Print ISSN 2287-979X
Online ISSN 2288-0011

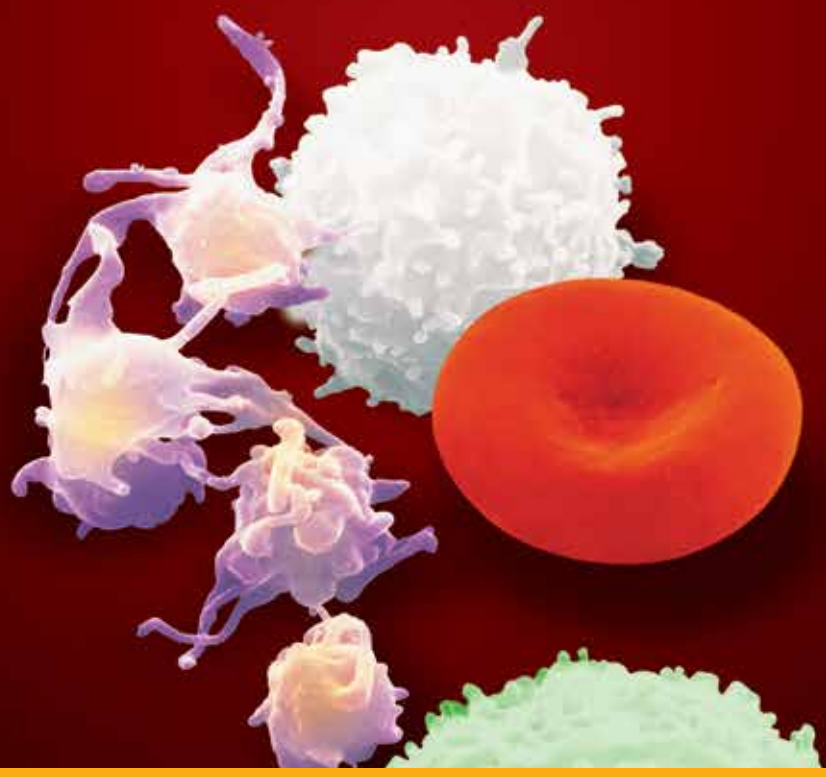
Vol. 57, No. S1, April 2022

BLOOD RESEARCH

bloodresearch.or.kr

2022 Korean Society of Hematology
International Conference
& 63rd Annual Meeting

Date : March 31(Thu.) - April 2(Sat.), 2022
Venue : Virtual



The Korean Society of Hematology

iCKSH 2022

2022 KOREAN SOCIETY OF HEMATOLOGY INTERNATIONAL CONFERENCE & 63rd ANNUAL MEETING

March 31 - April 2, 2022 VIRTUAL

ABSTRACT BOOK

BLOOD RESEARCH
Blood Res Vol. 57, No. S1, April 2022
bloodresearch.or.kr / p-ISSN 2287-979X / e-ISSN 2288-0011

BLOOD RESEARCH
Blood Res Vol. 57, No. S1, April 2022
bloodresearch.or.kr / p-ISSN 2287-979X / e-ISSN 2288-0011

About Blood Research

Blood Research is a peer-reviewed open-access journal and delivers important clinical, translational and basic study results in hematology and related fields to the readers worldwide. The areas covered by **Blood Research** include topics ranging from basic laboratory research to clinical studies, translational studies and precision medicine in the field of hematology. Any physicians or researchers throughout the world are welcome to submit a manuscript related to topics in hematology written in English. Our readership consists of clinical hematologists, hematopathologists, clinical oncologists, scientists in related fields, laboratory technicians, nurses and students.

All of the submitted manuscripts undergo intensive peer review by at least two independent reviewers and are selected based on the importance of the topic, originality of the work, quality of the content, and the compliance to the journal's format.

Blood Research publishes Original Articles, Review Articles, Editorials, Perspectives, Letters to the Editor, and Images of Hematology. It is published online (http://bloodresearch.or.kr) and in print quarterly (March 31, June 30, September 30, and December 31). All the articles published online are made publicly available in PDF files for free-of-charge. The printed copy of our Journal is distributed without charge to the members of the hematologic Societies. Corresponding author also receives the free copy of the journal in which his/her article was published.

Blood Research is indexed and covered by ESCI, PubMed Central, Scopus, KoreaMed Synapse, and CrossRef.

As the official journal of the Korean Society of Hematology, **Blood Research** has been published since 1966. As the international journal in the field of hematology, its former journal title, the Korean Journal of Hematology (p-ISSN 1738-7949, e-ISSN 2092-9129), has been changed to **Blood Research** since 2013.

The logo represents three types of cells (red blood cell, nucleated blood cell, and stem cell) in the field of hematology, and the earth, which overall signifies globalization and international scientific forum for blood research.

Open Access Policy

Disclaimer
No responsibility is assumed by the Societies for statements and opinions expressed by the contributors to the Journal.

Editorial Office

King's Garden Officetel 2-220,
24, Sajik-ro 8-gil, Jongno-gu, Seoul 03174, Korea
Tel: +82-2-516-6581, Fax: +82-2-516-6582,
E-mail: journal@bloodresearch.or.kr,
Homepage: http://bloodresearch.or.kr

This paper meets the requirements of KS X ISO 9706-1994 and ANSI/NISO Z.39.48-1992 (Permanence of Paper).
Printed by MEDrang Inc. 31st Floor, Prime Center, 85 Gwangnaru-ro 56-gil, Gwangjin-gu, Seoul 05116, Korea
Tel: +82-2-325-2093, Fax: +82-2-325-2095, E-mail: info@medrang.co.kr, Homepage: http://medrang.co.kr

CONTENTS

WELCOME MESSAGE

Dear Colleagues and Friends,

On behalf of the organizing committee, it is our great pleasure to invite you to participate in the 2022 Korean Society of Hematology (KSH) International Conference & 63rd Annual Meeting, hosted by KSH, from March 31 to April 2, 2022.

Held every year since 2018, the ICKSH conference shares up-to-date information and provides a unique opportunity for world class leaders in the field to debate vital and contentious issues in Hematology.

While many of us have endured personal and professional challenges over the course of the pandemic and the world is slowly taking the road to recovery, it remains our top priority and responsibility to ensure the health and safety of our participants. With this in mind, the ICKSH 2021 was held as a virtual event last year. Hoping to overcome all these difficulties, we are eagerly looking forward to meeting face to face in Seoul, Korea in the near future.

At the ICKSH 2022, our internationally renowned faculty will provide you with expert insights on the latest developments in benign hematologic diseases, various types of hematologic malignancies, coagulation/thrombosis related disorders and transfusion medicine, offering an unparalleled opportunity to explore the latest global updates.

We hope you to enjoy ICKSH 2022!

Dong-Wook Kim, MD., Ph.D.
Congress Chair
The Korean Society of Hematology

Je-Hwan Lee, MD., Ph.D.
President
The Korean Society of Hematology

ICKSH2022 ORGANIZING COMMITTEE

Congress Chair
Dong-Wook Kim
Uijeongbu Eulji Medical Center, Eulji University

President
Je-Hwan Lee
University of Ulsan College of Medicine

Auditor
Deog Yeon Jo
Chungnam National University College of Medicine

Auditor
Seok Lae Chae
Dongguk University College of Medicine

Secretary-General
Seongsoo Jang
University of Ulsan College of Medicine

Vice Secretary-General
Kyung-Nam Koh
University of Ulsan College of Medicine

Scientific Program Committee Chair
Jin Seok Kim
Yonsei University College of Medicine

Scientific Program Committee Vice-chair
Dong-Yeop Shin
Seoul National University College of Medicine

Finance Committee Chair
Seok Jin Kim
Sungkyunkwan University School of Medicine

Editor-in-Chief
Myung Geun Shin
Chonnam National University Medical School

Health Insurance Committee Chair
Yeung-Chul Mun
Ewha Womans University School of Medicine

Legislation Committee Chair
Yoon Hwan Chang
Seoul National University College of Medicine

International Cooperation Committee Chair
Keon Hee Yoo
Sungkyunkwan University School of Medicine

Research Committee Chair
Deok Hwan Yang
Chonnam National University Medical School

Medical Info. & Social Cooperation Committee Chair
Hyoung Jin Kang
Seoul National University College of Medicine

Medical Policy Committee Chair
Nack Gyun Chung
The Catholic University of Korea, College of Medicine

Public Relations Committee Chair
Young Kyung Lee
Hallym University College of Medicine

Education Committee Chair
Hyo Jung Kim
Hallym University College of Medicine

Membership Committee Chair
Chang-Ki Min
The Catholic University of Korea, College of Medicine

Textbook Committee Chair
Sung Hyun Kim
Dong-A University College of Medicine

Society Cooperation Committee Chair
Young Rok Do
Keimyung University School of Medicine

ICKSH2022 EXECUTIVE STEERING COMMITTEE

Congress Chair
Dong-Wook Kim
Uijeongbu Eulji Medical Center

President
Je-Hwan Lee
University of Ulsan College of Medicine

Secretary-General
Seongsoo Jang
University of Ulsan College of Medicine

Vice Secretary-General
Kyung-Nam Koh
University of Ulsan College of Medicine

Scientific Program Committee Chair
Jin Seok Kim
Yonsei University College of Medicine

Scientific Program Committee Vice-chair
Dong-Yeop Shin
Seoul National University College of Medicine

Finance Committee Chair
Seok Jin Kim
Sungkyunkwan University School of Medicine

International Cooperation Committee Chair
Keon Hee Yoo
Sungkyunkwan University School of Medicine

Research Committee Chair
Deok Hwan Yang
Chonnam National University Medical School

Public Relations Committee Chair
Young Kyung Lee
Hallym University College of Medicine

PROGRAM AT A GLANCE Thursday, March 31

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
08:00-09:00	Registration			
08:50-09:00	Opening Remark			
09:00-10:30	**JS01** KAI-KSH Joint Session	**SS01** Pediatric Disease	**SS02** Lymphoma (1) - B cell / CLL	**ES01** Platelet Disorder
	Next generation CAR-T cell therapy against hematological malignancies (Kyungho Choi, Korea)	Primary immune regulatory disorder for the pediatric hematologist and oncologist (Shanmuganathan Chandrakasan, USA)	Molecular classification of diffuse large B-cell lymphoma and novel treatment strategies (Daisuke Ennishi, Japan)	Diagnostic work up of inherited platelet disorder (Bohyun Kim, Korea)
	Effective conditioning regimen in adoptive T cell therapy of cancer (Chungyong Han, Korea)	Clonal evolution and somatic reversion in bone marrow failure (Akiko Shimamura, USA)	Novel immunotherapeutic antibodies for B-cell NHL (Gilles Salles, USA)	Recent advances in treatments of immune thrombocytopenia (Dae Sik Kim, Korea)
	Tissue resident memory T cells in multiple myeloma (Yoon Seok Choi, Korea)			
	T-cell-based immunotherapeutic strategies against EBV-positive malignancies using the novel TCR specific for LMP1 antigen (Tai-Gyu Kim, Korea)	Molecular landscape of pediatric AML (Soheil Meshinchi, USA)	Targeting B-cell receptor and BCL-2 in chronic lymphocytic leukemia (Susan M. O'Brien, USA)	Thrombocytopenia in pregnancy (Young Hoon Park, Korea)
10:30-11:15	**PLENARY LECTURE I** Immune landscape of hematological malignancies and functional screening tools (Satu Mustjoki, Finland)			
11:15-11:30	Break			

PROGRAM AT A GLANCE Thursday, March 31

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
11:30-12:10	[Satellite] **SY01** HANDOK	[Satellite] **SY02** astellas	[Satellite] **SY03** NOVARTIS	[Satellite] **SY04** Janssen
	What is the role of C5 inhibitors in PNH? (Jin Seok Kim, Korea)	Gilteritinib: ADMIRAL study and real world experience (Byung Sik Cho, Korea)	Role of CD19-directed CAR-T therapy in patients with DLBCL (Novartis Kymriah symposium) (Koji Izutsu, Japan)	Immunotherapy in multiple myeloma (Ajai Chari, USA)
12:10-12:40	E-poster Exhibition			
12:40-13:40	**Young Investigator Presentation**	**OP01** AML, MDS	**OP02** Lymphoma, Histiocytosis	**OP03** Laboratory Hematology
13:40-13:55	Break			
13:55-15:25	**AS01** Asian Session 1 - AA (13:55-14:55)	**SS03** MPN	**SS04** MM	**ES02** AML
	Korean treatment guideline for aplastic anemia (Jun Ho Jang, Korea)	Recent advances in molecular diagnosis, prognosis and monitoring of MPNs (Myungshin Kim, Korea)	Evolution of myeloma from the normal plasma cell to disease complexity (Niccolo Bolli, Italy)	Human AML stem cell: evolution of concept (Dong-Yeop Shin, Korea)
	Aplastic anemia immunosuppressive therapy in China (Zhao Xin, China)	Molecular mechanisms underlying the development of MPN by mutant calreticulin and the therapeutic potential of an antibody targeting mutant calreticulin (Norio Komatsu, Japan)	The power of ONE: immunology in the age of single cell genomics (Ido Amit, Israel)	Recent update of AML risk stratification (Hyoeun Shim, Korea)
	Clinical significance of detecting HLA-class I allele-lacking leukocytes in patients with aplastic anemia (Kohei Hosokawa, Japan)			
		Targeting pro-inflammatory signaling, including IL8, in myelofibrosis: the pathway into the clinic (Andrew J. Dunbar, USA)	Clinical implication of immune network in multiple myeloma (Je-Jung Lee, Korea)	FLT3 mutated AML (Jae-Sook Ahn, Korea)

PROGRAM AT A GLANCE Thursday, March 31

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
15:25-15:40	Break			
15:40-17:10	**JS02** **KOGO-KSH Joint Session**	**SS05** **CML**	**SS06** **Cell Therapy/ Transplantation**	**ES03** **Thrombosis/ Hemostasis**
	Developing single-cell data integration pipeline to find novel cell types and gene markers for immune diseases (Jong-Eun Park, Korea)	Resistance mechanism in CML (Kimmo Porkka, Finland)	Immune landscapes and chemotherapy resistance in AML (Sergio Rutella, UK)	Advances in laboratory assessment in thrombosis/hemostasis (Jaewoo Song, Korea)
	Detection of enhancer hijacking of oncogenes in multiple myeloma (Jin-Wu Nam, Korea)	Mutational landscape in CML (Simona Soverini, Italy)	Towards next-generation T cell engineering for cancer (Chan Hyuk Kim, Korea)	Cancer-associated thrombosis (Ho-Young Yhim, Korea)
	Pharmacogenetics of childhood acute lymphoblastic leukemia (Hyery Kim, Korea)			
	Evaluating leukemic structural variations using optical genome mapping (Saeam Shin, Korea)	CML/MPN stem cells and the bone marrow microenvironment (Steffen Koschmieder, Germany)	Endogenous retroviruses as a source of tumor antigens in solid tumors and acute myeloid leukemia (Stéphane Depil, France)	Recent advances in the management of immune mediated TTP (Sung Hwa Bae, Korea)

PROGRAM AT A GLANCE Friday, April 1

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
08:00-09:00	Registration			
09:00-10:30	**JS03** **ASH-KSH Joint Symposium - Histiocytosis**	**SS07** **Stem Cell Biology**	**SS08** **Thrombosis & Hemostasis**	**ES04** **Plasma Cell Disorder**
	Biologic and clinical consequences of the $BRAF^{V600E}$ mutation in Langerhans cell histiocytosis (Kenneth McClain, USA)	Losing sense of self and surroundings: hematopoietic stem cell aging and leukemic transformation (Emmanuelle Passegue, USA)	Mechanism of thrombosis and bleeding in viral infection: focusing on COVID-19 (Marcel Levi, UK)	Diagnosis and management of monoclonal gammopathy of clinical significance (Hyungwoo Cho, Korea)
	Advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis (Kim E. Nichols, USA)	Hematopoietic stem and progenitor cell signaling in the niche (Peter Kurre, USA)	COVID-19 vaccine related hematologic manifestations (Soo-Mee Bang, Korea)	Update in the POEMS syndrome (Yu Ri Kim, Korea)
	Current status of diagnosis and treatment of Langerhans cell histiocytosis in Korea (Kyung-Nam Koh, Korea)			
	Adult hemophagocytic lymphohistiocytosis in Korea (Seok Jin Kim, Korea)	Thrombopoietin as an expansion factor for hematopoietic stem cells (Toshio Suda, Japan)	Thrombotic thrombocytopenic purpura in 2022: novel therapies and focus on long term outcomes (Shruti Chaturvedi, USA)	Update in the primary plasma cell leukemia (Sung-Hoon Jung, Korea)
10:30-11:15	**PLENARY LECTURE II** Rational development of targeted therapies to cure molecular subtypes of DLBCL (Louis M. Staudt, USA)			
11:15-11:30	Break			

PROGRAM AT A GLANCE Friday, April 1

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
11:30-12:10	[Satellite] **SY05** KYOWA KIRIN Role of romiplostim in ITP and AA (Jun Ho Jang, Korea)	[Satellite] **SY06** Otsuka The updated information of ponatinib use in chronic myeloid leukemia (Jorge E. Cortes, USA)	[Satellite] **SY07** Roche Strategic treatment for diffuse large B-cell lymphoma; incorporating polatuzumab to DLBCL (Christopher Flowers, USA)	[Satellite] **SY08** Bristol Myers Squibb Celgene | A Bristol Myers Squibb Company Optimal treatment with IMiDs in Newly diagnosed multiple myeloma (Luciano J. Costa, USA)
12:10-12:40	E-poster Exhibition			
12:40-13:40	**OP04** ALL	**OP05** Anemia, BMF, CML, MPN	**OP06** MM	**OP07** Platelet, Transfusion
13:40-13:55	Break			
13:55-14:40	**Presidential Symposium** Toward precision medicine in AML (Hartmut Döhner, Germany)			

PROGRAM AT A GLANCE Friday, April 1

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
14:40-16:10	**MS01** **MOU Country Session - MM** (14:40-15:40)	**SS09** **MDS**	**SS10** **ALL**	**ES05** **AA and BMF**
	Managing multiple myeloma in a resource-limited region: diagnosis and treatment in Armenia (Yervand K. Hakobyan, Armenia)	Pathophysiology of spliceosome mutations in MDS (Andrea Pellagatti, UK)	Chemotherapy vs. allogeneic HSCT for Ph–negative adult ALL (Josep-Maria Ribera, Spain)	Genetics and genomics of bone marrow failure syndrome (Hyun-Young Kim, Korea)
	Renal involvement in plasma cell disorder: learning from real-life practice (Suporn Chun, Thailand)	Role of extracellular vesicles and miRNA in MDS (Sophie Park, France)	Clonal heterogeneity in ALL (Jan Cools, Belgium)	Aplastic anemia: transplant vs. non-transplant options (Ik-Chan Song, Korea)
	Treatment sequence decision in multiple myeloma considering reimbursement status (Youngil Koh, Korea)			
		Challenges in the diagnosis and treatment of overlap MDS/MPN syndromes (Antonio Almeida, Portugal)	Adoptive cellular immunotherapies based on chimeric antigen receptors (Pablo Menendez, Spain)	Overview of bone marrow failure syndrome (Meerim Park, Korea)
16:10-16:25	Break			

PROGRAM AT A GLANCE Friday, April 1

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
16:25-17:55	**JS04** **EHA-KSH Joint Symposium - CML**	**SS11** **Advanced Technology**	**SS12** **Benign Hematology (Anemia)**	**ES06** **Lymphoma**
	Failing a second-generation TKI: when the guidelines don't always help (Jane Apperley, UK)	Hematopoiesis and leukemia through the lens of single cell genomics (Lars Velten, Spain)	The iron-erythropoiesis cross-talk in health and disease (Antonella Nai, Italy)	Lymphoma pathology: basic immunohistochemistry for lymphoma diagnosis (Junhun Cho, Korea)
	Discontinuation of tyrosine kinase inhibitors in CML patients in clinical practice (Antonio Almeida, Portugal)	Computer vision in hematologic malignancies (Oscar Brück, Finland)	Autoimmune hemolytic anemia: state-of-the-art hypotheses on pathogenesis and their application to treatment (Bruno Fattizzo, Italy)	Staging and response assessment of lymphoma (Kwai Han Yoo, Korea)
	Second and later line therapy: the role of ponatinib in Korean patients with CML (Jeong-Ok Lee, Korea)			
	Stopping tyrosine kinase inhibitor in CML; perspectives from Korean data (Hawk Kim, Korea)	Hydrogel-based stamping technology for solution-free blood cell staining (Dongyoung Lee, Korea)	Cold agglutinin disease: an update on pathogenesis and future prospects on therapy (Sigbjørn Berentsen, Norway)	Treatment of indolent lymphoma (Seong Hyun Jeong, Korea)

PROGRAM AT A GLANCE Saturday, April 2

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
07:30-08:30	Business Meeting			
08:30-09:00	Working Party Reports			
09:00-10:30	**AS02** **Asian Hematology Session 2 - Pediatric ALL** (09:00-10:00)	**SS13** **AML**	**SS14** **Lymphoma (2) - T cell / HL**	**ES07** **Supportive Care**
	Ma-Spore ALL studies: truly Asia approach to curing childhood ALL (Allen E.J. Yeoh, Singapore)	AML microenvironment and FLT3 inhibitor resistance (Elie Traer, USA)	Genomic landscape of peripheral T-cell lymphomas (Keisuke Kataoka, Japan)	Comprehensive geriatric assessment in older patients for intensive chemotherapy (Jung-Yeon Choi, Korea)
	Childhood ALL in Thailand and multicenter studies of Thai pediatric oncology group (Samart Pakakasama, Thailand)	Targeting TP53 mutation in AML (David A. Sallman, USA)	T-cell lymphomas of follicular helper T-cell derivation: pathology, mechanisms and therapeutic implications (Laurence de Level, Switzerland)	Evaluation and management of platelet transfusion refractoriness (Dae-Hyun Ko, Korea)
	The adherence to MRD time points improves treatment outcomes of childhood ALL in Taiwan: the experience of TPOG-ALL-2013 protocol (Hsi-Che Liu, Taiwan)			
		Adaptive immune resistance and immune evasion by programmed death-1 homolog (PD-1H/VISTA) in AML (Tae Kon Kim, USA)	Targeted therapy to small molecules in peripheral T cell lymphomas (Deok Hwan Yang, Korea)	Advances in management of invasive fungal infections: perspectives on hematologic diseases (Dong-Gun Lee, Korea)
10:30-11:15	**PLENARY LECTURE III** Improving outcomes after CD19-targeted CAR T-cell therapy (Jordan Gauthier, USA)			
11:15-11:30	Break			
11:30-12:10	**Award Ceremony & Closing**			

VIRTUAL CONFERENCE INFORMATION

VIRTUAL CONFERENCE WEBSITE

http://virtual.icksh.org

REGISTRATION

Please log in using the ID and PW you used to pre-register on the ICKSH 2022 website. If you missed pre-registration, please register onsite.

>> On-Site Registration Days
March 31 - April 2, 2022

>> On-Site Registration Fees

- Overseas

Category	On-Site Registration Fees
General	USD 50
Resident / Trainee / Nurse / Student	USD 25

- Domestic

Category	On-Site Registration Fees	Note
KSH Member	KRW 50,000	Free for KSH members 65 years or above
Fellow / Nurse / Researcher	KRW 30,000	-
Student / Resident	KRW 20,000	-
Non-Member	KRW 150,000	-

* If you use multiple devices with the same ID, your login will be canceled automatically.

VIDEO LECTURES AND Q&A

All lectures and presentations are pre-recorded and broadcast during session time. After the videos are streamed, chairs and speakers have live Q&A and discussion.
Participants can watch VOD lectures for free for one month after the conference. VOD lectures are limited to lectures with consent for distribution.

SATELLITE SYMPOSIA

Please attend the satellite symposium hosted by each of our sponsors over the three-day period and get a point for the prize.

[SY01] Satellite Symposium 01

HANDOK

March 31 (Thursday), 11:30-12:10 / Room 1

Chair
Jun Ho Jang (Sungkyunkwan University, Korea)

Presentation
What is the role of C5 inhibitors in PNH?
Jin Seok Kim (Yonsei University College of Medicine, Korea)

VIRTUAL CONFERENCE INFORMATION

[SY02] Satellite Symposium 02

March 31 (Thursday), 11:30-12:10 / Room 2

Chair
Hyeoung-Joon Kim (Hwasun Chonnam National University Hospital, Korea)

Presentation
Gilteritinib: ADMIRAL study and real world experience
Byung Sik Cho (College of Medicine, The Catholic University of Korea, Korea)

[SY03] Satellite Symposium 03

March 31 (Thursday), 11:30-12:10 / Room 3

Chair
Sung-Soo Yoon (Seoul National University College of Medicine, Korea)

Presentation
Role of CD19-directed CAR-T therapy in patients with DLBCL (Novartis Kymriah symposium)
Koji Izutsu (National Cancer Center Hospital, Japan)

[SY04] Satellite Symposium 04

March 31 (Thursday), 11:30-12:10 / Room 4

Chair
Chang-Ki Min (Seoul St. Mary's Hospital, The Catholic University of Korea, Korea)

Presentation
Immunotherapy in multiple myeloma
Ajai Chari (Mount Sinai, USA)

[SY05] Satellite Symposium 05

April 1 (Friday), 11:30-12:10 / Room 1

Chair
Jong Wook Lee (Seoul St. Mary's Hospital, The Catholic University of Korea, Korea)

Presentation
Role of romiplostim in ITP and AA
Jun Ho Jang (Sungkyunkwan University, Korea)

[SY06] Satellite Symposium 06

April 1 (Friday), 11:30-12:10 / Room 2

Chair
Dong-Wook Kim (Uijeongbu Eulji Medical Center, Eulji University, Korea)

Presentation
The updated information of ponatinib use in chronic myeloid leukemia
Jorge E. Cortes (Georgia Cancer Center, USA)

[SY07] Satellite Symposium 07

April 1 (Friday), 11:30-12:10 / Room 3

Chair
Seok Jin Kim (Sungkyunkwan University School of Medicine, Korea)

Presentation
Strategic treatment for diffuse large B-cell lymphoma; incorporating polatuzumab to DLBCL
Christopher Flowers (The University of Texas MD Anderson Cancer Center, USA)

VIRTUAL CONFERENCE INFORMATION

[SY08] Satellite Symposium 08

Bristol Myers Squibb
Celgene | A Bristol Myers Squibb Company

April 1 (Friday), 11:30-12:10 / Room 4

Chair
Kihyun Kim (Sungkyunkwan University School of Medicine, Korea)

Presentation
Optimal treatment with IMiDs in newly diagnosed multiple myeloma
Luciano J. Costa (The University of Alabama at Birmingham, USA)

E-POSTER & ORAL PRESENTATIONS

All participants can view the E-posters and oral presentations in the E-Poster/Oral section of the ICKSH2022 virtual conference website. Participants will have an opportunity to win the Lucky Draw after viewing more than 50 of the E-posters.

VIRTUAL EXHIBITION HALL

Meet our sponsors virtually. If you visit e-booths and complete the stamp sheet, and win a chance to get prizes.

ICKSH 2022 SECRETARIAT OFFICE

Onsite	T. TBA T. TBA E. icksh@icksh.org
Post Conference	T. +82-2-566-6031 F. +82-2-566-6087 E. icksh@icksh.org

CME CREDIT INFORMATION (DOMESTIC PARTICIPANTS ONLY)

Please be sure that Korean participants who claim CME credit must press the Enter / Exit button when entering or leaving the session room to record the training time.

1) CME Credit Rating: By the Korean Medical Association

Category	March 31	April 1	April 2	Remarks
KMA CME Credit	6	6	2	-
KAIM CME Credit		2		During the conference period

2) Korean participants must attend the sessions and complete the viewing time everyday to get Daily CME credits.

3) After entering and exiting the session, please click the "Enter" and "Exit" buttons to record your attendance time. The entry/exit records for each session are required for the credit to be recognized.
* When moving between rooms, you must click the "Exit" button, and click the "Enter" button in the new room.

VIRTUAL CONFERENCE INFORMATION

4) Credits accrued per hour of attendance per day

Residence time	Recognition of Credit
From 1 hour or more to less than 2 hours	1 credit
From 2 hours or more to less than 3 hours	2 credit
From 3 hours or more to less than 4 hours	3 credit
From 4 hours or more to less than 5 hours	4 credit
From 5 hours or more to less than 6 hours	5 credit
From 6 hours or more	6 credit

** The training time you see on My page of the Virtual conference website includes the break time. The exact session viewing time will be counted after the conference.

EVENTS

We have exciting events for participants. Participants who complete the mission will win a prize!

ICKSH POINTS

>> Event Period: March 31 to April 2 (KST)
The Point Event Prizes will be given if you get 300P (points) a day! (200P on Saturday)
You can check your accumulated points on My Page of the virtual conference website.

HOW TO EARN POINTS

Action	Points
Enter the Platform (Log in)	100P/Day
Attend an Oral Session	100P/Day
Attend a Session (Except Satellite Symposia, Oral Sessions)	50P/Session
Attend the Closing Ceremony (Saturday Only)	50P
Submit the Conference Survey (Saturday Only)	50P

PRIZES

STARBUCKS CARD

For Korean participants and those living in Korea, KRW 10,000 (daily) Starbucks Gift Card will be given for the prize.

amazon.com gift card

For others, USD 10 (daily) Amazon eGift cards will be given for the prize.

E-POSTER LUCKY DRAW

View more than 50 of the e-posters and get the chance to be a winner!
>> Event Period: March 31 to April 2, 11:00(KST)
Eligibility to win the lucky draw is awarded after viewing more than 50 E-Posters.
Winners will be posted on the ICKSH2022 website after the conference and will be contacted individually.

PRIZES

For Korean participants and those residing in Korea, gifts will be given for the prize.

1 winner

Dyson Airwrap™ styler Complete

3 winners

Apple Watch SE (GPS, 44mm) or Galaxy Watch 4 Classic (Bluetooth, 46mm)

10 winners

LG TONE Free

amazon.com gift card

* For others, an Amazon eGift card in the amount of the product will be provided.

EVENTS

E-BOOTH STAMP TOUR

If you visit e-booths and complete the stamp sheet, the prizes will be given.
>> Event Period: March 31 to April 2 (KST)

ELIGIBILITY TO GET GIFTS: GET 21 STAMPS [DAILY]

Sponsor Level	How to Get Stamps
Diamond 8 E-Booths	Download 1 Leaflet & Watch 1 Advertisement (Each E-Booth)
Platinum 3 E-Booths	Download 1 Leaflet (Each E-Booth)
Gold 6 E-Booths	Download 1 Leaflet (Each E-Booth)
4 E-Booths of Silver & Bronze	Access E-Booth

PRIZES

MARCH 31

Hand Sanitizer

APRIL 1

Tea Set

APRIL 2

Car Air Freshener

* For others, an Amazon eGift card in the amount of the product will be provided.

SATELLITE SYMPOSIA EVENT

Attend the Satellite symposium and get an e-gift card!
>> Event Period: March 31 to April 1 (KST)
>> Daily Event: It is required to watch at least 30 minutes of the luncheon symposium.

PRIZES

For Korean participants and those residing in Korea, KRW 10,000 (Daily) Culture Land Certificate will be given for the prize.

For others, USD 10 (Daily) Amazon eGift cards will be given for the prize.

SPONSORS (Acknowledgements)

DIAMOND

Otsuka

NOVARTIS

KYOWA KIRIN

Roche

HANDOK

astellas

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Bristol Myers Squibb™
Celgene | A Bristol Myers Squibb Company

SPONSORS (Acknowledgements)

PLATINUM

AMGEN

Takeda

GC Pharma

GOLD

CELLTRION PHARM
CELLTRION

ANTENGENE

JW Pharmaceutical

MSD
INVENTING FOR LIFE

YUHAN

Pfizer

sanofi

abbvie

SPONSORS (Acknowledgements)

SILVER

Roche

BRONZE

sysmex
Lighting the way with diagnostics

DONG-A ST

ONO PHARMA KOREA

Bristol Myers Squibb™

DAEWOONG PHARMACEUTICAL CO.,LTD.

samyang

novo nordisk®

BD

BARD
has joined BD

EUSAPharma

KEY SPEAKERS

MARCH 31 (Thursday)

[PL01] Plenary Lecture 01

10:30 - 11:15 | Room 1

Immune landscape of hematological malignancies and functional screening tools

Satu Mustjoki
University of Helsinki, Finland

APRIL 1 (Friday)

[PL02] Plenary Lecture 02

10:30 - 11:15 | Room 1

Rational development of targeted therapies to cure molecular subtypes of DLBCL

Louis M. Staudt
National Cancer Institute, USA

APRIL 1 (Friday)

[PS] Presidential Symposium

13:55 - 14:40 | Room 1

Toward precision medicine in AML

Hartmut Döhner
University of Ulm, Germany

APRIL 2 (Saturday)

[PL03] Plenary Lecture 03

10:30 - 11:15 | Room 1

Improving outcomes after CD19-targeted CAR T-cell therapy

Jordan Gauthier
University of Washington, USA

DAILY PROGRAM

Thursday, March 31

Friday, April 1

Saturday April 2

DAILY PROGRAM Thursday, March 31

08:50-09:00 **Opening Remark**

09:00-10:30 **[JS01] KAI-KSH Joint Session** Room 1

Chairs Kyungho Choi (Seoul National University College of Medicine, Korea)
Seok-Goo Cho (The Catholic University of Korea, Korea)

JS01-1 Next generation CAR-T cell therapy against hematological malignancies
Kyungho Choi (Seoul National University College of Medicine, Korea)

JS01-2 Effective conditioning regimen in adoptive T cell therapy of cancer
Chungyong Han (National Cancer Center, Korea)

JS01-3 Tissue resident memory T cells in multiple myeloma
Yoon Seok Choi (Ajou University School of Medicine, Korea)

JS01-4 T-cell-based immunotherapeutic strategies against EBV-positive malignancies using the novel TCR specific for LMP1 antigen
Tai-Gyu Kim (The Catholic University of Korea, Korea)

09:00-10:30 **[SS01] Pediatric Disease** Room 2

Chairs Hye Lim Jung (Sungkyunkwan University School of Medicine, Korea)
Hyeon Jin Park (National Cancer Center, Korea)

SS01-1 Primary immune regulatory disorder for the pediatric hematologist and oncologist
Shanmuganathan Chandrakasan (Emory University School of Medicine, USA)

SS01-2 Clonal evolution and somatic reversion in bone marrow failure
Akiko Shimamura (Harvard Medical School, USA)

SS01-3 Molecular landscape of pediatric AML
Soheil Meshinchi (Fred Hutchinson Cancer Research Center, USA)

09:00-10:30 **[SS02] Lymphoma (1) - B cell / CLL** Room 3

Chairs Jae-Yong Kwak (Jeonbuk National University Medical School, Korea)
Deok Hwan Yang (Chonnam National University Medical School, Korea)

SS02-1 Molecular classification of diffuse large B-cell lymphoma and novel treatment strategies
Daisuke Ennishi (Okayama University Hospital, Japan)

SS02-2 Novel immunotherapeutic antibodies for B-cell NHL
Gilles Salles (Memorial Sloan Kettering Cancer Center, USA)

SS02-3 Targeting B-cell receptor and BCL-2 in chronic lymphocytic leukemia
Susan M. O'Brien (University of California, USA)

DAILY PROGRAM Thursday, March 31

09:00-10:30 **[ES01] Platelet Disorder** Room 4

Chairs Hyun Kyung Kim (Seoul National University College of Medicine, Korea)
Sung Hwa Bae (Daegu Catholic University Hospital, Korea)

ES01-1 Diagnostic work up of inherited platelet disorder
Bohyun Kim (Soonchunhyang University College of Medicine, Korea)

ES01-2 Recent advances in treatments of immune thrombocytopenia
Dae Sik Kim (Korea University Guro Hospital, Korea)

ES01-3 Thrombocytopenia in pregnancy
Young Hoon Park (Ewha Womans University Mokdong Hospital, Korea)

10:30-11:15 **[PL01] Plenary Lecture 01** Room 1

Chair Dong-Wook Kim (Uijeongbu Eulji Medical Center, Eulji University, Korea)

Immune landscape of hematological malignancies and functional screening tools
Satu Mustjoki (University of Helsinki, Finland)

11:15-11:30 Break

11:30-12:10 **[SY01] Handok** Room 1

Chair Jun Ho Jang (Sungkyunkwan University School of Medicine, Korea)

What is the role of C5 inhibitors in PNH?
Jin Seok Kim (Yonsei University College of Medicine, Korea)

11:30-12:10 **[SY02] Astellas** Room 2

Chair Hyeoung-Joon Kim (Hwasun Chonnam National University Hospital, Korea)

Gilteritinib: ADMIRAL study and real world experience
Byung Sik Cho (College of Medicine, The Catholic University of Korea, Korea)

11:30-12:10 **[SY03] Novartis** Room 3

Chair Sung-Soo Yoon (Seoul National University College of Medicine, Korea)

Role of CD19-directed CAR-T therapy in patients with DLBCL (Novartis Kymriah symposium)
Koji Izutsu (National Cancer Center Hospital, Japan)

DAILY PROGRAM Thursday, March 31

11:30-12:10 **[SY04] Janssen** Room 4

Chair Chang-Ki Min (Seoul St. Mary's Hospital, The Catholic University of Korea, Korea)

Immunotherapy in multiple myeloma
Ajai Chari (Mount Sinai, USA)

12:10-12:40 **E-poster Exhibition**

12:40-13:40 **[YI] Young Investigator Presentation** Room 1

Chairs Je-Hwan Lee (University of Ulsan College of Medicine, Korea)
Deok Hwan Yang (Chonnam National University Medical School, Korea)

YI-1 Establishment of a preclinical model for acquired resistance to FMS-like tyrosine kinase 3 (FLT3) inhibitors and development of a basis for overcoming the resistance in FLT3 mutated acute myeloid leukemia
Eun-Ji Choi (University of Ulsan College of Medicine, Korea)

YI-2 Identification of tyrosine kinase resistance mechanisms through next-generation sequencing analysis in chronic myeloid leukemia patients
Saeam Shin (Yonsei University College of Medicine, Korea)

YI-3 Correlation between cytomorphological findings and molecular genetic characteristics using digital imaging in patients with pre-myelodysplastic syndrome
Chang-Hun Park (Samsung Changwon Hospital, Korea)

YI-4 Clinical implication of plasma-derived circulating tumor DNA (ctDNA) changes in patients with advanced diffuse large B-cell lymphoma treated with immunochemotherapy
Ga-Young Song (Chonnam National University Medical School, Korea)

YI-5 A cohort study to investigate the correlation between the microbiome and diffuse large B cell lymphoma (DLBCL)
Sang Eun Yoon (Sungkyunkwan University School of Medicine, Korea)

YI-6 Analysis of marrow-infiltrating T cell subpopulation in newly diagnosed multiple myeloma
Myung-Won Lee (Chungnam National University College of Medicine, Korea)

YI-7 Multi-omics analysis of pediatric patients undergoing haploidentical hematopoietic stem cell transplantation with busulfun-based conditioning regimen and post-transplant cyclophosphamide
Kyung Taek Hong (Seoul National University College of Medicine, Korea)

YI-8 Development of acute GVHD biomarkers in pediatric patients
Sung Han Kang (Asan Medical Center, Korea)

12:40-13:40 **[OP01] AML, MDS** Room 2

Chairs Byung-Soo Kim (Korea University College of Medicine, Korea)
Dong-Yeop Shin (Seoul National University College of Medicine, Korea)

OP01-1 Potential prognostic significance of promoter methylation status of DNA repair genes at diagnosis in acute myeloid leukemia: analysis of TCGA-LAML cohort and patients in a single institution
Sholhui Park (Ewha Womans University School of Medicine, Korea)

DAILY PROGRAM Thursday, March 31

OP01-2 TP53-mutated AML with high variant allele frequency show better survival outcome with hypomethylating agents than with cytarabine-based induction
Hye Won Kook (Yonsei University College of Medicine, Korea)

OP01-3 WT1 gene expression in primary acute myeloid leukemia
Ishan Gupta (All India Institute of Medical Sciences, India)

OP01-4 Preliminary results by age group of treatment with CPX-351 plus venetoclax in adults with newly diagnosed AML: subgroup analysis of the v-fast trial
Vinod Pullarkat (City Of Hope Comprehensive Cancer Center, USA)

OP01-5 A randomized, phase II, comparative study with a parallel control for evaluating the efficacy and safety of 5-day azacitidine for patients with lower-risk MDS
Silvia Park (The Catholic University of Korea, Korea)

12:40-13:40 **[OP02] Lymphoma, Histiocytosis** Room 3

Chairs Ki-Seong Eom (College of Medicine, The Catholic University of Korea, Korea)
Sukjoong Oh (Hanyang University Seoul Hospital, Korea)

OP02-1 High incidence of MYD88 mutation associated with mutated IGHV gene in Korean chronic lymphocytic leukemias
Ari Ahn (The Catholic University of Korea, Korea)

OP02-2 First interim analysis results of ALPINE phase 3 study of zanubrutinib vs ibrutinib in R/R chronic lymphocytic leukemias/small lymphocytic leukemias
Won Seog Kim (Sungkyunkwan University School of Medicine, Korea)

OP02-3 CD 19 chimeric antigen receptor T cell therapy for relapsed/refractory B-cell lymphoid malignancies: the efficacies and safeties of tisa-cel in the real world
Sang Eun Yoon (Sungkyunkwan University School of Medicine, Korea)

OP02-4 Long-term real-world experience of Castleman's disease treatment
Gi June Min (The Catholic University of Korea, Korea)

OP02-5 Clinical analysis of modified HLH-04 regimen for the treatment of childhood hemophagocytic lymphohistiocytosis
Fenfen Cheng (Capital Medical University, China)

12:40-13:40 **[OP03] Laboratory Hematology** Room 4

Chairs Myung-Hyun Nam (Korea University Anam Hospital, Korea)
Young-Uk Cho (University of Ulsan College of Medicine, Korea)

OP03-1 Clinical-biochemical screening and genetic analysis of suspected inherited iron metabolism related anaemias using targeted NGS approach
Pankaj Sharma (PGIMER, India)

OP03-2 Comparison of clinical features, genetic alterations, and outcomes in patients with prefibrotic, overt primary myelofibrosis, and secondary myelofibrosis
Tong Yoon Kim (The Catholic University of Korea, Korea)

OP03-3 Flow cytometry of body fluid specimens: diagnostic value in hematologic malignancy
Smeeta G (All India Institute of Medical Sciences, India)

DAILY PROGRAM Thursday, March 31

OP03-4 Single-cell analysis of Multiple Myelomas refines bortezomib treatment responsiveness
Sung-Soo Park (The Catholic University of Korea, Korea)

OP03-5 Empagliflozin modulates CD4+ T cell differentiation via metabolic reprogramming in immune thrombocytopenia
Qin Jing (Shandong University, China)

13:40-13:55 Break

13:55-14:55 **[AS01] Asian Session I - AA** Room 1

Chairs Jong Wook Lee (Seoul St. Mary's Hospital, The Catholic University of Korea, Korea)
Hoon Kook (Chonnam National University Medical School, Korea)

AS01-1 Korean treatment guideline for aplastic anemia
Jun Ho Jang (Sungkyunkwan University School of Medicine, Korea)

AS01-2 Aplastic anemia immunosuppressive therapy in China
Zhao Xin (Institute of Hematology and Blood Diseases Hospital, China)

AS01-3 Clinical significance of detecting HLA-class I allele-lacking leukocytes in patients with aplastic anemia
Kohei Hosokawa (Kanazawa University, Japan)

13:55-15:25 **[SS03] MPN** Room 2

Chairs Chul Won Choi (Korea University Guro Hospital, Korea)
Sung-Yong Kim (Konkuk University School of Medicine, Korea)

SS03-1 Recent advances in molecular diagnosis, prognosis and monitoring of MPNs
Myungshin Kim (The Catholic University of Korea, Korea)

SS03-2 Molecular mechanisms underlying the development of MPN by mutant calreticulin and the therapeutic potential of an antibody targeting mutant calreticulin
Norio Komatsu (Juntendo University Graduate School of Medicine, Japan)

SS03-3 Targeting pro-inflammatory signaling, including IL8, in myelofibrosis: the pathway into the clinic
Andrew J. Dunbar (Memorial Sloan Kettering Cancer Center, USA)

13:55-15:25 **[SS04] MM** Room 3

Chairs Dong Soon Lee (Seoul National University College of Medicine, Korea)
Kihyun Kim (Sungkyunkwan University School of Medicine, Korea)

SS04-1 Evolution of myeloma from the normal plasma cell to disease complexity
Niccolo Bolli (University of Milan, Italy)

SS04-2 The power of ONE: immunology in the age of single cell genomics
Ido Amit (Weizmann Institute, Israel)

DAILY PROGRAM Thursday, March 31

SS04-3 **Clinical implications of immune networks in multiple myeloma**
Je-Jung Lee (Chonnam National University Medical School, Korea)

13:55-15:25 **[ES02] AML** Room 4

Chairs Dong-Yeop Shin (Seoul National University College of Medicine, Korea)
Byung Sik Cho (College of Medicine, The Catholic University of Korea, Korea)

ES02-1 **Human AML stem cell: evolution of concept**
Dong-Yeop Shin (Seoul National University College of Medicine, Korea)

ES02-2 **Recent update of AML risk stratification**
Hyoeun Shim (National Cancer Center, Korea)

ES02-3 **FLT3 mutated AML**
Jae-Sook Ahn (Chonnam National University Medical School, Korea)

15:25-15:40 **Break**

15:40-17:10 **[JS02] KOGO-KSH Joint Session** Room 1

Chairs Hae-Ock Lee (The Catholic University of Korea, Korea)
Sun-Young Kong (National Cancer Center, Korea)

JS02-1 **Developing single-cell data integration pipeline to find novel cell types and gene markers for immune diseases**
Jong-Eun Park (Korea Advanced Institute of Science and Technology, Korea)

JS02-2 **Detection of enhancer hijacking of oncogenes in multiple myeloma**
Jin-Wu Nam (Hanyang University, Korea)

JS02-3 **Pharmacogenetics of childhood acute lymphoblastic leukemia**
Hyery Kim (University of Ulsan College of Medicine, Korea)

JS02-4 **Evaluating leukemic structural variations using optical genome mapping**
Saeam Shin (Yonsei University College of Medicine, Korea)

15:40-17:10 **[SS05] CML** Room 2

Chairs Chul Won Jung (Sungkyunkwan University School of Medicine, Korea)
Won Sik Lee (Inje University College of Medicine, Korea)

SS05-1 **Resistance mechanism in CML**
Kimmo Porkka (Helsinki University Central Hospital, Finland)

SS05-2 **Mutational landscape in CML**
Simona Soverini (University of Bologna, Italy)

SS05-3 **CML/MPN stem cells and the bone marrow microenvironment**
Steffen Koschmieder (RWTH Aachen University, Germany)

DAILY PROGRAM Thursday, March 31

15:40-17:10 **[SS06] Cell Therapy / Transplantation** Room 3

Chairs Hyeon-Seok Eom (National Cancer Center, Korea)
Hyoung Jin Kang (Seoul National University College of Medicine, Korea)

SS06-1 Immune landscapes and chemotherapy resistance in AML
Sergio Rutella (Nottingham Trent University, UK)

SS06-2 Towards next-generation T cell engineering for cancer
Chan Hyuk Kim (Korea Advanced Institute of Science and Technology, Korea)

SS06-3 Endogenous retroviruses as a source of tumor antigens in solid tumors and acute myeloid leukemia
Stéphane Depil (Université Claude Bernard Lyon 1, France)

15:40-17:10 **[ES03] Thrombosis / Hemostasis** Room 4

Chairs Sung-Hyun Kim (Dong-A University College of Medicine, Korea)
Jin-Yeong Han (Dong-A University College of Medicine, Korea)

ES03-1 Advances in laboratory assessment in thrombosis/hemostasis
Jaewoo Song (Yonsei University College of Medicine, Korea)

ES03-2 Cancer-associated thrombosis
Ho-Young Yhim (Jeonbuk National University Medical School, Korea)

ES03-3 Recent advances in the management of immune mediated TTP
Sung Hwa Bae (Daegu Catholic University Hospital, Korea)

DAILY PROGRAM Friday, April 1

09:00-10:30 **[JS03] ASH-KSH Joint Symposium: Histiocytosis** Room 1

Chairs Jane Winter (Feinberg School of Medicine, USA)
Ho Joon Im (University of Ulsan College of Medicine, Korea)

JS03-1 Biologic and clinical consequences of the $BRAF^{V600E}$ mutation in Langerhans cell histiocytosis
Kenneth McClain (Texas Children's Cancer Center, USA)

JS03-2 Advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis
Kim E. Nichols (St. Jude Children's Research Hospital, USA)

JS03-3 Current status of diagnosis and treatment of Langerhans cell histiocytosis in Korea
Kyung-Nam Koh (University of Ulsan College of Medicine, Korea)

JS03-4 Adult hemophagocytic lymphohistiocytosis in Korea
Seok Jin Kim (Sungkyunkwan University School of Medicine, Korea)

09:00-10:30 **[SS07] Stem Cell Biology** Room 2

Chairs Myung Geun Shin (Chonnam National University Medical School, Korea)
June-Won Cheong (Yonsei University College of Medicine, Korea)

SS07-1 Losing sense of self and surroundings: hematopoietic stem cell aging and leukemic transformation
Emmanuelle Passegue (Columbia University Irving Medical Center, USA)

SS07-2 Hematopoietic stem and progenitor cell signaling in the niche
Peter Kurre (Children's Hospital of Philadelphia, USA)

SS07-3 Thrombopoietin as an expansion factor for hematopoietic stem cells
Toshio Suda (Kumamoto University, Japan)

09:00-10:30 **[SS08] Thrombosis & Hemostasis** Room 3

Chairs Soo-Mee Bang (Seoul National University College of Medicine, Korea)
Seongsoo Jang (University of Ulsan College of Medicine, Korea)

SS08-1 Mechanism of thrombosis and bleeding in viral infection: focusing on COVID-19
Marcel Levi (University College London Hospitals NHS Foundation Trust, UK)

SS08-2 COVID-19 vaccine related hematologic manifestations
Soo-Mee Bang (Seoul National University College of Medicine, Korea)

SS08-3 Thrombotic thrombocytopenic purpura in 2022 - novel therapies and focus on long term outcomes
Shruti Chaturvedi (Johns Hopkins University School of Medicine, USA)

09:00-10:30 **[ES04] Plasma Cell Disorder** Room 4

Chairs Je-Jung Lee (Chonnam National University Medical School, Korea)
Dok Hyun Yoon (University of Ulsan College of Medicine, Korea)

ES04-1 Diagnosis and management of monoclonal gammopathy of clinical significance
Hyungwoo Cho (University of Ulsan College of Medicine, Korea)

DAILY PROGRAM Friday, April 1

ES04-2 **Update in the POEMS syndrome**
Yu Ri Kim (Yonsei University College of Medicine, Korea)

ES04-2 **Update in the primary plasma cell leukemia**
Sung-Hoon Jung (Chonnam National University Hwasun Hospital, Korea)

10:30-11:15 **[PL02] Plenary Lecture 02** Room 1

Chair Sung-Soo Yoon (Seoul National University College of Medicine, Korea)

Rational development of targeted therapies to cure molecular subtypes of DLBCL
Louis M. Staudt (National Cancer Institute, USA)

11:15-11:30 Break

11:30-12:10 **[SY05] Kyowa Kirin** Room 1

Chair Jong Wook Lee (Seoul St. Mary's Hospital, The Catholic University of Korea, Korea)

Role of romiplostim in ITP and AA
Jun Ho Jang (Sungkyunkwan University School of Medicine, Korea)

11:30-12:10 **[SY06] Otsuka** Room 2

Chair Dong-Wook Kim (Uijeongbu Eulji Medical Center, Eulji University, Korea)

The updated information of ponatinib use in chronic myeloid leukemia
Jorge E. Cortes (Georgia Cancer Center, USA)

11:30-12:10 **[SY07] Roche** Room 3

Chair Seok Jin Kim (Sungkyunkwan University School of Medicine, Korea)

Strategic treatment for diffuse large B-cell lymphoma; incorporating polatuzumab to DLBCL
Christopher Flowers (The University of Texas MD Anderson Cancer Center, USA)

11:30-12:10 **[SY08] BMS-Celgene** Room 4

Chair Kihyun Kim (Sungkyunkwan University School of Medicine, Korea)

Optimal treatment with IMiDs in newly diagnosed multiple myeloma
Luciano J. Costa (The University of Alabama at Birmingham, USA)

DAILY PROGRAM Friday, April 1

12:10-12:40 **E-poster Exhibition**

12:40-13:40 **[OP04] ALL** Room 1

Chairs Inho Kim (Seoul National University Hospital, Korea)
Kyung-Nam Koh (University of Ulsan College of Medicine, Korea)

OP04-1 Expression pattern of non-homologous end joining DNA repair pathway genes and its clinical relevance in T-lineage acute lymphoblastic leukemia
Anita Chopra (All India Institute of Medical Sciences, India)

OP04-2 Interim analysis of the prospective phase II study of individualized 6-mercaptopurine dosing based on pharmacogenomics in childhood acute lymphoblastic leukemia
Hyery Kim (University of Ulsan College of Medicine, Korea)

OP04-3 Current treatment trends of infant Leukemia in Korea based on a retrospective multicenter reivew: the Korean society of hematology, pediatric all working group
Seung Min Hahn (Yonsei Cancer Center, Korea)

OP04-4 Prognostic impact of cytogenetic classification in adult all patients treated with intensive chemotherapy and allogeneic HCT-based post-remission therapy
Jae-Ho Yoon (The Catholic University of Korea, Korea)

OP04-5 DEFIFrance registry study: efficacy and safety of defibrotide for the treatment of severe/very severe VOD/SOS after hematopoietic cell transplantation
Mohamad Mohty (Hôpital St Antoine, Sorbonne University, France)

12:40-13:40 **[OP05] Anemia, BMF, CML, MPN** Room 2

Chairs Hawk Kim (Gachon University College of Medicine, Korea)
Sung-Eun Lee (The Catholic University of Korea, Korea)

OP05-1 Causal role of iron status on anemia and on cardiometabolic outcomes among UK whites and Taiwanese Han Chinese using hemoglobin-genetic risk scores
Vanessa Joy Timoteo (National Yang Ming Chiao Tung University and Academia Sinica, Taiwan)

OP05-2 Favorable outcomes of familial-mismatched donor transplantation using post-transplant cylophosphamide(PTCy) for pediatric severe aplastic anemia
Jae Won Yoo (The Catholic University of Korea, Korea)

OP05-3 The long-term efficacy and safety of eculizumab in patients with paroxysmal nocturnal hemoglobinuria; retrospective study on behalf of Korean society of hematology aplastic anemia working party
Jin Seok Kim (Yonsei University College of Medicine, Korea)

OP05-4 Response to chemotherapy in patients with juvenile Myelomonocytic Leukemia in Korea: The Korean pediatric hematology-oncology group(KPHOG)
Eun Sang Yi (Korea University College of Medicine, Korea)

OP05-5 A multicenter, open-label, phase IV clinical study for efficacy and safety evaluation of anagrelide in patients with treatment-naïve, high-risk essential thrombocythemia as a primary treatment
Ja Min Byun (Seoul National University Hospital, Korea)

DAILY PROGRAM Friday, April 1

12:40-13:40 **[OP06] MM** Room 3

Chairs Jeong Yeal Ahn (Gachon University Gil Medical Center, Korea)
Min Kyoung Kim (Yeungnam University Medical Center, Korea)

OP06-1 Prognostic role of the ratio of natural killer to regulatory T cells in multiple myeloma treating lenalidomide and dexamethasone
Seung Yeon Kim (The Catholic University of Korea, Korea)

OP06-2 Rejuvenation of antigen-specific CD8+ T cells using induced pluripotent stem cell technology and specific regulatory pathways for T cell commitment
Jooeun Bae (Harvard Medical School, USA)

OP06-3 Busulfan and thiotepa as a conditioning regimen for autologous stem cell transplantation in multiple myeloma: KMMWP-1801 study
Ga-Young Song (Chonnam National University Medical School, Korea)

OP06-4 Comparative analysis of single versus tandem autologous stem cell transplantation in patients with multiple myeloma in Korea: the KMM2102 study
Jongheon Jung (National Cancer Center, Korea)

OP06-5 Subcutaneous daratumumab with bortezomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed light chain (AL) amyloidosis: 18-month analysis of the phase 3 andromeda study
Kihyun Kim (Sungkyunkwan University School of Medicine, Korea)

12:40-13:40 **[OP07] Platelet, Transfusion** Room 4

Chairs Eun Sun Yoo (Ewha Womans University Seoul Hospital, Korea)
Jaewoo Song (Yonsei University College of Medicine, Korea)

OP07-1 2021 operation of the surveillance system of covid-19 vaccination induced thrombosis with thrombocytopenia syndrome in Korea
Daehyun Chu (University of Ulsan College of Medicine, Korea)

OP07-2 Validation of khorana score in cancer patients undergoing chemotherapy with east asian ethnicity
Junshik Hong (Seoul National University College of Medicine, Korea)

OP07-3 Acute transfusion reactions of pediatric blood transfusions at Chiang Mai university hospital
Pattira Rungruansarn (Chiang Mai University, Thailand)

OP07-4 Risk factors of platelet transfusion refractoriness in patients with AA/MDS who receive allogeneic hematopoietic stem cell transplantation
Jaeik Oh (Seoul National University Hospital, Korea)

OP07-5 Combining pharmacokinetics and comprehensive evaluation system to individualize the prophylaxis in pediatric patients with hemophilia A
Kun Huang (Capital Medical University, China)

13:40-13:55 Break

DAILY PROGRAM Friday, April 1

13:55-14:40 **[PS01] Presidential Symposium** Room 1

Chair Je-Hwan Lee (University of Ulsan College of Medicine, Korea)

Toward precision medicine in AML
Hartmut Döhner (University of Ulm, Germany)

14:40-15:40 **[MS01] MOU Country Session: MM** Room 1

Chairs Jae Hoon Lee (Gachon University Gil Medical Center, Korea)
Jin Seok Kim (Yonsei University College of Medicine, Korea)

MS01-1 Managing multiple myeloma in a resource-limited region: diagnosis and treatment in Armenia
Yervand K. Hakobyan (Armenian Hematology Association, Armenia)

MS01-2 Renal involvement in plasma cell disorder: learning from real-life practice
Suporn Chuncharunee (Ramathibodi hospital, Thailand)

MS01-3 Treatment sequence decision in multiple myeloma considering reimbursement status
Youngil Koh (Seoul National University Hospital, Korea)

14:40-16:10 **[SS09] MDS** Room 2

Chairs Yoo-Jin Kim (College of Medicine, The Catholic University of Korea, Korea)
Yoon Hwan Chang (Seoul National University Hospital, Korea)

SS09-1 Pathophysiology of spliceosome mutations in MDS
Andrea Pellagatti (University of Oxford, UK)

SS09-2 Role of extracellular vesicles and miRNA in myelodysplastic syndromes
Sophie Park (CHU de Grenoble Service hematologie clinique, France)

SS09-3 Challenges in the diagnosis and treatment of overlap MDS/MPN syndromes
Antonio Almeida (Hospital da Luz Lisboa, Portugal)

14:40-16:10 **[SS10] ALL** Room 3

Chairs Nack-Gyun Chung (The Catholic University of Korea, Korea)
Ho-Jin Shin (Pusan National University School of Medicine, Korea)

SS10-1 Chemotherapy vs. allogeneic HSCT for Ph–negative adult ALL
Josep-Maria Ribera (ICO-Hospital Germans Trias i Pujol, Spain)

SS10-2 Clonal heterogeneity in ALL
Jan Cools (Center for Human Genetics, Belgium)

SS10-3 Adoptive cellular immunotherapies based on chimeric antigen receptors
Pablo Menendez (Josep Carreras Leukemia Research Institute, Spain)

DAILY PROGRAM Friday, April 1

14:40-16:10 **[ES05] AA and BMF** Room 4

Chairs Myungshin Kim (The Catholic University of Korea, Korea)
Yeung-Chul Mun (Ewha Womans University College of Medicine, Korea)

ES05-1 Genetics and genomics of bone marrow failure syndrome
Hyun-Young Kim (Sungkyunkwan University School of Medicine, Korea)

ES05-2 Aplastic anemia: transplant vs non-transplant options
Ik-Chan Song (Chungnam National University Hospital, Korea)

ES05-3 Overview of bone marrow failure syndrome
Meerim Park (National Cancer Center, Korea)

16:10-16:25 Break

16:25-17:55 **[JS04] EHA-KSH Joint Symposium: CML** Room 1

Chairs Kimmo Porkka (Helsinki University Central Hospital, Finland)
Sang Kyun Sohn (Kyungpook National University School of Medicine, Korea)

JS04-1 Failing a second-generation TKI: when the guidelines don't always help
Jane Apperley (Imperial College London, UK)

JS04-2 Discontinuation of tyrosine kinase inhibitors in CML patients in clinical practice
Antonio Almeida (Hospital da Luz Lisboa, Portugal)

JS04-3 Second and later line therapy: the role of ponatinib in Korean patients with CML
Jeong-Ok Lee (Seoul National University Bundang Hospital, Korea)

JS04-4 Stopping tyrosine kinase inhibitor in CML; perspectives from Korean data
Hawk Kim (Gachon University College of Medicine, Korea)

16:25-17:55 **[SS11] Adv Technology** Room 2

Chairs Duck Cho (Sungkyunkwan University School of Medicine, Korea)
Ji-Myung Kim (Chungnam National University Hospital, Korea)

SS11-1 Hematopoiesis and leukemia through the lens of single cell genomics
Lars Velten (Centre for Genomic Regulation, Spain)

SS11-2 Computer vision in hematologic malignancies
Oscar Brück (University of Helsinki, Finland)

SS11-3 Hydrogel-based stamping technology for solution-free blood cell staining
Dongyoung Lee (Noul Co., Ltd, Korea)

DAILY PROGRAM Friday, April 1

16:25-17:55 **[SS12] Benign Hematology** Room 3

Chairs Deog-Yeon Jo (Chungnam National University College of Medicine, Korea)
Hyoung Soo Choi (Seoul National University College of Medicine, Korea)

SS12-1 The iron-erythropoiesis cross-talk in health and disease
Antonella Nai (San Raffaele Scientific Institute, Italy)

SS12-2 Autoimmune hemolytic anemia: state-of-the-art hypotheses on pathogenesis and their application to treatment
Bruno Fattizzo (Università degli Studi di Milano, Italy)

SS12-3 Cold agglutinin disease: an update on pathogenesis and future prospects on therapy
Sigbjørn Berentsen (Haugesund Hospital, Norway)

16:25-17:55 **[ES06] Lymphoma** Room 4

Chairs Jong Ho Won (Soonchunhyang University College of Medicine, Korea)
Young Rok Do (Keimyung University School of Medicine, Korea)

ES06-1 Lymphoma pathology: basic immunohistochemistry for lymphoma diagnosis
Junhun Cho (Sungkyunkwan University School of Medicine, Korea)

ES06-2 Staging and response assessment of lymphoma
Kwai Han Yoo (Gachon University Gil Medical Center, Korea)

ES06-3 Treatment of indolent lymphoma
Seong Hyun Jeong (Ajou University School of Medicine, Korea)

DAILY PROGRAM Saturday April 2

07:30-08:30 **Business Meeting** Room 1

08:30-09:00 **Working Party Reports** Room 1

09:00-10:00 **[AS02] Asian Session II - Pediatric ALL** Room 1

Chairs Chuhl Joo Lyu (Yonsei University Health System, Korea)
Keon Hee Yoo (Sungkyunkwan University School of Medicine, Korea)

AS02-1 Ma-Spore ALL studies: truly Asia approach to curing childhood ALL
Allen E.J. Yeoh (National University of Singapore, Singapore)

AS02-2 Childhood ALL in Thailand and multicenter studies of Thai pediatric oncology group
Samart Pakakasama (Mahidol University, Thailand)

AS02-3 The adherence to MRD time points improves treatment outcomes of childhood ALL in Taiwan: the experience of TPOG-ALL-2013 protocol
Hsi-Che Liu (Mackay Memorial Hospital, Taiwan)

09:00-10:30 **[SS13] AML** Room 2

Chairs Hee-Je Kim (The Catholic University of Korea, Korea)
Young Kyung Lee (Hallym University College of Medicine, Korea)

SS13-1 AML microenvironment and FLT3 inhibitor resistance
Elie Traer (Oregon Health & Science University, USA)

SS13-2 Targeting TP53 mutation in AML
David A. Sallman (H. Lee Moffitt Cancer Center and Research Institute, USA)

SS13-3 Adaptive immune resistance and immune evasion by programmed death-1 homolog (PD-1H/VISTA) in AML
Tae Kon Kim (Vanderbilt University Medical Center, USA)

09:00-10:30 **[SS14] Lymphoma (2) - T cell / HL** Room 3

Chairs Won Seog Kim (Sungkyunkwan University School of Medicine, Korea)
Ho-Young Yhim (Jeonbuk National University Medical School, Korea)

SS14-1 Genomic landscape of peripheral T-cell lymphomas
Keisuke Kataoka (National Cancer Center Research Institute, Japan)

SS14-2 T-cell lymphomas of follicular helper T-cell derivation: pathology, mechanisms and therapeutic implications
Laurence de Level (Lausanne University Hospital, Switzerland)

SS14-3 Targeted therapy to small molecules in peripheral T cell lymphomas
Deok Hwan Yang (Chonnam National University Medical School, Korea)

DAILY PROGRAM Saturday April 2

09:00-10:30 **[ES07] Supportive Care** Room 4

Chairs Seong Kyu Park (Soonchunhyang University Bucheon Hospital, Korea)
Hyo Jung Kim (Hallym University College of Medicine, Korea)

ES07-1 Comprehensive geriatric assessment in older patients for intensive chemotherapy
Jung-Yeon Choi (Seoul National University Bundang Hospital, Korea)

ES07-2 Evaluation and management of platelet transfusion refractoriness
Dae-Hyun Ko (University of Ulsan College of Medicine, Korea)

ES07-3 Advances in management of invasive fungal infections: perspectives on hematologic diseases
Dong-Gun Lee (Seoul St. Mary's Hospital, The Catholic University of Korea, Korea)

10:30-11:15 **[PL03] Plenary Lecture 03** Room 1

Chair Chuhl Joo Lyu (Yonsei University Health System, Korea)

Improving outcomes after CD19-targeted CAR T-cell therapy
Jordan Gauthier (University of Washington, USA)

11:15-11:30 Break

11:30-12:10 **Award Ceremony & Closing** Room 1

POSTER LIST

BEST POSTER

BP01 **Acute Myeloid Leukemia**

Identification of cell type-specific effects of DNMT3A mutations involved in relapse of acute myeloid leukemia

Seo-Gyeong Bae[1], Jihwan Park[1*], Jae-Sook Ahn[2,3], Hyeoung-Joon Kim[2,3] and Mi Yeon Kim[2,3]

[1]*School of Life Sciences, Gwangju Institute of Science and Technology (GIST), Korea*
[2]*Department of Internal Medicine, Chonnam National University Hwasun Hospital, Korea*
[3]*Genomic Research Center for Hematopoietic Diseases, Chonnam National University Hwasun Hospital, Korea*

BP02 **Myelodysplastic Syndrome**

DNA methylation-based biomarkers for azacitidine resistance in myelodysplastic syndrome

Da Yeon Kim[1,2] and Eun Ju Kim[1,2*]

[1]*Division of Radiation Biomedical Research, Korea Institute of Radiological and Medical Sciences, Korea*
[2]*Department of Radiological and Medico-Oncological Sciences, University of Science and Technology, Korea*

BP03 **Acute Lymphoblastic Leukemia**

Integrated targeted RNA fusion analysis and deep sequencing highlights diverse primary and secondary clonal abnormalities in a cohort of paired diagnosis-relapse pediatric B-cell acute lymphoblastic leukemia cases

Rozy Thakur

Pediatric Hematology-Oncology Lab-Advanced Pediatrics Centre, India

BP04 **Lymphoma**

A retrospective analysis of real-world outcomes of dose-adjusted EPOCH compared with CHOP based chemotherapy as frontline therapy for untreated PTCL

Sang-Bo Oh[1], Ho-Jin Shin[2*] and Do-Young Kim[2]

[1]*Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Medical Research Institute, Pusan National University Yangsan Hospital, Yangsan, Korea*
[2]*Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Medical Research Institute, Pusan National University Hospital, Busan, Korea*

BP05 **Multiple Myeloma**

First-line treatment with either VMP or RD for Transplant-ineligible patients with multiple myeloma: a pooled analysis of multicenter real-world data

Jung Yeon Lee[1], Young-Woo Jeon[2], Seung-Ah Yahng[3], Seung-Hwan Shin[4], Chang-Ki Min[1] and Sung-Soo Park[1*]

[1]*Department of Hematology, Catholic Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea*
[2]*Department of Hematology, Yeoido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea*
[3]*Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea*
[4]*Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea*

BP06 **Myeloproliferative Neoplasm**

Neutrophil–lymphocyte ratio and carotid plaque burden in patients with essential thrombocythemia and polycythemia vera

Seug Yun Yoon, Sun Young Jeong, Min-Young Lee, Kyoung-Ha Kim, Namsu Lee and Jong-Ho Won[*]

Division of Hematology & Medical Oncology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Seoul, Korea

BP07 **Laboratory Hematology**

Detection of recurrent, rare gene fusions and correlation with clinical manifestations in acute leukemia by targeted RNA-sequencing

Seo Wan Kim

Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea

BP08 **Anemia and Other Red Cell Disorders**

Characterization of alpha beta double negative T cells in children with acquired aplastic anemia

Hui Chen

Hematologic Disease Laboratory, Beijing Children's Hospital, China

BEST POSTER

BP09 **Platelet/ Hemostasis**

Levels of heparin induced anti-PF4 antibodies and endogenous glycosaminoglycans and their relationship with inflammatory biomarkers in pulmonary embolism patients

Bulent Kantarcioglu[1*], Amir Darki[2], Fakiha Siddiqui[1], Debra Hoppensteadt[1], Joseph Lewis[1], Roland Krämer[3] and Jawed Fareed[1]

[1]*Department of Pathology and Laboratory Medicine, Cardiovascular Research Institute, Health Sciences Division, Loyola University Chicago, USA*
[2]*Department of Internal Medicine, Division of Cardiovascular Disease, Loyola University Chicago, USA*
[3]*Institute of Inorganic Chemistry, Heidelberg University, Germany*

BP10 **Quality of Life**

Differences in comorbidities by trajectory groups as a reference in identifying patients at risk for late mortality in childhood cancer survivors

Hyery Kim[1], Hae Reong Kim[2], Sunghan Kang[1], Kyung-Nam Koh[1], Ho Joon Im[1] and Yu Rang Park[2*]

[1]*Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea*
[2]*Biomedical Systems Informatics, Yonsei University College of Medicine, Korea*

POSTER LIST

PP01-01 **RUNX1 mutation in children with acute myeloid leukemia of a single-center**
Hong Bo He, Hu Yong Zheng and Chao Gao
Hematology Center, Beijing Children's Hospital, China

PP01-02 **Establishment of a panel of biomarkers for immunophenotyping in acute leukemia**
Amar Ranjan, Harshita Dubey* and Pranay Tanwar
Lab Oncology Unit, AIIMS, New Delhi, India

PP01-03 **The prognostic impact of reduced variant burden in elderly patients with acute myeloid leukemia treated with decitabine**
Mihee Kim[1], Seo-Yeon Ahn[1], Sung-Hoon Jung[1], Ga-Young Song[1], TaeHyung Kim[3], Deok-Hwan Yang[1], Je-Jung Lee[1], Seung-Hyun Choi[2], MiYoen Kim[2], Hyeoung-Joon Kim[1,2], Dennis Dong Hwan Kim[4] and Jae-Sook Ahn[1,2*]
[1]Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea
[2]Genomic Research Center for Hematopoietic Diseases, Chonnam National University Hwasun Hospital, Korea
[3]Computer Science, University of Toronto, Canada
[4]Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Canada

PP01-04 **Therapeutic effect of metformin on acute myeloid leukemia through targeting AMPK/mTOR, cell cycle, apoptosis and autophagy**
Juan liu and Wenyu shi*
Oncology and hematology, Affiliated Hospital of Nantong University, China

PP01-05 **Epigenetic regulation and synthetic lethal targeting of genetically deficient acute myeloid leukemia by siRNA loaded customized polymeric and superparamagnetic multifunctional nanoparticles**
Anas Ahmad
Pharmacology, Chandigarh College of Pharmacy, India

PP01-06 **Investigation of genes and pathways associated with low platelet count in normal karyotype acute myeloid leukemia**
Chang-Hun Park[1] and Jae Won Yun[2*]
[1]Department of Laboratory Medicine & Genetics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Korea
[2]Veterans Medical Research Institute, Veterans Health Service Medical Center, Korea

PP01-07 **Clinical and molecular significance of multilineage dysplasia in acute myeloid leukemia: a single-center experience**
Hee Sue Park[2,4], Bo Ra Son[2,4] and Jihyun Kwon[1,3*]
[1]Internal Medicine, Chungbuk National University College of Medicine, Korea
[2]Laboratory Medicine, Chungbuk National University College of Medicine, Korea
[3]Internal Medicine, Chungbuk National University Hospital, Korea
[4]Laboratory Medicine, Chungbuk National University Hospital, Korea

PP01-09 **Stepwise combination of azacitidine and low-dose venetoclax in treatment-näive, critically ill elderly patient with acute myeloid leukemia: a case report**
Truc Phan[1,3], Thanh Nguyen Huu[3], Nghi Tran Phuong[3], Trang Nguyen Le[2], Kelly Smith[1,3,4] and Yi Hyeon Gyu[1,3*]
[1]Oncology & Hematology Dept, Vinmec Times City International Hospital, Viet Nam
[2]Pharmacy Dept, Vinmec Times City International Hospital, Viet Nam
[3]College of Health Science, Vin University, Viet Nam
[4]Perelman School of Medicine, University of Pennsylvania, USA

PP01-10 **Relevance of Wilms' tumor 1 (WT1) gene expression in AML patients among north Indian population**
Harsh Goel[1], Anita Chopra[1], Amar Ranjan[1], Ganesh Kumar Viswanathan[2], Aditya Kumar Gupta[3], Jagdish Prasad Meena[3], Sameer Bakhshi[4], Maroof Ahmad Khan[5] and Pranay Tanwar[1*]
[1]Laboratory Oncology Unit, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India
[2]Hematology, All India Institute of Medical Sciences, New Delhi, India
[3]Pediatric Oncology, All India Institute of Medical Sciences, New Delhi, India
[4]Medical Oncology, All India Institute of Medical Sciences, New Delhi, India
[5]Biostatistics, All India Institute of Medical Sciences, New Delhi, India

POSTER LIST

PP01-11 **Clinical outcomes in patients with relapsed/refractory acute myeloid leukemia treated with gilteritinib who received prior midostaurin or sorafenib**

Alexander E Perl[1*], Jessica K Altman[2], Naoko Hosono[3], Pau Montesinos[4], Nikolai Podoltsev[5], Giovanni Martinelli[6], Catherine C Smith[7], Mark J Levis[8], Christoph Röllig[9], Marco Groß-Langenhoff[10], Nahla Hasabou[11], Qiaoyang Lu[11], Ramon V Tiu[11] and Joon Seong Park[12]

[1]Abramson Cancer Center, University of Pennsylvania, USA
[2]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, USA
[3]Department of Internal Medicine, University of Fukui, Japan
[4]Department of Hematology, Hospital Universitario y Politécnico La Fe, Spain
[5]Department of Hematology, Yale School of Medicine, USA
[6]Research Department, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRST IRCCS, Italy
[7]Department of Hematology, University of California-San Francisco, USA
[8]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, USA
[9]Clinical Studies Department, Universitätsklinikum Carl Gustav Carus, Germany
[10]HEOR Department, Astellas Pharma GmbH, Germany
[11]Medical Department, Astellas Pharma US, USA
[12]Department of Hematology-Oncology, Ajou University Hospital, Korea

PP01-12 **Prognostic implications of Wilms' tumor 1 (WT1) gene expression in newly diagnosed cases of primary acute myeloid leukemia**

Pranay Tanwar[1*], Harsh Goel[1], Anita Chopra[1], Aditya Kumar Gupta[3], Jagdish Prasad Meena[3], Sameer Bakhshi[2] and Amar Ranjan[1]

[1]Laboratory Oncology, Dr. BRA-IRCH, AIIMS, New Delhi, India
[2]Medical Oncology, Dr BRA-IRCH, AIIMS, New Delhi, India
[3]Pediatrics, AIIMS, New Delhi, India

PP01-13 **Arsenic trioxide-based regimen versus autologous hematopoietic stem cell transplantation as post-remission therapy in relapsed acute promyelocytic leukemia**

Gi June Min, Byung-Sik Cho*, Daehun Kwag, Tong Yoon Kim, Jong Hyuk Lee, Joonyeop Lee, Sung-Soo Park, Silvia Park, Jae-Ho Yoon, Sung-Eun Lee, Ki-Seong Eom, Yoo-Jin Kim, Seok Lee, Chang-Ki Min, Seok-Goo Cho, Jong Wook Lee and Hee-Je Kim

Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea

PP01-14 **Diagnosis of acute promyelocytic leukemia with 3D microscope: toward an objective diagnosis**

Hyunji Kim[1], Seongsoo Jang[1*], Daehyun Chu[1], Miyoung Kim[1], Young-Uk Cho[1], Sang-Hyun Hwang[1], Chan-Jeoung Park[1] and YongKeun Park[2]

[1]Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[2]Department of Biological Sciences, KAIST, Korea

PP01-15 **Efficacy of cytarabine, daunorubicin plus etoposide as induction regimen for pediatric acute myeloid leukemia**

Huong-Giang Nguyen-Tran[1*], Tuan Nguyen[1] and Nghia Huynh[2]

[1]Hematology, Cho Ray Hospital, Viet Nam
[2]Hematology, Ho Chi Minh University of Medicine and Pharmacy, Viet Nam

PP01-16 **Genetic characteristics according to subgroup of acute myeloid leukemia with myelodysplasia-related changes**

Silvia Park[1], Dain Kang[2], Byung-Sik Cho[1], Hee-Je Kim[1], Yeojae Kim[2], Jong Mi Lee[3], Ari Ahn[3], Yonggoo Kim[3] and Myungshin Kim[3*]

[1]Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea
[2]Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea
[3]Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea

PP01-17 **Clinical significance of masked systemic mastocytosis with associated hematological neoplasm in AML with RUNX1: RUNX1T1**

Beom Joon Kim[1], Jee Soo Lee[2], Moon-Woo Seong[2], Soo Hyun Seo[1], Jinho Paik[4], Sang A Kim[3], Ji Yun Lee[3], Jeong Ok Lee[3], Soo Mee Bang[3], Yoon Hwan Chang[2] and Sang Mee Hwang[1*]

[1]Laboratory Medicine, Seoul National University Bundang Hospital, Korea
[2]Laboratory Medicine, Seoul National University Hospital, Korea
[3]Internal Medicine, Seoul National University Bundang Hospital, Korea
[4]Pathology, Seoul National University Bundang Hospital, Korea

POSTER LIST

PP01-18 **Incidence of therapy-related myeloid neoplasms and their risk factors for the selection of patients with an increased risk: a Korean nationwide study**

Hyerim Ha[1,2], Hyo Jeong Kim[3], Ju Hyun Park[3], Na Rae Lee[2] and Junshik Hong[1*]
[1]*Department of Internal Medicine, Seoul National University College of Medicine, Korea*
[2]*Department of Internal Medicine, Inha University Hospital, Korea*
[3]*National Evidence-based Healthcare Collaborating Agency (NECA), Korea*

PP01-19 **Induction of differentiation in acute myeloid leukemic stem cells by a natural compound: esculetin**

Ankit Mathur and Daman Saluja*
Dr. B.R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi, India

PP01-20 **Acute promyelocytic leukemia with cryptic IRF2BP2-RARA rearrangement in a patient with Germline DDX41 mutation: the first case in Korea**

Jae Joon Lee[1], Hyun-Young Kim[1], Jun Ho Jang[2], Sun-Hee Kim[1] and Hee-Jin Kim[1*]
[1]*Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*
[2]*Department of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

PP01-21 **Therapy-related myeloid neoplasm with Inv(11)(p15q22)/NUP98-DDX10 rearrangement: the first case in Korea**

Noorie Kang[1], Jae Joon Lee[1], Hyun-Young Kim[1], Chul Won Jung[2], Sun-Hee Kim[1] and Hee-Jin Kim[1*]
[1]*Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[2]*Department of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*

PP01-22 **Gene expression profiling of VASH1 and its prognostic role in acute myeloid leukemia**

Avanish Kumar Pandey[1], Sarita Kumari[1], Jay Singh[1], Mohit Arora[3], M Shadab Ali[4], Jayanth Kumar Palanichamy[3], Sameer Bakhshi[2], Atul Sharma[2], Mercilena Benjamin[1], Neha Thukral[1] and Anita Chopra[1*]
[1]*Laboratory Oncology Unit, Dr. BRA-IRCH, AIIMS, New Delhi, India*
[2]*Department of Medical Oncology, AIIMS, New Delhi, India*
[3]*Department of Biochemistry, AIIMS, New Delhi, India*
[4]*Department of Pulmonary, AIIMS, New Delhi, India*

PP01-23 **Clinical usefulness of next-generation sequencing panel for myeloid neoplasms**

A-Jin Lee, Sang-Gyung Kim*, Chang-Ho Jeon and Eun-Hyung Yoo
Department of laboratory medicine, Daegu Catholic University School of Medicine, Korea

PP01-24 **Differences of genetic alteration between pediatric and adult acute myeloid leukemia detected by panel-based next generation sequencing**

Jae Won Yoo[1], Tong Yoon Kim[2], Jong Mi Lee[3], Ari Ahn[3], Seongkoo Kim[1], Silvia Park[2], Jae Wook Lee[1], Myungshin Kim[3], Yonggoo Kim[3], Byung-Sik Cho[2], Hee-Je Kim[2], Nack-Gyun Chung[1] and Bin Cho[1*]
[1]*Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[2]*Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[3]*Laboratory medicine, Seoul St. Mary's Hospital College of Medicine, The Catholic University of Korea, Seoul, Korea*

PP01-25 **Allogeneic hematopoietic cell transplantation overcomes adverse prognosis in patients with low allelic ratio FLT3-ITD and NPM1 mutated AML**

Ga-Young Song[1], TaeHyung Kim[2,3], Seo-Yeon Ahn[1], Sung-Hoon Jung[1], Mihee Kim[1], Deok-Hwan Yang[1], Je-Jung Lee[1], Seung Hyun Choi[4], Mi Yeon Kim[4], Chul Won Jung[5], Jun-Ho Jang[5], Hee Je Kim[6], Joon Ho Moon[7], Sang Kyun Sohn[7], Jong-Ho Won[8], Seong-Kyu Park[8], Sung-Hyun Kim[9], Zhaolei Zhang[2,3,10], Jae-Sook Ahn[1,4], Dennis Dong Hwan Kim[11] and Hyeoung-Joon Kim[1,4*]
[1]*Department of Hematology-Oncology, Chonnam National University Hwasun Hospital and Chonnam National University Medical School, Korea*
[2]*Department of Computer Science, University of Toronto, Canada*
[3]*The Donnelly Centre for Cellular and Biomolecular Research, , University of Toronto, Canada*
[4]*Genomic Research Center for Hematopoietic Diseases, , Chonnam National University Hwasun Hospital, Korea*
[5]*Division of Hematology-Oncology, Samsung Medical Center, Korea*
[6]*Department of Hematology, The Catholic University of Korea, Korea*
[7]*Department of Hematology-Oncology, Kyungpook National University Hospital, Korea*
[8]*Department of Hematology-Oncology, Soon Chun Hyang University Hospital, Korea*
[9]*Department of Hematology-Oncology, Dong-A University College of Medicine, Korea*
[10]*Department of Molecular Genetics, University of Toronto, Canada*
[11]*Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Canada*

POSTER LIST

PP01-27 **Treatment outcomes of venetoclax and hypomethylating agents for newly diagnosed acute myeloid leukemia**
Eun-Ji Choi, Je-Hwan Lee*, Han-Seung Park, Jung-Hee Lee and Kyoo-Hyung Lee
Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea

PP01-28 **Cannabidiol exhibits anti-leukemic and anti-inflammatory activities through regulation of the NF-κB signaling pathway in human leukemia monocytic cell line**
Krai Daowtak[1,2], Thitiya Luetragoon[2], Kanchana Usuwanthim[2] and Ruttiros Khonkarn[3*]
[1]Unit of Hematology and Clinical Microscopy, Department of Medical Technology, Unit of Hematology and Clinical Microscopy, Department of Medical Technology, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand
[2]Cellular and Molecular Immunology Research Unit, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand
[3] Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, 50200, Thailand

PP01-30 **Risk of serious infections with the use of immunomodulatory drugs in multiple myeloma patients**
Md. Sarfaraj Hussain
Pharmacology and Toxicology, Lord Buddha Koshi Pharmacy College, Biajanathpur, Saharsa (Bihar) 852201, India

PP01-31 **An evaluation of the efficacy and safety of lenalidomide as monotherapy and as part of a combination regimen in the treatment of acute myeloid leukaemia**
Md. Sarfaraj Hussain
Pharmacology and Toxicology, Lord Buddha Koshi Pharmacy College, Biajanathpur, Saharsa (Bihar) 852201, India

PP01-32 **Early bone marrow assessment after 3+7 induction chemotherapy is predictable of outcome in AML with intermediate or adverse cytogenetics**
Daehun Kwag [1,2], Byung-Sik Cho [1,2], Tong Yoon Kim[1,2], Jong Hyuk Lee[1,2], Joonyeop Lee[1,2], Gi-June Min[1,2], Sung-Soo Park[1,2], Silvia Park [1,2], Young-Woo Jeon[3], Seung-Hwan Shin[4], Seung-Ah Yahng[5], Jae-Ho Yoon [1,2], Sung-Eun Lee [1,2], Ki-Seong Eom [1,2], Yoo-Jin Kim [1,2], Seok Lee [1,2], Chang-Ki Min [1,2], Seok-Goo Cho[1], Jong Wook Lee[1] and Hee-Je Kim[1,2*]
[1]Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea
[3]Department of Hematology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[4]Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[5]Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

PP01-33 **Decetabine plus venetoclax versus decetabine alone for older adults with newly diagnosed acute myeloid leukemia**
Daehun Kwag [1,2], Tong Yoon Kim[1,2], Jong Hyuk Lee[1,2], Joonyeop Lee[1,2], Gi-June Min[1,2], Sung-Soo Park[1,2], Silvia Park[1,2], Young-Woo Jeon[3], Seung-Hwan Shin[4], Seung-Ah Yahng[5], Jae-Ho Yoon[1,2], Sung-Eun Lee[1,2], Ki-Seong Eom[1,2], Yoo-Jin Kim[1,2], Seok Lee[1,2], Hee-Je Kim[1,2], Chang-Ki Min[1,2], Seok-Goo Cho[1], Jong Wook Lee[1] and Byung-Sik Cho [1,2*]
[1]Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea
[3]Department of Hematology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[4]Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[5]Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

PP01-34 **Real-world experience of gilteritinib in relapsed/refractory FLT3 mutated acute myeloid leukemia**
Jong Hyuk Lee, Daehun Kwag, Joonyeop Lee, Tong Yoon Kim, Gi-June Min, Sung-Soo Park, Silvia Park, Jae-Ho Yoon, Sung-Eun Lee, Byung-Sik Cho, Ki-Seong Eom, Yoo-Jin Kim, Seok Lee, Chang-Ki Min, Seok-Goo Cho, Jong Wook Lee, and Hee-Je Kim*
Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Banpo-daero 222, Seocho-Gu, Seoul, Korea

PP02-01 **Genetic mutations associated with blood count abnormalities in myeloid neoplasms**
Chantana Polprasert[1*], Pimjai Niparuck[2], Thanawat Rattanathammethee[3], Suporn Chuncharunee[2], Sirorat Kobbuaklee[1], Amornchai Suksusut[1], Theerin Lanamtieng[4], Sunisa Kongkiatkamon[1], Panisinee Lawasut[1], Thiti Asawapanumas[1], Kitsada Wudhikarn[1], Udomsak Bunworasate[1] and Ponlapat Rojnuckarin[1]
[1]Department of Medicine, Chulalongkorn University, Thailand
[2]Department of Medicine, Mahidol University, Thailand
[3]Department of Medicine, Chiangmai University, Thailand
[4]Department of Medicine, Khon kaen University, Thailand

POSTER LIST

PP02-02 **Increased apoptotic activity in patients with lower risk myelodysplastic syndrome**

Songyi Park[1], Dong-Yeop Shin[1,2,3*], Hee Sue Park[4], Soo Young Moon[5], Sung-Soo Yoon[1,3] and Dong-Soon Lee[3,6]
[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Hospital, Korea
[2]Biomedical Research Institute, Seoul National University Hospital, Korea
[3]Cancer Research Institute, Seoul National University College of Medicine, Korea
[4]Department of Laboratory Medicine, Chungbuk National University Hospital, Korea
[5]Department of Laboratory Medicine, Pusan National University Hospital, Korea
[6]Department of Laboratory Medicine, Korea Cancer Center Hospital, Korea

PP02-03 **DDX41-mutated myeloid neoplasms with propensity for higher-risk myelodysplastic syndrome and distinct bone marrow features depending on mutation type**

Youn Ji Hong[1], Young-Uk Cho[1*], Miyoung Kim[1], Seongsoo Jang[1], Chan-Jeoung Park[1], Eul-Ju Seo[1], Eun-Ji Choi[2], Je-Hwan Lee[2] and Kyoo-Hyung Lee[2]
[1]Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea
[2]Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea

PP02-04 **R-loop induced DNA damage and clinical features of DDX41- mutated Korean MDS**

Silvia Park[1], Won Chan Hwang[2], Kiboem Park[2], Jong Mi Lee[3], Myungshin Kim[3], Hongtae Kim[2] and Yoo-Jin Kim[1*]
[1]Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Biological Sciences, Ulsan National Institute of Science and Technology, Ulsan, Korea
[3]Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

PP02-05 **Survival analysis of post-transplant MDS according to relapse and treatment pattern**

Joonyeop Lee[1], Gi-June Min[1], Sung-Soo Park[1], Silvia Park[1], Seung-Ah Yahng[2], Young-Woo Jeon[3], Seung-Hwan Shin[4], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Seok Lee[1], Hee-Je Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Jong Wook Lee[1] and Yoo-Jin Kim[1*]
[1]Department of Hematology, Leukemia Research Institute, Seoul St. Mary's Hematology Hospital, College of Medicine, Korea
[2]Department of Hemato-oncology, Incheon St Mary's Hospital, College of Medicine, Korea
[3]Department of Hematology, Yeouido St. Mary's Hematology Hospital, College of Medicine, Korea
[4]Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, Korea

PP02-06 **Treatment outcomes of secondary acute myeloid leukemia from myelodysplastic syndrome, according to previous treatment history**

Daehun Kwag[1], Tong Yoon Kim[1], Jong Hyuk Lee[1], Joon yeop Lee[1], Gi June Min[1], Sung Soo Park[1], Silvia Park[1], Seung-Ah Yahng[2], Seung-Hwan Shin[3], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung Sik Cho[1,4], Ki-Seong Eom[1,4], Seok Lee[1,4], Hee-Je Kim[1,4], Chang-Ki Min[1,4], Jong Wook Lee[1] and Yoo-Jin Kim[1,4*]
[1] Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2] Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea
[3] Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[4] Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

PP03-01 **Clinical application of next-generation sequencing -based monitoring of minimal residual disease in childhood acute lymphoblastic leukemia**

Mai Huirong* and Li Qin
Department of Hematology and Oncology, Shenzhen Children's Hospital, China

PP03-03 **Pediatric leukemia: a systematic review of oral manifestations, post-treatment complications & oro-dental management**

Vaibhav Gupta* and Poonam Goel
National Institute of Pathology, India

PP03-04 **IKZF1 plus profile and outcome analysis in a cohort of paediatric B-cell acute lymphoblastic leukaemia cases**

Prateek Bhatia[1*], Minu Singh[1], Pragna Hc[1], Rozy Thakur[1], Amita Trehan[1] and Neelam Varma[2]
[1]Peditaric Hematology-Oncology Unit, Department of Pediatrics, Pgimer Chandigarh, India
[2]Hematology, Pgimer Chandigarh, India

PP03-06 **Genetic variation and relationship of homo sapiens t(4;11)(q21;q23) translocation breakpoint sequence, MLL-AF4 gene fusion, in acute lymphoblastic leukemia**

Ramlah Ramlah
Biology, Universitas Sulawesi Barat, Indonesia

POSTER LIST

PP03-07 **Prognostic utility of key copy number alterations in T cell acute lymphoblastic leukemia**
Sarita Kumari[2,5], Md Shadab Ali[1], Jay Singh[2], Mohit Arora[3], Deepak Verma[2], Dr. Sameer Bakhshi[4], Jayanth Kumar Palanichamy[3], Atul sharma[4], Inder Singh[6] and Anita Chopra[2*]
[1]Department of Pulmonary, Critical Care and Sleep Medicine, All India institute of medical Sciences, India
[2]Lab oncology unit BRA.IRCH, All India institute of medical Science, India
[3]Department of Biochemistry, All India institute of medical science, India
[4]Department of Medical Oncology, All India institute of medical science, India
[5]Department of Biotechnology, Gautam Buddha University, India
[6]Department of Neurology, All India institute of medical sciences, India

PP03-08 **Segmentation of red blood cell image based on cell morphology to detect iron deficiency anemia**
Elfiany Elfiany*, Rosmani Bahtiar and Bannure Bannure
Computational Science, Universitas Muhammadiyah Bulukumba, Indonesia

PP03-09 **Delineating CRLF2 positivity and its clinical significance in pediatric B-cell acute lymphoblastic leukemia**
Jay Singh[1], Mercillena Benjamin[1], Avanish Kumar Pandey[1], Sarita Kumari[1], Mohit Arora[3], Gunjan Sharma[3], Md. Shadab Ali[8], Deepak Verma[7], Sameer Bakhshi[2], Rachna Seth[4], Amitabh Singh[6], Jayanth Kumar Palanichamy[3], Inder Kumar Singh[5] and Anita Chopra[1*]
[1]Laboratory Oncology unit, Dr. BRAIRCH, AIIMS, New Delhi, India
[2]Department of Medical oncology, AIIMS, New Delhi, India
[3]Department of Biochemistry, AIIMS, New Delhi, India
[4]Department of Pediatrics, AIIMS, New Delhi, India
[5]Department of Neurology, AIIMS, New Delhi, India
[6]Department of Pediatrics, VMMC & Safdarjung Hospital, New Delhi, India
[7]Department of Oncology, School of Medicine, SKCCC, Johns Hopkins University, Baltimore, USA
[8]Department of Pulmonary, AIIMS, New Delhi, India

PP03-10 **High-throughput drug sensitivity analysis strategy and salvage autologous CD19 CAR-T therapy in second marrow relapse of acute lymphoblastic leukemia with NT5C2 mutation**
Xue Tang
Department of Hematology and Oncology, Shenzhen Children's Hospital, China

PP03-11 **Circular RNA (CircRNA) transcriptomic signature in T-cell acute lymphoblastic leukemia**
M Shadab Ali[1], Deepak Verma[2], Jay Singh[1], Sarita Kumari[1], Avanish K Pandey[1], Mercilena Benjamin[1] and Anita Chopra[1*]
[1]Lab Oncology Unit, Dr. BRAIRCH, All India Institute of Medical Sciences, New Delhi, India
[2]Department of Oncology, School of Medicine, SKCCC, Johns Hopkins University, Baltimore MD, USA

PP03-17 **A real world experience of clinical characteristics & treatment outcome of T-ALL: the Ampang experience**
Siew Lian Chong*, Kim Wah Ho, Tee Chuan Ong, Veena Selvaratnam and Sen Mui Tan
Department of Haematology, Ampang Hospital, Dr, Malaysia

PP03-18 **Role of SOX4 and KRAS activation in relapsed pediatric B- cell acute lymphoblastic leukemia**
Jae Wook Lee*, Jae Won Yoo, Seongkoo Kim, Pil-Sang Jang, Nack-Gyun Chung and Bin Cho
Division Hematology/Oncology, Department of Pediatrics, The Catholic University of Korea, Korea

PP03-19 **Clinical and genetic characteristics of IGH aberrations detected by FISH analysis in childhood B-lymphoblastic leukemia**
Sung Hee Min[1], Young Uk Cho[1], Seongsoo Jang[1], Chan Jeoung Park[1], Ho Joon IM[2], Kyoung-Nam Koh[2], Hyery Kim[2] and Eul Ju Seo[1*]
[1]Department of Laboratory Medicine, Asan Medical center, University of Ulsan College of Medicine, Korea
[2]Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

PP03-20 **Analysis of cerebrospinal fluid for malignant cells**
Saransh Verma, Amar Ranjan*, Harshita Dubey and Pranay Tanwar
Laboratory Oncology Unit, All India Institute of medical Sciences, New Delhi, India

PP03-21 **Evaluation of genetic alterations in HBB gene and unravel the Biochemical parameters among the sickle cell anemia (SCD) patients**
Krishnaswamy Rangaswamy [1*], Harysh Winster[1], Md.Younus Pasha [1], Dhivya Venkatesan[1], Balachandar Vellingiri[1] and Arul Narayanasamy [2]
[1]Department of Human Genetics & Molecular Bilogy, Bharathiar University, India
[2]Department of Zoology, Bharathiar University, India

POSTER LIST

PP03-22 **The outcome of blinatumomab in relapsed or refractory pediatric B-ALL: single center experience**
Hyun Jin Park[1,2,3], Kyung Taek Hong[1,2,3], Jung Yoon Choi[1,2,3], Hong Yul An[1,2,3], Bo Kyung Kim[1,2,3] and Hyoung Jin Kang[1,2,3*]
[1]*Department of Pediatrics, Seoul National University College of Medicine, Korea*
[2]*Seoul National University Cancer Research Institute, Korea*
[3]*Wide River Institute of Immunology, Korea*

PP03-24 **Comparison of mutational spectrum of IDH2, NRAS and TP53 genes in B-cell precursor lymphoblastic leukemia and acute myeloid leukemia**
Hee Sue Park[1,2], Bo Ra Son[1,2] and Jihyun Kwon[3]
[1]*Laboratory Medicine, Chungbuk National University Hospital, Korea*
[2]*Laboratory Medicine, Chungbuk National University, College of Medicine, Korea*
[3]*Internal Medicine, Chungbuk National University, College of Medicine, Korea*

PP03-25 **Efficacy and safety of decitabine in the management of acute myeloid leukemia**
Mohammad Asad Hussain
Health Outcomes Research, Jamia Millia Islamia, India

PP03-26 **Anti-leukemic effect of Umbelliferone β-D-galactopyranoside against DMBA induced leukemic rat model: possible mechanism of action**
Vikas Kumar[1*] and F Anwar[2]
[1]*Pharmaceutical Sciences, SHUATS, India*
[2]*Biochemistry, King Abdulaziz University, Saudi Arabia*

PP03-27 **A comparative study on digital dermatoglyphic patterns among adolescent with acute lymphoblastic leukemia in Guyana**
Ameet Kumar Jha
Department of Preclinical Sciences, Texila American University, Nepal

PP04-01 **A single-center report on treatment outcomes of patients with CML treated with TKIs with a survey of health-related quality of life**
Hee Jeong Cho, Jung Min Lee, Ju-Hyung Kim, Dong Won Baek, Joon Ho Moon and Sang-Kyun Sohn*
Department of Hematology/Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Korea

PP04-03 **Long-term outcomes of tyrosine kinase inhibitor discontinuation in chronic myeloid leukemia patients in real-world clinical practice**
Chang-Hoon Lee[1], So-Yeon Jeon[1], Ho-Young Yhim[1], Jeong-A Kim[2] and Jae-Yong Kwak[1*]
[1]*Department of Internal Medicine, Jeonbuk National University Hospital, Korea*
[2]*Hemato-oncology, St. Vincent Hospital, The Catholic University, Korea*

PP04-05 **Clinical and hematological profile of chronic myeloid leukemia in sub-himalayan region**
Rajeev Sandal, Pravesh Dhiman*, Manish Gupta , Sunil Sharma, Vikas Fotedar, Sidharth Vats and Purnima Thakur
Department of radiotherapy and oncology, Indira Gandhi Medical College , India

PP04-06 **Discontinuation of tyrosine kinase inhibitors based on BCR-ABL1 monitoring by digital droplet PCR in pediatric chronic myeloid leukemia**
Seongkoo Kim[1], Yeojae Kim [2], Jong Mi Lee[2,3], Ari Ahn[2,3], Jae Won Yoo[1], Jae Wook Lee[1], Bin Cho[1], Nack-Gyun Chung[1], Yonggoo Kim[2,3], Myungshin Kim[2,3]
[1] *Division Hematology/Oncology, Department of Pediatrics, The Catholic University of Korea, Seoul, Korea*
[2] *Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea*
[3] *Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea*

PP05-01 **Productivity of 18F-FDG-PET/CT diagnostic tool in the management of pediatric lymphoblastic lymphoma**
Ahmed Abdelsalam
Pediatric Hematology/Oncology, Children's Cancer Hospital Egypt (CCHE 57357), Pediatric Hematology/Oncology Consultant, Egypt

PP05-03 **A case of primary effusion lymphoma**
Dawpadee Dharmasena[1*], Sanka Vijayabandara[2] and Champika Bodinayake[2]
[1]*Teaching Hospital, Karapitiya, Galle, Senior Registrar in respiratory Medicine, Sri Lanka*
[2]*Teaching Hospital, Karapitiya, Galle, Consultant Physician, Sri Lanka*

POSTER LIST

PP05-04 **Bone marrow infiltration in non-hodgkin lymphoma: 18 F-FDG PET/CT versus bone marrow aspiration biopsy**

Manas Kumar Sahoo[1*], Smeeta G[2], Bhawna Jha[3] and Nagender Sharma[4]
[1]Nuclear Medicine, Medanta-the Medicity, Gurgaon, Senior Consultant, India
[2]Laboratory Oncology, All India Institute of Medical Sciences, New Delhi, India
[3]Hematopathology, Medanta-the Medicity, Gurgaon, India
[4]Medical & HematoOncology, Medanta-the Medicity, Gurgaon, India

PP05-05 **Diabetic foot ulcer as a manifestation of T-cell lymphoma: a case report**

Jumria Tandi Panggalo[1] and Riswan Arisandi[2]
[1]Resident Internal Medicine, Internal Medicine Department, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia
[2]Division of Hematology and Oncology, Internal Medicine Department, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia

PP05-06 **Flow cytometry v/s BM aspirate v/s BM biopsy as a screening tool for detection of marrow involvement by lymphoma: study at a tertiary cancer hospital**

Garima Jain[1*], Chandan Kumar[2], Pranay Tanwar[2] and Amar Ranjan[2]
[1]Pathology, National Institute of Pathology-ICMR, India
[2]Laboratory Oncology, AIIMS, New Delhi, India

PP05-07 **A retrospective analysis of the efficacy of low-dose metronomic cyclophosphamide for treatment in patients with low grade non-hodgkin lymphoma**

Boram Han, Bum Jun Kim, Ho Young Kim, Dae Young Zang and Hyo Jung Kim*
Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University Medical Center, Korea

PP05-08 **The endothelial activation and stress index (EASIX) score is an independent prognostic factor in patients with diffuse large B cell lymphoma**

Sungwoo Park[1], Gyeong-Won Lee[1*] and Seil Go[2]
[1]Division of Hematology and Oncology, Department of Internal Medicine, Gyeong-Sang National University Hospital, Gyeongsang National University School of Medicine, Korea
[2]Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Institute of Health Sciences, College of Medicine, Gyeongsang National University, Korea

PP05-09 **CC-95251, a novel anti-SIRPα antibody, enhances phagocytosis of non-hodgkin lymphoma (NHL) cells when combined with rituximab**

Henry Chan[1*], Christina Trout[2], David Mikolon[1], Preston Adams[1], Roberto Guzman[3], Gustavo Fenalti[4], Konstantinos Mavrommatis[5], Mahan Abbasian[6], Lawrence Dearth[1], Brian Fox[7], Pallavur Sivakumar[8] and Kandasamy Hariharan[1]
[1]Discovery Biotherapeutics, Bristol Myers Squibb, USA
[2]Formerly Research and Early Development Alliances, Bristol Myers Squibb, USA
[3]Exploratory Toxicology, Bristol Myers Squibb, USA
[4]Department of Crystallography, Bristol Myers Squibb, USA
[5]Computational Genomics, Bristol Myers Squibb, USA
[6]Formerly Discovery Biotherapeutics, Bristol Myers Squibb, USA
[7]Informatics and Predictive Sciences, Bristol Myers Squibb, USA
[8]Immuno-oncology and Cell Therapy Discovery, Bristol Myers Squibb, USA

PP05-10 **First clinical study of the anti -SIRPα Antibody CC-95251 combined with rituximab in patients with relapsed/refractory (R/R) non-hodgkin lymphoma (NHL)**

Paolo Strati[1*], Eliza Hawkes[2], Nilanjan Ghosh[3], Joseph Tuscano[4], Quincy Chu[5], Mary Ann Anderson[6], Amar Patel[7], Michael R. Burgess[7], Kristen Hege[7], Sapna Chhagan[7], Sarandeep Boyanapalli[8], Tracey Day[7], Frank Shen[9], Jin-Seok Kim[10] and Amitkumar Mehta[11]
[1]MD Anderson Cancer Center, The University of Texas, USA
[2]Austin Health, Austin Hospital, Australia
[3]Lymphoma Program, Levine Cancer Institute, USA
[4]Hematology and Oncology, University of California, Davis, USA
[5]Oncology, Cross Cancer Institute, Canada
[6]Clinical Hematology, Peter MacCallum Cancer Centre, Australia
[7]Early Clinical Development, Hematology/Oncology & Cell Therapy, Bristol Myers Squibb, USA
[8]Clinical Pharmacology and Pharmacometrics, Bristol Myers Squibb, USA
[9]Biostatistics, Bristol Myers Squibb, USA
[10]Severance Hospital, Yonsei University, Korea
[11]Comprehensive Cancer Center, University of Alabama at Birmingham, USA

POSTER LIST

PP05-11 **The clinical outcome of rituximab biosimilars versus rituximab originator with CHOP as first-line treatment for patients with DLBCL**
Amitawan Maneenut and Kannadit Prayongratana*
Hematology unit, Department of medicine, Phramongkutklao hospital, Thailand

PP05-12 **Bone marrow involvement in korean patients with various lymphoma types: a 21-year large single-center study**
Min-Sun Kim[1], Miyoung Kim[2*], Young-Uk Cho[2], Sang-Hyun Hwang[2], Seongsoo Jang[2], Han-Seung Park[3], Jung-Hee Lee[3], Dok Hyun Yoon[4], Cheolwon Suh[4], Hyery Kim[5], Kyung-Nam Koh[5], Ho Joon Im[5], Jooryung Huh[6] and Chan-Jeoung Park[2]
[1]Laboratory Medicine, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, Korea
[2]Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[3]Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[4]Oncology, Asan Medical Center, University of Ulsan College of Medicine, Korea
[5]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea
[6]Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

PP05-13 **MicroRNA-196a sensitizes B cell lymphoma cells to daunorubicin through FOXO1**
Hyun Ju Hwang[1], Soyoung Kim[1], Young-Ho Ahn[2], Eun Seok choi[3], Sung Han Kang[3], Hyeri Kim[3], Sang-Hyun Hwang[4], Seongsoo Jang[4], Ho Joon Im[3], Kyung-Nam Koh[3*] and Nayoung Kim[1]
[1]Asan Institute for Life Sciences, Asan Medical Center, Korea
[2]Department of Molecular Medicine, Ewha Womans University, Korea
[3]Department of Pediatrics, University of Ulsan College of Medicine, Korea
[4]Department of Laboratory Medicine, University of Ulsan College of Medicine, Korea

PP05-14 **Clinicopathological correlation of mantle cell lymphoma**
Harshita Dubey, Amar Ranjan* and Pranay Tanwar
Labortaory Oncology , Dr.B.R.A-IRCH, AIIMS, New Delhi, India

PP05-15 **Epigenetic priming improves salvage chemotherapy in diffuse large B-cell lymphoma via endogenous retrovirus-induced cGAS-STING activation**
Jun Liu[2], Ja Min Byun[1,2] Dong-Yeop Shin[1,2] Youngil Koh[1,2] Junshik Hong[1,2] and Sung-Soo Yoon[1,2]
[1]Department of Internal Medicine, Seoul National University College of Medicine, Korea
[2]Cancer Research Institute, Seoul National University College of Medicine, Korea

PP05-16 **Morphologic variant of hairy cell leukemia: a diagnostic challenge**
Go Eun Bae[1], Hyun-Young Kim[1], Seok Jin Kim[2], Duck Cho[1], Hee-Jin Kim[1] and Sun-Hee Kim[1*]
[1]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Department of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

PP05-17 **Diagnostic challenge for composite mature B cell lymphoma and CD8+ T cell lymphoma**
Sholhui Park[1], Min-Kyung So[1], Dong Jin Park[1], Min-Sun Cho[2], Seonggyu Byeon[3], Young Hoon Park[3], Yeung Chul Mun[3] and Jungwon Huh[1*]
[1]Department of Laboratory Medicine, College of Medicine, Ewha Womans University, Korea
[2]Department of Pathology, College of Medicine, Ewha Womans University, Korea
[3]Department of Internal Medicine, College of Medicine, Ewha Womans University, Korea

PP05-18 **Exosomal miR-155 and miR-21 in ibrutinib-resistant diffuse large B cell lymphoma cells**
Bon Park[1], Myung Eun Choi[1], Kyung Ju Ryu[1], Jung Yong Hong[2], Won Seog Kim[2], Chaehwa Park[1] and Seok Jin Kim[1,2*]
[1]Department of Health Sciences and Technology, Samsung Advanced Institute of Health Science and Technology, Sungkyunkwan University, Korea
[2]Department of Medicine, Samsung Medical Center, Sungkyunkwan University, Korea

PP05-20 **Impact of the epstein-barr virus positivity on consolidation radiotherapy (RT) for hodgkin's lymphoma**
Tong Yoon Kim[1], Seok-Goo Cho[1*], Daehun Kwag[1], Gi June Min[1], Sung-Soo Park[1], Silvia Park[1], Young-Woo Jeon[2], Seung-Hawn Shin[3], Seung-Ah Yahng[4], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Seok Lee[1], Chang-Ki Min[1], Jong-Wook Lee[1] and Hee-Je Kim[1]
[1]Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Hematology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[3]Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[4]Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

POSTER LIST

PP05-21 **Cytokine profile in patients with DLBCL: prognostic value of IL6 and C- reactive protein in predicting poor survival - a prospective study**
Gaurav Prakash*, Vaishali Agrawal, Nidhi Jain, Manupdesh Singh, Arihant Jain, Deepesh Lad, Aditya Jandial and Pankaj Malhotra
Clinical Hematology and Medical Oncology, Postgraduate Institute of Medical Education and Research , India

PP05-22 **Bloodless treatment of Jehovah's witness patients with lymphoma: single center experience**
Kyoung Ha Kim, Sun Young Jeong, Seug Yun Yoon, Min-Young Lee, Namsu Lee and Jong-Ho Won*
Internal Medicine, Soonchunhyang University College of Medicine, Soonchunhyang University Hospital, Seoul, Korea

PP05-23 **Long term effectiveness of autologous peripheral blood stem cell transplantation (Auto-PBSCT) using busulfan, melphalan, and thiotepa (BMT) regimen in patients with recurrent or refractory CNS lymphoma: single center experience**
Youngwoo Jeon[1,2], Gi June Min[3], Sung-Soo Park[3], Silvia Park[3], Jae-Ho Yoon[3], Sung-Eun Lee[3], Ki-Seong Eom[3] and Seok-Goo Cho[1,2,3*]
[1]Hematology, The Catholic University of Korea, Yeouido ST. Mary's Hospital, Korea
[2]Institute for Translational Research and Molecular Imaging, Catholic Institutes of Medical Science, College of Medicine, Seoul St. Mary's Hospital, Korea
[3]Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

PP06-01 **18F-FDG PET/CT for identifying the potential primary diseases and predicting prognosis of secondary hemophagocytic lympho-histiocytosis in children**
Ang Wei, Honghao Ma, Sitong Chen, Zhigang Li, Tianyou Wang and Rui Zhang*
Hematology center, Beijing children's hospital, China

PP06-02 **Clinical analysis of chronic active EBV infection involving gastrointestinal tract: a retrospective analysis of a single-center**
Ang Wei, Honghao Ma, Liping Zhang, Zhigang Li, Tianyou Wang and Rui Zhang*
Hematology center, Beijing children's hospital, China

PP06-03 **Clinical-biological characteristics and treatment outcome of children with multisystem Langerhans cell histiocytosis and secondary hemophagocytic lymphohistiocytosis**
Lingling Fu, Dong Wang, Honghao Ma And Rui Zhang*
Hematologic Diseases Laboratory, Hematology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China

PP06-04 **Clinical significance of soluble CD25 in cerebrospinal fluid in hemophagocytic lymphohistiocytosis with central nervous system involvement**
Wenxin Ou
Hemotology, Beijing Children's Hospital, China

PP06-05 **Effect analysis of Ruxolitinib combinations liposomal doxorubicin, etoposide methylprednisolone +/- PEG-asparaginase in treatment of refractory and relapsed hemophagocytic lymphohistiocytosis in children**
Ang Wei, Tianyou Wang* and Rui Zhang
Hematology center, Beijing children's hospital, China

PP06-06 **The role of pre-therapeutic 18F-FDG PET-CT in pediatric hemophagocytic lymphohistiocytosis with Epstein-Barr virus infection**
Liping Zhang, Ang Wei, Rui Zhang and Tianyou Wang
Hematology, Beijing Children's Hospital, China

PP06-07 **A case report of adult bone eosinophilic granuloma**
Altanshagai Boldbaatar[1], Ulzii-Orshikh Namkhai[2], Erdenetsetseg Battulga[3], Elbegjargal Erdenebaatar[1] and Khishigjargal Batsukh[1*]
[1]Center of Hematology, Blood and Marrow Transplantation, The First Central Hospital of Mongolia, Mongolia
[2]General Laboratory of Clinical Pathology, The First Central Hospital of Mongolia, Mongolia
[3]Diagnostic Imaging Center, The First Central Hospital of Mongolia, Mongolia

PP07-02 **Significance of LDH level in development of secondary plasma cell leukemia**
Harshita Dubey, Amar Ranjan* and Pranay Tanwar
Labortaory Oncology , Dr.B.R.A-IRCH, AIIMS, New Delhi, India

POSTER LIST

PP07-03 **Clinical benefit of measurable residual disease assessment by fragment analysis or next-generation sequencing in patients with multiple myeloma**

Hyunsoo Cho[1], Saeam Shin[2], Haerim Chung[1], Ji Eun Jang[1], Yu Ri Kim[1], June-Won Cheong[1], Yoo Hong Min[1], Seung-Tae Lee[2], Jong Rak Choi[2] and Jin Seok Kim[1*]
[1]Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Korea
[2]Department of Laboratory Medicine, Yonsei University College of Medicine, Korea

PP07-04 **Updated risk assessment and staging systems in multiple myeloma - real world scenario**

Ritu Gupta[1*], Akanksha Farswan[2], Anubha Gupta[2], Sriram K[3], Atul Sharma[4] and Lalit Kumar[4]
[1]Department of Laboratory Oncology, All India Institute of Medical Sciences (AIIMS), New Delhi, India
[2]SBILab, Department of Electronics and Communication, Indraprastha Institute of Information Technology-Delhi, New Delhi, India
[3]Department of Computational Biology, Indraprastha Institute of Information Technology-Delhi, New Delhi, India
[4]Department of Medical Oncology, All India Institute of Medical Sciences (AIIMS), New Delhi, India

PP07-05 **Light chain multiple myeloma presenting as AL amyloidosis**

Dawpadee Dharmasena*, Sanka Vijayabandara and Dhammika Palangasinghe
Teaching Hospital, Karapitiya, Galle, Sri Lanka

PP07-06 **Overexpression of PFKFB4 promotes adaptation to hypoxic microenvironment in multiple myeloma**

Jie Yang, Fei Wang and Baoan Chen*
Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, China

PP07-07 **Case series: Daratumumab monotherapy in relapsed and refractory multiple myeloma patients with severely compromised forced expiratory volume in one second**

Jin-Hyo Kim[2], Sung-Soo Park[1*], Jae-Ho Yoon[1], Sung-Eun Lee[1], Hee-Je Kim[1] and Chang-Ki Min[1]
[1]Department of Hematology, Seoul St. Mary's Hospital, The Catholic University, Korea
[2]College of Medicine, The Catholic University, Korea

PP07-08 **Multiple myeloma in borneo sarawak malaysia: a decade of experience in a single center**

Tze Shin Leong[1*], Adelyn Fen Ein Tee[1], Ching Tiong Ko[2], Grace Wan Chieng Lee[1] and Lee Ping Chew[1]
[1]Haematology Unit, Medical Department, Sarawak General Hospital, Malaysia
[2]Chemotherapy Drug Reconstitution Unit, Pharmacy Department, Sarawak General Hospital, Malaysia

PP07-10 **Talquetamab, a GPRC5D x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma: updated phase 1 results from monumental-1**

Amrita Krishnan[1*], Monique C. Minnema[2], Jesus G. Berdeja[3], Albert Oriol[4], Niels W.C.J. van de Donk[5], Paula Rodríguez-Otero[6], Elham Askari[7], María-Victoria Mateos[8], Luciano J. Costa[9], Raluca Verona[10], Joanne Ma[11], Suzette Girgis[11], Shiyi Yang[12], Brandi W. Hilder[13], Jeffery Russell[13], Jenna D. Goldberg[13] and Ajai Chari[14]
[1]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, USA
[2]Department of Hematology, University Medical Center Utrecht, Netherlands
[3]Center for Blood Cancer, Sarah Cannon Research Institute and Tennessee Oncology, USA
[4]Clinical Hematology Service - Clinical Trials Unit, Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Spain
[5]Department of Hematology, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Netherlands
[6]Central Clinical Trials Unit, Clínica Universidad de Navarra, Spain
[7]Hematology and Hemotherapy Service, Hospital Universitario Fundación Jiménez Díaz, Spain
[8]Hematology and Hemotherapy Service - Myeloma Unit, University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Spain
[9]Division of Hematology & Oncology, University of Alabama at Birmingham, USA
[10]Oncology Translational Research, Janssen R&D, USA
[11]Clinical Pharmacology, Janssen R&D, USA
[12]Clinical Biostatistics, Janssen R&D, USA
[13]Oncology, Janssen R&D, USA
[14]Medicine, Mount Sinai School of Medicine, USA

POSTER LIST

PP07-11 **The recovery of absolute lymphocyte count predicts a good prognosis in daratumumab-treated patients with relapsed/refractory multiple myeloma**

Hee Jeong Cho[1], Jae-Cheol Jo[2], Yoo Jin Lee[2], Myung Won Lee[3], Do-young Kim[4], Ho Jin Shin[4], Sung Nam Lim[5], Ji Hyun Lee[6], Sung Hwa Bae[7], Young Rok Do[8], Won Sik Lee[9], Min Kyung Kim[10], Jung Min Lee[1], Ju-Hyung Kim[1], Dong Won Baek[1], Sang-Kyun Sohn[1] and Joon Ho Moon[1*]

[1]Department of Hematology/Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Korea
[2]Ulsan University Hospital, University of Ulsan College of Medicine, Department of Hematology and Oncology, Korea
[3]Department of Hematology-Oncology, Chungnam National University Hospital, School of Medicine, Chungnam National University, Korea
[4]Department of Hematology-Oncology, Pusan National University Hospital, Pusan National University School of Medicine, Korea
[5]Department of Hematology-Oncology, Inje University Haeundae Paik Hospital, Korea
[6]Department of Hematology-Oncology, Dong-A University Hospital, Korea
[7]Department of Hematology-Oncology, Daegu Catholic University Hospital, Daegu Catholic University School of Medicine, Korea
[8]Department of Hematology-Oncology, Keimyung University School of Medicine, Korea
[9]Department of Hematology-Oncology, Inje University Busan Paik Hospital, Korea
[10]Department of Hematology-Oncology, Yeungnam University Hospital, Korea

PP07-12 **Galectin-1, Galectin-3, Galectin-9 and their role in monoclonal gammopathy of undetermined significance and multiple myeloma in residents of the Gomel region of Belarus**

Zhanna Kozich[1], Viktor Martinkov[1], Janna Pugacheva[1] and Natalya Klimkovich[2]

[1]Hematology Department, Republican Research Center for Radiation Medicine and Human Ecology, Belarus
[2]Hematology Department, Belarusian Medical Academy for Postgraduate Education, Belarus

PP07-13 **CC-92480 when combined with bortezomib/dexamethasone enhances cell-autonomous cytotoxicity through G_2/M transition blockade in multiple myeloma**

Chad C. Bjorklund[1*], Michael Amatangelo[1], Jian Kang[2], Hsiling Chiu[2], Archana Mukhopadhyay[1], Krista Wollerman[3], Michael Pourdehnad[4], Patrick Hagner[1] and Anjan Thakurta[1]

[1]Translational Medicine-Hematology, Bristol Myers Squibb, USA
[2]Research & Development, Bristol Myers Squibb, USA
[3]Pharmaceutical Development, Bristol Myers Squibb, USA
[4]Early Clinical Development, Hematology/Oncology and Cell Therapy, Bristol Myers Squibb, USA

PP07-14 **The GNRI (Geriatric Nutritional Risk Index) as a prognostic factor in patients with newly diagnosed multiple myeloma**

Sewon Lee[1], Seounggye Byeon[2], Yeung-Chul Mun[1] and Young Hoon Park[1*]

[1]Hematology-Oncology, Ewha Womans University College of Medicine, Mokdong Hospital, Korea
[2]Hematology-Oncology, Ewha Womans University College of Medicine, Seoul Hospital, Korea

PP07-15 **Treatment outcome and prognostic factors of newly diagnosed multiple myeloma receiving bortezomib-based induction in Hong Kong: an analysis of 448 patients**

Hoi Ki Karen Tang[1], Chi Yeung Fung[1], Yu Yan Hwang[1], Harold Lee[2], Sze Fai Yip[3], Howard Wong[4], Chi Kuen Lau[5], Kwan Hung Leung[6], Elaine Au[7], Bonnie Kho[4], Eric Tse[1], Joycelyn Sim[1], Yok Lam Kwong[1] and Chor Sang Chim[1*]

[1]Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong
[2]Department of Medicine, Princess Margaret Hospital, Hong Kong
[3]Department of Medicine, Tuen Mun Hospital, Hong Kong
[4]Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong
[5]Department of Medicine, Tseung Kwan O Hospital, Hong Kong
[6]Department of Medicine, United Christian Hospital, Hong Kong
[7]Department of Pathology, Queen Mary Hospital, University of Hong Kong, Hong Kong

PP07-16 **Favorable outcomes of 3-weekly daratumumab-based regimens in relapsed/refractory multiple myeloma: impact of MRD, rapid doubling time, LDH, triplets and quadruplets**

Cheong Ngai[1], Hoi Ki Karen Tang[1], Chi Yeung Fung[1], Yu Yan Hwang[1], Kai Chung Vincent Wong[2] and Chor Sang Chim[1*]

[1]Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong
[2]Department of Pharmacy, Queen Mary Hospital, University of Hong Kong, Hong Kong

POSTER LIST

PP07-17 **Effective substances for the treatment of multiple myeloma using a prohibitin-targeted chromanone compound derivatives**
Young Eun Lee[1,2], Ju Heon Park[1], Ha Jin Lim[1], Hye Ran Kim[3], Jong Hee Shin[1] and Myung Geun Shin[1,2*]
[1]Department of Laboratory Medicine, Chonnam National University Hwasun Hospital, Hwasun, Korea
[2]BioMedical Sciences Graduate Program (BMSGP), Chonnam National University and Chonnam National University Hwasun Hospital, Hwasun, Korea
[3]College of Korean Medicine, DongShin University, Naju, Korea

PP07-18 **Determinant factors for early mortality in newly diagnosed multiple myeloma patients**
Javad Alizargar
Nursing, Taipei University of Nursing and Health Sciences, Rep of China (Taiwan)

PP07-19 **Clinical profiles and survival outcomes of adult patients with multiple myeloma at a tertiary hospital in the Philippines**
Jeremiah Vallente*, Carlo Francisco Cortez and Ma. Angelina Mirasol
Department of Medicine, University of the Philippines - Philippine General Hospital, Philippines

PP07-20 **Treatment outcomes with reduced-dose bortezomib in adult patients with multiple myeloma: a single-center experience**
Jeremiah Vallente*, Carlo Francisco Cortez and Ma. Angelina Mirasol
Department of Medicine, University of the Philippines – Philippine General Hospital, Philippines

PP07-21 **Inhibition of mitochondrial thioredoxin by auranofin increases bortezomib-induced cell death through autophagy and mitochondrial ROS in multiple myeloma cell line**
Young Hoon Park, Jee Young Ahn and Yeung-Chul Mun*
Division of Hemato-Oncology, Department of Internal Medicine, Ewha Womans University Mokdong Hospital, Korea

PP07-23 **Real-world toxicity and efficacy of ixazomib, lenalidomide, and dexamethasone in Asian patients with relapsed and refractory multiple myeloma**
Ji Hyun Lee[1], Sung-hyun Kim[1], Hye Ryeon Kim[1], Joon Ho Moon[2], Chang-Ki Min[3], Je-Jung Lee [4], Ho-Jin Shin[5], Jae-Cheol Jo[6], Ji Yun Lee[7] and Ki-Hyun Kim[8]
[1]Department of Internal Medicine, Dong-A University College of Medicine, Korea
[2]Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea
[4]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea
[5]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[6]Department of Internal Medicine, Chonbuk National University Medical School, Korea
[7]Department of Internal Medicine, Pusan National University Hospital, Korea
[8]Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Korea

PP07-24 **Prognosis of chronic kidney disease stage 5 or under dialysis in asian multiple myeloma patients - on behalf of Korean multiple myeloma working party (KMM177 study)**
Ji Hyun Lee[1], Sung-HyunKim Kim[1], Ki-Hyun Kim[2], Chang-Ki Min[3], Je-Jung Lee [4], Sung-Hoon Jung[4], Sung-Soo Yoon[5], Dong-Yeop Shin[5], Ja Min Byun[5], Jae-Yong Kwak[6], Ho-Young Yhim[6], Byeong Seok Sohn[7], Jin Seok Kim[8], Hyo Jung Kim[9], Ho Sup Lee[10], Sung Hwa Bae[11], Gyeong-Won Lee[12], Sungwoo Park[12], Jae Hoon Lee[13], Min Kyoung Kim[14], Young Rok Do[15] and Jun Ho Yi[16]
[1]Department of Internal Medicine, Dong-A University College of Medicine, Korea
[2]Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea
[4]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea
[5]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[6]Department of Internal Medicine, Chonbuk National University Medical School, Korea
[7]Department of Internal Medicine, Pusan National University Hospital, Korea
[8]Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Korea
[9]Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Korea
[10]Department of Internal Medicine, Kosin University College of Medicine, Korea
[11]Department of Internal Medicine, Catholic University of Daegu School of Medicine, Korea
[12]Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, Korea
[13]Department of Internal Medicine, Gachon University Gil Medical Center, Korea
[14]Department of Medicine, Yeungnam University College of Medicine, Korea
[15]Division of Hematology-Oncology, School of Medicine, Keimyung University, Korea
[16]Division of Hematology-Oncology, Department of Medicine, Chung-Ang University, Korea

POSTER LIST

PP07-25 **The benefit of pomalidomide in RRMM with plasmacytomas - on behalf of Korean multiple myeloma working party (KMM1907 study)**

Ji Hyun Lee[1], Sung-Hyun Kim[1], Ki-Hyun Kim[2*], Chang-Ki Min[3], Sung-Soo Park[3], Je-Jung Lee[4], Sung-Hoon Jung[4], Sung-Soo Yoon[5], Ja Min Byun[5], Jae-Yong Kwak[6], Ho-Young Yhim[6] and Ho-Jin Shin[7]

[1]Department of Internal Medicine, Dong-A University College of Medicine, Korea
[2]Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea
[4]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea
[5]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[6]Department of Internal Medicine, Chonbuk National University Medical School, Korea
[7]Department of Internal Medicine, Pusan National University Hospital, Korea

PP07-26 **A pilot study to identify role of minimal residual disease in multiple myeloma patients who received autologous stem cell transplantation**

Sung-Soo Park[1], Jung Yeon Lee[2], Ari Ahn[2], Yonggoo Kim[2], Myungshin Kim[3] and Chang-Ki Min[1*]

[1]Department of Biochemistry, College of Medicine, Catholic University of Korea, Korea
[2]Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, Catholic University of Korea, Korea
[3]Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea

PP08-01 **Splenic infarction in patient with Philadelphia-negative myeloproliferative neoplasm**

Myung-Won Lee[1], Sang-Hoon Yeon[1], Hyewon Ryu[1], Ik-Chan Song[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1], Seon Young Kim[2], Kyung Sook Shin[3] and Deog-Yeon Jo[1*]

[1]Division of Hematology/Oncology, Department of Internal Medicine, Chungnam National University College of Medicine, Korea
[2]Department of Laboratory Medicine, Chungnam National University College of Medicine, Korea
[3]Department of Radiology, Chungnam National University College of Medicine, Korea

PP08-02 **Volumetric splenomegaly in patients with polycythemia vera**

Myung-Won Lee[1], Sang-Hoon Yeon[1], Hyewon Ryu[1], Ik-Chan Song[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1], Seon Young Kim[2], Jeoung Eun Lee[3], Kyung Sook Shin[3] and Deog-Yeon Jo[1*]

[1]Division of Hematology/Oncology, Department of Internal Medicine, Chungnam National University College of Medicine, Korea
[2]Department of Laboratory Medicine, Chungnam National University College of Medicine, Korea
[3]Department of Radiology, Chungnam National University College of Medicine, Korea

PP08-03 **Tuberculosis of the bone marrow in a patient with JAK2- positive myelofibrosis presenting with jaundice: a case report**

Joseph Emmanuelle Siatan[*] and Chrystal Anne Catli-Burog

Division of Internal Medicine, National Kidney and Transplant Institute, Philippines

PP08-04 **Myelofibrotic and leukemic transformation in 2016 WHO-defined Philadelphia-negative myeloproliferative neoplasm**

Ik-Chan Song, Sang Hoon Yeon, Myung-Won Lee, Hyewon Ryu, Hyo-Jin Lee, Hwan-Jung Yun, Seon Young Kim and Deog-Yeon Jo[*]

Department of Internal Medicine, Chungnam National University Hospital, Korea

PP08-05 **Real-world outcomes of ruxolitinib in patients with myelofibrosis focusing on RBC transfusion: a multicenter study from the MPN working party of the KSH**

Eunhee Jung[1], Junshik Hong[1*], Sung-Yong Kim[2], Young Park[3], Young Jin Yuh[4], Yeung-Chul Mun[5], Won-Sik Lee[4], Sung-Kyu Park[6] and Soo-Mee Bang[1]

[1]Department of Internal Medicine, Seoul National University College of Medicine, Korea
[2]Department of Internal Medicine, Konkuk University Medical Center, Korea
[3]Department of Internal Medicine, Korea University Anam Hospital, Korea
[4]Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Korea
[5]Department of Hematology-Oncology, Ewha Womans University College of Medicine, Korea
[6]Department of Internal Medicine, Soonchunhyang University College of Medicine, Korea

PP08-07 **Modified cell-based model of JAK2V617F mutation by using CRISPR/Cas9**

Rujira Mekchaaum[1], Supaporn Kalasin[1], Krai Daotak[1,2] and Nungruthai Nilsri[1,2*]

[1]Department of Medical Technology, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand
[2]Cellular and Molecular Immunology Research Unit, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand

POSTER LIST

PP09-01 **Pure red cell aplasia after ABO- mismatched allogeneic haematopoietic stem cell transplantation for very severe aplastic anaemia**
Ching Soon Teoh
Haematology, Hospital Pulau Pinang, Malaysia

PP09-03 **Application of next-generation sequencing to distinguish inherited from acquired in bone marrow failure syndrome: a single-center study**
WonKee Ahn, Seungmin Hahn, Jung Woo Han and Chuhl Joo Lyu*
Division of Pediatric Hemato-oncology, Department of Pediatrics, Yonsei University College of Medicine, Korea

PP09-04 **Comprehensive genetic analysis for patients with inherited bone marrow failure syndrome**
Jong Mi Lee[1,2], Hoon Seok Kim[1,2], Ari Ahn[1,2], Jisook Lim[1,2], Jae Won Yoo[3], Seongkoo Kim[3], Jae Wook Lee[3], Bin Cho[3], Nack-Gyun Chung[3], Myungshin Kim[1,2], Yonggoo Kim[1,2]
[1]Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[2]Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[3]Division Hematology/Oncology, Department of Pediatrics, The Catholic University of Korea, Seoul, Republic of Korea

PP10-01 **Performances of targeted RNA sequencing for the analysis of fusion, mutation, and expression in ph like B-ALL**
Jing Li
R&D, SINO-US diagnostics, China

PP10-02 **Novel usefulness of krebs von den lungen 6 (KL-6) for assessing bone marrow fibrosis**
Minjeong Nam[1], Mina Hur[2*], Mikyoung Park[3] and Hanah Kim[2]
[1]Laboratory Medicine, Korea University Anam Hospital, Korea
[2]Laboratory medicine, Konkuk University School of Medicine, Korea
[3]Laboratory medicine, Eunpyeong St. Mary's Hospital, Korea

PP10-03 **Diagnostic validity %Micro-R of the Sysmex Xn1000 for iron deficiency screening in adolescent female without anemia**
Ikky Nabila Nandinanti and Tri Ratnaningsih*
Departement of Clinical Pathology and Laboratory Medicine, Universitas Gadjah Mada, Indonesia

PP10-05 **Evaluation of somatic hypermutation status and cytogenetic abnormalities in Korean patients with chronic lymphocytic leukemia**
Heekang Choi[1], Haerim Chung[2], Hyunsoo Cho[2], Seung-Tae Lee[1], Jin Seok Kim[2] and Saeam Shin[1*]
[1]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul 03722, Korea
[2]Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul 03722, Korea

PP10-06 **Aplastic anemia and risk of incident atrial fibrillation - the good, the bad and the ugly**
Wei Syun Hu
Department, CMUH, Rep of China (Taiwan)

PP10-07 **Association of HTLV-1 bZIP factor with PICT1 impairs the nucleolar stress inducible RPL11/MDM2 complex**
Takayuki Ohshima
Faculty of Science and Engineering, Tokushima Bunri University, Japan

PP10-09 **Myeloproliferative Neoplasm (MPN)-associated gene mutations in non -MPN patients highlighting distinct features in plausible cases**
Daehyun Chu[1], Young-Uk Cho[1*], Seongsoo Jang[1], Miyoung Kim[1], Chan-Jeoung Park[1], Eul-Ju Seo[1], Eun-Ji Choi[2], Je-Hwan Lee[2] and Kyoo-Hyung Lee[2]
[1]Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea
[2]Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea

PP10-10 **Deep sequencing for BCR-ABL1 kinase domain variants analysis in chronic myeloid leukemia patients with TKI treatment**
Taekgyu Lee[1], Hyeon Ah Lee[1], Saeam Shin[2*], Seung-Tae Lee[2] and Jong Rak Choi[2]
[1]Department of Laboratory Medicine, Graduate School of Medical Science, Brain Korea 21 PLUS Project, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea

POSTER LIST

PP10-11 **Routine use of targeted RNA sequencing in leukemia patients and comparative evaluation with commercially available panels**
Young Eun Lee[1,2], Ha Jin Lim[1], Ji Hu Jeon[1], Ju Heon Park[1], Hye Ran Kim[3], Jong Hee Shin[1] and Myung Geun Shin[1*]
[1]Department of Laboratory Medicine, Chonnam National University and Chonnam National University Hwasun Hospital, Hwasun, Korea
[2]BioMedical Sciences Graduate Program (BMSGP), Chonnam National University and Chonnam National University Hwasun Hospital, Hwasun, Korea
[3]College of Korean Medicine, DongShin University, Naju, Korea

PP10-12 **Hemoglobin concentration, leukocyte and platelet counts in patients with gestational diabetes**
Nhu Cao Thi Bich, Thao Nguyen Van*, Tung Tran Thanh, Tuan Nguyen Huu, Thao Nguyen Thi, Ha Vy The, An Pham Thi Thuy, Diem Pham Ngoc and Trung Thai Minh
Hematology, Cho Ray hospital, Viet Nam

PP10-13 **Establishment of next-generation sequencing protocol for highly sensitive tracking of minimal residual disease in B-lymphoblastic leukemia**
Hyeon Ah Lee[1], Jin Ju Kim[2], Saeam Shin[2*], Seung-Tae Lee[2] and Jong Rak Choi[2]
[1]Department of Laboratory Medicine, Graduate School of Medical Science, Brain Korea 21 PLUS Project, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea

PP10-14 **Higher value of hemoglobin in optical methods of hematology analyzer ADVIA 2120 in diagnosing anemia**
Adika Zhulhi Arjana and Tri Ratnaningsih*
Clinical Pathology and Laboratory Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia

PP10-15 **Diagnostic validity of percentage of hypochromic red cells (% HYPO) for iron deficiency screening without anemia**
Andri Christianalusi and Tri Ratnaningsih*
Departement of Clinical Pathology and Laboratory Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada Yogyakarta, Indonesia

PP10-17 **Correlation of reticulocyte hemoglobin content (CHr) and iron status parameters**
Pradita Sri Mitasari and Tri Ratnaningsih*
Clinical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

PP10-18 **Validation of a machine learning expert supporting system, immunogenius, using immunohistochemistry results of 3000 Korean patients with lymphoid neoplasms**
Yosep Chong[1], Jamshid Abdul-Ghafar[1], Hye-Ra Jung[2], Seung-Sook Lee[3], and Gyeongsin Park[2]
[1]Department of Hospital Pathology, The Catholic University of Korea College of Medicine, Seoul, Korea
[2]Department of Pathology, Keimyung University, Daegu, Korea
[3]Department of Pathology, Korea Institute of Radiological and Medical Sciences, Seoul, Korea

PP11-01 **Iron deficiency anaemia presenting as idiopathic intracranial hypertension**
Sanka Vijayabandara*, Dawpadee Dharmasena and Malika Udugama
Teaching Hospital, Karapitiya, Galle, Sri Lanka

PP11-02 **Risk factors associated with anemia among teens in Laguna, Philippines**
Cherry Ann Durante[1*], Rufo Jr. Calixtro[2] and Estrella San Juan[1]
[1]Nursing, University of Perpetual Help - Dr. Jose G. Tamayo Medical University, Philippines
[2]Research, University of Perpetual Help - Dr. Jose G. Tamayo Medical University, Philippines

PP11-05 **Impairment of invasion and maturation and decreased selectivity of plasmodium falciparum in G6PD Viangchan and Mahidol variants**
Duangdao Palasuwan[1], Attakorn Palasuwan[1], Kanyarat Boonpeng[1], Mallika Imwong[2], Kasem Kulkeaw[3*] and Nutpakal Ketprasit[4]
[1]Oxidation in Red Cell Disorders Research Unit, Department of Clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, Thailand
[2]Department of Molecular Tropical Medicine and Genetics, Faculty of Tropical Medicine, Mahidol University, Thailand
[3]Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand
[4]Department of Biochemistry and Pharmacology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Australia

PP11-08 **Association of hematologic parameters with TMPRSS6 gene variations in iron deficiency anemia patients**
Azadeh Alizargar
Electrical Engineering and computer science, National Taipei University of Technology, Rep of China (Taiwan)

POSTER LIST

PP11-09 **Identification of genetic alterations in TMPRSS6 gene of anaemic patients from tribal region of Tamil Nadu, India**
Balachandar vellingiri[1*], Dhivya Venkatesan[1], Nimmisha Eruppakotte[1], Soumya Kizhakkillach[1], Harsha Ganesan[1], Arul Narayanasamy[2] and Abilash Valsala Gopalakrishnan[3]
[1]Department of Human Genetics & Molecular Biology, Bharathiar University, India
[2]Department of Zoology, Bharathiar Univeristy, India
[3]Department of Biomedical Sciences, Vellore Institute of Technology (VIT), India

PP11-11 **Identification of CYP2A6 alteration and its effect on sickle cell anaemia (SCA) in tribal population of Tamil Nadu, India**
Dhivya V[1], Soumya K[1], Harsha G[1], Krishnaswamy R[1], Arul N[1] and Balachandar V[1*]
[1]Human Molecular Cytogenetics and Stem Cell Laboratory, Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore 641046, Tamil Nadu, India
[2]Disease Proteomics Laboratory, Department of Zoology, Bharathiar University, Coimbatore 641046, Tamil Nadu, India

PP11-12 **Risk factors of anemia in pregnancy woman: primary healthcare centre**
Fitri Rachmawati Putri
Medika Mulya Hospital, Indonesia

PP11-13 **Diagnostic performance of % hypo as discriminator parameter of iron deficiency and hemoglobinopaties**
Rhaina Khairani
Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

PP11-14 **Favism a common but rare seen cause for hemolytic anemia for glucose-6-phosphate dehydrogenase (G6PD) deficiency: a case report**
Jian An Boo* and Shi Chyn Lim
Department of Paediatrics, Hospital Sultanah Bahiyah Alor Setar, Malaysia

PP11-15 **How Do current health expenditure per capita, labor force participation rate, GDP per capita relate to the prevalence of anemia among pregnant and non-pregnant women in the Philippines?**
Putri Ayu
Economics, Andalas University, Indonesia

PP11-17 **Analysis of the influence of the prevalence of anemia among pregnant women, current health expenditure and stunting on the prevalence of anemia among children in the Philippines**
Derizal Derizal[1*] and Putri Ayu[2]
[1]Economics, State Islamic Institute of Bukittinggi, Indonesia
[2]Economics, Andalas University, Indonesia

PP11-18 **The effect of analysis nutritional status and blood adding tablets on anemia in pregnancy**
Andi Makkasau[1], Sumiyati Sumiyati[2] and Andi Nursanti[3*]
[1]Management, Bina Generasi Bangsa of College Foundation, Indonesia
[2]Nursing, Bina Generasi Bangsa of College Foundation, Indonesia
[3]Pharmacy, Andini Persada College of Health Sciences Indonesia, Indonesia

PP12-01 **Single nucleotide polymorphisms of the HIF1A gene are associated with sensitivity of glucocorticoid treatment in pediatric ITP patients**
Hao Gu, Runhui Wu* and Zhenping Chen
Hematology center, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, China

PP12-02 **Efficacy and safety of two different low-dose rituximab regimens for chinese children patients with primary immune thrombocytopenia**
Xiaojing Zhu, Xingjuan Xie, Jialu Zhang and Runhui Wu*
Hematology, Beijing Children's Hospital Affiliated to Capital Medical University, China

PP12-03 **Comparison of AggreGuide A-100 with platelet function tests and thromboelastrography in patient with ischemic stroke**
Hyunjung Kim, Hey Kyung Lee and Young Woo Kim*
Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

POSTER LIST

PP12-04 **Rare acquired bleeding disorders in adolescents and young adults**
Young Shil Park
Department of Pediatrics, Kyung Hee University Hospital at Gangdong, Korea

PP12-05 **Incidence of complications in Korean patients with haemophilia A based on the Korean health insurance review and assessment service database: a study by the Korean pediatric hematology oncology group (KPHOG)**
Ye Jee Shim[1*] and Young Bae Choi[2]
[1]Department of Pediatrics, Keimyung University School of Medicine, Keimyung University Dongsan Hospital, Daegu, Korea
[2]Department of Pediatrics, Ajou University School of Medicine, Ajou University Hospital, Suwon, Korea

PP12-06 **CD4+CD25+FOXP3+, CD8+ predict development of chronic disease in newly diagnosed idiopathic Thrombocytopenia**
Zhi Wang[1,2,3], Zhenping Chen[1,2,3], Hao Gu[1,2,3], Jingyao Zhang[1,2,3], Shuyue Dong[1,2,3], Xinjuan Xie[1,2,3], LIngling Fu[1,2,3], Jlalu Zhang[1,2,3] and Runhui Wu[1,2,3*]
[1]Department of Hematology and Oncology, Beijing Children's Hospital, Capital Medical University, China
[2]Beijing Key Laboratory of Pediatric Hematology Oncology, National Center for Children's Health, China
[3]Key Laboratory of Major Diseases in Children, Ministry of Education, National Key Discipline of Pediatrics, Capital Medical University, China

PP12-07 **Case of acquired hemophilia a post Covid-19 vaccination**
Guang Yong Chong* and Nor Rafeah Tumian
Department of Hematology, Hospital Canselor Tuanku Muhriz University Kebangsaan, Malaysia

PP12-08 **Effect of anti-nuclear antibody positivity on adult newly diagnosed immune thrombocytopenia prognosis**
Ngoc-Sang Nguyen*, Tuan Nguyen, Thanh-Thanh Suzanne and Tung Tran
Hemotology, Cho Ray Hospital, Viet Nam

PP12-09 **Eltrombopag affects interferon-induced antiviral response through iron metabolism pathway**
Yuefen Hu, Sai Ma and Jun Peng*
Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China

PP12-10 **Piper betel ethanolic extract prolongs prothrombin time (PT) in plasma of Group O and Group A blood donors**
Evana Kamarudin
Medical Laboratory Department, University Technology MARA (UiTM), Malaysia

PP12-12 **Clinical characteristics of hemophilia in Korea – data from the Korean bleeding disorder registry (KBDR)**
Jung Woo Han[1,2], Hee Jo Baek[3], Young Shil Park[4], Sang Kyu Park[5], Ki Young Yoo[6], Eun Jin Choi[7], Ji Yoon Kim[8], Soon Ki Kim[9*]
[1] Department of Pediatrics, Yonsei University College of Medicine, Korea
[2] Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Seoul, Korea
[3] Department of Pediatrics, Hwasun Hospital, Chonnam National University, Korea
[4] Department of Pediatrics, Kyung Hee University School of Medicine, Korea
[5] Department of Pediatrics, School of Medicine, University of Ulsan, Korea
[6] Seoul Clinic, Korea Hemophilia Foundation, Korea
[7] Department of Pediatrics, Daegu Catholic University School of Medicine, Korea
[8] Department of Pediatrics, Kyungpook National University School of Medicine, Korea
[9] Department of Pediatrics, College of Medicine, Inha University, Korea

PP12-13 **Increased TCRαβ+ double-negative T Cells in pediatric Primary Immune Thrombocytopenia**
Xingjuan Xie[1], Runhui Wu[2*], Zhenping Chen[1], Hui Chen[1], Hao Gu[1] and Jingyao Ma[2]
[1]Hematology and Oncology Laboratory, Beijing Pediatric Research Institute, Beijing Children's Hospital, National Center for Children's Health, Beijing, China
[2]Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

PP12-14 **FOXO1 SNPs are associated with the severity and clinical outcome of pediatric immune thrombocytopenia in the Chinese population**
Xingjuan Xie[1], Zhenping Chen[1*], Runhui Wu[2], Hao Gu[2] and Jingyao Ma[2]
[1]Hematology and Oncology Laboratory, Beijing Pediatric Research Institute, Beijing Children's Hospital, National Center for Children's Health, Beijing, China
[2]Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

POSTER LIST

PP12-15 **The metformin effect in adult patients with ITP and pre-existing T2DM**
Chaoyang Li, Ming Hou, Qi Feng* and Jun Peng
Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China

PP12-16 **Treatment and bleeding complications of cancer-associated venous thromboembolism: a Korean population-based study**
Sang-A Kim[1], Ju Hyun Lee[1], Ji Yun Lee[1], Hun-Gyu Hwang[2], Yang-Ki Kim[3], Ho-Young Yhim[4], Junshik Hong[5], Jeong-Ok Lee[1] and Soo-Mee Bang[1*]
[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Korea
[2]Division of Pulmonology, Department of Internal Medicine, Soonchunhyang University, School of Medicine, Gumi Hospital, Korea
[3]Division of Pulmonology, Department of Internal Medicine, Soonchunhyang University, School of Medicine, Seoul Hospital, Korea
[4]Division of Hematology and Medical Oncology, Department of Internal Medicine, Jeonbuk National University Medical School, Korea
[5]Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Hospital, Korea

PP12-17 **Evaluation of guidelines for childhood primary immune thrombocytopenia**
Jialu Zhang
Hematology Center, Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

PP12-18 **Adapted guideline for the diagnosis and treatment of primary immune thrombocytopenia in children in China (2021 edition): recommendations external review**
Jialu Zhang
Hematology Center, Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

PP12-19 **Immune thrombocytopenia and incidence of H. pylori infection - a prospective study from India**
Rajeev Sandal [1], Gaurav Parkash[2*], Pankaj Malhotra[2], Shamoli Bhattacharya [2], Neelam Varma[2], Jasmina Ahluwalia[2] and Vishal Sharma[2]
[1]Department of radiotherapy and oncology, Indira Gandhi Medical College, India
[2]Department of clinical Hematology and Medical Oncology, PGIMER, Chandigarh, India

PP12-22 **To predict the pretest probability score in deep vein thrombosis (DVT) - a single center study**
Madiha Abid[1*], Munira Borhany[2], Sidra Zafar[1] and Tahir Shamsi[2]
[1]Research and Development, National Institute of Blood disease and Bone Marrow Transplantation, Pakistan
[2]Clinical Hematology, National Institute of Blood disease and Bone Marrow Transplantation, Pakistan

PP12-23 **Management of chronic adult ITP patients: a single center study**
Sidra Zafar[1*], Munira Borhany[2], Madiha Abid[1] and Tahir Shamsi[2]
[1]Research and Development, National Institute of Blood disease and Bone Marrow Transplantation, Pakistan
[2]Clinical Hematology, National Institute of Blood disease and Bone Marrow Transplantation, Pakistan

PP12-24 **An escalating treatment strategy for children with chronic immune thrombocytopenia: prospective clinical study from a single center**
Jialu Zhang
Hematology Center, Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

PP12-25 **HDAC3 single-nucleotide polymorphism rs2530223 is associated with increased susceptibility and severity of primary immune thrombocytopenia**
Leng Shaoqiu, MD, Liu Anli, MD, Wang Shuwen, MD, Peng J, MD
Department of Hematology, Qilu hospital, Jinan, China

PP13-01 **Outcome of allogenic hematopoietic stem cell transplantation for pediatric acute lymphoblastic leukemia: a retrospective analysis of a single-center**
Hongbo He, Huyong Zheng and Bin Wang
Hematology Center, Beijing Children's Hospital, China

PP13-03 **Early infectious complications among adult autologous hematopoietic stem cell transplant recipients at the national kidney and transplant institute**
Ernest Matthew Paggabao* and Lynn Bonifacio
Internal Medicine, National Kidney and Transplant Institute, Philippines

POSTER LIST

PP13-05 **Haploidentical stem cell transplantation using post cyclophosphamide: a single –center initial experience in Viet Nam**
Van Man Huynh
Stem Cell Transplantation, Blood Transfusion and Hematology Hospital, Viet Nam

PP13-07 **Efficacy of imatinib mesylate in patients with steroid-refractory chronic graft-versus-host disease**
Dong Won Baek[1], Hee Jeong Cho[1], Ju-Hyung Kim[1], Jae Sook Ahn[2], Hyung Joon Kim[2], Sung Nam Lim[3], Jun Won Cheong[4], Sung-Yong Kim[5], Ho Sup Lee[6], Jong Ho Won[7], Ho-Young Yhim[8], Joon Ho Moon[1] and Sang Kyun Sohn[1*]
[1]Department of Hematology/Oncology, Kyungpook National University Hospital, Korea
[2]Department of Hematology/Oncology, Chonnam National University Hwasun Hospital, Korea
[3]Department of Hematology/Oncology, Inje University Haeundae Paik Hospital, Korea
[4]Department of Hematology/Oncology, Severance Hospital, Korea
[5]Division of Hematology, Department of Internal Medicine, Konkuk University Medical Center, Korea
[6]Department of Hematology/Oncology, Kosin University Gosper Hospital, Korea
[7]Department of Hematology/Oncology, SoonChunHyang University Hospital, Korea
[8]Department of Internal Medicine, Jeonbuk National University Medical School, Korea

PP13-09 **Immune reconstitution following autologous hematopoietic stem cell transplantation: a study from AIIMS**
Mohini Mendiratta[1], Vineet Govinda Gupta[1], Sandeep Rai[2], Saroj Singh[2], Lalit Kumar[1], Ritu Gupta[2], Gajendra Smeeta[2] and Ranjit Kumar Sahoo[1*]
[1]Medical Oncology, All India Institute of Medical Sciences, India
[2]Laboratory Oncology, All India Institute of Medical Sciences, India

PP13-10 **Post-transplant cyclophosphamide for GVHD prophylaxis in haploidentical peripheral blood stem cell transplantation**
Jinhang Kim, Nanyoung Yun and Jeong-A Kim*
Hematology, St. Vincent Hospital, College of Medicine, The Catholic University of Korea, Korea

PP13-11 **Outcome of infant younger than 1 year with acute lymphoblastic or myeloid leukemia following intensive chemotherapy and hematopoietic stem cell transplantation**
Bo Kyung Kim, Kyung Taek Hong, Jung Yoon Choi, Hong Yul An, Hyun Jin Park and Hyoung Jin Kang*
Pediatrics, Seoul National University College of Medicine, Korea

PP13-12 **Symptomatic diarrhoeal and non-symptomatic clostridioides difficile infection (CDI) in hematopoietic stem cell transplantation recipients**
Alka Khadwal
Clinical Hematology & Medical Oncology, Post Graduate Institute of Medical Education & Research, Chandigarh, India

PP13-13 **The management and protocol of bone marrow transplantation (BMT) in the era of the COVID-19 pandemic: strategy to minimize risk of exposure to hazards**
Lintong Hottua Simbolon[1], Aprilia Grace A. Maay[2]
[1]Alumnus of University of Lampung, Indonesia
[1]Public Health, Institute of Health, Papua, Indonesia

PP14-01 **Expansion of human megakaryocyte-axis progeny via aryl hydrocarbon receptor antagonism of CH223191**
Dongchan Kim[1,2], Dong-Yeop Shin[1,2,3]*, Jun Liu[1,2], Na-rae Jeong[1,2], Youngil Koh[1,2,3], Junshik Hong[1,2,3], Xinxin Huang[4], Hal E. Broxmeyer[5] and Sung-Soo Yoon[1,2,3]
[1]Cancer Research Institute, College of Medicine, Seoul National University, Seoul, Republic of Korea
[2]Center for Medical Innovation of Biomedical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea
[3]Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea
[4]Institutes of Biomedical Sciences, Fudan University, Shanghai, China
[5]Department of Microbiology and Immunology, Indiana University School of Medicine (IUSM), Indianapolis, Indiana, USA

PP14-02 **Genetic variation of method of producing human liver stem cells or projenitor cells by direct reprogramming**
Haerani Haerani
Midwifery, Sekolah Tinggi Ilmu Kesehatan Bina Bangsa Majene, Indonesia

POSTER LIST

PP14-03 **BAFF blockade attenuates acute graft-versus-host disease directly via the dual regulation of T- and B-cell homeostasis**
Youngwoo Jeon[1,2], Jung-Yeon Lim[3], Keon-Il Lim[2], Nayoun Kim[2] and Seok-Goo Cho[1,2,4*]
[1]Hematology, The Catholic University of Korea, Yeouido ST. Mary's Hospital, Korea
[2]Institute for Translational Research and Molecular Imaging, Catholic Institutes of Medical Science, College of Medicine, Seoul St. Mary's Hospital, Korea
[3]Department of biomedical laboratory science, Inje University, Kimhae, South Korea, Korea
[4]Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

PP15-01 **Mesenchymal stem cells application improves face hyperpigmentation**
Mahmood Saba
Human Genetics & Molecular Biology, University of Health Sciences, Pakistan

PP15-02 **A combination of immunoadjuvant nanocomplex and dendritic cell vaccine in the presence of immune checkpoint blockade for effective cancer immunotherapy**
Manh Cuong VO[1], Sung-Hoon Jung[1], In-Kyu Park[2] and Je-Jung Lee[1*]
[1]Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Jeollanamdo, Korea
[2]Biomedical Science, Chonnam National University Medical School, Korea

PP15-03 **Antitumor activity of activated marrow-infiltrating lymphocytes in patients with multiple myeloma**
Manh-Cuong VO, Sung-Hoon Jung and Je-Jung Lee*
Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Korea

PP15-04 **Potent antimyeloma efficacy of dendritic cell therapy in combination with pomalidomide and programmed death ligand 1 blockade in a preclinical model of multiple myeloma**
Van-Tan Nguyen, Tan-Huy Chu, Manh-Cuong Vo, Sung-Hoon Jung and Je-Jung Lee*
Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea

PP15-05 **Novel IL-15 dendritic cells have a potent immunomodulatory effect in cancer immunotherapy**
Hoyoon Shin, Tan-Huy Chu, Manh-Cuong Vo, Sung-Hoon Jung and Je-Jung Lee*
Hematology-Oncology, Chonnam National University Medical School and Chonnam National University Hwasun Hospital, Korea

PP15-07 **Filterless- filter: microfluidic approach for cell separation and concentration**
Myeongwoo Kang[1], Taehwan Shin[1], Yujin Lee[1], Sunggyu Shin[1], Seungjung Song[1], Sungyoung Choi[2], Seong Soo A. An[3], Jaewoo Song[4], In Bum Suh[5] and Hoyoung Yun[1*]
[1]R&D, Curiosis Inc., Korea
[2]Department of Biomedical Engineering, Hanyang University, Korea
[3]Department of BionanoTechnology, Gachon University, Korea
[4]Department of Laboratory Medicine, Yonsei University College of Medicine, Korea
[5]Department of Laboratory Medicine, Kangwon National University College of Medicine, Korea

PP15-08 **Analysis of bone marrow mesenchymal stem cells for its protective effect on leber's hereditary optic neuropathy (LHON)**
Mohana Devi Subramaniam* and Aswathy P Nair
SN ONGC Department of Genetics and Molecular Biology, Vision Research Foundation, CHennai, India

PP15-09 **Material-based system for stem cell implant: aim to increase stem cell survival by drug**
Saher Khan
Uttar Pradesh Rajarshi Tandon Open University, Uttar Pradesh Rajarshi Tandon Open University, Uttar Pradesh, India

PP16-01 **Anaphylactic shock to a hematological disorder patient during transfusion of a platelet apheresis unit stored in platelet additive solution: a rare case report**
Bala Bhasker
Transfusion medicine, Sparsh Hospital, India

PP16-04 **Detection of anti-B Antibodies in a patient with A1B blood group: a case report and literature review**
Hee-Jeong Youk[1], Jin Seok Kim[1], Hyungsuk Kim[2], Sang-Hyun Hwang[1], Heung-Bum Oh[1], Yousun Chung[3] and Dae-Hyun Ko[1*]
[1]Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[2]Department of Laboratory Medicine, Seoul National University Hospital, Seoul, Korea
[3]Department of Laboratory Medicine, Kangdong Sacred Heart Hospital, Seoul, Korea

POSTER LIST

PP16-05 **The effect of plasma transfusion platelet to red blood cell ratio on mortality and morbidity: update meta-analysis**
Steven Irving[1*], Bastomy Eka Rezkita[1], Rabbinu Rangga Pribadi[2] and Marcellus Simadibrata[2]
1Department of General Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
2Division of Gastroenterology, Pancreatobiliary, and Digestive Endoscopy, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia

PP16-07 **Clinical significance of hemagglutination grades determined using the IH-1000 automated blood typing system: real world data**
Bosung Park[1], Jin Seok Kim[1], Hee-Jeong Youk[1], Yousun Chung[2], Hyungsuk Kim[3], Sang-Hyun Hwang[1], Heung-Bum Oh[1] and Dae-Hyun Ko[1*]
[1]Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea
[2]Laboratory Medicine, Kangdong Sacred Heart Hospital, Korea
[3]Laboratory Medicine, Seoul National University Hospital, Korea

PP16-09 **Effects of vitamin-C and L-carnitine as additives in stored erythrocytes**
Masannagari Pallavi
Biotechnology, JAIN (Deemed-to-be University), India

PP16-12 **Effect of patient characteristics on outcome of platelet transfusion in haemato-oncological patients**
Rahul Katharia*, Vasundhara Singh, Rajendra Chaudhary and Priti Elhence
Department of Transfusion Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

PP17-01 **Summary and analysis of 13 RAS-associated autoimmune leukoproliferative disease clinical features**
Lingling Fu, Jie Ma, Jiafeng Yao, Rui Zhang, Yunyun Wei, Bixi Yang, Ruixin Wang, Hongmin Li and Runhui Wu*
Hematologic Diseases Laboratory, Hematology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China

PP17-02 **Effectiveness of sirolimus in partial DiGeorge syndrome with refractory immune cytopenia: spot of elevated TCRαβ+ CD4-CD8-double-negative T cells**
Hao Gu, Runhui Wu* and Zhenping Chen
Hematology center, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, China

PP17-03 **Effectiveness of sirolimus in a novel CTLA-4 haploinsufficiency with ALPS phenotype**
Hao Gu, Wenjun Mou, Zhenping Chen and Runhui Wu
Hematology center, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, China

PP17-04 **Analysis of the relationship between the expression levels of neutrophil gelatinase-associated lipocalin and cytokine genes in bone marrow**
Sungchul Mun[1], Min-Chul Park[2] and Chi-Hyun Cho[3*]
[1]Industrial Engineering, Jeonju University, Korea
[2]Center for Opto-Electronic materials and devices, Korea Institute of Science and Technology, Korea
[3]Laboratory Medicine, Korea University Ansan Hospital, Korea

PP17-06 **Prolonged duration of the SARS-CoV-2 viral shedding in patients with oncohematological diseases**
Igor Stoma[1*] and Maria Shapetska[2]
[1]Infectious Diseases, Gomel state medical university, Belarus
[2]Hematology №3, Minsk scientific and practical center of surgery, transplantology and hematology, Belarus

PP17-07 **Incidence of pregnancy-associated venous thromboembolism: second nationwide study**
Hun-Gyu Hwang[1], Ju Hyun Lee[2] and Soo-Mee Bang[2*]
[1]Department of Internal Medicine, Soonchunhyang University, School of Medicine, Gumi Hospital, Korea
[2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Korea

PP17-08 **Pregnancy and the barriers in preventing anemia during Covid-19: result from a qualitative study of nurse-midwives perception in rural area**
Mahyuddin Mahyuddin
Sociology, State Islamic Institute of Parepare, Indonesia

POSTER LIST

PP17-09 **Machine learning in gene expression microarrays for leukemia cancer classification**
Rifaldy Fajar*, Nana Indri Kurniastuti, Dewi Mustika Sari and Maria Rosalia
Computational Bioloy and Medicine Laboratory, Yogyakarta State University, Indonesia

PP17-10 **Clinical characteristics and real world burden of Kimura's disease in Korea**
Hyun Jung Lee[1], Myung Hee Chang[2*], Do Yeon Kim[1], Dal Yong Kim[1] and Yueun Lee[1]
[1]Internal Medicine, Dongguk University Ilsan Hospital, Korea
[2]Internal Medicine, National Health Insurance Sevice Ilsan Hospital, Korea

PP17-11 **Epstein-Barr virus-related lymphoproliferative disease mimicking acute leukemia after mRNA COVID-19 vaccination**
Jae Hyun Cha[1], Myung-Hyun Nam[1*], Ka-Won Kang[2], Yunjung Cho[1] and Byung Soo Kim[2]
[1]Department of Laboratory Medicine, Anam Hospital, Korea University School of Medicine, Seoul, Korea
[2]Division of Hematology-Oncology, Department of Internal Medicine, Anam Hospital, Korea University School of Medicine, Seoul, Korea

PP17-16 **Consideration of differences in SARS-CoV-2 vaccination strategies in patients with hematologic malignancies**
Young Sok Ji[1], Sung Hee Lim[1], Jina Yun[1], Se Hyung Kim[1], Chan Kyu Kim[1], Jong Ho Won[2] and Seong Kyu Park[1*]
[1]Hematology/Oncology, Soonchunhyang University Bucheon Hospital, Korea
[2]Hematology/Oncology, Soonchunhyang University Seoul Hospital, Korea

PP17-17 **Xanthohumol suppresses interleukin-1β secretion and prevents inflammation through inhibition of NLRP3 inflammasome**
Cheng Zhang
Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, China

PP17-18 **Anticoagulation in patients with antiphospholipid syndrome-related venous thromboembolism: a nationwide study**
Hun-Gyu Hwang[1], Ju Hyun Lee[2], San-A Kim[2], Yang-Ki Kim[3], Myung-Shin Kim[1], Junshik Hong[4], Ho-Young Yhim[5] and Soo-Mee Bang[2*]
[1]Department of Internal Medicine, Soonchunhyang University, School of Medicine, Gumi Hospital, Korea
[2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Korea
[3]Department of Internal Medicine, Soonchunhyang University, School of Medicine, Seoul Hospital, Korea
[4]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[5]Department of Internal Medicine, Chunbuk National University Medical School, Korea

PP17-19 **Molecular abnormalities and their correlation with the prognosis of younger Indian patients with de novo myelodysplastic syndromes: AIIMS study**
Rekha Chaubey[1], Sudha Sazawal[1], Manoranjan Mahapatra[1], Sunita Chhikara[1], RM Pandey[2], Ashish Datt Upadhyay[2], Renu Saxena[1]
[1] Department of Hematology,All India Institute of Medical Sciences, India
[2] Department of Biostatistics, All India Institute of Medical Sciences, India

PP18-01 **Acute critical illness and cancer risk: implications from a nationwide population based study in Asia**
Wei Syun Hu
CMUH, Rep of China (Taiwan)

PP18-02 **Comparison of CHA 2 DS 2-VASc, CHADS 2 and HATCH scores for the prediction of new-onset atrial fibrillation in cancer patients: novel messages for hematologist**
Wei Syun Hu
CMUH, Rep of China (Taiwan)

PP18-04 **Factors associated with quality of life in patients with leukemia**
Elaheh Alizargar
Public Health, National Yangming Jiaotong University, Rep of China (Taiwan)

PP18-06 **Self efficacy approach for the prevention of acute lymphoblastic leukemia (ALL) in Indonesia**
Mega Dwi Septivani
Department of Science Management, Alumnae of Universitas Gadjah Mada, Indonesia

PLENARY LECTURE & PRESIDENTIAL SYMPOSIUM

PL01

Immune landscape of hematological malignancies and functional screening tools

Satu Mustjoki
University of Helsinki, Finland

Recent advances in the understanding of the immune response against cancer have provided novel cancer treatments, while undiscovered therapeutic potential still exists. Immune checkpoint inhibitors, particularly anti–PD-1 antibodies, have shown great potential in a variety of cancers, and are currently approved in over 15 cancer indications. CAR T cell therapies have also been approved and successfully used in B-cell malignancies. Currently emerging immuno-oncological (IO) therapies comprise antibodies targeting other immune checkpoint molecules, and various adoptive T and NK cell therapies. Despite impressive results, immunotherapy shows efficacy only in a subset of patients, and refractoriness and acquired resistance occur. As novel immunologic treatments are expensive, and severe side effects emerge, better biomarkers are needed to guide patient selection (personalized medicine) and to provide on-treatment indicators of response.

Recently we have performed an extensive immunogenomic analysis relying on large multi-omics datasets including over 8,000 transcriptomes of hematological cancers to investigate how immunological features are linked to cancer subtypes and patient survival.[1] Further, with the high-throughput profiling of over 500 drugs and genome-scale CRISPR-Cas9 loss-of-function screens we have discovered drug classes which either inhibit or potentiate CART cytotoxicity.[2]

During the presentation I will describe, how genomic features are associated with the immunogenicity of myeloid malignancies and novel immunotherapy targets can be discovered using unbiased functional screens for molecules that regulate the interaction between cancer cells and immune cells. Further, as currently approved cancer drugs may have great potential to enhance cancer immunotherapy, I will show examples how novel compounds that sensitize malignant cells to immune cell-mediated destruction can be discovered using high-throughput compound screening.

1. Dufva O, Polonen P, Bruck O, Keranen MAI, Klievink J, Mehtonen J, Huuhtanen J, Kumar A, Malani D, Siitonen S, Kankainen M, Ghimire B, Lahtela J, Mattila P, Vaha-Koskela M, Wennerberg K, Granberg K, Leivonen SK, Meriranta L, Heckman C, Leppa S, Nykter M, Lohi O, Heinaniemi M, Mustjoki S. Immunogenomic Landscape of Hematological Malignancies. Cancer Cell. 2020;38(3):380-399 e313.

2. Dufva O, Koski J, Maliniemi P, Ianevski A, Klievink J, Leitner J, Polonen P, Hohtari H, Saeed K, Hannunen T, Ellonen P, Steinberger P, Kankainen M, Aittokallio T, Keranen MAI, Korhonen M, Mustjoki S. Integrated drug profiling and CRISPR screening identify essential pathways for CAR T-cell cytotoxicity. Blood. 2020;135(9):597-609.

PL02

Rational development of targeted therapies to cure molecular subtypes of DLBCL

Louis M. Staudt
National Cancer Institute, USA

Chronic active B cell receptor (BCR) signaling is a key survival pathway in diffuse large B cell lymphoma (DLBCL), particularly in the ABC gene expression subgroup. The BTK kinase inhibitor ibrutinib kills ABC DLBCL cells by blocking this pathway and decreasing downstream NF-kB activation. A phase II trial of ibrutinib monotherapy in relapsed/refractory DLBCL demonstrated frequent responses in the ABC but not GCB subgroup. This prompted a phase III trial ("Phoenix") in previously untreated patients with non-GCB DLBCL testing the effect of adding ibrutinib to R-CHOP chemotherapy. Younger patients (age<60) had significantly improved progression-free and overall survival when receiving ibrutinib, but the molecular basis for this benefit is unknown. Recent multi-platform genetic profiling revealed a genetic taxonomy of DLBCL that subdivides the ABC subgroup into 4 genetic subtypes that are characterized by recurrent genetic aberrations, distinctive gene expression signatures, and differential responses to R-CHOP chemotherapy. The exceptional benefit of ibrutinib in particular DLBCL genetic subtypes will be discussed. Beyond chemotherapy, we are developing potentially curative therapies for lymphomas by combining targeted agents that block key survival pathways in the malignant cells. Recent progress in developing a therapeutic regimen combining 5 targeted agents will also be discussed.

PL03

Improving outcomes after CD19-targeted CAR T-cell therapy

Jordan Gauthier
University of Washington, USA

In this talk I will share my past and current work aimed at improving the outcomes of patients treated with T cells engineered with CD19-targeted chimeric antigen receptors (CD19 CAR T cells). I will summarize our extensive experience using defined-composition CD19 CAR T cells from approximately 200 patients with relapsed or refractory (R/R) B-cell malignancies treated on a phase I/II clinical trial at our institution. While gradually transforming the management of R/R B-cell malignancies, CD19 CAR T-cell therapy still fails to induce durable responses in most patients. In addition, a significant proportion of patients experience severe toxicities (cytokine release syndrome, neurologic toxicity), limiting access to CAR T-cell therapy to specialized centers. First, I will present our data modeling the independent impact of the CD19 CAR T-cell product type on outcomes in patients with R/R aggressive B-cell non-Hodgkin lymphoma. Next, I will discuss several strategies we investigated in clinical trials to improve outcomes after CD19 CAR T-cell therapy: i) combinatorial approaches with Bruton tyrosine kinase inhibitors and checkpoint inhibitors; ii) T cells engineered with a fully human CD19-targeted single chain variable fragment; iii) Toxicity prevention with the IL-1R antagonist anakinra.

PS01

Toward precision medicine in AML

Hartmut Döhner
University of Ulm, Germany

With the new sequencing technologies enormous progress has been made in deciphering the genetic landscape of acute myeloid leukemia (AML), thereby unraveling the enormous molecular heterogeneity of the disease and identifying new therapeutic targets. The development of precision medicine in AML is currently best illustrated by the successful development of FLT3-, IDH1/IDH2- and Bcl-2 inhibitors. When applied as single agents, most of these novel drugs only have modest clinical activity, but combining these drugs with current standard of care, such as intensive induction chemotherapy with daunorubicin/cytarabine ('3+7') or with the hyomethylating agents (HMA) azacitidine and decitabine, has demonstrated marked synergistic efficacy. However, despite significant improvements in outcome, the increment in response rates and in particular in survival remains modest. Numerous other new agents, including immunotherapies with bi-specific antibodies and antibody-drug conjugates, are in clinical development that hold promise to enlarge our portfolio of anti-leukemic drugs.

There remain quite a few challenges for the further successful development of precision medicine in AML, such as how to best and safely combine new agents (e.g. the development of less intensive triple therapies in older, unfit patients), or to circumvent primary and secondary resistance mechanisms. Finally, AML is a rare disease and conducting randomized phase 2/3 trials in particular in molecular subsets of the disease increasingly requires international collaborative efforts. The presentation will provide an update on the current status and promising new avenues for precision medicine in AML.

JOINT SYMPOSIUM

JS01-1

Next Generation CAR-T cell therapy against hematological malignancies

Kyungho Choi
Seoul National University College of Medicine

Chimeric Antigen Receptor (CAR) is an artificial receptor, in which a tumor antigen-binding antibody is fused with signaling domains of T cells. When the CAR gene is introduced to peripheral blood T cells from tumor patients, a large number of tumor-specific T cells which express CAR molecules (CAR-T cells) are able to be generated in a short period of time. These CAR T cells are infused back to the patient for T cell-mediated tumor eradication. The CAR-T cell therapy had a great success in treatment of the refractory and relapsing acute lymphoblastic leukemia leading to commercial development of several CAR-T cell drugs in the US. However, this remarkable therapeutic efficacy of the CAR-T cells is restricted to some blood tumors such as CD19(+) leukemias. The hurdles in this field include low therapeutic efficacy due to immunosuppressive tumor microenvironment and on-target off-tumor toxicity of CAR-T cells due to low-level expression of tumor antigens in normal tissues.
In this talk, I will introduce our recent experimental models to overcome those hurdles in CAR-T cell therapy on hematological malignancies.

JS01-2

Effective conditioning regimen in adoptive T cell therapy of cancer

Chungyong Han
National Cancer Center, Korea

Adoptive T cell therapy (ACT), a strategy for cancer treatment, has shown impressive therapeutic potential in hematologic cancer and melanoma. The strategy involves administration of tumor- reactive T cells such as T cells engineered with chimeric antigen receptor and the T cell receptor (TCR). Lymphodepletion pre-conditioning, which is generally performed before the T cell infusion, enhances the efficacy of ACT by increasing the graft rate of the T cells. However, the function of the transferred T cells is affected by immune-suppressive cells that repopulate after lymphodepletion. We designed a post-conditioning regimen that involves transient treatment with CD4-depleting antibody. In ACT of murine melanoma, the combination of cyclophosphamide pre-conditioning and anti-CD4 post-conditioning significantly enhanced anti-tumor efficacy. The combination regimen accelerated the expansion of CD8+ T cells and increased the proportion of IL-18Rα-high T cell subset which induced strong anti-tumor immune response in an IL-18/TCR signaling dependent manner. This study demonstrates the clinical relevance of anti-CD4 post-conditioning in ACT and provides insights into the function of IL-18Rα-high CD8+ T cells in cancer immunology

JS01-3

Tissue resident memory T cells in multiple myeloma

Yoon Seok Choi
Ajou University School of Medicine, Korea

Bone marrow (BM) is a primary lymphoid organ, a site of lymphocyte development. Even after development, mature T cells are more abundant in BM than in the peripheral circulation and $CD8^+$ T cell population occupies a large proportion than $CD4^+$ T cell population.

Recently, tissue resident memory T cells (T_{RM} cells) are discovered as a lineage of T cells specialized for function within tissues. Emerging evidence has shown that T_{RM} cells have a specialized role in the control of various tumors. A high frequency of T_{RM} cells in tumor correlates with favorable clinical outcome in cancer patients and studies in murine models have shown that T_{RM} cells are necessary for optimal immunologic control of tumors.

To date, there have been very few reports on the T_{RM} cells in the context of hematologic malignancies in human. We have been investigating the functional characteristics of BM-residing $CD8^+$ T cells in patients with multiple myeloma. $CD8^+$ T cells in the BM of MM patients contains sub-population expressing CD69, a marker of tissue residency, in a high frequency. Indeed, $CD69^+CD8^+$ T cells in BM have transcriptomic signature of T_{RM} cells with higher expression level of genes associated with tissue residency. Also, the myeloma (tumor) antigen-specific $CD8^+$ cells was more enriched in this $CD69^+CD8^+$ T cells than the $CD69^-$ counterpart. Interestingly, this population showed phenotypes consistent with profoundly exhausted $CD8^+$ T cells expressing several immune checkpoint receptors, indicating their active role in the immunosuppressive milieu of MM microenvironment.

In this presentation, the clinical implication of T_{RM} cells in the BM of patients with multiple myeloma (MM), especially in the advent of various T cell-directed immunotherapies, will be discussed.

JS01-4

T-cell-based immunotherapeutic strategies against EBV-positive malignancies using the novel TCR specific for LMP1 antigen

Tai-Gyu Kim
The Catholic University of Korea, Korea

Adoptive transfer of genetically engineered T-cells to express antigen-specific T-cell receptor (TCR) is a feasible and effective therapeutic approach for numerous types of cancers, including Epstein– Barr virus (EBV)-associated malignancies. In this study, a TCR gene transfer regimen was established to rapidly and reliably generate T-cells specific to EBV-encoded latent membrane protein- 1 (LMP1). A novel TCR specific to LMP1 (LMP1-TCR) was isolated from HLA-A*0201 transgenic mice that were immunized with the minimal epitope LMP1166 (TLLVDLLWL), and LMP1-TCR- transduced peripheral blood lymphocytes were evaluated for functional specificities. Both human CD8 and CD4 T-cells expressing the LMP1-TCR provoked high levels of cytokine secretion and cytolytic activity towards peptide-pulsed and LMP1-expressing tumor cells. Notably, recognition of these T-cells to peptide-pulsed cells was maintained at low concentration of peptide, implying that the LMP1-TCR has high avidity. Infusion of these engineered T-cells revealed remarkable therapeutic effects and inhibition of tumor growth in a preclinical xenogeneic model. Furthermore, explosive ex vivo proliferation of functional TCR-transduced T-cells was induced with artificial antigen-presenting cells that express costimulatory molecules CD80 and 4-1BBL.These data suggest that the novel TCR-targeting LMP1 might allow the potential design of T-cell-based immunotherapeutic strategies against EBV-positive malignancies.

JS02-1

Developing single-cell data integration pipeline to find novel cell types and gene markers for immune diseases

Jong-Eun Park
Korea Advanced Institute of Science and Technology, Korea

Since the first single-cell transcriptome analysis in 2009, the throughput of single-cell transcriptomics techniques has grown exponentially, allowing for a single study to characterize millions of cells. This technique is now being applied to various domains in biology, including human development, aging and pathologies. The human cell atlas initiative is a global network to bring all human single-cell data into a single map. As a part of this collaborative effort, we have built a map of human thymus across human lifetime, unraveling the process of birth and death of human organ. Meanwhile, to seamlessly integrate data with complex batch structure, we have developed a computational algorithm named BBKNN, which can be used to efficiently integrate large-scale dataset across multiple organs, timelines and diseases. With this pipeline, we have been building population-level single-cell atlas on multiple pathologies including inflammatory diseases and cancer tissues, which unveils new disease associated cell types and gene expression patterns. Especially, we have newly identified DC subtypes which are associated with the neuroinflammation and generalize our finding by analyzing multiple single-cell datasets on inflammatory diseases.

JS02-2

Detection of enhancer hijacking of oncogenes in multiple myeloma

Jin-Wu Nam
Hanyang University, Korea

Genome rearrangements often result in copy number alterations of cancer-related genes and cause the formation of cancer-related fusion genes. A previous report found that more than half of multiple myeloma (MM) cases showed that translocations that hijacked the IGH super-enhancer to be near the oncogene locus. Although the enhancer hijacking of oncogenes may direct the dramatic reduction of immunoglobulin (IG) genes in malignant tumor cells in the MM cases, the relationship between the genomic rearrangments and the transcriptomic complexity still remained unexplored. Here, we observed a frequent hijacking of the IGH super-enhancers, E and the 3'RR enhancers, to the 4p16, 6p21, 11q13, and 22q11 loci in 14 out of our 26 MM cases. Consequently, the target genes—FGFR3, NSD2, CCND1, CCND3, MYEOV, and SUSD2— near the translocations accompanying enhancer hijacking were highly upregulated relative to those in cases with no translocations. The enhancer hijacking events during the IGH rearrangements well reflected the upregulation of target genes according to the translocation position but the significant downregulation of IG genes, which led to the increases of transcriptomic complexity.

JS02-3

Pharmacogenetics of childhood acute lymphoblastic leukemia

Hyery Kim
University of Ulsan College of Medicine, Korea

Despite improvements in combination drug therapy and risk stratification, approximately 20% of pediatric patients with acute lymphoblastic leukemia (ALL) still experience drug resistance and treatment failure due to drug toxicities. In European populations, about 50% of thiopurine-induced cytotoxic adverse reactions, such as severe neutropenia and leukopenia, are explained by NUDT15 and TPMT genetic variants. According to the established guideline from the Clinical Pharmacogenetics Implementation Consortium (CPIC), the thiopurine dose is pharmacogenetically titrated based on the known risk variants of NUDT15 and TPMT. However, a substantial proportion of patients with leukemia presenting no genetic variation in NUDT15 or TPMT still experience life- threatening toxicities, which may result in dose reduction and/or discontinuation of thiopurine, resulting in therapeutic failure and relapse of leukemia.

Throughout the multicenter study, we have investigated a novel pharmacogenetic (PGx) markers and interactions associated with thiopurine intolerance from hematological toxicities using whole-exome sequencing in childhood patients with ALL. We used the gene-wise variant burden (GVB) method, which quantitates the cumulative variant burden of one or more genes into a single score with dimensionality reduction, thus providing a reliable frame for multiple gene-interaction analysis. The categorical nature of the traditional star allele haplotype-based method can complement the quantitative nature of the GVB method for evaluating the complex interplay of multiple genes/variants. For instance, designating three categories [i.e., poor (PM), intermediate (IM), and normal (NM) metabolizers] per gene creates an exponentially increasing complexity of 3N for a drug with N-gene PGx interactions. NUDT15 and TPMT have been assigned nine PGx subgroups for thiopurine, which will increase exponentially following new PGx discoveries across different ethnic groups.

We identified and evaluated the deterministic effect and their interaction of novel candidate PGx variants on the last-cycle 6-mercaptopurine (6-MP) dose intensity percentage (DIP) tolerated by pediatric patients with ALL. We identified CRIM1 rs3821169 homozygote in East Asians as a novel risk variant of thiopurine-induced hematological toxicities. Heterozygotes of the variant have revealed only mild effects on thiopurine toxicity, with an unknown clinical impact. The traditional two-gene model (NUDT15 and TPMT) for predicting the tolerated 6-MP DIP < 25% was outperformed by the three-gene model that included CRIM1, in terms of the area under the receiver operating characteristic curve (0.734 vs. 0.665), prediction accuracy (0.759 vs. 0.756), sensitivity (0.636 vs. 0.523), positive predictive value (0.315 vs. 0.288), and negative predictive value (0.931 vs. 0.913). Furthermore, four-gene-interplay models including NUDT15, TPMT, CRIM1, and IL6 revealed the best odds ratio (8.06) and potential population impact [relative risk (5.73), population attributable fraction (58%), number needed to treat (3.67), and number needed to genotype (12.50)]. Interplay between IL6 rs13306435 and CRIM1 rs3821169 was suggested as an independent and/or additive genetic determinant of thiopurine intolerance beyond NUDT15 and TPMT in pediatric ALL.

JS02-4

Evaluating leukemic structural variations using optical genome mapping

Saeam Shin
Yonsei University College of Medicine, Korea

Among various genetic variations, structural variations of chromosomes play an essential role in the pathogenesis of cancer development and progression. Especially in hematologic malignancies, it is well known that one of the major mechanisms of oncogenesis is the formation of fusion genes due to chromosomal rearrangements, which induces the loss of control of cell division and proliferation. Thus, structural variations are dealt with as important markers of diagnosis, selecting target therapy, and predicting prognosis through risk stratification in hematologic malignancies. Conventional methods for detecting structural variations, including G-banding karyotyping, fluorescence in situ hybridization, chromosomal microarray, and reverse-transcription polymerase chain reaction, have limitations. The short-read next-generation sequencing platform has limitations in precisely analyzing structural variations that are large in size and homologous elements such as repetitive sequences and pseudogenes. There is growing interest in single-molecule strategies, exploring long reads from tens to hundreds of kilobases. Optical mapping is a technique for constructing ordered, genome-wide, high-resolution maps from ultra-high-molecular-weight DNA labeled fluorescent probes. This mapping technique enables de novo assembly and gap filling, and it can detect structural variations that are up to tens of kilobases long. Optical mapping can overcome the limitations of conventional methods and detect structural variations with higher resolution in much less time. Moreover, the optical mapping may uncover novel chromosomal aberrations used as additional diagnosis markers, target therapy, and prognosis prediction.

JS03-1

Biologic and clinical consequences of the $BRAF^{V600E}$ mutation in Langerhans cell Histiocytosis

Kenneth L. McClain
Texas Children's Cancer Center, USA

Langerhans cell histiocytosis (LCH) is caused by mutations of the MAP Kinase pathway (BRAFV600E, MAPK1, BRAF insertions, deletions, and others) It is hypothesized that mutations in the least differentiated (bone marrow stem) cells lead to diffuse disease especially in the liver, spleen, and bone marrow resulting in the clinical category of high risk disease (high risk of treatment failure and death). Mutations in more differentiated cells can lead to multiple lesions in a single organ system, such as bone or skin, or single lesions. Targeted therapy of patients with BRAF or MEK inhibitors can bring rapid clinical responses, but a majority of patients will relapse when the inhibitors are withdrawn. Over the past 3 years some important discoveries have uncovered some mysteries of the pathologic LCH cells and why these patients have poor responses to standard chemotherapy or MAPKinase inhibitors. MAPKinase mutations have wide-spread effects on the biology of histiocytes and lymphocytes. The pathologic dendritic cells accumulate in lesions because of down-regulated CCR7 which is supposed to direct antigen presenting cells to lymph nodes. BCLX is also down- regulated leading to inability of the caspase cell death program to be activated by therapies. A senescence program is activated which makes cells resistant to inhibitors. The histiocytes in LCH express elevated levels of the Programmed Cell Death Ligand (PDL-1) and the lymphocytes express Programmed Death Receptor (PD-1) leading to an exhausted phenotype for CD8 lymphocytes. The dysfunctional state helps explain why all of the neoplastic histiocytes are not eliminated with MAPKinase inhibitors alone.

JS03-2

Advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis

Kim E. Nichols
St. Jude Children's Research Hospital, USA

Hemophagocytic lymphohistiocysis (HLH) comprises a group of inherited ("primary") and non- inherited ("secondary") disorders of the immune system characterized by the dysregulated activation of T cells and macrophages that copiously secrete cytokines and mediate significant tissue damage. Historically, HLH has been challenging to diagnose due the similarity of its manifestations to those seen in other more common disorders. Similarly, HLH has proven challenging to cure with a large proportion of patients dying due to disease or the complications of its treatment. Thanks to the dedicated efforts of clinical and basic investigators working in the field, the last 25 years have witnessed tremendous advances in our understanding of normal immune cell function and the pathogenesis of HLH. Together, this knowledge has informed many novel and innovative approaches to HLH diagnosis and treatment. Several of these advances will be discussed in this presentation including: 1) development of flow cytometric methods for the rapid detection of primary HLH; 2) development of multi-agent chemo-immunotherapeutic, immune cell-depleting, and cytokine- targeting regimens for the treatment of HLH; and 3) implementation of reduced intensity conditioning approaches for use in hematopoietic stem cell transplantation.

JS03-3

Current status of diagnosis and treatment of Langerhans cell histiocytosis in Korea

Kyung-Nam Koh
University of Ulsan College of Medicine, Korea

Langerhans cell histiocytosis (LCH) has a wide range of clinical presentations, and its clinical course varies widely from spontaneous regression to severe disseminated disease with the risk of permanent consequences. Although the pathogenesis of LCH has been a conundrum, recent advances have led to a better understanding of the molecular pathogenesis and ontogeny of the disease. Advanced genomic analyses have suggested that LCH is a disorder of MAPK pathway mutations. Due to the rarity of LCH, collaborative, cooperative group trials, especially those of Histiocyte Society, have contributed to the development of the treatment protocol. However, optimal treatment for recurrent or high-risk LCH has not yet been established.

The Korea Histiocytosis Working Party (KHWP) reported the outcome of a large, retrospective multicenter study in Korean children with LCH. A nationwide, multicenter, prospective registry of LCH was launched in 2013 with the support of the Korean Centers for Disease Control to overcome the limitation of the retrospective study and better understand its pathobiology and clinical course. The registry has collected patients' information with LCH, using iCReaT (internet-based clinical research and trial management system), a web-based data entry system. The goal of the registry is to produce epidemiologic and clinical data to reveal the current status of diagnosis and treatment of LCH, leading to developing an optimal treatment strategy for LCH in Korea. The KHWP is also trying to establish Korean guidelines for the diagnosis and treatment of LCH. Furthermore, the introduction of genomic sequencing and targeted agents is changing the landscape of diagnosis and treatment of LCH in real-world clinical practice.

This lecture will cover the current status and future perspectives in multicenter efforts to establish better diagnostic and therapeutic strategies for LCH in Korea. In addition, data on genomic alterations of Korean LCH patients will be presented.

JS03-4

Adult hemophagocytic lymphohistiocytosis in Korea

Seok Jin Kim
Samsung Medical Center, Korea

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome caused by uncontrolled immune activation leading to multiple organ failure. Impaired immune function, including natural killer (NK) or T cells, is a critical factor contributing to the occurrence of HLH, where macrophages are excessively activated to induce hemophagocytosis as well as a cytokine storm resulting in fever, organomegaly, and cytopenia. Primary HLH, also known as familial HLH, is mainly observed in infants and children and results from genetic defects in NK- and T-cell cytotoxicity such as genes related to cytotoxic granule exocytosis, whereas secondary HLH is mostly found in adults with various clinical situations such as malignancy, infections, and autoimmune diseases. The occurrence of secondary HLH may be influenced by many trigger factors and underlying disorders, and little is known about the underlying mechanisms and causality. Furthermore, there are limited data regarding the incidence of secondary HLH in adults because the initial clinical presentation is usually obscure and overlaps with other conditions, resulting in multi-organ failure such as sepsis.
Therefore, we have conducted a prospective cohort study for patients with suspected secondary HLH. In this cohort, we tried to diagnose secondary HLH in adult patients with symptoms and signs suspicious of HLH according to the HLH-2004 criteria, and then initiate immediate treatment for HLH to improve associated outcomes of critically ill patients. This lecture summarizes the experience with our prospective cohort study and the landscape of adult HLH in Korea including the feasibility of HLH-2004 criteria for the diagnosis of secondary HLH and biomarkers for predicting the prognosis of adult HLH.

Keywords: Hemophagocytic Lymphohistiocytosis, Diagnosis, Treatment, Prognosis

JS04-1

Failing a second-generation TKI: when the guidelines don't always help

Jane Apperley
Imperial College London, UK

The majority of patients with chronic myeloid leukemia (CML) respond well to tyrosine kinase inhibition (TKI) and will have a life expectancy similar to unaffected age-matched individuals. National and international recommendations for patient management are widely available and regularly updated. These guidelines are, as far as possible, evidence based and understandably utilise the results emanating from well-designed and executed clinical trials. Advice regarding diagnostic investigations, molecular monitoring, response criteria and first and second line treatments is robust and easy to follow. Management becomes more difficult when patients require several changes in TKI because of intolerance and/or resistance, or where co-morbidities limit the choice of subsequent TKI. In these patients, in whom the goal at diagnosis of treatment free remission now seems unrealistic, our overall aim must remain the prevention of disease progression. The challenge becomes the balance of efficacy versus tolerability. For patients with multiple intolerance to TKI, strategies such as dose reduction with increased frequency of molecular monitoring become a pragmatic 'real-world' choice. Those with true resistance pose a different challenge. Worldwide most patients still receive imatinib as their first-line treatment and some 30% will demonstrate resistance, defined as failure to achieve pre-defined levels of response at certain timepoints or loss of a previous response despite good compliance. After an obligatory investigation for a kinase domain mutation these patients will move onto a second generation TKI (2GTKI), the precise choice dictated by local drug availability, previous adverse events, pre-existing co-morbidities and patient preference, and some 50% will respond durably. Increasingly, newly diagnosed patients begin treatment with a 2GTKI and approximately 15% will have resistance, In these individuals, second-line management is equivalent to third-line treatment in those who started with imatinib, and here the guidelines are less prescriptive and less supported by published studies. Choosing an alternative 2GTKI for patients who are resistant to the first 2GTKI is largely futile in terms of achieving durable molecular remissions, but moving to a third generation TKI (3GTKI) is often a difficult choice given the more serious side effects associated with more potent agents. The recently published OPTIC study investigated the efficacy and safety of three different doses of ponatinib, the most widely available 3GTKI: rather surprisingly there was little difference in the toxicity of the varying doses and less surprisingly, the higher dose was more effective. Further analyses within this study have identified the need to start with the higher dose (45mg daily) in patients with kinase domain mutations and in those whose response to the most recent TKI was at best complete haematological remission. The explanation for the lower incidence of arterial thrombotic events compared to the original Phase 2 study is less clear, but may reflect physician awareness, patient selection and better management of underlying co-morbidities. Asciminib has now been licensed and is available as a third line option in some countries. The recent ASCEMBL randomized study of asciminib versus bosutinib in third or subsequent line treatment has shown improved efficacy of asciminib compared to bosutinib, and to date, the adverse event profile of asciminib seems acceptable. These recent data provide a better understanding of the use of 3GTKI in patients at risk of disease progression and should increase patient and physician confidence in earlier instigation when necessary.

JS04-2

Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia patients in clinical practice

Antonio Almeida
Hospital da Luz Lisboa, Portugal

The main goal of Chronic Myeloid Leukemia (CML) therapy was prevention of progression to ensure best overall survival, which required lifelong treatment. In recent years, treatment-free remission (TFR) has become an important goal and several Tyrosine Kinase Inhibitors (TKI) discontinuation studies have shown that around 50% of patients with a durable deep molecular response (DMR) successfully interrupt TKI for at least 3 years without loss of major molecular response.
However, the exact conditions which determine the greatest probability of successful TFR remain poorly defined. Different studies have tried to guide clinical decision-making regarding this topic but there are some points that differ, namely with respect to the recommended duration of TKI therapy and the appropriate molecular response and its duration prior to treatment interruption.
Perhaps the most important finding of all TKI treatment interruption studies is the confirmation that, with adequate monitoring, this practice is safe. The requisites are access to reliable and timely molecular monitoring and the possibility to immediately restart TKI if MMR is lost. Under these conditions there have been no progressions in the study population during the treatment-free period. The majority of published studies have included patients treated with Imatinib. More recently several studies have studied treatment interruption in patients treated with second generation TKI, both in the second- and first-line setting. All these studies confirm that this practice is safe, but several unanswered questions remain. The most important of these is which TKI treatment strategy is most favorable to successful long-term TFR. It is also not clear if the British strategy, which involves reducing TKI dosing prior to interruption, is indeed more efficacious than the sudden stopping strategy adopted by most other studies. Finally, it is very important to identify which patients will benefit the most from TFR and how their treatment should be tailored to that end.
In an era when an "operational cure" has become a reality for CML patients without needing to receive a bone marrow transplant, our experience from treatment interruption has led us to search for deeper knowledge about this fascinating disease and the roles BCR-ABL, stem cells and the immune system have in its pathophysiology.

JS04-3

Second and later line therapy: the role of ponatinib in Korean patients with CML

Jeong-Ok Lee
Seoul National University Bundang Hospital, Korea

JS04-4

Stopping tyrosine kinase inhibitor in chronic myeloid leukemia; perspectives from Korean data

Hawk Kim
Gachon University College of Medicine, Korea

The objectives of treating chronic myeloid leukemia (CML) have changed from the prolonging overall survival by achieving adequate cytogenetic/molecular responses to treatment free remission (TFR) which became of the new therapeutic target by European LeukemiaNet 2017 recommendation. There are many clinical trials for TFR in CML patients taking second generation tyrosine kinase inhibitors (TKIs) as well as imatinib. Early Korean retrospective data in 2012 for stopping imatinib analyzed 14 patients defining TFR as maintenance of complete molecular response (CMR; currently molecularly undetectable leukemia [MUL]). The overall probability of persistence of CMR at 1 year was 28.6% (95% Confidence Interval [CI], 16.5–40.7). The duration of IM therapy after achieving a CMR showed a marginally significant trends for overall probability for CMR persistence (P = 0.076). Long-term follow up retrospective multicenter data were published in 2016. The criterion of TFR was the undetectable minimal residual disease (UMRD) persistence. Nineteen patients were enrolled and the estimated UMRD persistence rate at 5 years was 23.7% (95% CI 13.2–34.2). The rate of UMRD persistence at 5 years was significantly lower in patients with a high- risk Sokal score at diagnosis than in those with low- to intermediate-risk Sokal scores (0 vs. 40.9%, $p < 0.001$).

The first prospective TFR study in Korea was Korean imatinib stop study (KIDS) published in 2013. KIDS study defined TFR failure as 2 consecutive losses of major molecular response (MMR). The TFR rate was the overall 12- month and 24-month probability of sustained MMR was 62.2% and 58.5%, respectively. Follow up data of KIDS showed

The Korean Society of Hematology Chronic Myeloid Leukemia Working Party (CMLWP) conducted a retrospective TFR study was ASTER study that enrolled 93 patients. TFR at 5 years was 47.9 % and 44.4 %, for MR3.0 loss and UMRD loss, respectively. A prospective multicenter study of TFR (Digital CML study) was conducted by CMLWP. The study was closed after enrolling total 78 patients. After TKI discontinuation, digital polymerase chain reaction (dPCR) was measured at regular intervals to check the relationship between changes in BCR/ABL1 levels and molecular recurrence survival, and to select a patient group that can safely discontinue TKI.

New prospective TFR studies of CMLWP are ASTER-P as a first TFR trial and ASTER-A as a second TFR trial. CMLWP will publish a new Korean guideline for CML treatment and TFR in consideration of these Korean data.

ASIAN/MOU COUNTRY SESSION

AS01-1

Korean treatment guideline for aplastic anemia

Jun Ho Jang
Sungkyunkwan University, Korea

Acquired aplastic anemia (AA) is a rare, life-threatening bone marrow failure (BMF) disorder that affects patients of all ages and is caused by lymphocyte destruction of early hematopoietic cells. Diagnosis of AA requires a comprehensive approach with prompt evaluation for inherited and secondary causes of bone marrow aplasia, while providing aggressive supportive care. The choice of frontline therapy is determined by many factors including severity, age, donor availability, and other therapies. For newly diagnosed severe aplastic anemia, bone marrow transplant should be done in all pediatric patients and in younger adult patients when a matched sibling or unrelated donor is available. Frontline therapy in older adult patients and in all patients lacking a matched sibling donor involves immunosuppressive therapy (IST) with rabbit antithymocyte globulin and cyclosporine A. Recent improvements in upfront therapy include the emerging benefits of eltrombopag combined with initial IST. For the relapsed or refractory patients, several therapeutic options exist, with improving outcomes of haploidentical bone marrow transplantation as well as the addition of eltrombopag to the non-transplant AA.

AS01-2

Aplastic anemia immunosuppressive therapy in China

Zhao Xin
Institute of Hematology and Blood Diseases Hospital, China

The incidence of aplastic anemia (AA) is relatively higher in Asia. China has a large population, so there are many AA patients. Hematopoietic stem cell transplantation is the first choice for young patients with HLA matched sibling donors, but the choice is limited in China due to one child policy implemented for a period. Therefore, majority patients were treated immunosuppressive therapy (IST).

Hematologists in China began to use antithymocyte globulin (ATG) combined with cyclosporine in severe aplastic anemia (SAA) since 1990s. We have experienced horse ATG, rabbit ATG (rATG) and porcine ATG (pATG). Currently, rATG and pATG are the two kinds mainly be used, and the response rate achieves 60-70% in SAA. pATG may have more advantages in the elderly. Medium- dose cyclophosphamide (CTX) shows good efficacy and safety in Chinese SAA patients. In addition, the regimen including ATG, CTX and human umbilical cord blood cells also showed very good efficacy.

TPO receptor agonists have a history of more than 10 years in China. Some studies showed that rhTPO combined with IST can improve the efficacy of SAA patients. There are also eltrobopag, herombopag and avatrombopag in Chinese market. The response rate is up to 80% using eltrombopag and IST as first-line treatment for SAA, with a CR rate of nearly 30%. In IST-refractory SAAs, the response rate of herombopag is comparable to eltrombopag. The clinical trial of herombopag combined with IST as first-line treatment for SAA is under way. There is limited data on the treatment of AA with avatrombopag.

Despite multiple studies report prognostic factors for AA to IST, there is no scoring system that enables clinicians to quantify the patient's indicators to assess the patient's benefit after IST. To establish such a system, we analyzed the clinical data from the largest hematological clinical center in China. A global analysis was performed, and critical prognostic variables were evaluated to generate a consensus scoring system. This prognostic system should prove useful for more precise treatment choice and analysis of therapeutic trials in AA.

AS01-3

Clinical significance of detecting HLA-class I allele-lacking leukocytes in patients with aplastic anemia

Kohei Hosokawa
Kanazawa University, Japan

The presence of such HLA class I allele-lacking leukocytes [HLA(-) cells] provides compelling evidence that cytotoxic T-lymphocytes are involved in the development of AA. However, the clinical significance and precise mechanisms underlying clonal hematopoiesis by HLA(-) HSPCs remain unknown.

We identified a common nonsense mutation at codon19 (c.19C>T, p.R7X) in exon1 (Exon1mut) of different HLA-A and HLA -B alleles in HLA(-) cells from AA patients. Screening of 353 AA patients using a novel droplet digital PCR (ddPCR) assay revealed Exon1mut in 101 (29%) of the patients. Eighty-two percent of AA patients with Exon1mut responded to immunosuppressive therapy (IST). The detection of Exon1mut using the ddPCR assay thus serves as a powerful tool for diagnosing the immune pathophysiology of patients with bone marrow failure.

We studied the prognosis of 633 AA patients including 127 patients with HLA(-) cells followed for a long period. The prognosis survey revealed that clonal evolution to MDS/AML did not occur in any of the 127 patients with HLA(-) cells, after a median follow-up period of 51 months. In contrast, 17 AA patients without HLA(-) cells eventually evolved to MDS/AML. The presence of HLA(-) cells represented independent negative predictors of clonal evolution to MDS/AML.

We studied clonal predominance of HLA(-) cells relative to that of GPI(-) cells in 13 AA patients in convalescence who possessed both marker(-) leukocytes. Longitudinal studies of 7 patients showed a gradual decrease in the percentage of HLA(-) granulocytes, with a reciprocal increase in the GPI(-) granulocytes in 4 patients responding to cyclosporine (CsA) and an increase in the HLA(-) granulocytes with a stable or declining GPI(-) granulocytes in 3 patients in sustained remission off CsA therapy. The findings indicate that GPI(-) HSCs may lose survival advantage and become less predominant than HLA(-) HSCs in AA patients off IST when they possess both marker(-) cells, and suggest a lower risk of developing secondary PNH.

In summary, detecting HLA(-) leukocytes is therefore essential in the management of AA patients, and help physicians to choose appropriate therapy.

AS02-1

Ma-Spore ALL studies: truly Asia approach to curing childhood ALL

Allen E.J. Yeoh
National University of Singapore, Singapore

Despite its deceptively similar morphology under light microscopy, ALL is highly heterogeneous. Its heterogeneity is underlined by >20 distinct genetic drivers; each genetic driver conferring its own distinct risk of relapse. Whole genome transcriptomic sequencing using RNA-Seq can help define exactly each's patient genetic aberration that is driving his ALL. Increasingly study groups like St Jude Total 17 and Ma-Spore ALL 2020 study are using RNA-Seq to better define the genetic drivers and refine the risk stratification.

Low risk ALL is characterized by low risk of relapse. Features of low risk ALL include:

1. NCI standard risk – age 1-10 and WBC <50,000/uL at presentation.
2. Favorable genetics – Hyperdiploidy and ETV6-RUNX1
3. Rapid early response to therapy as defined by end of induction MRD <0.01%.
4. CNS 1 disease

There are considerable interactions between the first 3 low risk factors.

It is increasingly clear that further intensification of therapy does not improve outcome for low-risk ALL. COG AALL0331 study showed that children with ALL with all of the above low risk features (SR-low) did exceedingly well with 3-drug induction, mild consolidation and one block of COG Protocol II. Intensification with 4-additional doses of PEG-L-asp although marginally reduced the risk of relapse, did not improve overall outcome. UKALL 2003 SR arm showed that 2 blocks of delayed intensification Protocol II yielded similar outcome as one block.

As a result, many groups have started to reduce the intensity of therapy for low risk ALL. Ma-Spore ALL 2010 Standard Risk arm completely eliminated anthracyclines in low risk ALL patients, reducing toxicity without compromising outcomes. COG AALL0932 showed that in NCI SR ALL, 4 weekly dexa/vincristine pulse did not improve outcome compared to 12 weekly dexa/vincristine pulses.

In this talk, I will review some of the world's experience in managing low risk ALL and suggest that for this low risk group, giving less chemotherapy can actually achieve more.

AS02-2

Childhood acute lymphoblastic leukemia in Thailand and multicenter studies of Thai pediatric oncology group

Samart Pakakasama
Mahidol University, Thailand

Acute lymphoblastic leukemia (ALL) is the most common malignancy in Thai children aged less than 15 years old. Our institution previously used modified St Jude Children Research Total therapy protocols. We adjusted types and dosages of some chemotherapeutic drugs to be appropriate to our context. The event-free survival (EFS) rates of the modified Total Therapy XIIIB were 82.8%, 81.7% and 81.7% at 5, 10 and 15 years whereas EFS rates of the modified Total Therapy XV were 84%, 80.8% and 80.8%, respectively.

With advances in genetic studies, the treatment outcomes of childhood ALL have been improving. Genetic abnormalities identify patients' risk and are used for providing the most effective treatment schemes especially specific targeted therapy. We have implemented genetic analysis for leukemic cells including cytogenetics, RT-PCR for common chromosomal translocations, FISH for TEL- AML1 and MLL rearrangement and IKAROS gene deletion. Pharmacogenetic testing for TPMT and NUDT15 polymorphisms are analyzed and used for individually adjusting mercaptopurine dosage.

Thai Pediatric Oncology Group (Thai POG) has developed ALL treatment protocols aiming for comfortable use in both medical schools and regional hospitals all over the country. Therefore, treatment intensity was less than other ALL protocols. In 2006, Thai POG ALL protocols simply classified the patients into standard and high risk ALL. The 5-year EFS rates in standard and high- risk patients were 66.5% and 51.2%. Currently, we have used updated ALL protocols stratified into standard, high and very high-risk treatment protocols. MRD and genetic abnormalities are incorporated into criteria for risk classification. Data and outcomes of the patients enrolled in these protocols have been collecting and analyzing.

AS02-3

The adherence to MRD time points improves treatment outcomes of childhood ALL in Taiwan: the experience of TPOG-ALL-2013 protocol

Hsi-Che Liu
Mackay Memorial Hospital, Taiwan

The Taiwan Pediatric Oncology Group (TPOG) launched the first nationwide study TPOG-ALL-881 Protocol for ALL treatment in 1988. The TPOG-ALL-2013 protocol (TPOG-2013), adapted from the St. Jude Total Therapy XV Study and Total Therapy XVI Study, was opened since January 2013. This is the first MRD-directed protocol for treatment of childhood ALL in Taiwan. According to TPOG-2013, two MRD measurements were scheduled on days 15-19 of induction (MRD1 time point, TP1) and days 35-42, end of induction (MRD2 time point, TP2) to make the definitive risk stratification to guide subsequent therapy.

As of December 31, 2020, 900 newly diagnosed ALLs were enrolled with last follow-up on October 31, 2021. The median follow-up time of 814 surviving patients was 4.4 years (range, 0.8-9.0 years). The outcomes were compared with those of TPOG-ALL-2002 protocol (TPOG-2002) (N=1347, between January 2002 and December 2012), which did not integrate the MRD monitoring. There were no significant differences in gender, age, WBC counts, and lineage at diagnosis between the patients treated with TPOG-2002 and TPOG-2013. The 5-year event-free survival (EFS) (% ± SE) was significantly improved from 74.9 ± 1.2 of TPOG-2002 to 84.8 ± 1.4 of TPOG-2013 ($P < 0.0001$). Further, the cumulative incidences (% ± SE) of isolated CNS relapse and any CNS relapse significantly decreased from 4.0 ± 0.6 to 1.3 ± 0.4 ($P < 0.0001$) and from 5.8 ± 0.7 to 2.9 ± 0.7 ($P = 0.0003$), respectively.

The issue of non-adherence to MRD monitoring emerged since the implementation of MRD-directed TPOG-2013. For further analysis, 662 (74%) patients with exact adherence (EA) to both TPs were assigned as MRD EA group; 234 (26%) patients who were non-adherence (NA) to either one of TPs as MRD NA group; and four patients were excluded for the comparative outcome analysis. The major causes of non-adherence for both TPs were delaying MRD monitoring due to neutropenic fever and documented infections. In MRD EA group, 14.5% of patients were upgraded to higher-risk treatment groups based on their MRD results. There were significant differences in outcomes between MRD EA and MRD NA groups: the 5-year EFS were 87.3 ± 1.6 and 79.4 ± 2.9, respectively ($P = 0.007$), overall survival (OS) were 92.0 ± 1.2 and 81.5 ± 2.7, respectively ($P = 0.00014$).

In conclusion, contemporary MRD-directed therapy has improved the treatment outcomes of childhood ALL in Taiwan. The adherence to MRD time points remains a significantly prognostic predictor in the era of MRD-guided treatment.

MS01-1

Managing multiple myeloma in a resource-limited region: diagnosis and treatment in Armenia

Yervand K. Hakobyan
Armenian Hematology Association, Armenia

Multiple myeloma (MM) is the second most common blood cancer in adults leading to 117,000 deaths every year. Major breakthroughs in clinical research of the past decades transformed the diagnosis and treatment of MM improving the survival rates and overall quality of life of patients. Unfortunately, scientific advancements are not distributed equally around the globe leading to disparities in the treatment outcomes between different regions of the world. Management of MM in low- and middle- income countries represents a big challenge for healthcare providers considering the economic, technological, and infrastructural restraints in comparison to developed countries. Many standards of practice, including diagnostic tools and therapeutic regimens, are not available in developing regions of the world. As an example of an upper-middle-income country, Armenia has been witnessing considerable progress in the diagnosis and treatment of MM, including but not limited to the establishment of autologous stem cell transplant (ASCT), accessibility to modern anti-myeloma medications, and improved diagnostic and monitoring workup. Despite significant improvements, there is still a need for refinement in the management of MM. The aim of this review article is to discuss the latest developments and the current diagnosis and treatment of MM in Armenia as an example of a resource-limited region.

MS01-2

Renal involvement in plasma cell disorder: learning from real-life practice

Suporn Chuncharunee
Ramathibodi Hospital, Thailand

A variety of renal diseases have now been described in association with monoclonal gammopathy. These spectrum of diseases include cast nephropathy, light chain nephropathy (LCCN) and monoclonal gammopathy of renal significance (MGRS). Monoclonal gammopathy-related nephropathies are most common in patients with symptomatic multiple myeloma. LCCN may cause other monoclonal gammopathy-related kidney lesions such as AL amyloidosis, light chain deposition disease. Early detection and effective treatment is crucial to reverse myeloma-associated renal impairment and improved survival. The International Kidney and Monoclonal Gammopathy Research Group (IKMG) redefines MGRS as a clonal proliferative disorder that produces a nephrotoxic monoclonal immunoglobulin and does not meet previously defined haematological criteria for treatment of a specific malignancy. The diagnosis of immunoglobulin-related disease is established by kidney biopsy and immunofluorescence studies. Combination of dexamethasone with the proteasome inhibitor bortezomib is considered as the standard treatment. The randomized study that compared a doublet (bortezomib-dexamethasone) with a triplet regimen (cyclophosphamide- bortezomib-dexamethasone) did not show a beneficial effect for renal outcomes. Furthermore, monoclonal anti-CD38 monoclonal antibodies, which significantly improve the efficacy is a promising agent in treatment of LCCN and amyloidosis.
This presentation will focus on the cases with light chain-nephropathy, amyloidosis and light chain deposition disease. Therapeutic approach of each case will be addressed.

References:
1. Leung N, Bridoux F, Vecihi Batuman V. et al The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. Nat Rev Nephrol. 2019;15:45–59.
2. Bridoux F, Arnulf B, Karlin L. et al.Randomized Trial Comparing Double Versus Triple Bortezomib-Based Regimen in Patients With Multiple Myeloma and Acute Kidney Injury Due to Cast Nephropathy J Clin Oncol2020;38:2647-2657
3. Bridoux F. Leung N, Belmouaz M, et al. Management of acute kidney injury in symptomatic multiple myeloma. Kidney International (2021) 99, 570–580

MS01-3

Treatment sequence decision in multiple myeloma considering reimbursement status

Youngil Koh
Seoul National University Hospital, Korea

Multiple myeloma (MM) is a characteristic disease with long disease course with median overall survival (OS) over 7 years. MM treatments are divided into several classes including induction, maintenance/consolidation, and salvage. For induction treatment, NCCN recommended regimens includes VRD (Bortezomib, Lenalidomide, and dexamethasone) or anti-CD38 combination. After induction with or without autologous stem cell transplantation (ASCT), maintenance with lenalidomide or consolidation with ixazomib is recommended to lengthen progression free survival (PFS).

However, these costly treatments are not always accessible for patients in many countries, which makes a practical treatment scheme considering drug assessment to be essential for individual countries. To make things more complicated, recent advances in the drug development including T- cell engagers, antibody-drug conjugates (ADC), and chimeric antigen receptor (CAR) based treatments are changing a paradigm in MM treatment journey. Even some of these treatments seems to cure MM in relapsed/refractory setting. Hence, practical treatment scheme should be made considering the accessibility to the upcoming treatments in years.

In this talk, I will be discussing how to make a practical scheme for treating MM in a country where drug access is not perfect to optimize outcome of MM patients. Conditioning regimen for ASCT, value of maintenance/consolidation, optimal treatment sequences will be covered.

SCIENTIFIC SESSION

SS01-1

Primary immune regulatory disorder for the pediatric hematologist and oncologist

Shanmuganathan Chandrakasan
Emory University School of Medicine, USA

The spectrum of Primary Immune Regulatory Disorders (PIRD) has widened over the last decade. An array of monogenic immune defects marked by autoimmunity, lymphoproliferation, and hyperinflammation rather than infections have been described. Increasingly, pediatric hematologists and oncologists are among the first subspecialists these patients might present to. Hence, understanding different manifestations of this disease spectrum, its evaluation, and management is critical for the early identification and proper management of these patients. The talk will give an overview of the spectrum of primary immune regulatory disorders, including ALPS and ALPS-like syndromes, IPEX and IPEX-like disorders, CVID and CVID-like, and late-onset combined immunodeficiency (CID) disorders. The talk will also focus on recent advances in immunobiology and genetics of Evans syndrome, hyperinflammatory disorders, and those associated with increased susceptibility to lymphoid malignancies.

SS01-2

Clonal evolution and somatic reversion in bone marrow failure

Akiko Shimamura
Harvard Medical School, USA

Early diagnosis of germline genetic causes of bone marrow failure informs medical management and treatment decisions. This talk will review indications for germline genetic testing and explore some of the challenges of genetic testing. We will also explore recent advances in our understanding of clonal evolution to myeloid malignancies as well as genetic somatic reversion in bone marrow failure conditions.

SS01-3

Molecular landscape of pediatric AML

Soheil Meshinchi
Fred Hutchinson Cancer Research Center, USA

Acute myeloid leukemia (AML) is the disease of elderly, where more than 80% of all cases of AML diagnosed in patients older than 60 years of age. Until recently, it was assumed that childhood AML is a less common variant of the adult disease. Recent studies into the underlying biology of childhood AML has defined the genomic and transcriptome of AML in younger patients and contrasted the underlying mechanism of disease to those in older adults. These studies have demonstrated that childhood AML is vastly different than the adult disease, with structural alterations including translocations/fusion transcripts leading to the generation of fusion oncoproteins are the predominant mechanism of disease in younger patients. As many of these disease defining fusions are associated with clinical outcome in children, comprehensive knowledge of such fusions, many of which are cryptic, can inform most appropriate risk and target based therapeutic interventions. Accurate identification of patients at high risk of relapse allows for allocation of patients to allogeneic stem cell transplantation in first CR prior to impending relapse. In this presentation we will review the most recent genomic and transcriptomic discoveries in childhood AML, their prognostic implications, therapeutic targets and most appropriate incorporation into the pediatric AML clinical trials.

SS02-1

Molecular classification of diffuse large B-cell lymphoma and novel treatment strategies

Daisuke Ennishi
Okayama University Hospital, Japan

Diffuse large B-cell lymphoma (DLBCL) represents a largest number of entities among lymphoid cancers, which are an aggregate of clinically and biologically diverse diseases. In particular, it is thought that various molecular genetic abnormalities are involved in the tumorigenesis of disease development. Due to recent advances in multi-omics analyses, gene expression profile reflecting cell-of-origin and tumor microenvironment, and recurrent genetic abnormalities have been discovered, which is important aspect for the development of future new therapeutic drugs and indications for clinical trials, ultimately leading to the precision medicine in the area of DLBCL.

SS02-2

Novel immunotherapeutic antibodies for B-cell NHL

Gilles Salles
Memorial Sloan Kettering Cancer Center, USA

More than 20 years ago, the introduction of rituximab transformed the treatment of patients with B-cell lymphoma and significantly improved their outcome. More recently, different types of antibodies directed against several B-cell antigens have been developed and allowed further progresses in the field.

The antibody drug conjugate polatuzumab vedotin was developed as a single agent, then combined with bendamustine and rituximab for patients with diffuse large B-cell lymphoma (DLBCL) in the relapsed/refractory setting. In a randomized phase 2 study, the addition of polatuzumab vedotin to BR resulted in a significant improvement of complete response rate, progression-free survival, and overall survival. Furthermore, the recent randomized phase 3 study POLARIX (Tilly et al., NEJM 2021) in patients with newly diagnosed DLBCL (with an IPI score 2 to 5) has shown that substituting vincristine with polatuzumab vedotin within the R-CHOP regimen resulted in a significant prolongation of progression-free survival. This new combination (pola-R-CHP) was shown to have a similar toxicity profile compared to R-CHOP.

The antibody directed against CD19 tafasitamab has been used in combination with lenalidomide in the L-MIND regimen. In patient with relapsed or refractory DLBCL, this combination has shown a 58% overall response rate with 40% of the patients achieving a complete response. Interestingly, patient with a complete response had a very prolonged duration of the efficacy of the treatment: at 3 years about 80% of them remained free of disease recurrence. This combination is now evaluated within different combinations in various situations and B-cell entities.

Another class of antibodies has been recently developed cold bispecific antibodies. The underlying concept is to recognize specifically the tumor cell with one arm of the antibody (targeting a B-cell antigen), while the second arm will engage the T-cell receptor (via CD3) to activate T-cells cytotoxic activity against lymphoma cells. Several bispecific antibodies directed against CD20 and CD3 are currently in active development, with promising results in different B-cell malignancies: DLBCL as well as follicular and mantle cell lymphomas. Response rates appear variable among the different studies and the response durability, while encouraging in some studies, needs to be further ascertained. The rapid activation of T-cells results during the first infusions in a cytokine release syndrome, rapidly reversible and manageable. Combination of bispecific antibodies with other new agents (immunotherapies) or classical cytotoxic agents are currently under active development. We will review recent results regarding the efficacy and safety of these different drugs and to fit in our current therapeutic strategies.

SS02-3

Targeting B-cell receptor and BCL-2 in chronic lymphocytic leukemia

Susan M. O'Brien
University of California, USA

Treatment for relapse of CLL is obviously dependent on what the patient received as initial therapy. In patients who have received prior chemo immunotherapy, a B-cell receptor inhibitor (BTKi) or Venetoclax +/- antibody are both options. If patients are treated initially with a BTKi, most of those who progress will progress on therapy, thus not allowing treatment with another second generation BTKi.

For patients progressing on a BTKi, switching to venetoclax provides an excellent option. In the clinical trial of venetoclax continuous therapy for patients who had failed a prior BCR inhibitor, 59 of 91 patients (65%) treated with ibrutinib responded, impressive data given that the median number of prior regimens was four and that 45% of the patients had a P53 abnormality. Subsequently, the Murano trial led to the approval of venetoclax and rituximab for relapsed CLL as a fixed duration therapy of two years. However, the relapsed population being treated here had predominantly received prior chemoimmunotherapy so this did not provide specific data for response rates in those refractory to a BTKi. Real world data looked at a total of 141 CLL patients who received venetoclax for relapsed CLL. Prior to venetoclax initiation, 89% had received a BTKi. The overall response rate to venetoclax was 72%.

The CLL14 trial led to the approval of venetoclax and obinutuzumab as a fixed duration one year therapy for frontline patients with CLL. Since that trial is quite recent there is very little data on patients relapsing and their subsequent response to any treatment. Here the options may be more variable since as the venetoclax is fixed duration, it's likely that most of these patients will have been off venetoclax for several years at the time they recur. This raises the distinct option of retreating with either single agent venetoclax or in combination with antibody. The largest series thus far examining the response to a BTKi in BTKi naive patients who had received venetoclax, comes from real world data. In that data cohort, 84% of patients achieved a response.

Finally, there is now data for the use of non-covalent BTKi for the treatment of relapsed CLL. Pirtobrutinib showed excellent efficacy in vitro against xenografts containing a BTK mutation. In the phase one trial the response rate was 62%; responses appeared to improve over time and the short follow-up did not provide information on durability. Of note was that there was no MTD reached and the toxicity was quite minimal, some of the usual side effects of BTKi such as atrial fibrillation and hypertension were not seen.

SS03-1

Recent advances in molecular diagnosis, prognosis and monitoring of myeloproliferative neoplasms

Myungshin Kim
The Catholic University of Korea, Korea

Myeloproliferative neoplasms (MPNs) are characterized by the clonal proliferation of hematopoietic cells that are fully differentiated and functional. MPNs are mainly classified into polycythemia vera, essential thrombocythemia and primary myelofibrosis, according to disease manifestations. Some rare disease categories, such as chronic neutrophilic leukemia and chronic eosinophilic leukemia, are also considered MPNs, in addition to those MPNs that are unclassified. The diagnosis of MPN and the distinction of its disease categories are based on blood cell counts, bone marrow morphology and molecular testing. As a result of increasingly available and economical next-generation sequencing technologies, mutational studies have revealed the prognostic relevance of a few somatic mutations in terms of thrombotic risk and risk of transformation. Finally, knowledge of the mutational landscape not only can potentially be used as a prognostic factor of MPN, but also can help identify targets for directed therapy. Here, we will provide an update of the Recent advances on how molecular testing can improve the diagnosis and prognosis of patients with MPN and present recent advances that may have prognostic value in the near future.

SS03-2

Molecular mechanisms underlying the development of MPN by mutant calreticulin and the therapeutic potential of an antibody targeting mutant calreticulin

Norio Komatsu
Juntendo University Graduate School of Medicine, Japan

Somatic mutations in the calreticulin (CALR) gene, which encodes a molecular chaperone, have been reported in patients with JAK2- and MPL-unmutated essential thrombocythemia and primary myelofibrosis, a subcategory of myeloproliferative neoplasms (MPNs). Our group and others have shown that the expression of mutant CALR results in the transformation of cells through interactions with and the activation of the thrombopoietin receptor, MPL (Blood 2016). We recently demonstrated that mutant, but not wild-type, CALR forms a homomultimeric complex, and showed that an interaction between mutant CALR molecules within the homomultimeric complex was required for the binding and activation of MPL on the cell surface (Leukemia 2018 and Leukemia 2020). Therefore, mutant CALR serves as a "fake" ligand for MPL. Since the c-terminal mutant sequence is unique to mutant CALR, it has potential as a therapeutic target for mutant CALR-positive MPN patients. Based on these findings, we developed the monoclonal antibody, B3, which specifically recognizes mutant, but not wild-type, CALR. A flow cytometric analysis revealed that B3 recognized mutant CALR expressed on the cell surface. Furthermore, B3 exhibited a strong binding capacity to the antigen in a surface plasmon resonance analysis. These results promoted us to develop the mouse chimeric antibody, B3-chimera, and examine its potential as a therapeutic reagent against MPNs in vivo. When ET model animals created by the bone marrow transplantation of LSK (Lin-Sca1+c-Kit+) cells transduced with CALR del52 were intraperitoneally treated with B3-chimera, thrombocytosis induced by CALR del52 was markedly suppressed. Furthermore, the number of megakaryocytes in bone marrow was markedly reduced in animals treated with B3-chimera. These results indicate that the B3-chimera antibody has therapeutic potential for mutant CALR-positive MPN patients with thrombocytosis.

SS03-3

Targeting pro-inflammatory signaling, including IL8, in myelofibrosis: the pathway into the clinic

Andrew J. Dunbar
Memorial Sloan Kettering Cancer Center, USA

Pro-inflammatory signaling is a hallmark feature of human cancer, including in myeloproliferative neoplasms (MPNs), most notably myelofibrosis (MF). Dysregulated inflammatory signaling contributes to fibrotic progression in MF; however, the individual cytokine mediators elicited by malignant MPN cells to promote collagen-producing fibrosis and disease evolution remain yet to be fully elucidated.

Previously we identified a critical role for combined constitutive JAK/STAT and aberrant NF-κB pro-inflammatory signaling in myelofibrosis development, and recent clinical studies suggest synergistic targeting of these pathways leads to improved outcomes in MF. Using single-cell transcriptional and cytokine-secretion studies of primary MF patient cells and two separate murine models of myelofibrosis, we extend this previous work and delineate the role of CXCL8 (IL8)-/CXCR2 signaling in MF pathogenesis and bone marrow fibrosis progression. MF patient hematopoietic stem/progenitor cells are enriched in a CXCL8/CXCR2 gene signature and display dose-dependent proliferation and fitness in response to exogenous CXCL8 ligand in vitro. Genetic deletion of Cxcr2 in the hMPLW515L adoptive transfer model abrogates fibrosis and extends overall survival, and pharmacologic inhibition of the CXCR1/2 pathway improves hematologic parameters, attenuates bone marrow fibrosis, and synergizes with JAK inhibitor (JAKi) therapy. Our mechanistic insights provide a rationale for therapeutic targeting of the CXCL8/CXCR2 pathway in MF patients at risk for continued fibrotic progression.

SS04-1

Evolution of myeloma from the normal plasma cell to disease complexity

Niccolo Bolli
University of Milan, Italy

The knowledge of cancer origin and the subsequent tracking of disease evolution represent unmet needs that will soon be within clinical reach. This will provide the opportunity to improve patient's stratification and to personalize treatments based on cancer biology along its life history. Multiple myeloma (MM) is an hematological cancer characterized by uncontrolled accumulation of clonal plasma cells within the bone marrow. However, the cell of origin is a B-lymphocyte acquiring aberrant genomic events in the germinal center of a lymph node as off-target events during somatic- hypermutation and class-switch recombination driven by activation-induced-deaminase. Whether pre-germinal center events are also required for transformation, and which additional events are required for disease progression is still matter of debate. Indeed, MM has a long preclinical phase whose better understanding may lead to progress in clinical management of the disease. In this talk, I will focus on the molecular pathogenesis of multiple myeloma (MM), describing novel insights into modes and timing of disease initiation. I will dissect the genomics of the preclinical and pre-malignant phases, elucidating how knowledge of the genomics of the disease and the composition of the microenvironment allow stratification of patients based on risk of disease progression. Then, I will describe cell-intrinsic and cell-extrinsic drivers of MM evolution to symptomatic disease. I will explain the genetic heterogeneity of MM as one of the major drivers of disease. As early treatment in asymptomatic phases is gaining traction in the clinic, a better understanding of the molecular pathogenesis of myeloma progression would allow stratification of patients based on their risk of progression, thus rationalizing efficacy and cost of clinical interventions. By integrating an evolutionary view of myeloma biology with the recent acquisitions on its clonal heterogeneity, I envision a way to drive the clinical management of the disease based on its detailed biological features more than surrogates of disease burden.

SS04-2

The power of ONE: immunology in the age of single cell genomics

Ido Amit
Weizmann Institute, Israel

The immune system is a complex, dynamic and plastic network composed of various interacting cell types that are constantly sensing and responding to environmental cues. From very early on, the immunology field has invested great efforts to characterize the various immune cell types and elucidate their functions. However, accumulating evidence indicates that current technologies and classification schemes are limited in their ability to account for the functional heterogeneity of immune processes. Single cell genomics hold the potential to revolutionize the way we characterize complex immune cell assemblies and study their spatial organization, dynamics, clonal distribution, pathways, and crosstalk. This emerging field can greatly affect basic and translational research of the immune system. I will discuss how recent single cell genomic studies are changing our perspective of various immune related pathologies from cancer to autoimmune disease and neurodegeneration. Finally, I will consider recent and forthcoming technological and analytical advances in single cell genomics and their huge potential impact on the future of immunology research and immunotherapy.

SS04-3

Clinical implications of immune networks in multiple myeloma

Je-Jung Lee
Chonnam National University Medical School, Korea

Multiple myeloma (MM) is characterized by generalized immune dysregulation, such as functional hypogammaglobulinemia and defects in T cell immunity, natural killer (NK) cell function, and antigen-presenting capacities of dendritic cells, resulting in susceptibility to infection as well as tumor progression. Additionally, there is a rise in immune suppressor cells, such as regulatory T cells and myeloid-derived suppressor cells, in the bone marrow microenvironment. In the COVID-19 pandemic era, this immune dysfunction, especially in humoral immunity, in MM induce to increase the susceptibility of MM patients to infections and decrease the response to vaccination. The impairment in the function of several immune cells favors the tumor escape from immune surveillance and contributes to induce myeloma cell growth and survival. Immunotherapy has recently emerged as a promising and innovative treatment option to prolong survival of MM patients, and monoclonal antibodies, vaccines, NK cells, and genetically engineered cells (CAR T cells and CAR NK cells) may represent a new era for the treatment of myeloma. In this presentation, I will briefly discuss clinical implications of immune networks in the aspect of our translational researches in the field of MM.

SS05-1

Resistance mechanism in chronic myeloid leukemia

Kimmo Porkka
Helsinki University Central Hospital, Finland

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasia associated with a molecular alteration, the fusion gene BCR-ABL1, that encodes the tyrosine kinase oncoprotein BCR-ABL1. This led to the development of practice-changing drugs - tyrosine kinase inhibitors (TKI) - with imatinib being the first TKI approved.
Although the vast majority of CML patients respond to TKIs, resistance to this targeted therapy contributes to therapeutic failure and relapse. In this presentation, I will review the molecular mechanisms and other factors (e.g., patient drug adherence) involved in TKI resistance, the methodologies to access these mechanisms, and the current therapeutic approaches to circumvent TKI resistance in CML.

SS05-2

Mutational landscape in CML

Simona Soverini
University of Bologna, Italy

The natural history of chronic myeloid leukemia (CML) is a progression from an initial, rather indolent phase (chronic phase ; CP) to an acute, inexorably lethal phase (blast crisis ; BC). Tyrosine kinase inhibitors (TKIs) have only partially changed this naturally history, since a small but not negligible proportion of patients still progress from CP to BC even in the TKI era. BC is characterized by a high degree of genetic instability, fostering the accumulation of additional chromosomal abnormalities and mutations, that may decrease oncogenic addiction to BCR-ABL1 and are considered the main reason why TKIs are markedly less effective. In contrast, for long time, CP has been considered relatively genetically 'homogeneous', with no alterations additional to the Philadelphia chromosome (if not in <5% of patients). The advent of high throughput technologies, and of next generation sequencing in particular, has challenged this 'old' view. Recent studies have indeed shown that several newly diagnosed CP patients may have fusion transcripts and genomic rearrangements additional to BCR-ABL1 as well as mutations in known cancere genes, and that these patients have high risk disease. This has sparked efforts to create international networks and pooling high throughput data in an attempt to investigate, in large cohorts of CML patients, whether these alterations may serve as biomarkers, and be incorporated in novel algorithms aimed to optimize risk- adapted therapeutic approaches.

SS05-3

CML/MPN stem cells and the bone marrow microenvironment

Steffen Koschmieder
RWTH Aachen University, Germany

Myeloproliferative neoplasms (MPN), including chronic myeloid leukemia (CML), are chronic malignant disorders of the hematopoietic stem cell in the bone marrow (BM). They arise from driver mutations such as the BCR-ABL fusion gene or mutations in the genes encoding JAK2 (mostly JAK2V617F), calreticulin (CALR), or the thrombopoietin receptor (MPL). They are characterized by increased cell proliferation in the BM, giving rise to increased white blood cells, red blood cells, and/or platelets in the peripheral blood. Extramedullary hematopoiesis typically develops, and most patients present with splenomegaly. During the course of the disease, patients are at an incrased trisk to develop myelofibrosis, thrombotic and hemorrhagic complications, and progression of the disease (accelerated phase, blast crisis).
However, it is becoming increasingly clear that CML/MPN is not confined to alterations of the hematopoietic lineage. Essentially all non-hematopoietic cells in the BM microenvironment are implicated in the inititiation, maintenance, and progression of the disease, including mesenchymal stromal cells, endothelial cells, osteoblasts, and even neuronal cells. They contribute to the malignant process by producing an excess of inflammatory cytokines (interleukin-6 [IL-6], IL-8, lipocalin-2, TNFa, etc), prothrombotic molecules (e.g. P-selectin, von Willebrand factor), and fibrosis-inducing factors (e.g. TGF-beta). Single-cell RNA-sequencing and other modern techniques that allow detection of single-cell transcriptomes and cell-cell interactions in both hematopoietic cells and cells of the BM microenvironment are revolutionizing our understanding of MPN disease development. Also, novel cellular systems, including patient-derived disease-specific induced pluripotent stem cells (iPSC) allow us to study CML/MPN pathogenesis in clonal human cells, both in the presence and absence of the disease-driving oncogenes. Together, these innovations have already led to novel therapies targeting both the malignant clone and the contributing cells of the microenvironment. This presentation will summarize these our current understanding of the contributation of both CML/MPN stem cells and the BM microenvironment to the disease pathophysiology, diagnosis, prognosis, and treatment of CML/MPN.

SS06-1

Immune landscapes and chemotherapy resistance in AML

Sergio Rutella
Nottingham Trent University, UK

Chemotherapy remains the standard of care for most patients with acute myeloid leukaemia (AML). The 5-year overall survival from first relapse for patients with AML is only 10%. The investigation of new molecularly targeted and immuno-modulating agents therefore remains a high priority.

Our multi-institutional, multi-cohort study was undertaken to characterise the immune ecosystem of AML in a spatially resolved manner using the nCounter™ and GeoMx Digital Spatial Profiling (DSP) platforms (NanoString Technologies, USA), with the goal to identify oncogenic drivers of immune infiltration and to implement new immunotherapy agents for patients with specific immunologic subtypes of AML.

Using 442 primary bone marrow samples from three independent cohorts of children and adults with AML, we defined immune-infiltrated and immune-depleted disease classes and revealed critical differences in immune gene expression across age groups and molecular disease subtypes. Interferon (IFN)- g -related mRNA profiles were predictive for both chemotherapy resistance

In a separate set of studies, GeoMx DSP of FFPE BM allowed the identification of protein co- localization patterns with prognostic relevance in T-cell-infiltrated AML that were correlated with TP53 mutational status. Compared with AML subgroups with other risk-defining molecular lesions, patients with newly diagnosed, TP53-mutant AML showed high T-cell infiltration and high expression of actionable immune checkpoints and IFN- g signalling molecules, as well as transcriptomic features of immune exhaustion and senescence.

Correlative analyses in patients with relapsed/refractory AML treated with flotetuzumab, an investigational CD123×CD3 bispecific DART® molecule for redirecting host T cells to AML (NCT#02152956), identified immune gene sets that support the prediction of therapeutic responses.

Finally, in situ transcriptomic and proteomic analyses on the GeoMx DSP platform showed the formation of immunological synapses between CD3+ T cells and CD123+ AML blasts (or 'CD3 hotspots'), and the up-regulation of type I IFN signalling molecule STING in bone marrow FFPE collected on-treatment.

In conclusion, our study has identified unique immunological features with prognostic relevance in patients with AML. From a clinical standpoint, 'immune enriched' AMLs might be less responsive to conventional chemotherapy but amenable to immunotherapy approaches with T-cell engagers.

SS06-2

Towards next-generation T cell engineering for cancer

Chan Hyuk Kim
Korea Advanced Institute of Science and Technology, Korea

CD19-targeting chimeric antigen receptor (CAR) T cells have become an important therapeutic option for patients with relapsed and refractory B cell malignancies. However, recent clinical data indicate that a significant portion of patients still do not benefit from the therapy owing to various resistance mechanisms, including high expression of multiple inhibitory immune checkpoint receptors on activated CAR T cells. Here, we report a lentiviral two-in-one CAR T approach in which two checkpoint receptors are downregulated simultaneously by a dual short-hairpin RNA cassette integrated into a CAR vector. Using this system, we evaluated CD19-targeting CAR T cells in the context of four different checkpoint combinations—PD-1/TIM-3, PD-1/LAG-3, PD-1/CTLA-4 and PD-1/TIGIT—and found that CAR T cells with PD-1/TIGIT downregulation uniquely exerted synergistic antitumor effects in mouse xenograft models compared with PD 1 single downregulation, and maintained cytolytic and proliferative capacity upon repeated antigen exposure. Importantly, functional and phenotypic analyses of CAR T cells as well as analyses of transcriptomic profiles suggested that downregulation of PD-1 enhances short-term effector function, whereas downregulation of TIGIT is primarily responsible for maintaining a less-differentiated/exhausted state, providing a potential mechanism for the observed synergy. The PD-1/TIGIT–downregulated CAR T cells generated from diffuse large B-cell lymphoma patient-derived T cells using a clinically applicable manufacturing process also showed robust antitumor activity and significantly improved persistence in vivo compared with conventional CD19-targeting CAR T cells. Overall, our results demonstrate that the cell-intrinsic PD-1/TIGIT dual downregulation strategy may prove effective in overcoming immune checkpoint-mediated resistance in CAR T therapy.

SS06-3

Endogenous retroviruses as a source of tumor antigens in solid tumors and acute myeloid leukemia

Stéphane Depil
Université Claude Bernard Lyon 1, France

Human endogenous retroviruses (HERVs) represent 8% of the human genome. HERVs are silenced by epigenetic mechanisms in normal cells but are aberrantly expressed by tumor cells. Given their viral origin, HERV products may represent tumor antigens relevant for cancer immunotherapy.

We developed a systematic bioinformatics-based approach to identify shared CD8+ T cell epitopes derived from cancer-associated HERVs in solid tumors. Six HLA-A2 epitope candidates among the most commonly shared epitopes with evidence of translation were selected for further immunological evaluation. In vitro priming assays showed the induction of specific CD8+ T cells leading to polyfunctional T cell responses. The functionality of the sorted T cell clones was confirmed by Elispot (GrzB+ IFN-γ+) before TCR sequencing. Interestingly, these TCRs were predicted to interact with a high affinity with their respective MHC-peptide complexes in 3D models. This was confirmed by measurement of the functional avidity, which was in the same order as CMV-specific T cell clones. HERV-specific CD8+ T cells induced specific cell death of HLA-A2+ cancer cell lines presenting HERV epitopes on HLA molecules, as demonstrated by mass spectrometry . Furthermore, HERV- specific CD8+ T cells were identified by dextramer-staining among tumor infiltrating lymphocytes (TILs) from HLA-A2+ breast and ovarian cancer patients. Finally, we showed that HERV-specific T cells can lyse patient-derived organoids.

In parallel, we also evaluated HERV expression in Acute Myeloid Leukemia (AML). We used a complete database of 14,968 HERVs functional units to provide a thorough analysis of HERVs in normal and AML bone marrow cells. We found that HERV retrotranscriptome accurately characterizes normal and leukemic cell subpopulations, including leukemia stem cells, in line with different epigenetic profiles. We then showed that HERV expression separates distinct AML subtypes of different prognosis. We selected CD8+ T cell epitopes derived from AML-specific HERVs and we showed that patients' marrow infiltrating lymphocytes at diagnosis also contain naturally occurring CD8+ T cells against HERV epitopes. Furthermore, we demonstrated that HERV-specific CD8+ T cells specifically recognize AML cells.

In conclusion, our bioinformatics-based approach allowed us to identify shared HERV-derived CD8+ T cell epitopes specifically expressed by tumor cells and inducing high avidity T cell clones able to kill tumor cells in a class I-restricted manner. The detection of TILs recognizing HERV peptides suggests natural presentation of these epitopes in the tumors. These HERV-derived epitopes may thus represent relevant targets for the development of new immunotherapeutic approaches, especially in tumors with a low or moderate mutational burden. We are currently developing a therapeutic vaccine as well as TCR engineered T cells specific for these HERV epitopes.

SS07-1

Losing sense of self and surroundings: hematopoietic stem cell aging and leukemic transformation

Emmanuelle Passegue
Columbia University Irving Medical Center, USA

This lecture has no abstract.

SS07-2

Hematopoietic stem and progenitor cell signaling in the niche

Peter Kurre
Children's Hospital of Philadelphia, USA

Lifelong hematopoietic function is maintained by a pool of hematopoietic stem and progenitor cells (HSPC) capable of self-renewal and differentiation. The prevailing model of HSPC and bone marrow (BM) niche cells as an operationally defined unit of hematopoiesis is built on the signaling activity of cytokines, chemokines and other growth factors, that guard functional integrity and adapt HSPC output under stress and injury. Work in our own and other laboratories over the past decade has examined the role of nanoscale extracellular vesicles (EVs) as an alternative dynamic platform for regulation of hematopoietic function of the niche. EV crosstalk in the leukemic BM reveals paracrine and endocrine regulation of residual healthy HSPC and niche cells by leukemia cell-derived EVs containing selectively enriched protein and micro (mi-) RNA cargo. Acute myeloid leukemia (AML) derived EV miRNAs deregulate key signaling pathways (mTOR) and translationally suppress critical transcription factors (c-Myb) active in hematopoietic stem- or progenitor cells in vitro and in xenograft models, respectively. These effects are reversible upon transfer to a naïve BM niche. However, additional recent studies in congenic models of AML reveal more durable effects from vesicle trafficking between leukemic cells and residual HSPC. Here we observe that AML- EV trafficking converts HSPC into long lived hubs of compartmental inflammation, not unlike experimental models of inflammation using LPS or synthetic RNA (poly I:C). Ongoing work aims to delineate the inflammatory secretome and functional impact of HSPC during leukemic remission. Altogether, our studies identify a role for AML EVs in deregulating hematopoiesis in the BM niche and promoting sustained compartmental inflammation in the bone marrow.

SS07-3

Thrombopoietin as an expansion factor for hematopoietic stem cells

Toshio Suda
Kumamoto University, Japan

Cellular metabolism in hematopoietic stem cells (HSCs) is an area of intense research interest, but the metabolic requirements of HSCs and their adaptations to their niches during development have remained largely unaddressed. Distinctive from other tissue stem cells, HSCs transition through multiple hematopoietic sites during development. This transition requires drastic metabolic shifts, insinuating the capacity of HSCs to meet the physiological demand of hematopoiesis. In this review, we highlight how mitochondrial metabolism determines HSC fate, and especially focus on the links between mitochondria, endoplasmic reticulum (ER), and lysosomes in HSC metabolism.
In order to gain a detailed understanding of regulating HSC quiescence, we will focus on Thpo (Thrombopoietin)-Mpl (Receptor) signaling. We analyzed Thpo-/- and Thpofl/fl;AlbCre+/- HSCs in detail. Thpo-/- HSCs were apoptotic and impaired in mitochondria bioenergetics. Thpofl/fl;AlbCre+/- HSCs exhibited a similar HSC phenotype yet with a lesser extent of damage. Administration of Romiplostim restored mitochondria function and induced quiescence in Thpo-/- HSCs. Moreover, Thpo-/- HSCs did not exhaust and exhibited reconstitution potential even after continuous stimulation with Romiplostim. Our data reveal that a subpopulation of HSCs which escape Thpo-deprivation acquiesce quiescence through Thpo-Mpl signaling in a dose-dependent manner which process involves the modification of metabolism.

SS08-1

Mechanisms of thrombosis and bleeding in viral infection: focusing on COVID-19

Marcel Levi
University College London Hospitals NHS Foundation Trust, UK

Viral infections are often associated with coagulopathy and consequent clinical manifestations. Examples are CMV infections, severe influenza, viral hemorrhagic fevers, and most recently, COVID-19.

Patients with severe COVID-19 infections frequently manifest coagulation abnormalities that are associated with respiratory deterioration and death. In addition, many patients with severe COVID-19 infections develop thromboembolic complications, which seem to be related to the coagulopathy. It has been suggested that undiagnosed pulmonary embolism contribute to a sudden deterioration of pulmonary oxygen exchange that is sometimes seen in patients with COVID-19 infections.

The coagulation changes associated with COVID-19 mimics other systemic coagulopathies that are regularly seen during severe infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy (TMA). However, at the same time, the clinical and laboratory characteristics of the coagulation changes in COVID are distinctly different from the common presentation of these conditions.

Severe COVID-19 infections seem to cause a profound coagulation abnormality caused by inflammation-induced changes in coagulation in combination with severe endothelial cell injury with consequent massive release of von Willebrand factor and plasminogen activators. This coagulopathy likely contributes to pulmonary microvascular thrombosis, broncho-alveolar fibrin deposition (which is a hallmark of adult respiratory distress syndrome (ARDS)) and thromboembolic complications. Venous thrombosis is common in patients with severe COVID-19 with incidences up to 30% in some studies. There is ample evidence supporting the use of prophylactic dose low molecular weight (LMW) heparin as prophylaxis for venous thromboembolism in critically ill medical patients. In view of the hypercoagulable state of severe COVID-19 patients and the possibly increased risk of thrombosis, all patients with COVID-19 that are admitted to the hospital should receive this prophylactic treatment. Higher dose thromboprophylaxis have been studied in randomized controlled trials with modest success in non-ICU patients but are currently not advocate in critically ill patients on the ICU.

SS08-2

COVID-19 vaccine related hematologic manifestations

Soo-Mee Bang
Seoul National University College of Medicine, Korea

SS08-3

Thrombotic thrombocytopenic purpura in 2022 - novel therapies and focus on long term outcomes

Shruti Chaturvedi
Johns Hopkins University School of Medicine, USA

Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy caused by ADAMTS13 deficiency. TTP used to be a universally fatal disorder; however, rapid diagnosis and treatment with plasma exchange and immunosuppression has improved survival of acute TTP episodes to > 90%. Recent insights into TTP pathogenesis have led to the development of novel therapies targeting pathogenic anti-ADAMTS13 antibody production, von Willebrand factor (VWF)- platelet interactions, and ADAMTS13 replacement. TTP is now understood as a chronic disease characterized by recurrent episodes of thrombotic microangiopathy. TTP survivors are also at increased risk for a number of long-term complications such as stroke, cognitive impairment, cardiovascular disease, poor quality of life and shortened survival. This talk will discuss current ideas on the pathophysiology, diagnosis, and management of TTP with a focus on targeted therapies and emerging treatment paradigms. Strategies to optimize long term outcomes will also be discussed.

SS09-1

Pathophysiology of spliceosome mutations in MDS

Andrea Pellagatti
University of Oxford, UK

The myelodysplastic syndromes (MDS) are common myeloid malignancies. Mutations in genes encoding different components of the spliceosome (including SF3B1, SRSF2, U2AF1 and ZRSR2) occur in over half of MDS patients and result in aberrant pre-mRNA splicing of many target genes, indicating that aberrant spliceosome function plays a major role in MDS disease pathogenesis. Recent functional studies have illuminated the impact on hematopoiesis of some aberrantly spliced target genes associated with splicing factor mutations. Emerging data show that some of the downstream effects of different mutated splicing factors converge on common cellular pathways/processes, such as hyperactivation of NF-κB signaling and increased R-loops, providing novel insights into MDS disease pathophysiology. The combination of induced pluripotent stem cell (iPSC) and CRISPR/Cas9 technologies has been harnessed for the modeling and study of clonal evolution of myeloid malignancies, including the investigation of the impact of splicing factor gene mutations on the cellular phenotype. The aberrantly spliced target genes and the dysregulated pathways and cellular processes associated with splicing factor mutations provided the rationale for new potential therapeutic approaches to target splicing factor mutant MDS cells.

SS09-2

Role of extracellular vesicles and miRNA in myelodysplastic syndromes

Sophie Park
CHU de Grenoble Service hematologie clinique, France

Myelodysplastic syndromes (MDS) are due to oligoclonal involvement of the hematopoietic stem cell resulting in dysplasia of the myeloid lineages, blood cytopenias and frequent progression to acute leukemia. Many mutations described in genes controlling epigenetic regulation are responsible for the genesis of MDS. But recent work also shows that abnormalities in the medullary microenvironment, including mesenchymal stromal cells (MSCs), can induce and propagate MDS suggesting the idea of close intercellular communication between the niche and hematopoietic cells. One way of communication between cells are extracellar vesicles (EVs).
In this presentation, I will present two MDS models demonstrating the role of EVs in the physiopathogenesis of MDS.
1) In low risk MDS, we found an underexpression of DICER1 in MDS MSCs from primary samples of total marrow and in expanding MSCs by flow cytometry and RTqPCR. This underexpression of DICER1 is accompanied by deregulation of the microRNA profile within MDS MSCs demonstrated by transcriptomic study of MDSs from MDS vs controls. We discovered a possible therapeutic target: miR-486-5p, which we found constantly overexpressed in MDS MSCs. One of the ways for MSCs to influence hematopoietic stem cells may be through the secretion of extracellular vesicles (EVs). These EVs are heterogeneous and can be defined by their size. We were more particularly interested in small extracellular vesicles (sEVs) containing the exosomal fraction which is known to be able to transport microRNA, mRNA and proteins between cells. We found this miR-486-5p transported as a cargo in the sEVs secreted from MSCs to CD34+. In addition, we show in a co-incubation model (sEVs with CD34+ from healthy subjects), that sEVs from MDS MSCs induce more apoptosis, more oxidative stress as well as more DNA damage in the HSCs. Using RNA sequencing of CD34+ cells from healthy donor over expressing miR-486-5p, we found that the upregulation of this miRNA leads to the activation of TNFα, innate immune and inflammatory pathways. Whole genome sequencing of healthy donor CD34+ incubated with sEVs from MDS-derived MSC showed that sEVs induce a mutational signature seen in cancer process.
2) Chronic myelomonocytic leukemia (CMML) is a myeloid hematological malignancy with overlapping features of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN). The knowledge of the role of the tumor microenvironment (TME), particularly mesenchymal stromal cells (MSCs), in MDS pathogenesis is increasing. Generally, cancer is associated with a procoagulant state participating in tumor development. Monocytes release procoagulant, tissue factor (TF)–bearing microparticles. We hypothesized that MSCs and clonal CMML monocytes release procoagulant extracellular vesicles (EVs) within the CMML TME, inducing a procoagulant state that could modify hematopoietic stem cell (HSC) homeostasis. We isolated and cultured MSCs and monocytes from CMML patients and MSCs from healthy donors (HDs). Their medium EVs and small EVs (sEVs) were collected after iterative ultracentrifugations and characterized by nanoparticle tracking analysis. Their impact on hemostasis was studied with a thrombin generation assay and fibrinography. CMML or HD HSCs were exposed to sEVs from either CMML or HD MSCs. CMML MSC sEVs increased HD HSC procoagulant activity, suggesting a transfer of TF from the CMML TME to HD HSCs. The presence of TF on sEVs was shown by electron microscopy and western blot. Moreover, CMML monocyte EVs conferred a procoagulant activity to HD MSCs, which was reversed by an anti-TF antibody, suggesting the presence of TF on the EVs. Our findings revealed a procoagulant "climate" within the CMML environment related to TF-bearing sEVs secreted by CMML MSCs and monocytes. Overall, we confirm here that bone marrow microenvironment highly participates to the MDS pathogenesis by a dysregulation of miRNA pattern of the niche stromal cells and via cell-to-cell communication by extracellular vesicles which carry miRNA and proteins to modulate the fate of hematopoietic stem cells.

References:
*Extracellular vesicles from myelodysplastic mesenchymal stromal cells induce DNA damage and mutagenesis of hematopoietic stem cells through miRNA transfer. Meunier M, Guttin A, Ancelet S, Laurin D, Zannoni J, Lefebvre C, Tondeur S, Persoons V, Pezet M, Pernet-Gallay K, Chuffart F, Rousseaux S, Testard Q, Thevenon J, Jouzier C, Deleuze JF, Laulagnier K, Sadoul R, Chatellard C, Hainaut P, Polack B, Cahn JY, Issartel JP, Park S. Leukemia. 2020 Aug;34(8):2249-2253. doi: 10.1038/s41375-020-0738-8. Epub 2020 Feb 12.
*Tumor microenvironment and clonal monocytes from chronic myelomonocytic leukemia induce a procoagulant climate within the tumor niche. N. Mauz , J. Zannoni , L. Seyve , M. Meunier, K. Pernet-Gallay, J. Brault , C. Jouzier, D. Laurin, JY Cahn , F. Cognasse , B.Polack, Sophie Park. Blood advances, 2019 Jun 25;3(12):1868-1880. doi: 10.1182/bloodadvances.2018026955.

SS09-3

Challenges in the diagnosis and treatment of overlap MDS/MPN syndromes

Antonio Almeida
Hospital da Luz Lisboa, Portugal

CMML is paradigmatic of MDS/MPN overlap syndromes. It is a rare disorder, comprising approximately 10% of all MDS cases. The median age of presentation is 65-75, and males are affected twice as commonly as females. The most common presenting features are a direct consequence of the underlying cytopenias: fatigue, susceptibility to infections and hemorrhage. Patients with more proliferative forms of the disease may present with abdominal symptoms related to splenomegaly and with constitutional symptoms associated with a hypercatabolic state: night sweats, fevers ad weight loss. More rarely patients may present with monocytic skin infiltrates or in the transformed form of the disease as AML. CMML is a pathogenetically diverse disease which lacks a specific, reliable molecular marker. There are no recurrent cytogenetic aberrations associated with this condition and most of the cytogenetic changes are those described in other forms of MDS (trisomy 8, monosomy 7 and complex karyotypes). Mutations have been described in genes involved in proliferative pathways, such as RAS, JAK2 and CBL, in tumor suppressor genes (RUNX1, TET2, ASXL1 and NPM1) and in epigenetic regulators (IHD1, IDH2 and EZH2). In addition, promoter DNA hypermethylation is found in MDS, particularly of genes within the WNT and MAPK signaling pathways. Often, multiple abnormalities are present, but these are probably secondary and the precise initiating event is not known.

In addition to the genetic aberrations detailed above, it is essential to exclude chronic infections (tuberculosis, fungal or protozoal infections, among other chronic infections) and inflammatory diseases (SLE, sarcoidosis, storage disorders) in the investigation of a patient with monocytosis as these may mimic the clinical and laboratory findings of CMML.

In general, median survival is in the range of 12 - 24 months and approximately one third of patients, depending on the series, progress to acute leukemia. Although stem cell transplantation presently represents the only potentially curative therapeutic strategy, advanced age and associated comorbidities at diagnosis often preclude this procedure.

Consequently, until recently most patients were treated with best supportive care. This includes transfusional support and erythropoiesis stimulating agents, which are usually ineffective in CMML. Patients with proliferative disease have been treated with cytotoxic agents, such as hydroxycarbamide, etoposide and cytarabine, among others, with poor response rates and significant worsening of the citopenias.

Investigations into the molecular pathophysiology of CMML have revealed marked DNA hypermethylation. This finding has been used to test the of hypomethylating agents such as 5- azacitidine (AZA) and Decitabine (DAC). Their efficacy has been firmly established in patients with higher risk MDS. The numbers of CMML patients included in large trials with these agents were few, with less than ten patients treated in the AZA trials. However, several recent reports in the literature have shown generally good safety and efficacy profiles. This experience has led to the increasing use of hypomethylating agents in all forms of CMML, including proliferative disease.

The remainder subtypes of MDS/MPN share the poor prognosis seen in CMML. Molecular markers have facilitated the diagnosis of MDS/MPN-RS-t, generally harboring JAK2 mutations, and aCML, harboring GCSF-receptor mutations. However, no directed treatment options are currently available, and most patients are treated with supportive care, highlighting the need for better knowledge of disease pathophysiology which will enable the development of better treatments.

SS10-1

Chemotherapy versus, allogeneic HSCT for Philadelphia chromosome–negative adult lymphoblastic leukemia

Josep-Maria Ribera
ICO-Hospital Germans Trias i Pujol, Spain

Therapy outcome in adults with acute lymphoblastic leukemia (ALL) has substantially improved in the last decade, with complete remission (CR) and long-term overall survival (OS) rates of around 90% and 40%-50%, respectively. Treatment of Philadelphia chromosome-negative (Ph-neg) ALL in adults is still based on conventional multidrug chemotherapy followed or not by (usually allogeneic) hematopoietic stem cell transplantation (allo-HSCT). Significant improvements have been achieved in recent years from the use of improved targeted therapy and immunotherapy in CR patients with positive measurable residual disease (MRD) and even in newly diagnosed patients with ALL. If these approaches will reduce (or eliminate in some cases) the need of allo-HSCT is still a matter of research. There is clear evidence that adult patients with standard-risk (SR) ALL at baseline and end-of- induction and/or end-of-consolidation MRD levels <0.01%, are best managed with conventional chemotherapy, whereas patients with poor MRD clearance are best treated with allo-HSCT. However, is not clear whether this same principle can be applied to patients with high-risk (HR) features at diagnosis, for whom allo-HSCT has been classically considered as the standard post-consolidation therapy. In this sense, it is important to note that allo-HSCT only benefitted MRD-positive patients in two studies from the French GRAALL Group.

The allocation of adult patients with Ph-negative ALL to chemotherapy or to allo-HSCT as post- consolidation therapy according to MRD levels has been addressed in some prospective trials, two of them from the Italian NILG Group and two from the Spanish PETHEMA group. All trials showed that there was a subset of Ph-neg adult patients with good MRD clearance after induction and/or after consolidation that achieve OS rates of 60-70% without allo-HSCT. The last trial of the PETHEMA Group showed a clear relationship between the early deep clearance of MRD and OS, with OS over 80% in HR patients who showed a MRD level <0.01% at mid induction treatment. The GMALL Group is currently conducting a randomized trial evaluating the allo-HSCT vs. standard therapy in Ph-negative ALL patients with HR features and molecular CR after induction.

Apart of MRD level, some studies have shown that genetic features of ALL have independent prognostic significance, with differences in these features for BCP-ALL and for T-ALL. Other studies have shown that the absolute relapse rate associated with a specific MRD value varied significantly according to the genetic subtype of ALL. Thus, integration of genetic subtype/subclone-specific MRD might potentially allow for more refined risk stratification.

There are some unanswered questions on the role of allo-HSCT in first complete remission in adults with Ph-neg ALL. Will MRD clearance with immunotherapy avoid allo-HSCT in CR1? Will CAR T therapy administered in early phases in patients with HR features and positive MRD avoid the need for HSCT in CR1? Will prophylactic therapy after allo-HCST be necessary in HR ALL patients to decrease the 20-30% relapse after transplant?

In summary, it is highly probable that the incorporation of targeted therapies and immunotherapy in frontline therapy of ALL, combined with genetic and MRD-based stratification of therapy, will contribute to best define the role of allo-HSCT in ALL management and will improve the outcome of adult patients with ALL.

SS10-2

Clonal heterogeneity in acute lymphoblastic leukemia

Jan Cools
Center for Human Genetics, Belgium

Acute lymphoblastic leukemia (ALL) is an aggressive leukemia that is most frequent in children and is characterized by the presence of chromosomal rearrangements and additional mutations. We used single-cell targeted DNA sequencing (Tapestri, Mission Bio) and single-cell RNA-sequencing (10x Genomics) to determine the clonal heterogeneity in bone marrow and peripheral blood of 20 ALL cases (12 B-ALL and 8 T-ALL) at diagnosis. We also monitored the clonal evolution during chemotherapy treatment.
We designed a custom ALL panel and obtained accurate single-nucleotide variant and small insertion-deletion mutation calling for 305 amplicons covering 110 genes in about 4400 cells per sample and time point. In T-ALL, we typically observed a major clone at diagnosis (>35% of the cells) accompanied by several minor clones of which some were less than 1% of the total number of cells. Four patients had >2 NOTCH1 mutations, some of which present in minor clones, indicating a strong pressure to acquire NOTCH1 mutations in developing T-ALL cells. We also detected multiple mutations in the JAK/STAT pathway in T-ALL, either as a stepwise accumulation of mutations in the same cells or as the acquisition of mutations in different cells. In B-ALL, we observed that only half of the cases showed the presence of subclones based on SNV detection. Cases with PAX5 alterations or hyperdiploidy showed multiple clones (1 to 7) at diagnosis, defined by a variety of mutations in the JAK-STAT, RAS or FLT3 signaling pathways.
By analyzing longitudinal samples, we detected the presence and clonal nature of residual leukemic cells and clones with a minor presence at diagnosis that evolved to clinically relevant major clones at later disease stages. Single-cell RNA-sequencing confirmed the presence of residual leukemia cells in the samples obtained during treatment and also illustrated the kinetics of restoration of normal blood cells during chemotherapy treatment. We conclude that single-cell DNA amplicon sequencing is a sensitive assay to detect clonal architecture and evolution of the malignant cells in ALL.

Reference

Albertí-Servera L, Demeyer S, Govaerts I, Swings T, De Bie J, Gielen O, Brociner M, Michaux L, Maertens J, Uyttebroeck A, De Keersmaecker K, Boeckx N, Segers H, Cools J. Single-cell DNA amplicon sequencing reveals clonal heterogeneity and evolution in T-cell acute lymphoblastic leukemia. Blood. 2021;137(6):801-811.

SS10-3

Adoptive cellular immunotherapies based on chimeric antigen receptors

Pablo Menendez
University of Barcelona, Spain

Here, I will review the current state-of-the-art of adoptive cellular immunotherapies using T-cells redirected to tumor associated antigens through the use of chimeric antigen receptors (CAR). I will review also the generation of BiTE-secreting T-cells and their advantages and will review current clinical data in B-ALL, T-ALL and AML. We will also discuss the current drawbacks in applying CAR T-cells to solid tumors.

SS11-1

Hematopoiesis and leukemia through the lens of single cell genomics

Lars Velten
Centre for Genomic Regulation, Spain

Blood formation is a process of fundamental biomedical importance. In recent years, data from new single-cell techniques have allowed us and others to propose new models of hematopoietic stem cell differentiation, clarify the composition of the hematopoietic stem cell niche, and shed light on the molecular consequences of pre-leukemic and leukemic mutations in the human stem cell compartment. In my talk, I will provide an overview of the power of single cell genomics approaches in hematology.

SS11-2

Computer vision in hematological malignancies

Oscar Brück
University of Helsinki, Finland

Background
Following excellent results in pathology and radiology, deep learning -based image analysis is increasingly applied to support routine diagnostics. However, there is an unmet need in hematology for automated machine vision to speed up and standardize routine diagnostics. Moreover, the full potential of May-Grünwald-Giemsa (MGG) and hematoxylin-eosin (H&E)-stained bone marrow (BM) samples in describing the clinical course of hematological diseases has likely not been unveiled.

Methods
In study I (Brück et al, 2021), 236 MDS, 87 MDS/MPN, and 11 control BM biopsies were stained with H&E and digitized with a slide scanner. Clinical data, cytogenetics profiles and results of a clinical targeted myeloid sequencing panel were collected. Morphological features were extracted with convolutional neural networks and used to predict genetic and cytogenetic aberrations, survival and patient demographics with multivariate regression models.
In study II, we digitize routine clinical MGG-stained samples with a two-phase strategy (10x and 100x) using an automated slide scanner. Digital images are transferred to a clinical database and automatically labelled with essential clinical information. From images, white blood cells are detected and classified with a regional convolutional neural network. Moreover, images are automatically classified by their clinical urgency.

Results
In study I, we could predict the occurrence of TET2 [area under the receiver operating curve (AUROC) = 0.94] and spliceosome mutations (0.89) as well as chromosome 7 monosomy (0.89). We found that the probability of a mutation correlated with its variant allele frequency emphasizing the algorithms' ability to identify relevant morphologic patterns.
In study II, we show how 400 slides can be digitized weekly achieving a digital slide archive of 12 000 samples as of October 2021. Moreover, we achieved over 0.90 classification accuracy for multiple white blood cell types.

Conclusions
Image analysis of BM samples represent an understudied and promising avenue that can possibly help to improve our understanding of hematological diseases and automate diagnostics, disease monitoring and treatment response prediction.

Keywords
Computer vision, MGG, H&E, bone marrow, machine learning

SS11-3

Hydrogel-based stamping technology for solution-free blood cell staining

Dongyoung Lee
Noul Co., Ltd, Korea

An accurate microscopical analysis of blood smears requires a reproducible and convenient method of staining. Solution-based staining procedures can be cumbersome. Especially in low- and middle- income countries, the lack of skilled technicians and adequate laboratory facilities, as well as insufficient water and reagent quality, often become confounding factors. To overcome these obstacles, we developed a new cell staining method based on sequential stamping of agarose gel patches that contain eosin, methylene blue/oxidized methylene blue, Azure B, and buffer, respectively. Our method, termed "hydrogel staining", provides a simple, reproducible, solution-free, and inexpensive approach to stain blood cells. We have optimized incubation times to achieve the optimal transfer of dyes to fixed blood cells on a glass slide, with outcomes comparable to conventional solution-based methods for white blood cells and malaria-infected red blood cells. This hydrogel staining method does not require special skills to produce excellent quality stained blood film slides. The new method could enhance the accuracy of microscopical examination of blood smears, especially in resource-limited settings.

SS12-1

The iron-erythropoiesis cross-talk in health and disease

Antonella Nai
San Raffaele Scientific Institute, Italy

Iron and erythropoiesis are reciprocally regulated. Erythropoiesis requires about 25mg of iron daily for the production of more than 200 billion red blood cells. Iron is not only essential for heme/hemoglobin synthesis, but also for the control of the production of erythropoietin (EPO), the cytokine that drives erythropoiesis. On a reciprocal side, erythropoiesis controls iron homeostasis regulating the transcription of hepcidin (HAMP), the master regulator of iron metabolism. To signal iron needs to the liver, erythroid cells release in the circulation erythroferrone (ERFE), an EPO target gene, that inhibits HAMP sequestering its activating ligands. A recently identified link between iron homeostasis and erythropoiesis is Transferrin Receptor 2, that reciprocally regulates EPO signaling and hepcidin expression based on available iron.
The understanding of the mutual crosstalk between iron homeostasis and erythropoiesis significantly improved in the last years, leading to pinpointing novel players and to the elucidation of the pathophysiology of disorders deriving from its deregulation. One example is represented by iron loading anemias, characterized by excessive ERFE production and hepcidin suppression. The other and opposite is the iron deficiency/iron restricted erythropoiesis that occurs in genetic IRIDA and acquired inflammatory disorders, due to excessive hepcidin production.
This lecture will give an overview on the mechanisms governing this complex system, with a focus on innovative therapeutic approaches.

SS12-2

Autoimmune hemolytic anemia : state-of-the-art hypotheses on pathogenesis and their application to treatment

Bruno Fattizzo
Università degli Studi di Milano, Italy

Autoimmune hemolytic anemia (AIHA) is a highly heterogeneous disease due to increased destruction of autologous erythrocytes by autoantibodies with or without complement involvement. Other pathogenic mechanisms include hyper-activation of cellular immune effectors, cytokine dysregulation and ineffective marrow compensation. AIHAs may be primary or associated with lymphoproliferative and autoimmune diseases, infections, immunodeficiencies, solid tumors, transplants, and drugs. The direct antiglobulin test (DAT) is the cornerstone of diagnosis, allowing the distinction into warm forms (wAIHA), cold agglutinin disease (CAD), and other more rare forms such as mixed AIHA, IgA driven AIHA, AIHA due to warm IgM, and DAT negative cases. The immunologic mechanisms responsible for erythrocyte destruction in the various AIHAs are different and therefore therapy is quite dissimilar. In wAIHA, steroids represent first line therapy, followed by rituximab and splenectomy. Conventional immunosuppressive drugs (azathioprine, cyclophosphamide, cyclosporine) are now considered in third line. In CAD steroids are useful only at high/unacceptable doses and splenectomy is uneffective. Rituximab is advised in first line, followed by rituximab plus bendamustine and bortezomib. Several new drugs are under development, including B-cell directed therapies (ibrutinib, venetoclax, parsaclisib), and inhibitors of complement (sutimlimab, pegcetacoplan), spleen tyrosine kinases (fostamatinib), or neonatal Fc receptor. In this talk, the main pathogenic mechanisms, the classification and current treatment of the various forms of AIHA will be addressed.

SS12-3

Cold agglutinin disease: an update on pathogenesis and future prospects on therapy

Sigbjørn Berentsen
Haugesund Hospital, Norway

Cold agglutinin disease (CAD) is a type of autoimmune hemolytic anemia and a low-proliferating clonal bone marrow lymphoproliferative disorder. CAD is a well-defined clinico-pathologic entity that should be distinguished from cold agglutinin syndrome (CAS), which occurs secondary to specific infections or aggressive lymphoma and will not be further addressed here. The typical clinical features of CAD are hemolytic anemia, cold-induced circulatory symptoms, fatigue (only partly explained by the anemia), and, often, exacerbations during diseases with acute phase reaction. The causative autoantibodies in CAD, cold agglutinins, are monoclonal, most often IgM kappa. Hemolysis is mostly extravascular and entirely mediated by complement classical pathway activation. Not all patients need drug treatment. Corticosteroids should not be used to treat CAD. First-line therapy is rituximab plus bendamustine or rituximab monotherapy, depending on individual patient characteristics. Newer B-cell directed treatments have also yielded promising results, in particular Bruton tyrosine kinase inhibitors. An alternative, attractive approach is upstream classical pathway inhibition, which has shown favorable results when using the C1s inhibitor sutimlimab. Other classical pathway inhibitors are also promising. Thus, several treatment options are currently available or will appear in the near future, and the choice of therapy should be individualized. Patients with CAD requiring therapy should be considered for prospective trials if available.

SS13-1

AML microenvironment and FLT3 inhibitor resistance

Elie Traer
Oregon Health & Science University, USA

Activating mutations in the FLT3 gene are the most common mutations in acute myeloid leukemia (AML). FLT3 mutations drive leukemia cell proliferation and are associated with higher rates of relapse and less favorable prognosis. Gilteritinib is a recently FDA-approved FLT3 inhibitor and has good initial efficacy in patients. However, despite effective inhibition of FLT3, residual cells survive in the marrow microenvironment and over time these early resistant cells evolve intrinsic resistance mechanisms to gilteritinib limiting the durability of response.

We utilized a two-step model to study the temporal evolution of gilteritinib resistance. To model initial extrinsic early resistance, we cultured the FLT3-ITD+ AML cell lines, MOLM-14 and MV4;11, with ligands secreted by the bone marrow microenvironment: fibroblast growth factor 2 (FGF2) and FLT3 ligand (FL). MOLM14 cells were cultured with 100 nM gilteritinib in media alone, or media supplemented with 10 ng/ml FGF2 or FLT3 ligand. After 7 weeks, only cultures supplemented with FGF2 or FL resumed growth, which we called early resistance. We then removed ligand, which transiently restored sensitivity to gilteritinib, however after 2 months the cells resumed exponential growth, which we termed late resistance (intrinsic resistance).

We used a comprehensive approach of proteomics, phospho-proteomics, whole exome sequencing (WES), CRISPR, metabolomics, and small molecule screening to interrogate the evolution of early to late resistance in both early and late resistant cell lines. WES identified NRAS mutations in the majority of late resistant cultures (14/16) and gatekeeper FLT mutations were found in the other 2, consistent with mutations found in patients treated with gilteritinib on the Admiral trial (McMahon et al., Cancer Discov., 2019). To identify if NRAS mutations were pre-existing, ddPCR was used to measure NRAS mutations at low level (<0.1%) in early resistant cultures and parental cells, but did not become the dominant mechanism of resistance until FGF2 or FL ligand was removed. Moreover, when NRAS mutations were introduced into MOLM14 cells by lentivirus, cells remained sensitive to 100 nM gilteritinib and required over a month of continuous culture to become resistant and resume growth, indicating that NRAS mutations alone are not sufficient for gilteritinib resistance.

We analyzed both early and late resistant lines with genome-wide resensitization CRISPR/Cas screening. CRISPR/Cas screening revealed that NRAS was the most important gene in late resistance, consistent with expansion of NRAS mutations. In contrast, early resistance revealed multiple hits in metabolic and cell cycle pathways. Global and phospho-proteomics identified very distinct expression profiles between early and late resistant cells, with numerous aberrations in metabolic and cell cycle proteins in early resistance, and prominent activation of MAPK signaling pathways in late resistance. The unique metabolic signatures (lipid signaling in particular) was verified by metabolomic analyses. Aurora Kinase B protein (AURKB) signaling was also increased in early resistance, and early resistant cells were uniquely sensitivity to AURKB small molecule inhibitors and genetic deletion by CRISPR.

We then evaluated primary leukemia cells from 11 patients before and after 1-2 months of gilteritinib to evaluate early resistance in primary samples. Leukemia cells were isolated by CD33 and CD34 beads and subjected to a targeted proteomic analysis. In agreement with our cell line model, early resistant cells had a distinct protein profile, with significant alteration of cell cycle and lipid metabolism proteins after gilterinitib treatment. Primary patient samples also demonstrated robust sensitivity to AURKB inhibitors after gilteritinib exposure. Our results suggest that exploiting the unique sensitivities of residual leukemia cells prior to expansion of resistance mutations may be an effective clinical strategy.

SS13-2

Targeting TP53 mutation in AML

David A. Sallman
H. Lee Moffitt Cancer Center and Research Institute, USA

Myelodysplastic syndromes (MDS) represent a heterogeneous group of malignant stem cell neoplasms hallmarked by ineffective hematopoiesis and risk of leukemic transformation. Of all somatic mutations identified in MDS, TP53 mutations are associated with the most inferior outcomes across independent studies with a median OS of 6-12 months despite standard of care therapies.1,2 Importantly, there is little, if any, significant difference between TP53 mutant MDS and AML as most often patients are oligoblastic and outcomes to standard and novel therapy have been similar to date. Notably, the variant allele frequency (VAF) and/or allelic status of TP53 to be strongly concordant with disease phenotype and further stratifies survival over binary mutation analysis alone.1,3-5 Importantly, clearance of TP53 (i.e. VAF <5%) predicted for improved OS whereas clonal expansion significantly predicted for inferior OS which remained predictive of OS in multivariate analysis. Importantly, clearance of TP53 in the setting of therapy, i.e. HMA therapy or allogeneic stem cell transplantation, has also been identified to be a positive predictor of outcomes6. APR-246 (eprenetapopt) is a novel small molecule anti-cancer compound that reactivates mutated and non- functional p53 and targets the cellular redox balance, two Achilles heels of cancer cells. APR-246 is a pro-drug that spontaneously releases the active drug species, methylene quinuclidinone (MQ), at physiologic pH. MQ forms a covalent bond with cysteine residues in p53 and the binding event thermodynamically stabilizes p53 protein, shifting the dynamic equilibrium away from the unfolded/misfolded state and toward the wild-type p53 conformation. Additionally, APR-246 has p53 independent activity via an increase in reactive oxygen species as well as more recent data identifying early cell death by APR-246 is mediated via ferroptosis7,8. We have conducted a Phase 1b/2 combination study of sequential APR-246 and azacitidine in HMA-naïve, TP53 mutant MDS and oligoblastic AML (≤30% blasts; ClinicalTrials.gov identifier NCT03072043). The phase 1b/2 results showed the combination to be well tolerated with no dose-limiting toxicities and a recommended phase 2 dose of APR-246 as a fixed dose of 4500mg days 1-4 in combination with AZA9. Treatment related APR-246 side effects include nausea, vomiting, dizziness and transient neuropathy; the majority of which were G1/G2. The overall response rate was 71% with 44% achieving CR. Overall, 19/55 (35%) patients underwent allogeneic stem cell transplant, with a median overall survival of 14.7 months. Similar data have also recently been reported by the GFM showing comparable response rates and long-term data will be presented at the upcoming ASH 2021 meeting which highlight particularly improved outcomes in patients who achieve CR and/or TP53 VAF clearance and are bridged to transplant with a median OS that was not reached10. These data support the ongoing phase 3 study of APR-246 in combination with azacitidine versus azacitidine alone (NCT03745716). Unfortunately, the trial has failed to meet its primary endpoint of increase CR (33.3% in combination vs 22.4% in control arm; P=0.13) although survival follow-up is ongoing and these data are yet to be formally presented to help evaluate for differential responses from the earlier phase 2 studies. Additionally, novel triplet therapy with venetoclax as well as azacitidine in combination with APR- 246 as post-transplant maintenance are being investigated and will be presented at the ASH 2021 annual meeting (NCT04214860/NCT03931291). Lastly, a 2nd generation oral agent (APR-548) has entered the clinic in late 2021. In addition, there are several additional azacitidine combinations which are ongoing in MDS and AML patients where molecular subset data are available. In TP53 mutant AML, azacitidine in combination with venetoclax did achieve an increased CR/CRi rate of 47%, although these patients had a short median duration of CR/CRi of 5.6 months and a median OS of 7.2 months, similar to survival outcome data with single agent HMA, with recent data showing TP53 as a major driver of resistance to venetoclax.11,12 This combination is ongoing in MDS patients (NCT02942290). More recently, azacitidine in combination with magrolimab, an inhibitor of the macrophage immune checkpoint CD47, was presented at the 2020 EHA congress showing very high response rates in MDS patients (91% ORR, 42%, CR), including high responses in TP53 mutant MDS patients (NCT03248479). More recently, data was presented on the TP53 mutant AML cohort at ASH of 2020. Importantly, in the TP53 mutant AML cohort of evaluable patients (n=29), the CR/CRi rate was 59% with a median OS of 12.9 months to date although follow up was short (median follow up of 4.7 months). Patients have achieved high depth of response with a 44% complete cytogenetic response and 29% MRD negativity. These data support the ongoing phase 3 open-label study of azacitidine + magrolimab vs azacitidine + venetoclax in unfit AML patients and versus induction chemotherapy in fit patients with a primary endpoint of OS in the non-intensive group (NCT04778397). Importantly, additional novel triplet strategies are underway for both all-comer elderly AML patients and TP53 specific patient populations (e.g. azacitidine + magrolimab + venetoclax). TP53 mutant MDS/AML patients represent a molecular cohort with very poor outcomes and lack of disease modifying therapy. The clonal burden of TP53 is intimately associated with outcomes in this patient group and novel therapies targeting this mutation are urgently needed. The treatment landscape of these patients is encouraging as the combination of azacitidine with APR-246 or magrolimab have been well tolerated and produced significantly improved response rates. Ideally, future translational data will further elucidate the underpinnings driving the poor outcomes for this molecular subgroup to lead to additional novel therapeutic strategies.

SS13-3

Adaptive immune resistance and immune evasion by programmed death-1 homolog (PD-1H/VISTA) in acute myeloid leukemia

Tae Kon Kim
Vanderbilt University Medical Center, USA

Immune response can recognize, respond to and eliminate cancer cells. During cancer progression, however, various cellular and molecular mechanisms are developed, especially in the tumor site, to adapt to the changes of the immune environment and eventually to overcome immune attack, allowing continuous growth of cancer. These mechanisms, collectively called "adaptive immune resistance", are initiated and prompted due to growth of cancer cells, which could be derived from either cancer cells or host cells owing to a long period of adaption, these mechanisms of adaptive immune resistance diversify, leading to remarkable heterogeneity. The first clearly defined and therapeutically validated adaptive immune resistance is selective induction of PD-L1, co-inhibitory molecule by interferon-gamma in the tumor tissue as a result of anti-tumor immunity. This paradoxical role of immune response shed the light on the complexity of adaptive immune resistance mechanisms and understanding the role of co-inhibitory molecules in immune evasion led to the clinical application of PD-1 and PD-L1 blockade by monoclonal antibodies (herein anti-PD therapy). However, anti-PD therapy as a single agent in AML has shown minimal response rates, indicating different mechanisms of immune evasion operate in human AML. Programmed Death-1 Homolog (PD-1H, also known as VISTA) is a co-inhibitory immunoglobulin broadly found in hematopoietic cells. To determine the expression of PD-1H surface protein in human AML, we performed immunohistochemical staining with a mAb specific to human PD-1H in AML bone marrow (BM) core biopsies. PD-1H surface protein was expressed in most AML samples, but PD-L1 expression was universally undetectable. Based on flow cytometry, PD-1H surface protein was expressed in normal myeloid cells but rarely in resting T cells. More importantly, PD-1H surface protein was highly expressed in CD34+ and CD33+ blasts. In contrast, normal CD34+ progenitor cells in BM from healthy donors had minimal expression of PD-1H surface protein. In studies employing syngeneic and humanized AML mouse models, overexpression of PD-1H promoted the growth of AML cells, mainly by evading T cell-mediated immune responses. Importantly, ablation of AML cell surface PD-1H by antibody blockade or genetic targeting significantly inhibited AML progression by promoting T cell activity. In addition, the genetic deletion of PD-1H from normal myeloid cells inhibited AML progression as well. Our findings provide the basis for PD-1H as an attractive therapeutic target to treat human AML.

SS14-1

Genomic landscape of peripheral T-cell lymphomas

Keisuke Kataoka
National Cancer Center Research Institute, Japan

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of mature T-cell neoplasm. Among PTCLs, the most common in Western countries is PTCL, not otherwise specified (NOS), accounting for approximately 30% of all PTCLs. Combining whole-exome and deep targeted-capture sequencing of more than 130 cases, we delineated the entire picture of genetic alterations in PTCL, NOS. Of note is the identification of a previously undescribed molecular subtype characterized by TP53 and/or CDKN2A mutations and deletions in PTCL, NOS without showing a T follicular helper cell phenotype. This subtype exhibited different prognosis and unique genetic features, including extensive chromosomal instability, which preferentially affected molecules involved in immune escape and transcriptional regulation.

Among PTCLs, the most common entity in Japan is adult T-cell leukemia/lymphoma (ATL), which is an aggressive peripheral T-cell lymphoma associated with human T-cell leukemia virus type-1 (HTLV-1) infection. We previously performed an integrated molecular study, in which whole-exome, transcriptome, and targeted resequencing, as well as array-based copy number analysis were performed. We found recurrent genetic alterations in T-cell receptor/NF-κ B signaling, T-cell trafficking, and other T-cell-related pathways as well as immunosurveillance. Although our previous study discovered many driver mutations and copy number alterations, the whole-genome landscape of ATL still remains elusive. To address this issue, we have recently performed high-depth whole-genome sequencing (WGS) of 150 ATL samples. WGS presented a substantially different overview of driver alterations compared with WES. Particularly, we identified novel alterations, such as long-isoform specific mutations of CIC and C-terminal truncation of REL. In vitro and in vivo analyses also revealed a functional role of these alterations in T-cell lymphomagenesis. Therefore, our WGS analysis not only identifies novel somatic alterations, but also extends the overview of ATL genome, which can lead to future improvement of patient management.

Taken together, our findings provide novel insights into genetic and molecular heterogeneity in PTCLs, which should help to devise a novel molecular classification and to exploit a new therapeutic strategy for these malignancies

SS14-2

T-cell lymphomas of follicular helper T-cell derivation: pathology, mechanisms and therapeutic implications

Laurence de Level
Lausanne University Hospital, Switzerland

Lymphomas derived from CD4+ follicular helper T-cells (TFH cells) represent the largest group of nodal T-cell lymphomas. They comprise three entities, namely angioimmunoblastic T-cell lymphoma (AITL), follicular T-cell lymphoma (F-TCL) and nodal lymphoma with a TFH phenotype (PTCL- TFH). AITL typically manifests with systemic symptoms and biological abnormalities and consists of a polymorphous infiltrate comprising a usually small population of TFH neoplastic cells within an abundant polymorphous microenvironment associated to proliferation of veinules and follicular dendritic cells. F-TCL and PTCL-TFH usually lack a prominent microenvironment. F-TCL shows a nodular pattern of growth reminiscent of follicular lymphoma or progressive transformation of germinal centers, and PTCL-TFH may feature an interfollicular "T-zone" pattern. In addition to sharing a TFH immunophenotype and gene expression signature, the three TFH lymphomas disclose a homogeneous mutational landscape which recapitulates a multi-step oncogenic process. This typically consists of epigenetic deregulation (TET2 +/- DNMT3A inactivating mutations, often occurring at early stages in hematopoietic progenitors), and second-hit mutations including a hotspot RHOAG17V mutation (50-80% of cases) or other gain-of-function mutations targeting the TCR signaling pathway (PLCG1, CD28, PI3K components, CARD11…). Moreover, fusions involving SYK and ITK, CD28 and CTLA4 or CD28 and ICOS are detected at lower frequency and IDH2R172 mutations resulting in production of an oncometabolite are found in 25-30% of AITLs. The prognostic impact of the variations in the mutational landscape appears limited. Transgenic mouse models with expression of RHOAG17V in the T-cell compartment demonstrated the role of RHOAG17V in TFH differentiation, and in inducing autoimmunity. However, additional TET2 inactivation is required for lymphoma development, and these mouse tumors are dependent on ICOS/PI3K/MTOR signaling. In humans there is now evidence that AITL emerges in a background of TET2 and/or DNMT3 mutated clonal hematopoiesis, a scenario which explains the co-occurrence of AITL and myeloid neoplasms in some patients. Our current understanding of TFH lymphomas pathogenesis supports therapeutical targeting epigenetic changes in these diseases, and promising results have been yet reported with the use of hypomethalyting agents (5-azacytidine) or histone deacetylase inhibitors in relapsed/refractory patients.

SS14-3

Targeted therapy to small molecules in peripheral T cell lymphomas

Deok Hwan Yang
Chonnam National University Medical School, Korea

Peripheral T cell lymphomas (PTCLs) are heterogeneous groups of aggressive lymphomas, which T-cell phenotype itself associated with unfavorable prognostic factors when compare to patients with B-cell phenotype lymphomas. However, significant advances were recently made to overcome these obstacles based on well conducted prospective studies with combined novel agents. Pralatrexate, a unique antifolate, romidepsin, a histone deacetylase inhibitor, and brentuximab vedotin, an immunoconjugate of anti-CD30 improved the prognosis and survivals in PTCLs. Furthermore, new understanding of the biology and molecular pathogenesis using next-generation sequencing (NGS) assessment could enable the selective targeted therapy and have demonstrated the clinical efficacy and tolerability in both frontline and relapsed clinical settings. This review will summarize the gene expression profiles of PTCLs and discuss wide-ranging novel agents which mainly targeting intracellular pathway and mitochondrial anti-apoptosis in PTCLs.

SATELLITE SYMPOSIUM

SY01

What is the role of C5 inhibitors in PNH?

Jin Seok Kim
Yonsei University College of Medicine, Korea

Paroxysmal nocturnal hemoglobinuria (PNH) is regarded as a life-threatening disease characterized by intravascular hemolysis. In PNH, hemolysis is mostly mediated by the alternative pathway of the complement system. Therefore, the inhibition of complement is the best strategy against this disease. Allogeneic bone marrow transplantation was the only applicable treatment option for young and fit patients with PNH before the approval of eculizumab. The therapeutic alternatives for elderly or unfit patients were only supportive care such as blood transfusion, iron supplementation, anti-thrombosis therapy.

Eculizumab, the first humanized monoclonal antibody that blocks terminal complement C5 activation, is the first approved medication for PNH. Clinical studies have confirmed that eculizumab can effectively control hemolysis in PNH patients. The overall survival of patients with PNH has become similar to those of the general population after the availability of eculizumab. Therefore, eculizumab treatment dramatically improved the clinical outcome of PNH patients, but there are many unsolved various problems such as extravascular hemolysis (EVH), breakthrough hemolysis (BTH), or meningococcal infection. The Korean Society of Hematology Aplastic Anemia Working Party retrospectively recruited adult PNH patients who received eculizumab from 14 institutions between December 2009, and January 2020. This analysis included baseline characteristics, treatment efficacy, and safety in PNH patients treated with eculizumab. These data demonstrated that eculizumab showed sustained effectiveness with outstanding control of hemolysis-related manifestations in patients with PNH with a high disease burden and severe symptoms and signs. The incidence of EVH was 28.75% (approximately 1/3 of these patients required intervention) and BTH was 18.75%. Treatment adherence to eculizumab was excellent and no AE was leading to drug discontinuation.

Ravulizumab is a terminal complement component 5 (C5) inhibitor shown to have a similar efficacy and safety profile to eculizumab in adults with PNH. Ravulizumab has a longer half-life (about 40 days) than eculizumab (about 11 days) and has the advantage of a longer administration interval (every-8-week). Because the incidence of BTH is also significantly lower in the ravulizumab group due to the better effective control of the free C5 concentration, ravulizumab is considered as the current standard treatment option for PNH patients.

Next-generation complement inhibitors, such as other types of C5 inhibitors, anti-Factor B/Factor D, and C3 inhibitors, are on the clinical trial.

SY02

Gilteritinib: ADMIRAL study and real world experience

Byung Sik Cho
College of Medicine, The Catholic University of Korea, Korea

Aberrant FLT3 receptor signaling has important implications for the biology and clinical management of acute myeloid leukemia (AML). Patients with FLT3-mutated AML frequently present with critical illness, are more likely to relapse after treatment, and have worse clinical outcomes than those without FLT3 mutations. Researchers have made efforts to develop tyrosine kinase inhibitors that could effectively target FLT3 and improve clinical outcomes. Gilteritinib is a novel compound that entered the field late, but moved through the developmental process with remarkable speed. Gilteritinib received marketing approval from the US Food and Drug Administration (FDA) on 28 November 2018, based on an interim analysis of the ADMIRAL clinical trial. Full results of the ADMIRAL trial were published on 2019. Single-agent gilteritinib, a potent and selective oral FLT3 inhibitor, improved the survival of patients with relapsed or refractory FLT3-mutated AML compared with standard chemotherapy. However, as monotherapy, FLT3 inhibition, with gilteritinib is unlikely to result in a high cure rate for this population. Gilteritinib will likely improve the cure rates for patients with FLT3-mutated AML, but only when incorporated into a broader treatment regimen, which could include chemotherapy, other targeted agents, and immunotherapy, including allogeneic transplant. A number of such clinical studies with various combinations and settings have already been launched. In Korea, FDA approved gilteritinib for patients with relapsed or refractory FLT3-mutated AML and insurance coverage is imminent. This talk will reflect on the core results of the ADMIRAL trial and share early real world experiences of gilteritinib in Korea.

SY03

Role of CD19-directed CAR-T therapy in patients with DLBCL

Koji Izutsu
National Cancer Center Hospital, Japan

Survival of patients with DLBCL relapsed after autologous hematopoietic stem-cell transplantation or refractory to salvage chemotherapy is extremely poor. CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) has been developed to improve outcome of those patients. Now, three CAR-T products are commercially available for DLBCL, namely tisagenlecluce l (tisa-cel), axicabtagene ciloleucel (axi-cel), and lisocabtagene maraleucel (liso-cel). They use different CAR gene construct including co-stimulatory domain, vector for transduction of CAR gene, and manufacturing process.

Tisa-cel is a 4-1BB-based CAR-T, and it is unique in that it uses mononuclear cells cryopreserved at clinical sites for manufacturing. Its efficacy and safety in patients with relapsed/refractory DLBCL were evaluated in the JULIET trial, which included167 patients. The median time from enrollment to infusion was reported to be 54 days and bridging therapy was allowed during manufacturing of a CAR-T product (Schuster SJ et al. N Engl J Med 2019). Recently, long-term outcomes of this study with a median follow-up of 40 months was published (Schuster SJ et al. Lancet Oncol 2021). Overall response rate was 53% with a complete response (CR) rate of 39%. It seems that duration of response curve in patients who achieved CR as best overall response after tisa-cel infusion reaches plateau at >70%, suggesting "cure" in nearly 30% of patients who received tisa-cel. Adverse events of special interest occurring within the first 8 weeks after infusion at any grade included cytokine release syndrome (CRS) (57%), prolonged cytopenias (45%), infections (37%) and neurological events (20%). Grade 3 or worse CRS and neurological events were observed in 23% and 11%, respectively. Subgroup analysis suggested that patients with transformed follicular lymphoma and normal baseline serum lactose dehydrogenase (LDH) level were associated with better progression-free survival (PFS). However, PFS with serum LDH level >2xULN was very poor. These efficacy and safety data suggest that CAR-T is a promising option as a third-line therapy for DLBCL.

In Japan, tisa-cel was approved for third-line DLBCL in March, 2019 and it is covered by public health insurance. As of July, 2021, 253 patients (including patients with acute lymphoblastic leukemia) were treated with tisa-cel. Axi-cel and liso-cel were also approved for the similar indication in 2021 and is introduced into clinical practice. However, number of institutions providing CAR-T is still limited.

SY04

Immunotherapy in multiple myeloma

Ajai Chari
Mount Sinai, USA

Despite multiple myeloma cells being responsible for the first monoclonal antibodies used in humans in 1988, the first monoclonal antibody for multiple myeloma was not approved until several decades later in 2015. Now there are 3 naked antibodies and also the first antibody drug conjugate, belantamab mafadotin, which targets the B cell maturation antigen (BCMA), was also approved by the FDA for the treatment of relapsed/refractory multiple myeloma. There is even more excitement about bispecific antibodies targeting either BCMA (numerous agents under investigation), GPRC5d (talquetamab), or FCRh5 (cevostamab) – all of which are demonstrating remarkable single activity with overall response rates of 60-80% at the recommended phase 2 doses with manageable low grade cytokine release syndrome (CRS). Side effects of bispecifics are target specific with hypogammaglobulinemia/infections – including lack of COVID vaccine responses, associated with BCMA and perhaps FcRH5 whereas talquemetab has associated rashes, nail changes, and dysgeusia/weight loss. Aside from bispecifics, which are off-the-shelf T cell redirectors, chimeric antigen receptor therapies (CARTs) are demonstrating outstanding ORRs of 73 TO 98% with PFS/OS ranging from 8.6 months./24.8 months for ide-cel to greater than 2 years and not reached for ciltacel. Low grade CRS is common with these 2 FDA approved CART constructs but Grade 3+ CRS is uncommon, less than 5%. Neurotoxicity, however is more common with CARTs- all grades approximately 20% with grade 3+ 3 to 9%. This an exciting time for myeloma patients and combination strategies are already generating exciting data whereas more robust data for the movement of these agents into earlier lines of therapy are eagerly awaited. Data from novel agents such as trispecifics and DARPins are eagerly awaited.

SY05

Role of romiplostim in ITP and AA

Jun Ho Jang
Sungkyunkwan University School of Medicine, Korea

The management of ITP has in recent years been transformed from reliance on immunosuppressants and splenectomy to targeted therapy with thrombopoietin receptor agonists (TPO-RA) that directly stimulate platelet production in the bone marrow. This has reduced the long-term infective complications and toxicities associated with the use of potent immunosuppressants and splenectomy. The welltolerated romiplostim, itself a novel drug construct called peptibody, has established itself, alongside other TPO-RA as the preferred 2nd line therapy in major international guidelines on treatment of ITP.
In recent phase II/III, multicenter, open-label study, romiplastim was effective to AA patients who are refractory to IST. Hematological response at week 27 was 84%. Trilineage response was 39% at week 53. The most common treatment-related adverse events (AEs) were headache and muscle spasms.
Other study showed high dose romiplostim was highly effective in AA patients refractory to eltrombopag. Sequential therapy with eltrombopag followed by romiplastim may further improve the prognosis of AA patients refractory to conventional therapy.
High-dose romiplostim is effective and well tolerated in the treatment of patients with AA refractory to IST.

SY06

The updated information of ponatinib use in chronic myeloid leukemia

Jorge E. Cortes
Georgia Cancer Center, USA

SY07

Strategic treatment for diffuse large B-cell lymphoma; incorporating polatuzumab to DLBCL

Christopher Flowers
The University of Texas MD Anderson Cancer Center, USA

SY08

Optimal treatment with IMiDs in newly diagnosed multiple myeloma

Luciano J. Costa
The University of Alabama at Birmingham, USA

Thalidomide was the first immune modulating agent (IMiD) to enter the multiple myeloma (MM) therapeutic landscape but its impact was hindered by the toxicity profile, particularly peripheral neuropathy. Lenalidomide is a second generation IMiD with more favorable toxicity profile that has become a fixture in the management of patients with newly diagnosed MM (NDMM). For patients with NDMM not amenable to AHCT, lenalidomide in combination with dexamethasone (Rd) was proved superior to the combination of melphalan, prednisone and thalidomide in the FIRST trial. Rd became the foundation for successful combination in this setting, including bortezomib (V) Rd, as demonstrated in the S0777 trial and Rd in combination with daratumumab (DRd) as demonstrated in the MAIA trial. For patients amenable to AHCT, lenalidomide is established as the optimal partner for a proteasome inhibitor (PI) during induction and consolidation, as elegantly demonstrated in the FORTE trial and by long term outcomes of the IFM-2009 trial. Much of the benefit of lenalidomide relates to its long term tolerability. In fact, lenalidomide forms the current cornerstone of continuous therapy in MM, given its benefit in PFS and OS demonstrated in both transplant-eligible and nontransplant-eligible population. The success of long term lenalidomide therapy depends on proper dosing, prevention and management of toxicities. Adjustments are necessary for patients with renal dysfunction. Patients should receive prophylaxis for venous thromboembolism. Ongoing management of cytopenias is a necessity and adjustments are common. While the increase in risk of second primary malignancy is of much lower magnitude that the impact of lenalidomide on MM progression and death, age-appropriate screening is indicated.

ORAL PRESENTATION

OP01-1

Potential prognostic significance of promoter methylation status of DNA repair genes at diagnosis in acute myeloid leukemia: analysis of TCGA-LAML cohort and patients in a single institution

Sholhui Park[1], Yeung Chul Mun[3], Chu-Myung Seong[3] and Jungwon Huh[1*]

[1] Department of Laboratory Medicine, College of Medicine, Ewha Womans University, Korea

[3] Department of Internal Medicine, College of Medicine, Ewha Womans University, Korea

Background: Dysregulation of DNA damage response and altered DNA methylation in acute myeloid leukemia (AML) have been reported. Methylation is an attractive therapeutic target in that they have the potential to be restored to normal using targeting inhibitors. However, the impact of methylation of DNA repair genes has not yet been fully searched. Therefore, we aimed to predict the prognosis of non-APL AML patients based on the promoter methylation levels of DNA repair genes through The Cancer Genome Atlas AML project (TCGA-LAML) data and patients in a single institution. In addition, this study aimed to compare the degree of methylation of DNA repair genes between subgroups of AML, and to investigate their potential as prognostic factors.

Method: We utilized the TCGA-LAML cohort (174 non-APL AML) for the methylation data of 22 DNA repair genes. The TCGA-LAML 174 non-APL AML patients included 22 in favorable risk group, 102 in intermediate risk group, and 50 in poor risk group according to cytogenetics and molecular abnormalities. The beta values of methylation data of DNA repair genes (Illumina Infinium Human Methylation 450, TCGA Level 3 DNA methylation) were obtained. The M values were derived from the beta values to analyze the methylation status of DNA repair genes. To validate the TCGA-LAML, diagnostic bone marrow materials from 34 non-APL AML patients were enrolled in Ewha study group between 2013 and 2018. Eleven favorable risk AML, 14 intermediate risk AML and 9 adverse risk. The promoter methylation status of DNA repair genes in Ewha study group was assessed using commercially available EpiTect Methyl II PCR Array Human DNA Repair, Signature panel (Qiagen, CA, USA).

Results: In the TCGA-LAML cohort, through univariate analysis, the hypermethylation of MLH1, RAD51, and ATM showed superior overall survival (OS) than non-hypermethylated groups, while hypermethylation of RAD23A, RAD23B, MLH1, MSH2, BRCA1, BRCA2, RAD50, and PARP1 was associated with poor OS. In the Ewha study group, promoter hypermethylation of 7 genes, RAD23B, XPC, MLH1, PMS2, ATM, MRE11A, and LIG3, showed significantly poor OS than non-hypermethylated patients. In the comprehensive evaluation of 7 genes, the patient who showed hypermethylation in at least one gene showed an inferior OS than the patient in whom all seven genes were non-hypermethylated. In the TCGA cohort, the methylation levels of DNA repair genes pertaining to significantly different OS were analyzed for the AML cytogenetic risk groups. Most of the genes analyzed showed differential methylation levels between AML cytogenetic risk subgroups. In multivariate analysis, hypermethylation of MLH1 and RAD51 showed better OS than non-hypermethylated patients, but hypermethylation of MSH2 and RAD50 showed worse OS than non-hypermethylated patients in the TCGA-LAML cohort. The age, stem cell transplant status, cytogenetic risk group in AML patients were also confirmed to be independent risk factors from this analysis.

Conclusion: Based on a study by the TCGA-LAML cohort and the Ewha study group, the prognosis can vary depending on the degree of promoter methylation of DNA repair genes in non-APL AML patients. Methylation of 4 DNA repair genes, such as MLH1, RAD51, MSH2, and RAD50, has potential to be independent risk factors in non-APL AML patients.

Keyword: DNA repair gene, Promoter methylation, Acute myeloid leukemia, Prognosis, Biomarker

Table1. Multivariate analysis of the promoter hypermethylation of MLH1 (cg10990993), RAD51 (cg13422654), MSH2 (cg11311499), and RAD50 (cg14597804) in TCGA-LAML

	Univarite		Multivariate (2 gene combined)	
Parameter	HR (95% CI)	*P*	HR (95% CI)	*P*
Age*			1.02 (1.00-1.03)	0.0196
Stem cell transplant	0.45 (0.31-0.65)	<0.0001	0.36 (0.23-0.56)	<0.0001
Cytogenetic risk (reference favorable)				
Intermediate	3.28 (2.04-5.27)	0.0001	3.20 (1.42-7.21)	0.0049
Adverse	4.92 (2.80-8.65)		5.89 (2.51-13.84)	<0.0001
Promoter hypermethylation				
MLH1	0.42 (0.22-0.80)	0.0087		
RAD51	0.28 (0.15-0.55)	0.0002		
MLH1 or RAD51			0.77 (0.29-2.02)	0.5909
MLH1 and RAD51			0.32 (0.12-0.80)	0.0148
MSH2	1.52 (1.06-2.18)	0.0232		
RAD50	1.97 (1.03-3.79)	0.0414		
MSH2 or RAD50			1.95 (1.28-2.97)	0.0018
MSH2 or RAD50			3.86 (1.67-8.91)	0.0016

*Continuous variable

OP01-2

TP53-mutated AML with high variant allele frequency show better survival outcome with hypomethylating agents than with cytarabine-based induction

Hye Won Kook[1], Hyunsoo Cho[1], Haerim Chung[1], Ji Eun Jang[1], Yu Ri Kim[1], Jin Seok Kim[1], Shin Young Hyun[1], Doh Yu Hwang[1], Saeam Shin[2], Dong-Yeop Shin[3], Jae-Sook Ahn[4], Yoo Hong Min[1] and June-Won Cheong[1*]

[1] Department of Internal Medicine, Yonsei University College of Medicine, Korea

[2] Department of Laboratory Medicine, Yonsei University College of Medicine, Korea

[3] Department of Internal Medicine, Seoul National University Hospital, Korea

[4] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea

Background: TP53 mutation, detected in 5~10% of newly diagnosed acute myeloid leukemia (AML), is well known for the resistance to conventional chemotherapies and dismal outcome in AML. Recent progress in next-generation sequencing (NGS) has enabled detailed exploration of the mutational landscapes of AML. Variant allele frequencies (VAFs) have become available, which reflects the clonal burden of the detected mutations. However, there are few studies that have evaluated the prognostic impact of VAF on outcome of AML. We conducted a multicenter retrospective study of VAF-available TP53-mutated AML patients to better understand the impact of the allelic burden of TP53 mutation on clinical outcomes and its application on deciding treatment options.

Method: A total of 53 patients were diagnosed with TP53-mutated AML in 3 Severance Hospitals belonging to Yonsei University Health System, Seoul National University Hospital, and Chonnam National University Hwasun Hospital from July 2017 to December 2021. Among them, 44 patients receiving chemotherapy were retrospectively analyzed. Patients were divided into two groups, Higher VAF (VAF>42.5%) group and Lower VAF (VAF≤42.5%) group, according to median VAF. For initial treatment, 27 patients received Cytarabine based intensive chemotherapy and 16 received hypomethylating agent (HMA) based less intensive treatment. The prognostic impact of the TP53 mutation VAF on outcomes were analyzed. Clinical characteristics and treatment outcomes including complete remission (CR) rates, event free survival (EFS), and overall survival (OS) were analyzed.

Results: The Higher VAF group showed higher PB blast percentage than the Lower VAF group (12% vs 2%, p=0.018). There was no difference between the two groups in other characteristics including age, sex, karyotype, and secondary AML diagnosis. (Table 1). Though the percentage of alive patients was lower in the Higher VAF group than the Lower VAF group (0.0% vs 23.8%, p=0.057), there was no significant difference in OS and EFS between the two groups (p=0.757). Subgroup analysis revealed that in the Lower VAF group, there was no difference in OS between the HMA group and the Cytarabine group (2.8 vs 3.8 months, p=0.666). However, in the Higher VAF group, the HMA group showed longer OS than the Cytarabine group (9.9 vs 6.5 months, p=0.037, Figure 1) despite of older age (71 vs 55 years, p=0.002). There was no difference in karyotype, secondary AML diagnosis, BM blast percentage and TP53 VAF. CR rates to first line therapy were 50% vs 20% in the HMA group and Cytarabine group (p=0.053).

Conclusion: In our study, there was no direct impact of TP53 VAF on OS and EFS. However, better outcomes with HMA compared to Cytarabine with longer OS and higher response rates were demonstrated in the Higher VAF group. It has been previously proposed that TP53 mutation might prime cells to have response to Decitabine. Better outcomes with HMA in the group with higher TP53 allelic burden from our study support the idea that TP53 mutation may confer sensitivity to HMA. Further studies to elucidate the mechanism are necessary. TP53-mutated AML with high VAF may benefit from induction with HMA than with Cytarabine, but further studies are needed for validation.

Keyword: TP53, AML, Variant allele frequency, Prognosis, Hypomethylating agent

	ALL patients *(N=44)	Lower VAF Group (N=21)	Higher VAF Group (N=21)	p value
Patient Characteristics				
Median Age (range)	62 (28-83)	64 (30-83)	60 (28-79)	0.281
Sex				
Male	29 (65.9)	15 (76.2)	11 (52.4)	0.107
Female	15 (34.1)	5 (23.8)	10 (47.6)	
Clinical parameters				
WBC (*10^9 /L) (range)	4.25 (0.64-194.70)	2.70 (0.88-194.70)	11.16 (0.64-110.42)	0.532
PB blasts (%) (range)	2 (0-96)	2 (0-81)	12 (0-96)	**0.018**
Hb (g/dL) (range)	7.4 (3.4-13.0)	7.5 (3.4-13.0)	7.4 (4.0-11.2)	0.894
Plts (*109 /L) (range)	35 (7-743)	34 (7-743)	41 (12-254)	0.831
BM blasts (%) (range)	37.4 (20.0-92.5)	27.4 (20.0-92.0)	51.4 (22.0-92.5)	0.126
LDH (IU/L) (range)	544 (106-11267)	433 (106-11267)	567 (200-4707)	0.679
Diagnosis				
AML	32 (72.7)	13 (61.9)	18 (85.7)	0.079
secondary AML	12 (27.3)	8 (38.1)	3 (14.3)	
Presence of Dysplasias	21 (47.7)	12 (57.1)	9 (42.9)	0.272
Cytogenetics				
Normal Karyotype	5 (11.4)	1 (4.8)	4 (19.0)	0.188
Complex Karyotype	31 (70.5)	13 (61.9)	16 (76.2)	0.583
Risk				

Favorable	1 (2.3)	1 (4.8)	0 (0)	
Intermediate	7 (15.9)	2 (9.5)	5 (23.8)	0.334
Adverse	34 (84.1)	16 (76.2)	16 (76.2)	
Median TP53 VAF (%) (range)	42.52 (2.85 - 97.90)	27.1 (2.85 - 41.04)	68.92 (43.00 - 97.90)	
Two TP53 mutations	5 (11.4)	3 (14.3)	2 (9.5)	0.634
Treatment				
Induction				
Cytarabine-based	27 (61.3)	12 (57.1)	15 (71.4)	
HMA-based	16 (36.4)	7 (38.1)	6 (28.6)	0.445
Venetoclax	1 (2.2)	1 (4.8)	0	
Allo-SCT	13 (44.8)	5 (41.7)	8 (47.1)	0.774
Outcome				
CR1 achievement (First cycle chemo-therapy only)	12 (27.3)	6 (28.6)	6 (28.6)	0.166
CR1 achieve-ment(Salvage chemotherapy included)	20 (47.6)	10 (47.6)	10 (47.6)	0.103
Survival	5 (11.9)	5 (23.8)	0 (0)	0.057
Relapse	15 (60)	5 (45.5)	10 (71.4)	0.188
Median OS (months)	5.9	3.8	7.4	0.757
Median EFS (months)	7.5	10.5	7.5	0.211

Table 1. Clinical Characteristics and Treatment Outcomes of all patients.

* Two patients had whole gene deletions with unavailable variant allele frequency.

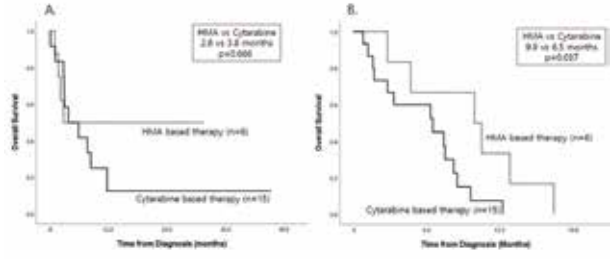


Figure 1. Survival Outcomes based on Chemotherapy Regimens in VAF≤42.5% group (A) and VAF>42.5% group (B).

OP01-3

WT1 gene expression in primary acute myeloid leukemia

Ishan Gupta[1], Harsh Goel[2], Pranay Tanwar[2*], Dimpy Gupta[2], Anita Chopra[2], Amar Ranjan Singh[2] and Sameer Bakhshi[3]

[1] M.B.B.S. Student, All India Institute of Medical Sciences (AIIMS), New Delhi, India

[2] Laboratory Oncology Unit, Dr. B.R.A. Institute Rotary Cancer Hospital (BRAIRCH), All India Institute of Medical Sciences (AIIMS), New Delhi, India

[3] Department of Medical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital (BRAIRCH), All India Institute of Medical Sciences (AIIMS), New Delhi, India

Background: Acute myeloid leukemia (AML) is a heterogenous disease which shows variation in response to therapy and survival. Prognosis is determined by age, cytogenetics, and performance status. Genetic mutations in KIT, NPM1 (nucleophosmin 1), FLT3 (Fms-like tyrosine kinase 3), WT1 (Wilms Tumor 1) and CEBPA (CCAAT enhancer-binding protein-α) are newer prognostic markers. In the present study, we assessed WT1 gene expression along with other mutations such as AML-ETO, CBFB-MYH11, NPM1, FLT3-ITD and PML-RARA as biomarkers for therapy response in primary AML.

Method: A total of 108 cases of diagnosed AML, with blast percentage of ≥20% blasts in peripheral blood smear or bone marrow on Day 0 and treated with induction therapy for 28 days following which morphological remission occured (blast percentage ≤5%) were enrolled. RNA was extracted from blood/bone marrow samples at diagnosis (Day 0) and on Day 28. Haematological workup and flowcytometric immunophenotypes were done. WT1 expression was done using real-time qPCR, and was normalized against endogenous control genes: HBG2, β2microglobulin and GAPDH. Detection of mutations including AML-ETO, CBFB-MYH11, NPM1, FLT3-ITD and PML-RARA was done in 45 cases. Cytogenetics was done in 38 cases and FISH for PML-RARA in 8 cases.

Results: WT1 expression was seen to be reduced at Day 28 in 93/108 (86.1%) cases; whereas in 17/108(15.7%) cases, WT1 expression was seen to have increased at Day 28 as compared to Day 0 levels. Blast count percentage in these 17 cases varied from 29% to 78%. AML-ETO mutation was detected in 13/45(28.9%) cases, CBFB-MYH11 in 3/45(6.7%) cases, NPM1 mutations in 5/45(11.1%) cases and FLT3-ITD in 7/45(15.5%) cases. PML-RARA mutation was detected in 8 cases of APML [confirmed by cytogenetics and FISH in 6/8 cases].

Conclusion: There was significant reduction in expression of WT1 in more than 85% of cases with morphological remission at the end of induction therapy. Blast count percentage along with WT1 expression can act as prognostic markers for assessment of remission. Molecular analysis in AML cases has diagnostic as well as prognostic role. More prospective studies with larger sample size may help to shed more light on this aspect.

Keyword: Acute myeloid leukemia, Prognostic factors, Real-time qPCR, WT1 (Wilms Tumor 1) gene

	ALL patients * (N=44)	Lower VAF Group (N=21)	Higher VAF Group (N=21)	p value
Patient Characteristics				
Median Age (range)	62 (28-83)	64 (30-83)	60 (28-79)	0.281
Sex				
Male	29 (65.9)	15 (76.2)	11 (52.4)	0.107
Female	15 (34.1)	5 (23.8)	10 (47.6)	
Clinical parameters				
WBC (*10^9 /L) (range)	4.25 (0.64-194.70)	2.70 (0.88-194.70)	11.16 (0.64-110.42)	0.532
PB blasts (%) (range)	2 (0-96)	2 (0-81)	12 (0-96)	**0.018**
Hb (g/dL) (range)	7.4 (3.4-13.0)	7.5 (3.4-13.0)	7.4 (4.0-11.2)	0.894
Plts (*10^9 /L) (range)	35 (7-743)	34 (7-743)	41 (12-254)	0.831
BM blasts (%) (range)	37.4 (20.0-92.5)	27.4 (20.0-92.0)	51.4 (22.0-92.5)	0.126
LDH (IU/L) (range)	544 (106-11267)	433 (106-11267)	567 (200-4707)	0.679
Diagnosis				
AML	32 (72.7)	13 (61.9)	18 (85.7)	0.079
secondary AML	12 (27.3)	8 (38.1)	3 (14.3)	
Presence of Dysplasias	21 (47.7)	12 (57.1)	9 (42.9)	0.272
Cytogenetics				
Normal Karyotype	5 (11.4)	1 (4.8)	4 (19.0)	0.188
Complex Karyotype	31 (70.5)	13 (61.9)	16 (76.2)	0.583
Risk				
Favorable	1 (2.3)	1 (4.8)	0 (0)	0.334
Intermediate	7 (15.9)	2 (9.5)	5 (23.8)	
Adverse	34 (84.1)	16 (76.2)	16 (76.2)	
Median TP53 VAF (%) (range)	42.52 (2.85 - 97.90)	27.1 (2.85 - 41.04)	68.92 (43.00 - 97.90)	
Two TP53 mutations	5 (11.4)	3 (14.3)	2 (9.5)	0.634
Treatment				
Induction				
Cytarabine-based	27 (61.3)	12 (57.1)	15 (71.4)	0.445
HMA-based	16 (36.4)	7 (38.1)	6 (28.6)	
Venetoclax	1 (2.2)	1 (4.8)	0	
Allo-SCT	13 (44.8)	5 (41.7)	8 (47.1)	0.774
Outcome				
CR1 achievement (First cycle chemotherapy only)	12 (27.3)	6 (28.6)	6 (28.6)	0.166
CR1 achievement (Salvage chemotherapy included)	20 (47.6)	10 (47.6)	10 (47.6)	0.103
Survival	5 (11.9)	5 (23.8)	0 (0)	**0.057**
Relapse	15 (60)	5 (45.5)	10 (71.4)	0.188
Median OS (months)	5.9	3.8	7.4	0.757
Median EFS (months)	7.5	10.5	7.5	0.211

Table 1. Clinical Characteristics and Treatment Outcomes of all patients.
* Two patients had whole gene deletions with unavailable variant allele frequency.

OP01-4

Preliminary results by age group of treatment with CPX-351 plus venetoclax in adults with newly diagnosed AML: subgroup analysis of the V-FAST trial

Vinod Pullarkat[1], Mark Levis[2], Gabriel Mannis[3], Tara L. Lin[4], Janet Pong[5*], Stefan Faderl[6], Divya Chakravarthy[6], Vijayalakshmi Chandrasekaran[7], Ronald S. Cheung[6] and Harry P. Erba[8]

[1] Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

[2] Hematologic Malignancies and Bone Marrow Transplantation Program, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

[3] Department of Hematology, Stanford University Medical Center, Palo Alto, CA, USA

[4] Department of Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS, USA

[5] Department of Partner Markets, Jazz Pharmaceuticals, Oxford, UK

[6] Department of Clinical Development, Jazz Pharmaceuticals, Palo Alto, CA, USA

[7] Department of Biostatistics, Jazz Pharmaceuticals, Philadelphia, PA, USA

[8] Division of Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA

Background: CPX-351 (United States: Vyxeos®; Europe: Vyxeos® liposomal), a dual-drug liposomal encapsulation of daunorubicin + cytarabine in a synergistic 1:5 molar ratio, is approved in Europe for the treatment of newly diagnosed therapy-related AML or AML with myelodysplasia-related changes in adults in Europe and for patients aged ≥1 year in the United States. In a phase 3 study in older adults with newly diagnosed, high-risk/secondary AML, after 5 years of follow-up CPX-351 significantly improved median survival and remission rates versus 7+3 cytarabine/daunorubicin, with a comparable safety profile. Preclinical data suggest CPX-351 may have synergistic activity with the BCL-2 inhibitor venetoclax (VEN), and interim results from the V-FAST (Vyxeos – First Phase Assessment with Targeted Agents) study have demonstrated the safety and preliminary efficacy of CPX-351 + VEN. Herein, we report preliminary results of an age-based analysis of adults treated with CPX-351 + VEN in the V-FAST study.

Method: V-FAST is an ongoing, open-label, multi-arm, non-randomised, phase 1b master trial (NCT04075747) to evaluate the safety and preliminary efficacy of CPX-351 combined with targeted agents (VEN, midostaurin, enasidenib). Each arm had a 3+3 dose-exploration phase (n≤12) and expansion phase (n=20) to determine the recommended phase 2 dose (RP2D), safety, and initial efficacy of the combination. Eligible adults in the CPX-351 + VEN arm were aged 18–75 years with newly diagnosed AML, were fit for intensive chemotherapy, had an ECOG status of 0–2, and had wild type FLT3 and IDH2. The RP2D of this arm was dose level 1: CPX-351 100 units/m2 on Days 1, 3, and 5 + VEN 400 mg on Days 1–14 of induction 1. At this dose level, 1 of 6 patients in the dose-exploration phase experienced 2 dose-limiting toxicities (grade 4 neutropenia and thrombocytopaenia that extended beyond 49 days); no dose adjustments were required, and the study enrolled additional patients into the expansion phase.

Results: A total of 21 evaluable patients (14 younger [18–59 years], 7 older [60–75 years]) received CPX-351 + VEN. Baseline characteristics are shown in the Table. TEAEs in ≥50% of younger adults were neutropenia (57%), febrile neutropenia (50%), and constipation (50%); TEAEs in ≥50% of older adults were febrile neutropenia (86%), thrombocytopaenia (86%), nausea (71%), and diarrhoea (57%). Grade ≥3 TEAEs in both age groups were primarily haematological events. Six younger and 1 older patients died during the study, including 2 younger and 1 older patients who died within 60 days. Median (IQR) platelet recovery times were 36.5 (36, 40) and 30.5 (27, 79.5) days in younger and older patients with complete remission (CR) or CR with incomplete platelet or neutrophil recovery (CRi); median (IQR) neutrophil recovery times were 36 (35, 37) and 33.5 (30.5, 48.5) days, respectively. CR+CRi was achieved by 6/14 (43%) and 4/6 (67%) evaluable younger and older adults; 5/14 (36%) and 3/6 (50%) achieved CR.

Conclusion: This analysis of preliminary results by age group from the V-FAST study supports the conclusion that the combination of CPX-351 + VEN is equally feasible with a manageable safety profile in younger and older adults with newly diagnosed AML. Promising remission rates were also reported for both age groups.

Keyword: Adult, Chemotherapy, Clinical, Combination therapy, Targeted agents, Acute myeloid leukemia

Table. Baseline Characteristics Of Patients Who Received CPX-351 + VEN By Age Group

	Aged 18–59 years (n=14)	Aged 60–75 years (n=7)	All ages (n=21)
Median (range) age, years	51.5 (35, 59)	68 (64, 69)	54 (35, 69)
Male, n (%)	8 (57)	4 (57)	12 (57)
Risk group, n (%)[a]			
Favourable	1 (7)	1 (14)	2 (10)
Intermediate	6 (43)	0	6 (29)
Poor	6 (43)	6 (86)	12 (57)
Mutated *TP53*, n (%)	4 (29)	2 (29)	6 (29)
AML subtype, n (%)			
de novo AML	9 (64)	5 (71)	14 (67)
AML with antecedent disorder	4 (29)	2 (29)	6 (29)
Therapy-related AML	2 (14)	0	2 (10)
Prior HMA for MDS, n (%)	0	0	0
ECOG PS, n (%)			
0	7 (50)	2 (29)	9 (43)
1	6 (43)	4 (57)	10 (48)
2	1 (7)	1 (14)	2 (10)

VEN, venetoclax; AML, acute myeloid leukaemia; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status.
n=number of patients who received ≥1 dose of study drug and had sufficient data to be included in the analysis.
[a]Risk classification is unknown for 1 patient aged 18–59 years.

OP01-5

A randomized, phase II, comparative study with a parallel control for evaluating the efficacy and safety of 5-day azacitidine for patients with lower-risk MDS

Silvia Park[1], Daehun Kwag[1], Eun-Ji Choi[2], Kyoo-Hyung Lee[2], Je-Hwan Lee[2], Dong-Yeop Shin[3], Junshik Hong[3], Sung-Soo Yoon[3] and Yoo-Jin Kim[1]

[1] Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[2] Department of Biological Sciences, Ulsan National Institute of Science and Technology, Ulsan, Korea

[3] Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Azacitidine has shown survival benefit in patients with higher-risk myelodysplastic syndrome (MDS) from a phase III randomized trial. Although the use of this agent is less well studied for lower-risk MDS (LrMDS), findings from previous studies suggest that azacitidine is a feasible option for LrMDS to improve hematologic outcomes and transfusion dependence. The standard dosing schedule of azacitidine (75mg/m2/day for 7 days) is commonly used for LrMDS, but optimal dosing schedule, providing comparable efficacy with lesser toxicities which could be more critical for LrMDS, has yet to be validated. Given that a low dosing schedule was reported to be feasible for LrMDS but has never been compared to the standard dosing schedule, this study was designed in a prospective manner.

Method: This study was a Phase II, multicenter, randomized, open-label clinical trial for LrMDS patients to explore the efficacy of 5-day azacitidine as compared to a 7-day standard regimen. Patients were randomly assigned to one of two treatment arms and received subcutaneous azacitidine until disease progression, relapse, unacceptable toxicity, or voluntary withdrawal of consent occurred. Patients presenting with the following conditions were eligible: adult patients (≥ 18 years) diagnosed with FAB criteria defined MDS, and low- or INT-1 risk according to IPSS; hemoglobin (Hb) < 10.0 g/dL or transfusion dependence (at least one RBC transfusion every 8 weeks), platelet count < 100×109/L, or absolute neutrophil count (ANC) < 1.80×109/L. The primary endpoint of the study was the comparison of the response rate between the two dosing schedules.

Results: Because of the slow accrual of patients, we stopped the study on May 15, 2020. By the date, 55 patients were registered, but 2 patients were excluded from the analysis as they did not meet the inclusion criteria. Random assignment of the remaining 53 patients was as follows; 25 and 28 patients were allocated to 5-day and 7-day regimen, respectively. A total of 47 patients (88.7%) received at least two treatment cycles and 30 patients (56.6%) completed six treatment cycles. Overall, the median age was 59 years (range, 23 to 80 years) and MDS-RCMD (n=27, 50.9%) and RAEB-1 (n=15, 28.3%) comprised the most. The composition of IPSS risk score was 0 (n=8, 15.1%), 0.5 (n=23, 43.4%) and 1.0 (n=22, 41.5%). The median percentage of BM blast was 3.0% (range, 0.0-10.0%) and the median ANC, Hb level and platelet count was assessed as 0.84×109/L, 8.4 g/dL and 121×109/L, respectively. When the 5-day and 7-day groups were compared, there was no difference in clinical factors including age, sex, MDS subtypes, IPSS score, BM blast, ANC, hemoglobin level, platelet count, while total white blood cell (WBC) count was higher in 5-day group as compared to 7-day group (p=0.041). The median cycles in both treatment arms were the same and six cycles. In all, the ORR was 43.4% (23 out of 53), with 11.3% of patients achieving a CR (6/53), and hematological improvement (HI) was seen in 41.5% (22/53). According to treatment arms, ORR was 48.0% and 39.3% (p=0.552) and HI was observed in 44.0% and 39.3% (p=0.617) in the 5-day and 7-day regimen. The median cycles to best response was 3 cycles (range, 1-8); 2.5 cycles for 5-day regimen (range, 1-8) vs 3.0 cycles for 7-day regimen (range, 1-8) (p=0.671). Overall, the most common reason for withdrawal was no response/disease progression/loss of response (n=35, 66.0%) followed by adverse events (AEs) (n=6, 11.3%). The percentage of patients who discontinued treatment due to AEs or lack of response did not significantly differ by treatment arms, and were 12.0% and 10.7% for AEs (p=0.883) and

68.0% and 64.3% for lack of response (p=0.776) in the 5-day and 7-day regimen. After the median follow-up period of 67.7 months for survivors, the median OS was not reached in both treatment arms and OS at 5 years was estimated to be 72.9% and 67.4% in the 5-day and 7-day regimen, respectively (p=0.901).

Conclusion: The efficacy of 5-day azacitidine was comparable to 7-day azacitidine in the context of overall response rate, hematologic improvement and survival in patients with lower-risk MDS by IPSS.

Keyword: Myelodysplastic syndrome, IPSS lower risk, Azacitidine, 5-day schedule

OP02-1

High incidence of MYD88 mutation associated with mutated IGHV gene in Korean chronic lymphocytic leukemia

Ari Ahn[1], Hoon Seok Kim[1], Jong Mi Lee[1], Tong-Yoon Kim[2], Ki-Seong Eom[2], Yonggoo Kim[1,3] and Myungshin Kim[1,3*]

[1] Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

[2] Department of Hematology, College of Medicine, The Catholic University of Korea, Seoul, Korea

[3] Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Chronic lymphocytic leukemia (CLL) is the most frequent leukemia in adults in Western countries, but is very rare in Asian cohorts as well as Korea. CLL has no specific genetic markers, but several biological features, including immunoglobulin heavy chain variable (IGHV) gene mutational status, cytogenetic abnormalities, or the expression of several proteins in the leukemic lymphocytes have been related to patient outcome. IGHV genes are mutated in 50-70% of cases and high somatic hypermutation (SHM) rate (≥2%) is associated with good prognosis in CLL. The reported MYD88 mutation rate is variable in CLL patients, ranging from 1.5 to 12.6%. The MYD88 mutation has been postulated to be an early clonal event and driver mutation in CLL, but the biological and clinical relevance of MYD88 mutations in CLL was controversial. In addition, the clinicopathological characterization of the canonical L265P MYD88 mutation vs. mutations in other sites of MYD88 within the context of CLL is still not established.

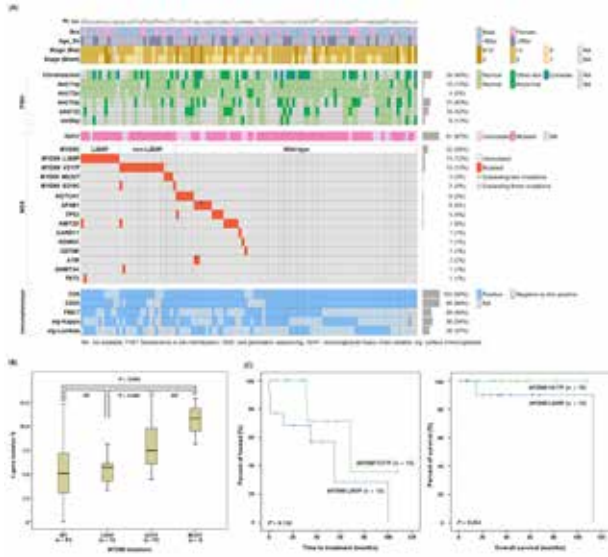
Method: In this study, we investigated the clinical and genetic characteristics of CLL in the Korean population. In total, 113 patients diagnosed with naïve CLL in the Seoul St. Mary's Hospital from March 2018 to December 2021 were included in the study. All patients underwent flow cytometric immunophenotyping and next-generation sequencing (NGS) based on a 43-gene mutations panel. We also identified IGH gene rearrangements and assessed the extent of SHM in IGHV gene using LymphoTrack® IGHV Leader Somatic Hypermutation Assay or IGH FR1 Assay kits (InVivoScribe, San Diego, CA). IGHV sequences with <98% identity to the germline sequence (V gene mutation ≥2%) were classified as mutated IGHV, while those with ≥98% identity to the germline sequence were classified (V gene mutation <2%) as unmutated IGHV according to European Research Initiative on CLL (ERIC) recommendation. Among them, 80 patients underwent conventional karyotyping and 105 patients underwent fluorescence in situ hybridization (FISH) with five DNA probes for the detection of del(13q14), trisomy 12, del(11q22), del(17p13), and del(6q23). To investigate the impact of IGHV and MYD88 mutations in CLL patients, we evaluated time to treatment (TTT) and overall survival (OS) in patients with and without IGHV and MYD88 mutations.

Results: The median age at diagnosis was 59.0 years (age range: 32–87 years). The population was predominantly male with a male-to-female ratio of 2:1. Pathogenic variants were identified in 59 patients (52.2%), and 32 (28.3%) patients were found to have MYD88 mutations, including 13 with L265P, 14 with V217F, 3 with M232T, 1 with S219C, and 1 with both S219C and V217F mutations. Except for 8 cases where SHM could not be evaluated in IGHV Leader and IGH FR1 Assay kits, 91 out of 105 patients (86.7%) showed IGHV mutation. The MYD88-mutated group more frequently showed atypical immunophenotypes including CD5-negative, CD23-negative, or FMC7-strong positive expression, and less frequently showed cytogenetic abnormalities than those in the wild-type group ($P < 0.001$ and $P = 0.010$, respectively). Patients with MYD88 mutations preferentially carried mutated IGHV genes (MYD88 mutated: 29/29 vs. MYD88 wild-type: 62/76, $P = 0.010$) (Figure A). In addition, compared to the group with L265P MYD88 mutation, the V gene mutational load was higher in the group with V217F and M232T MYD88 mutations, and group with L265P MYD88 mutation had no difference with wild-type group ($P = 0.002$, $P = 0.146$, and $P = 0.584$, respectively) (Figure B). With a median follow-up of 27.0 months, MYD88 mutations showed no significant impact on either TTT or OS. However, in MYD88 mutated patients, patients with V217F mutation showed a tendency of better prognosis of TTT and OS than those with L265P mutation ($P = 0.132$ and $P = 0.254$, respectively) (Figure C). Patients with mutated IGHV showed superior prognosis of TTT and OS compared to those with unmutated IGHV ($P = 0.038$ and $P = 0.014$, respectively).

Conclusion: We observed a high frequency of MYD88 mutations and IGHV somatic hypermutations in Korean patients with CLL compared with that in the populations of predominately European descent. Patients with MYD88-mutated CLL showed atypical immunophenotypes, and MYD88 mutations tended to be mutually exclusive with cytogenetic abnormalities. All MYD88-mutated patients belonged to the IGHV-mutated group, and the V gene mutational load of non-L265P mutation group was higher than that of

L265P group, which may be a molecular sign of favorable prognosis of CLL. These findings can explain some of the clinicopathological characterization differences between Asian and Western populations with CLL.

Keyword: Chronic lymphocytic leukemia, MYD88, IGHV, Somatic hypermutation, L265P, Korea



OP02-2

First interim analysis results of ALPINE phase 3 study of zanubrutinib vs ibrutinib in R/R chronic lymphocytic leukemia/small lymphocytic lymphoma

Won Seog Kim[1,2*], Peter Hillmen[3], Barbara Eichhorst[4,5], Jennifer R. Brown[6], Nicole Lamanna[7], Susan O'Brien[8], Constantine S. Tam[9,10,11,12], Lugui Qiu[13], Maciej Kazmierczak[14], Keshu Zhou[15], Martin Šimkovič[16,17], Jiri Mayer[18], Amanda Gillespie-Twardy[19], Mazyar Shadman[20,21], Alessandra Ferrajoli[22], Peter S. Ganly[23], Robert Weinkove[24,25], Tommi Salmi[26], Meng Ji[27], Jessica Yecies[28], Kenneth Wu[29], William Novotny[28], Jane Huang[28] and Wojciech Jurczak[30]

[1] Department of Hematology and Oncology, Sungkyunkwan University School of Medicine, Korea

[2] Department of Hematology and Oncology, Samsung Medical Center, Korea

[3] Department of Haematology, St James's University Hospital, UK

[4] Department I of Internal Medicine, University of Cologne, Germa

[5] Department I of Internal Medicine, Center for Integrated Oncology Aachen, Germany

[6] Department of Medical Oncology, Dana-Farber Cancer Institute, USA

[7] Department of Medicine, Division of Hematology/Oncology, Herbert Irving Comprehensive Cancer Center, Columbia University, USA

[8] Department of Hematology and Oncology, Chao Family Comprehensive Cancer Center, University of California, USA

[9] Department of Haematology, Peter MacCallum Cancer Centre, Australia

[10] Department of Haematology, University of Melbourne, Australia

[11] Department of Haematology, St Vincent's Hospital, Australia

[12] Department of Haematology, Royal Melbourne Hospital, Australia

[13] Department of Lymphoma & Myeloma, Chinese Academy of Medi cal Sciences, Peking Union Medical College, China

[14] Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poland

[15] Department of Hematology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, China

[16] 4th Department of Internal Medicine - Hematology, University Hospital, Czech

[17] Faculty of Medicine, Charles University, Czech

[18] Department of Internal Medicine-Hematology and Oncology, Masaryk University and University Hospital, Czech

[19] Medical Oncology and Hematology, Blue Ridge Cancer Care, US

[20] Clinical Research Division, Fred Hutchinson Cancer Research Center, USA

[21] Department of Medicine, University of Washington, USA

[22] Department of Leukemia, The University of Texas MD Anderson Cancer Center, USA

[23] Department of Haematology, Christchurch Hospital, New Zealan

[24] Hematology, Wellington Blood and Cancer Centre, Capital and Coast District Health Board, New Zealand

[25] Hematology, Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, New Zealand

[26] Hematology Clinical Development , BeiGene Switzerland GmbH, Switzerland

[27] Hematology Clinical Development , BeiGene (Beijing) Co., Ltd., China

[28] Hematology Clinical Development , BeiGene USA, Inc., USA

[29] Department of Biostatistics for Heme Clinical Development, BeiGene USA, Inc., USA

[30] Lymphoid Malignancies, Maria Sklodowska-Curie National Research Institute of Oncology, Poland

Background: Treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has been transformed with the advent of effective inhibitors of B-cell receptor signaling, such as Bruton tyrosine kinase (BTK) inhibitors. The first-generation BTK inhibitor ibrutinib is a standard of care in CLL/SLL. Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC and EGFR family kinases. Activity and tolerability of zanubrutinib in patients (pts) with CLL/SLL has been demonstrated in early phase trials. ALPINE (BGB-3111-305; NCT03734016) is a global, randomized, phase 3 study of zanubrutinib vs ibrutinib in pts with relapsed/refractory (R/R) CLL/SLL. Here we present the results of a pre-planned

interim analysis scheduled approximately 12 mo after the first 415 out of 652 pts were enrolled.

Method: Patients with R/R CLL/SLL were randomly assigned 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily until disease progression. Randomization was stratified by age (<65 yrs vs ≥65 yrs), geographic region, refractory status, and del17p/TP53 mutation status. The primary endpoint was overall response rate (ORR) as determined by investigators using the 2008 iwCLL guidelines for CLL and the Lugano criteria for SLL. Sample size was calculated to provide 90% power to demonstrate non-inferiority of zanubrutinib to ibrutinib response ratio at the non-inferiority margin of 0.8558. A hierarchical testing approach was implemented to test the superiority of zanubrutinib over ibrutinib in ORR if non-inferiority was demonstrated.

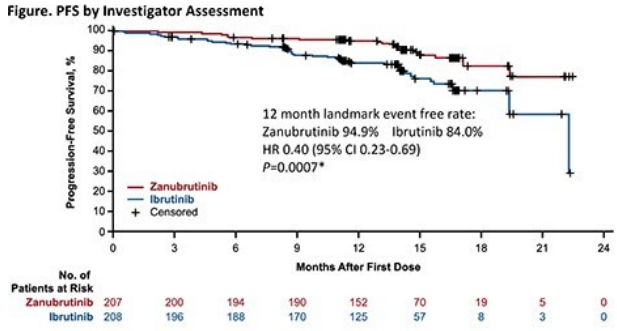
Results: Between 5 Nov 2018 and 20 Dec 2019, 415 pts were randomized. Treatment groups were well balanced for demographic and disease characteristics: age ≥65 yrs 62.3% vs 61.5%, male 68.6% vs 75%, >3 prior lines of therapy 7.2% vs 10.1%, del17p 11.6% vs 12.5%, TP53 mutated without del17p 8.2% vs 5.8%, in zanubrutinib and ibrutinib arms, respectively. At a median follow-up of 15 mo, ORR was significantly higher with zanubrutinib vs ibrutinib (78.3% vs 62.5%, 2-sided P=0.0006 compared with pre-specified alpha of 0.0099 for interim analysis). ORR was higher in pts with del11q (83.6% vs 69.1%) and del17p (83.3% vs 53.8%) with zanubrutinib, as were overall 12-mo progression-free survival (PFS) (94.9% vs 84.0%; Figure) and overall survival rates (97.0% vs 92.7%). The rate of atrial fibrillation/flutter, a pre-specified safety endpoint, was significantly lower with zanubrutinib vs ibrutinib (2.5% vs 10.1%, 2-sided P=0.0014, compared with pre-specified alpha of 0.0099 for interim analysis). Rates of major bleeding (2.9% vs 3.9%) and adverse events leading to discontinuation (7.8% vs 13.0%) or death (3.9% vs 5.8%) were also lower with zanubrutinib. Rate of neutropenia was higher with zanubrutinib (28.4% vs 21.7%), while grade ≥3 infections were lower with zanubrutinib (12.7% vs 17.9%).

Conclusion: In this interim analysis of a randomized, phase 3 ALPINE study in pts with R/R CLL/SLL, zanubrutinib was shown to have a superior response rate, an improved PFS, and a lower rate of atrial fibrillation/flutter compared with ibrutinib. These data confirm that more selective BTK inhibition, with more complete and sustained BTK occupancy, results in improved efficacy and safety outcomes.

Funding/Acknowledgement Statement: This study was sponsored by BeiGene, Ltd. Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and funded by the study sponsor.

Keyword: Chronic lymphocytic leukemia, Small lymphocytic lymphoma, BTK inhibitor, Refractory, Relapsed

Figure. PFS by Investigator Assessment



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.

OP02-3

CD 19 chimeric antigen receptor T cell therapy for relapsed/refractory B-cell lymphoid malignancies: the efficacies and safeties of tisa-cel in the real world

Sang Eun Yoon[1], Junhun Cho[2], Kyungmin Huh[3], Ju-Hong Min[4], Hyun-Young Kim[5], Eun-Suk Kang[5], Duck Cho[5], Jong Wook Chang[6], Seok Jin Kim[1,7] and Won Seog Kim[1,7*]

[1] Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[2] Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[3] Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[4] Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[5] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[6] Cell & Gene Therapy Institute, Samsung Medical Center, Korea
[7] Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University School of Medicine, Korea

Background: Chimeric antigen receptor (CAR) T-cell therapy, which modifies the host's T cells to recognize and fight cancer cells, has changed the therapeutic strategies for patients with relapsed or refractory (R/R) B-cell lymphoid malignancies, including diffuse large B-cell lymphoma (DLBCL) and acute B-cell lymphoblastic leukemia/lymphoma (B-ALL). Thus, FDA has approved three second-generation CD19 CAR-T cells (axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel) for R/R B-cell lymphoid malignancies as a salvage treatment option. Since tisa-cel was approved for the treat-

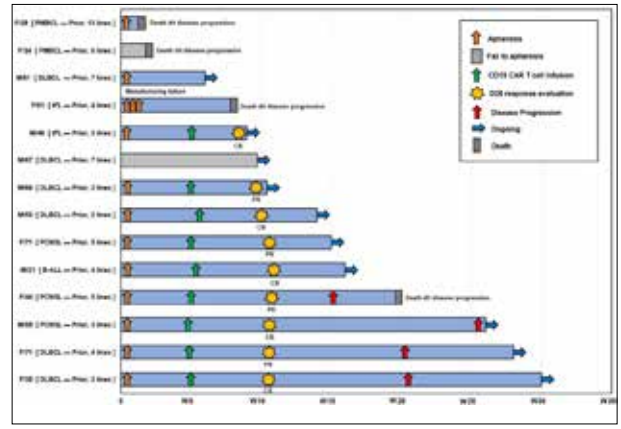
ment of adult patients with R/R DLBCL and pediatric/adolescent patients with R/R B-ALL in 2021, our center has used tisa-cel as a salvage treatment for patients with R/R DLBCL and B-ALL. Herein, we reported our experience with tisa-cel as the first Korean real-world data.

Method: In 2021, a total of 14 patients were enrolled into the tisa-cel treatment registry and their pre-treatment clinical and laboratory characteristics were analyzed. After apheresis, bridging chemotherapy was allowed and the lymphocyte depletion chemothertapy consisting of fludarabine and cyclophosphamide was done prior to the infusion of tis-cel. The first response evaluation was done at 28 days after CAR T-cell infusion, according to the Lugano recommendation for response assessment. In addition, the grading of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) was measured and managed through the American Society for Transplantation and Cellular Therapy (ASTCT) criteria. The data cutoff date was January 10th, 2022, and the median follow-up duration was 15 weeks (95% Confidence Interval: 11.8-18.2 weeks).

Results: The clinical characteristics of 14 patients, 9 patients received tisa-cel infusion whereas five patients could not receive tisa-cel because two patients did not undergo apheresis due to disease progression and three patients failed to manufacture after apheresis. The number of patients aged over 60 was 6 (42.9%), and the proportion between males and females was equal (50% versus 50%). Three (21.4%) patients estimated ECOG PS 2. Seven (50%) patients showed anemia, 3 (21.4%) showed thrombocytopenia, and 10 (71.4%) patients did not recover neutropenia until apheresis. Furthermore, the majority of patients (n = 11, 78.6%) presented over 300/uL of lymphocyte count. 64.3% (n = 9) of patients presented elevated LDH levels. Although hyperferritinemia and high CRP levels showed four patients (28.6%), it was not related to active or chronic infection issues. Of 14 patients, 42.9% (n = 6) had RR-DLBCL, 14.3% (n = 2) had RR-PMBCL, and 21.5% (n = 3) showed RR-PCNSL or secondary CNS lymphoma. Moreover, two patients had transformed follicular lymphoma (tFL), and another diagnosed RR-B-ALL. With a median of 4 prior lines of therapy and a range between 2 and 13 therapies, 42.9% of patients (n = 6) were receiving five or over prior lines of therapy. Among the infused patients (n = 9), treatment lines were median 3 (range 2-5). Furthermore, five patients (35.7%) underwent autologous stem cell transplantation (Auto-SCT), and a patient received allogeneic stem cell transplantation (Allo-SCT). Overall time duration from apheresis to tisa-cel infusion was estimated at the median of 35 days (range 31-41). After apheresis, six patients underwent bridge chemotherapies due to disease control during a long manufacturing time, such as rituximab plus bendamustine with or without polatuzumab (n = 3), lenalidomide (n = 1), ibrutinib (n = 1), and intrathecal methotrexate (n = 1). Finally, nine patients received CD19 CAR-T cells, which succeeded in manufacturing, and the median cell doses were 3.0 ×108 cells/kg (range, 1.4×108 to 3.9 ×108 cells/kg). At 28 days, the response rate was 100% (5CR, 4PR). Moreover, at the median follow-up 15 weeks, the response rate was 55.5% (3CR, 2PR). Among five patients who achieved CR or PR, a patient diagnosed RR-B-ALL showed MRD negative in bone marrow aspiration. The median time to response (DOR) was 17 weeks (95% CI 15.4-18.6). Of 3 patients who experienced disease progression at 15 weeks after CAR-T cell infusion, 2 received local radiotherapy, and 1 received pembrolizumab as the salvage line. Another patient experienced disease progression at ten weeks and passed away. In terms of safety, 75% (n = 6) showed all grade CRS, and 25% presented grade 3 CRS. Grade 3/4 ICANS were identified 25%. Two patients required admission to the intensive care unit due to grade 3 ICANS with CRS. Of them, one recovered within three days after administration of tocilizumab and steroids. However, in another ICU admission case with RR-PCNSL, it was ambiguous to separate neutropenic fever, sepsis, disease progression, or ICANS with CRS. Thus, all supportive care such as antibiotics, tocilizumab, steroids, inotropic, and ventilator care was provided for the patient. Although the patient recovered after 10 days and achieved PR at day 28 response evaluation, eventually, she passed away due to disease progression at the 20 weeks. All patients recovered after receiving tocilizumab (n =6, 75%) and steroids (n = 2, 25%) according to ASTCT guidelines.

Conclusion: We evaluated the real-world efficacies and safeties of the patients treated with tisa-cel. The patients who received tisa-cel showed about a 100% response rate at 28 days after infusion, and the response rate at the median follow-up date was 50%. In addition, there were no new safety issues observed compared to previous data. Even though our results had too small cases with a short follow-up duration, tisa-cel showed excellent treatment outcomes and manageable toxicities. Thus, we recommend that tisa-cel is an encouraging treatment option for patients with relapsed/refractory B-cell lymphoid malignancies.

Keyword: Diffuse large B-cell lymphoma, Tisagenleucel, Chimeric antigen receptor T cell



OP02-4

Long-term real-world experience of Castleman's disease treatment

Gi-June Min[1], Seok-Goo Cho[1*], Young-Woo Jeon[2], Tong Yoon Kim[1], Daehun Kwag[1], Jong Hyuk Lee[1], Joonyeop Lee[1], Sung-Soo Park[1], Silvia Park[1], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Seok Lee[1], Hee-Je Kim[1], Chang-Ki Min[1] and Jong Wook Lee[1]

[1] Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea

[2] Department of Hematology, Yeouido St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, 10, 63-ro, Yeongdeungpo-gu, Seoul, Korea

Background: Castleman disease (CD) is a refractory lymphoproliferative disorder of unknown origin, and it presents as unicentric CD (UCD; localized form) or multicentric CD (MCD; systemic form). CD can also be pathologically classified into hyaline-vascular (HV), plasma cell (PC), and mixed phenotypes. The clinical manifestations and management strategies of CD are distinct and depend on the clinical and pathological subtypes. Unlike UCD, MCD presents with multiple peripheral lymphadenopathies and systemic symptoms of fever, night sweats, weight loss, and fatigue, and its manifestation essentially results from proinflammatory hypercytokinemia of interleukin-6 (IL-6). Patients with human immunodeficiency virus (HIV)-negative and human herpesvirus type 8 (HHV-8)-negative MCD with unknown etiology and pathophysiology are considered to have idiopathic MCD (iMCD). This study presents real-world experience-based long-term clinical outcomes of various CD subtypes.

Method: In this retrospective study, we enrolled 88 patients diagnosed with CD (34 with UCD and 54 with MCD) from January 2006 to December 2020 at St Mary's Hematology Hospital, Seoul, South Korea. The median patient age was 44 years (range, 18–84 years), and there was a slight predominance of female patients (53.4%). Among the patients, 51.1% (n=45) were pathologically classified as having the HV type, 44.3% (n=39) were classified as having the PC type, and 4.5% (n=4) were classified as having the mixed type. Two patients were identified as HHV-8 positive, but no HIV-positive MCD patients were enrolled. For treatment, surgical resection for an isolated nodal or extranodal mass; radiotherapy; steroid pulse therapy; cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like chemotherapy; or intravenous siltuximab therapy (11 mg/kg at a 3-week interval) was considered, except in 9 patients who either had no presenting symptoms (n=4) or refused treatment (n=5). Before 2015, siltuximab was unavailable for MCD treatment in Korea. Therefore, CHOP-like chemotherapy was usually applied in severe cases. Treatment response was evaluated according to consensus treatment guidelines (Blood. 2018;132(20):2115-2124).

Results: During a median follow-up of 53.5 months (range, 4.0–192.0 months), the overall survival rate was 90.2% (95% confidence interval [CI], 77.1–96.0). In our cohort, there was no significant difference in survival outcomes between UCD and MCD (100% vs. 85.8%, p=0.073). Among the 34 patients with UCD, 32 received initial surgical resection of solitary lymphadenopathy for diagnosis and treatment, and all of them achieved complete remission (CR). The remaining patients were diagnosed with a core-needle biopsy and underwent long-term observation due to a lack of systemic symptoms and laboratory abnormalities, despite stable disease (SD) of a nodal mass on computed tomography (CT). The treatment strategies for the 54 patients with MCD were heterogeneous as follows: observation (n=7), radiotherapy (n=3), steroid pulse (n=3), or CHOP-like regimen-based chemotherapy (n=4) only, and siltuximab treatment (n=27). Of seven patients who did not receive treatment, 2 showed partial remission (PR), and 5 showed SD. All patients who received radiotherapy (presented with minimal symptoms and localized lymphadenopathies) achieved CR. Among 18 patients who received steroid pulse therapy, 7, 4, and 7 showed PR, SD, and PD, respectively. Moreover, 5 of the 7 PD patients received second-line siltuximab therapy, but the remaining two died because of combined septic shock. Among 11 patients treated with a CHOP-like regimen, 4 achieved CR, and 7 received second-line siltuximab therapy due to disease progression. Siltuximab treatment was used in MCD patients with systemic symptoms and laboratory abnormalities. Among them, 55.6% (n=15) were treated with siltuximab as first-line therapy, and 44.4% (n=12) were treated as second-line therapy after previous chemotherapy (n=7) or steroid pulse therapy (n=5). On average, improvements in clinical symptoms, laboratory parameters, and radiologic parameters of MCD among responders were observed after 1, 3, and 18 cycles of siltuximab treatment, respectively. Siltuximab demonstrated a favorable safety profile, and prolonged treatment (median, 39 cycles; range, 2–173 cycles) was well tolerated. In univariate analysis, old age (≥60 years), poor performance status (ECOG 2), and splenomegaly were risk factors related to MCD patient survival. Prognostic factors showing clinical significance in univariate analysis were subjected to multivariate analysis using a Cox regression model. As a result, age ≥60 years and splenomegaly were significantly affected survival.

Conclusion: In this retrospective study with a relatively large sample consisting of Korean patients, we identified the clinical characteristics and prognosis of UCD and MCD patients. UCD patients had favorable outcomes with surgical resection of a solitary mass, and in MCD patients, old age and splenomegaly were identified as independent prognostic factors. Further well-designed prospective studies are needed to confirm the prognostic factors and investigate the optimal treatment for CD patients.

Keyword: Castleman disease, Interleukin-6, Age, Splenomegaly, Siltuximab, Steroid

OP02-5

Clinical analysis of modified HLH-04 regimen for the treatment of childhood hemophagocytic lymphohistiocytosis

Honghao Ma, Rui Zhang* and Fenfen Cheng

Hematology Center, Beijing Children's Hospital, Capital Medical University, China

Background: Hemophagocytic lymphohistiocytosis (HLH) is a group of clinical syndromes triggered by the abnormal activation and proliferation of lymphocytes and monocyte-phagocyte system, and the release of a large number of inflammatory factors. It is mainly divided into primary and There are two major categories of secondary. HLH is a clinical acute and critical illness that seriously threatens the lives of children. The 5-year survival rate (overall survival, OS) of untreated children is less than 10%, so early diagnosis and treatment are needed. The application of etoposide (VP-16) is the first major breakthrough in the treatment of HLH, which works by clearing abnormally activated T cells. The currently commonly used HLH treatment regimens are the HLH-94 and HLH-04 regimens formulated by the International Tissue Cell Association, including VP-16, in addition to dexamethasone (Dex) and cyclosporin A (cyclosporin A, CsA) , And intrathecal injection of methotrexate (MTX). This program will increase the five-year survival rate of children to about 60%. Bone marrow suppression is one of the common adverse reactions of VP-16, which can lead to severe infection and even death in children. The long-term complication of VP16 is the secondary tumor. In the standard HLH-94/04 regimen, the conventional dosage of VP-16 is 150mg/m2, twice a week in the first and second weeks, the adverse reactions of VP-16 are dose-dependent, and chemotherapy in children is found in the clinic Severe bone marrow suppression is prone to occur in the 3rd week, and it is easy to merge with serious infection. Dex plays an important role in the treatment of HLH because of its suppression of the immune regulation function of T cells and its ability to penetrate the blood-brain barrier. However, Dex, as a long-acting and potent glucocorticoid, can cause adverse reactions such as secondary infections, hypertension, diabetes, and osteoporosis. Methylprednisolone is a medium-acting glucocorticoid, which also has a good anti-inflammatory effect. It has a fast onset, feasible shock therapy, and has less inhibitory effect on the hypothalamus-pituitary-adrenal axis [5]. The chemical structure of methylprednisolone has 8 hydrogen bonds and 3 methyl groups. It has good fat solubility and can pass through the blood-brain barrier. It has one less fluoride side chain than Dex. It has strong fat solubility and may be permeable to the blood-brain barrier. Better. CsA has strong immunosuppressive ability, but its onset time is slow, it needs to reach a certain blood concentration before it can take effect, and it has high toxicity, including nephrotoxicity, liver toxicity, neurotoxicity and cardiotoxicity. In order to reduce chemotherapy-related complications and mortality during the HLH-04 regimen chemotherapy, Beijing Children's Hospital has adopted the modified HLH-04 regimen to treat children with HLH since 2016. Now, we are analyzing the effects of children receiving the modified HLH-04 treatment at Beijing Children's Hospital. Clinical data to analyze the effectiveness and safety of the program.

Method: To retrospectively analyze the efficacy and prognosis of hemophagocytic lymphohistiocytosis (HLH) in children treated with the modified HLH-04 regimen (reducing the dose and frequency of etoposide, using methylprednisolone instead of dexamethasone, and eliminating cyclosporine) admitted to the Hematology Oncology Center of Beijing Children's Hospital from January 2016 to December 2017. The efficacy and prognosis of HLH in children treated with methylprednisolone instead of dexamethasone and eliminating cyclosporine were analyzed in a historical control analysis with children previously treated with the standard HLH-04 regimen.

Results: A total of 110 children with HLH were treated with the modified HLH-04 regimen, with a median age of 2.25 years (0.1-13.8 years), 65 males and 45 females (male-to-female ratio 1.56:1), 85 survived and 25 died, and the overall survival rates (overall survival, OS) at 2 months and 3 years were 83.2% and 75.3%, respectively. The efficacy was comparable to that of the HLH-04 regimen (2-month: 83.2% vs. 76.2%, P=0.198; 3-year: 75.3% vs. 54.1%, P=0.059). Bone marrow suppression occurred mainly in the first 3 weeks, with a lower incidence than in the HLH-04 regimen (47.3% vs. 62.7%, P=0.027). Death was mainly due to multiple organ failure (72%) due to progression of the primary disease, with post-chemotherapy myelosuppression and secondary infection as its main complications. Compared to the HLH-04 regimen, the rate of fungal infections was lower (3.6% vs. 13.7%, P = 0.008) and fewer children died from post-chemotherapy adverse effects (8.0% vs. 30.3%, P = 0.038).

Conclusion: The modified HLH-04 regimen reduced the chemotherapy dose, had no worse overall efficacy than the HLH-04 regimen, and significantly reduced the rate of chemotherapy-associated fungal infections and mortality.

Keyword: Hemophagocytic lymphohistiocytosis, Children, Modified HLH-04 protocol, Efficacy

OP03-1

Clinical-biochemical screening and genetic analysis of suspected inherited iron metabolism related anaemias using targeted NGS approach

Pankaj Sharma[1], Amita Trehan[1], Minu Singh[1], Reena Das[2] and Prateek Bhatia[1*]

[1] Pediatrics,PGIMER, India

[2] Hematology, PGIMER, India

Background: Inherited iron metabolism related anaemias are a heterogeneous group of disorders usually characterized by microcytic hypochromic anaemia with atypical iron profile and mutations in genes related with iron absorption, transport, utilization and storage in body. In current study, we carried out structured genetic analysis of a cohort of suspected URIDA and congenital sideroblastic anaemia cases using targeted NGS panel-based approach.

Method: We prospectively screened around 291 cases of paediatric microcytic hypochromic anaemia over a period of two years (2019-2021) and enrolled a final cohort of 64 cases with normal HPLC, ESR, CRP, tTg, with clinical oral iron refractoriness or atypical iron profile (high ferritin and TSAT or low iron and normal-high ferritin) for genetic analysis. Complete iron profile testing (S.iron, ferritin, TIBC and TSAT) was performed by chemiluminescent immunoassay on EM-200 analyser. Hepcidin-25 was performed using Hepcidin bioactive ELISA kits. Targeted NGS based analysis was performed using a custom panel of 27 genes related with iron metabolism and sideroblastic anaemia phenotype on an Ion Torrent S5 platform. Bioinformatics analysis was performed using Ion Torrent Suite and Ion Reporter software.

Results: The cases were divided into two cohorts: iron refractoriness (n=29) and atypical iron profile (35). In iron refractoriness cohort the mean age was 6 years, mean HB was 6.8gm/dl and 54 % patients had no response to iron supplements while 46% had minimal response. On NGS panel only one patient had a compound heterozygous pathogenic mutation consistent with classical IRIDA, 2 had haploinsufficient/hetrozygous form of IRIDA, while 8 cases had multiple SNP's and 14 cases had SNP's with splice site SNP in the TMPRSS6 gene. In 2 cases a non-IRIDA defect was unmasked with one having SLC19A2 and another LARS2 mutations. Two cases were negative for any mutation or SNP in TMPRSS6 gene. On a case control study we showed the presence of multiple SNPs plus splice site INDEL to be associated with oral iron refractoriness with a high odds ratio of 6.48 and a significant p-value. In atypical iron profile cohort the mean age was 4 years (0.4-15 years) with M:F ratio 4:1. The mean Hb 7.3gm/dl (4.8-10.2) with 9 having severe anaemia (<7gm/dl), 2 mild and 20 moderate (7-10gm/dl). 9 were transfusion dependent. 5 cases had syndromic presentation and one had family history of recurrent foetal loss. 13/15 cases had ringed siderobalsts (4-70%) on BM examination. Iron profile revealed high serum iron, ferritin and high TSAT disproportionate to transfusions in 15 cases, while rest 16 had low-normal serum iron and high ferritins without obvious secondary cause. On NGS analysis, 9/13 (69%) cases with RS had mutations; 5 (55%) had ALAS2, 2 in SLC25A38 gene and 1 each in SLC19A2 and FECH gene. In rest 18 cases, 5 (29%) revealed mutations in monogenic/digenic combination with compound heterozygous STEAP-3 related inherited anaemia in 1, BMP-6 related isolated hyperferritinaemia in 2 cases, a STEAP-3 and BMP-6 digenic mutation in 1 case and a novel mutation in mitoferrin-2 gene in 1 case. In 16 cases where no mutation could be identified in targeted NGS, we performed whole exome sequencing. WES analysis revealed pathogenic mutation in 5 cases in non-iron metabolism related genes which can have heterogeneous clinical overlap with iron related disorders

Conclusion: A targeted NGS- Iron related Gene Panel evaluation is must in all cases of URIDA and Atypical Iron with RS as the frequency of picking up a mutation/deleterious SNP is high including unmasking of a non-URIDA defect in upto 7% cases. However for Atypical Iron cases without RS/Bone marrow evaluation or other systemic features- A WES Could be the preferred genetic test upfront considering diverse heterogeneity of iron defects and overlap with other systemic Mendelian disorders

Keyword: IRIDA, NGS, Sideroblastic Anaemia, IRIDA, Hepcidin, Rare-disorders

OP03-2

Comparison of clinical features, genetic alterations, and outcomes in patients with prefibrotic, overt primary myelofibrosis, and secondary myelofibrosis

Tong Yoon Kim, Sung-Eun Lee*, Daehun Kwag, Jong-Hyuk Lee, Joonyeop Lee, Gi June Min, Sung-Soo Park, Silvia Park, Jae-Ho Yoon, Byung-Sik Cho, Ki-Seong Eom, Yoo-Jin Kim, Seok Lee, Chang-Ki Min, Hee-Je Kim, Seok-Goo Cho and Jong Wook Lee

Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: The Philadelphia-negative myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders characterized by an overproduction of differentiated hematopoietic cells and include three major subcategories i.e., polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). PV and ET can evolve to secondary forms of MF, known as postpolycythemia vera (PPV-MF) and postessential thrombocythemia (PET-MF) myelofibrosis, as part of their natural history. Moreover, the 2016 WHO classification dictated prefibrotic PMF (pre-PMF) and overt PMF. However, the clinical, prognostic, and molecular characteristics of secondary MF (2nd-MF) and moreover, current information about differences between pre-PMF and overt PMF are quite scanty. To

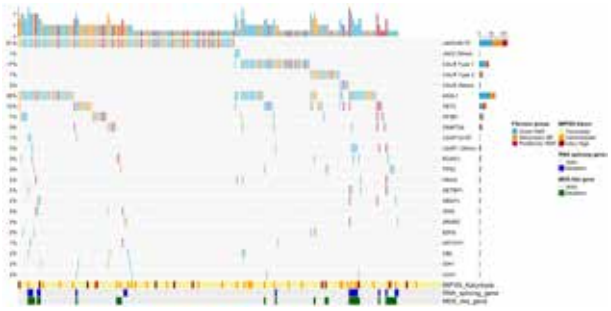
assess the importance of distinguishing them in the clinical practice, we evaluated the clinical features, genetic alterations, and outcomes in patients with prefibrotic, overt PMF, and 2nd-MF

Method: A total of 229 patients who diagnosed with MF between June 2017 and June 2021 and had genetic profile using NGS were included in this study. Progression is defined as leukemic transformation in secondary MF and overt PMF groups, while in Pre-PMF group, progression defined as the time to overt PMF or leukemic transformation.

Results: Among 229 patients, 67 (29%), 122 (53%), and 40 (18%) patients were confirmed by 2nd-MF, overt PMF, and Pre-PMF, respectively. We analyzed 90 gene mutations and cytogenetics. JAK2V617F mutation was differently distributed in 2nd-MF and PMF groups (64.2% and 44.3%, P = 0.014), while CALR and MPL were similarly distributed. With regard to nondriver mutations, ASXL1 mutation showed differences in PMF versus 2nd-MF (36.1% vs 28.4%, P = 0.02) and in PMF versus Pre-PMF (36.1% versus 7.5%, P = 0.001). After a median follow-up of 2.7 years (range, 0.2 to 19.9 years) for survivors, 3-year overall survival were 91.5%, 85.3%, and 94.8% in 2nd-MF, overt PMF, and Pre-PMF groups. (P = 0.026). Scoring systems including IPSS, DIPSS, DIPSS-plus, MIPSS70 MIPSS70-ver2, GIPSSS, and MYSEC-PM could discriminate the overall survival in PMF but not in 2nd-MF and Pre-PMF. On the other hand, when we applied the molecular grouping by SF3B1 wild-type and SRSF2 or RUNX1 or U2AF1 or ASXL1 or TP53 mutations into 2nd-MF and Pre-PMF, PFS could discriminated by this mutant group in PMF (P <0.001), 2nd-MF (P = 0.028) and pre-PMF (P = 0.047). In addition, this molecular grouping was associated with poor progression-free survival for Pre-PMF (P = 0.047).

Conclusion: We showed that current risk stratifications are still important for predicting outcome in patients with overt PMF. However, a widely known genetic scoring system in overt PMF could not predict in 2nd-MF and Pre-PMF. In this context, we suggested the mutation profiles which could be widely applied in MF patients including Pre-PMF. Further studies are needed to identify accurate characteristics in patients with prefibrotic, overt PMF, and 2nd-MF.

Keyword: Genetic alterations, Prefibrotic primary myelofibrosis, Overt primary myelofibrosis, Secondary myelofibrosis



OP03-3

Flow cytometry of body fluid specimens: diagnostic value in hematologic malignancy

Smeeta G[1*], Nupur Das[1], Ritu Gupta[2], Sanjeev Kumar Gupta[3], Sandeep Rai[4], Saroj Singh[4], Ranjit Kumar Sahoo[5], Sameer Bakhshi[6], Atul Sharma[6] And Lalit Kumar[6]

[1] Laboratory Oncology Unit, Dr B.R. Ambedkar IRCH, All India Institute of Medical Sciences, New Delhi, Assistant Professor, India

[2] Laboratory Oncology Unit, Dr B.R. Ambedkar IRCH, All India Institute of Medical Sciences, New Delhi, Professor, India

[3] Laboratory Oncology Unit, Dr B.R. Ambedkar IRCH, All India Institute of Medical Sciences, New Delhi, Additional Professor, India

[4] Laboratory Oncology Unit, Dr B.R. Ambedkar IRCH, All India Institute of Medical Sciences, New Delhi, Technical Officer, India

[5] Medical Oncology, Dr B.R. Ambedkar IRCH, All India Institute of Medical Sciences, New Delhi, Additional Professor, India

[6] Medical Oncology, Dr B.R. Ambedkar IRCH, All India Institute of Medical Sciences, New Delhi, Professor, India

Background: Multiparametric flow cytometric immunophenotyping (FCMI) is a powerful diagnostic tool for detecting hematologic malignancies in variety of sample specimens as peripheral blood, bone marrow, body fluids, fine needle aspiration samples and solid tissues (e.g. lymph node or small tissue section). FCMI in body fluids is a rapid, reproducible, sensitive, and quantitative method for immunophenotyping of cells and its in addition to morphological analysis is feasible and rewarding in relation to the diagnostic yield, especially when combined with other ancillary techniques, such as immunohistochemical and molecular methods. In this study we evaluate the diagnostic yield of flow cytometry in detecting hematologic malignancies in body fluid specimens of patients for suspected involvement.

Method: We reviewed flowcytometric immunophenotyping results of body fluid submitted to our flow cytometry laboratory including cerebrospinal fluid (CSF), pleural fluid (PF) and ascitic fluid (AF). All the samples were collected in sterile container and processed within 4 hours as per standard operative procedures followed in our laboratory. Immunophenotyping was done using 3 laser, 10 colour Gallios flow cytometer from Beckman and Coulter, La Brea, CA. Panel of antibodies for diagnosis included: CD45, CD34, cMPO, CD13, CD33, CD117, CD123, CD64, CD14, CD11b, CD16, CD36, CD4, sCD3, cCD3, CD2, CD5, CD7, CD8, CD10, CD1a, TdT, cCD79a, CD19, CD20, CD22, FMC7, CD23, CD200, CD38, CD56, CD57, CD94, CD138, CD81, IgM, surface immunoglobulin light chain (kappa, lambda) and TCR receptors (alpha beta and gamma delta).

Results: A total of 171 samples with suspected hematological malignancies were evaluated, of which FCMI detected 68 positive (CSF:

38, PF: 25, AF: 5). Five cases showed indeterminate results and 2 cases were failed for adequacy. On FCMI, spectrum of cases included: 37 cases of B cell malignancies, 21 cases of T cell malignancies and 10 cases of myeloid malignancies (table 1). Diagnosis of nine B-NHL (2 high grade and 7 low grade B-NHL) and two T-NHL cases were not further classified on flowcytometry, out of which final diagnosis was confirmed on 9 cases on corresponding histopathological correlation. Out of 30 non-leukemic cases, FCMI diagnosed the unknown primary without corresponding histopathology in 11 cases (4 T-LBL, 3 Burkitt lymphoma, 1 each of myeloid sarcoma, NK cell lymphoblastic lymphoma/leukemia and NK-T cell lymphoma). Ten cases (14.7%) had minimal involvement (<10% neoplastic cells on FCMI) were picked up which would have missed on morphology. Out of 17 B-ALL, 10 T-ALL and 5 AML cases with CSF involvement, 9 cases of B-ALL and 1 case each of T-ALL and AML had isolated CNS relapse.

Conclusion: FCMI is very useful both in the setting of a known disease and for unknown primary hematological malignancy diagnoses in body fluid specimens, permitting appropriate cancer staging and management. Diagnosis in body fluid samples in low volumes and cell contents specimens as CSF or cases with minimal involvement by neoplastic cells or in cases of indolent lymphoma subtypes may be challenging on morphological evaluation. Thus incorporation of FCMI into routine cytopathologic diagnostics is useful in such scenario to reach final diagnosis.

Keyword: Flow cytometric immunophenotyping, Hematological malignancies, Cerebrospinal fluid, Pleural fluid, Ascitic fluid

Table 1: Distribution of cases on flow cytometric immunophenotyping

Categories	Types	No of Cases
B cell	B-acute lymphoblastic lymphoma	17
	Chronic lymphocytic leukemia	3
	Burkitt lymphoma	3
	Mantle cell lymphoma	2
	Follicular lymphoma	1
	Primary mediastinal B cell lymphoma	1
	Plasmablastic lymphoma	1
	B-non Hodgkins lymphoma(high grade)	3
	B- non Hodgkins lymphoma	6
T and NK Cell	T- acute lymphoblastic lymphoma	10
	T-lymphoblastic lymphoma	7
	T- non Hodgkins lymphoma	2
	NK cell lymphoblastic lymphoma/leukemia	1
	NK-T cell lymphoma	1
MYELOID	Acute myeloid leukemia	5
	Isolated Myeloid Sarcoma	2
	Blastic plasmacytoid dendritic cell neoplasm	1
	CML-blast crisis (myeloid)	1
	CML- blast crisis (B-lymphoid)	1

OP03-4

Single-cell analysis of multiple myelomas refines bortezomib treatment responsiveness

Sung-Soo Park[2], Seung-Hyun Jung[1], Ji-Young Lim[2], Seon Yong Sohn[1], Jeongeun Si[3], Sug Hyung Lee[4], Yeun-Jun Chung[5] and Chang-Ki Min[2*]

[1] Department of Biochemistry, College of Medicine, Catholic University of Korea, Korea
[2] Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, Catholic University of Korea, Korea
[3] Precision Medicine Research Center/IRCGP, College of Medicine, Catholic University of Korea, Korea
[4] Department of Pathology, College of Medicine, Catholic University of Korea, Korea
[5] Department of Microbiology, College of Medicine, Catholic University of Korea, Korea

Background: Both the tumor and tumor microenvironment (TME) are crucial for pathogenesis and chemotherapy resistance in multiple myeloma (MM). Bortezomib, commonly used for MM treatment, works on both MM and TME cells but innate and acquired resistance may develop.

Method: By single-cell RNA-sequencing (scRNA-seq), we investigated bone marrow aspirates of 18 treatment-naïve MM patients who later received bortezomib-based treatments. Twelve plasma cell populations (normal and malignant) and TME cells were identified. Suboptimal responders (SORs) exhibited higher copy number alteration burdens than optimal responders (ORs). Forty-four differentially expressed genes for SORs based on scRNA-seq data were further analyzed in an independent cohort of 90 treatment-naïve MMs, where 24 genes were validated.

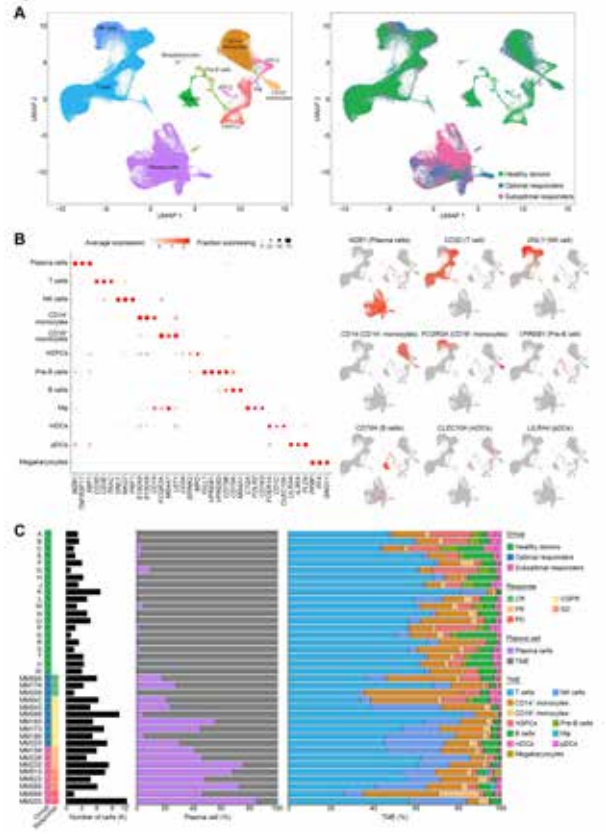
Results: A combined model of three clinical variables (older age, low absolute lymphocyte count, and no autologous stem cell transplantation) and 24 genes were associated with bortezomib responsiveness and poor prognosis. In T cells, cytotoxic memory, proliferating, and dysfunctional subsets were significantly enriched in SORs. Moreover, we identified three monocyte subsets associated with bortezomib responsiveness and an MM-specific NK cell trajectory that ended with an MM-specific subset. The scRNA-seq predicted interaction of GAS6-MERTK, ALCAM-CD6, and BAG6-NCR gene networks. Of note, tumor cells from ORs and SORs were the most prominent sources of ALCAM on effector T cells and BAG6 on NK cells, respectively.

Conclusion: Our study identified cellular subsets, gene signatures, and interactions of tumor and TME for bortezomib responsiveness, indicating that single-cell markers in both tumor and TME besides

clinical variables are essential for predicting treatment responsiveness in MM.

Keyword: Multiple myeloma, Bortezomib, Single-cell RNA-sequencing, Drug response prediction, Bone marrow microenvironment

Figure 1



OP03-5

Empagliflozin modulates CD4+ T Cell differentiation via metabolic reprogramming in immune thrombocytopenia

Qin Jing

Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong university, China

Background: Immune thrombocytopenia is an acquired autoimmune disease, in which the imbalance of T cell subsets plays the central role in the pathogenesis. Since T cells highly depend on metabolism for their function, we hypothesized that the dysfunction of T cells may be due to the impairment of metabolism within T cells. Empagliflozin, a sodium-glucose cotransporter 2 inhibitor, has been shown effects on other cells beyond glucose-lowering. However, the effects of empagliflozin on T cells remain unknown. We aim to explore the effect of SGLT2 inhibitor-empagliflozin on the CD4+ T cells differentiation in ITP patients.

Method: (1) Flow cytometry was performed to compare the proportion of CD4+ subsets after empagliflozin treatment. (2) Seahorse assay was performed to measure the glycolysis and oxidative phosphorylation. (3) Quantitative real-time PCR (qRT-PCR) was used to confirm the metabolic result by measure the mRNA expression of glycolysis-related genes. (4) Western blotting was made to test protein expression. (5) The active ITP mice model was used to confirm the results.

Results: Our results demonstrated for the first time that the increased glycolysis in T cells resulted in the imbalanced T cell population, while empagliflozin can affect CD4+ T subset differentiation by inhibiting Th1 and Th17 and increasing Tregs, and the regulation is through reversing the metabolic reprogramming of CD4+ T cells via inhibiting mTOR pathway. Empagliflozin effectively reversed thrombocytopenia by increasing platelet count significantly compared with the control group in active ITP mice model.

Conclusion: We proposed that empagliflozin could be used as a potential therapeutic option for ITP by modulating metabolic reprogramming in CD4+ T cells.

OP04-1

Expression pattern of non-homologous end joining DNA repair pathway genes and its clinical relevance in T-lineage acute lymphoblastic leukemia

Anita Chopra[1*], Sarita Kumari[1], Jay Singh[1], Mohit Arora[3], Shadab Ali[4], Avanish Kumar Pandey[1], Sameer Bakhshi[2], Jayanth Kumar Palanichamy[3], Atul Sharma[2], Pranay Tanwar[1] and Amar Ranjan Singh[1]

[1] Lab oncology unit, BRA IRCH, All India institute of medical sciences, India

[2] Department of medical oncology, All India institute of medical sciences, India

[3] Department of Biochemistry, All India institute of medical sciences, India

[4] Department of pulmonary medicine and sleep disorder, All India institute of medical sciences, India

Background: T-lineage acute lymphoblastic leukemia (T-ALL) is a molecularly heterogeneous malignancy characterized by transformation and differentiation blockage at different stages of T cell development. Efficient DNA repair has been shown to enable leukemic cells to survive the damaging effects of therapeutics, therefore, understanding of DNA repair alterations in leukemia may provide novel druggable targets and prognostic biomarkers. Notably, the developing T cells display variable abilities to repair DNA damage, therefore, it is important to determine whether the variable ability of T cells to repair DNA damage also translates into the corresponding subtype of T-ALL. Several components of different DNA repair pathways have been recently identified to play a critical role in ALL pathophysiology and drug resistance. However, the clinical significance of major DNA double-strand break repair pathway - Non-Homologous End Joining (NHEJ) in T-ALL remains to be studied in detail.

Method: In this prospective study, we assessed the gene expression pattern of 21 genes involved in the NHEJ pathway including six core genes, accessory genes, and other regulators such as MRN complex genes in 207 T-ALL patients. To determine the changes in the expression pattern of NHEJ genes during T-ALL, gene expression was assessed at different time points - at diagnosis, post-induction therapy (day 28), and at relapse. Quantitative real-time PCR was used to assess the expression of these genes and the data was normalized by using ABL1 as housekeeping gene. We further determined the association of NHEJ pathway gene expression pattern with clinical and molecular features.

Results: We observed higher expression of TOX, WRN, NHEJ1, APLF, TDP2, and reduced expression of XRCC4, POLL, PRKDC, APTX, PNKP, XRCC5, DCLRC1C, MRE11, XRCC6, NBN in diagnostic T-ALL samples compared to normal control bone marrow. Further, PRKDC, RAD50, and XRCC6 displayed lesser expression in the prednisolone resistant cases compared to the sensitive cases. In post-induction samples, XRCC4, POLL, WRN, POLM, APTX, PNKP, XRCC5, DCLRC1C, XRCC6, NBN, TDP1 exhibited higher expression and TOX, LIG4, MRE11 exhibited reduced expression compared to diagnostic samples. XRCC4, PRKDC, NHEJ1, PNKP, XRCC5, DCLRC1C, MRE11, XRCC6, NBN, and TDP1 exhibited higher expression in relapse samples compared to diagnostic samples. The clinical significance of the expression of NHEJ genes was also explored. Low expression of XRCC4, PRKDC, RAD50, XRCC5, XRCC6 and TDP1 gene was associated with immature immunophenotype (IPT) as compared to cortical and mature IPT. Patients with early thymic precursor (ETP-ALL) IPT more frequently had a lesser expression of XRCC4, PRKDC, RAD50, LIG4, APTX, MRE11, XRCC6 and TDP1 gene compared to other IPT groups. In diagnostic samples, higher XRCC4 expression was associated with better overall survival (OS) and even free survival (EFS). Additionally, low WRN expression was associated with poor EFS and relapse-free survival (RFS). Interestingly, high DCLRC1C expression was associated with favorable OS, EFS, and RFS.

Conclusion: We observed a distinct expression profile of NHEJ genes among different subtypes of T-ALL patients possibly explaining the different extents of DNA repair among patients with different immunological subtypes and in response to therapy. Interestingly, this depicted a clear change in the DNA repair responses in leukemia patients before and post chemotherapy. Gene expression pattern of NHEJ genes emerged as the predictor of OS, EFS and RFS in T-ALL patients that might be helpful in the improvement of the treatment outcome in T-ALL therapy.

Keyword: NHEJ, DNA repair, Leukemia, T-ALL

OP04-2

Interim analysis of the prospective phase II study of individualized 6-mercaptopurine dosing based on pharmacogenomics in childhood acute lymphoblastic leukemia

Hyery Kim[1], Jung Yoon Choi[2], Sunghan Kang[1], Kyung Nam Koh[1], Kyung Taek Hong[3], Hyoung Jin Kang[2], Kun Hee Yoo[3], Seungwon You[4], Yoomi Pari[4], Byung-Joo Min[4], Ju Han Kim[4] and Ho Joon Im[1*]

[1] Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea
[2] Pediatrics, Seoul National University College of Medicine, Korea
[3] Pediatrics, Sungkyunkwan University School of Medicine, Korea
[4] Biomedical Informatics, Seoul National University College of Medicine, Korea

Background: To improve treatment outcomes of childhood acute lymphoblastic leukemia (ALL), constant 6-mercaptopurine (6MP) dose titration is essential to maintain steady drug exposure, while minimizing myelosuppression. It is well known that there is a difference in the tolerable 6MP dose for each individual depending on the variants of NUDT15 and TPMT, which are pharmacogenomic markers related to 6MP. However, as the tolerated dose of 6MP for Asian patients is lower than that of Western patients, a study on whether the same guidelines can be applied is needed. The purpose of this study was to compare the incidence of side effects after applying the individually adjusted 6MP starting dose according to the results of NUDT15 and TPMT.

Method: This single-arm, multicenter prospective phase II study was conducted at three institutions in Korea. Patients undergoing maintenance therapy including 6MP enrolled. Whole exome sequencing was carried out with genomic DNA. During maintenance

phase, 6MP were administered at an individually adjusted starting dose base on each participant's NUDT15 and TPMT variants. Dose of daily 6MP was 50 mg/m2/day (original dose) for patients with both NUDT15 and TPMT wild-type or with TPMT heterozygote, 30 mg/m2/day for NUDT15 intermediate activity (NUDT15 variant allele heterozygous), 10 mg/m2/day for NUDT15 low activity (NUDT15 variant allele homozygote), and 10 mg/m2/day for 3 times a week for homozygous TPMT variants. As a primary and secondary endpoint, the duration of treatment discontinuation, the frequency of neutropenia, presence of neutropenic fever during maintenance therapy, and recurrence rate were compared with historical controls. As historical controls, data from 254 patients from 3 participating institutions who received maintenance therapy from 2001 to 2018 were used.

Results: Total 72 patients were enrolled from July 2019 until December 2021. There were 40 males, and 32 females. The median age of the patients was 6 years (range, 2~16 year). The immunophenotypes of ALL was B-ALL in 40 patients, T-ALL in 10, Mixed phenotype in 1, and unspecified ALL in 1 patient. This interim analysis was conducted on 52 patients who underwent maintenance therapy for at least 1 year after enrollment in this study. No patient had known pharmacogenetic variants in TPMT. The NUDT15 phenotypes based on diplotypes included normal activity (n=41), and intermediate activity (n=9), occurring in 78.8, and 17.3%, respectively. The number of days discontinued due to any toxicity during the 1st cycle of maintenance therapy was median 7 days (max 59 days) in all patients, and that of the study group was significantly shorter than in historical controls, with a median 0 day vs. 8 day (P=0.03). The frequency of neutropenia during the 1st cycle between two groups was not statistically different, however, among patients with NUDT15 intermediate activity, the frequency of neutropenia was significantly lower in the study group (P=0.03). The frequency of neutropenic fever (NF) and fever without neutropenia during the 1st cycle did not differ between the two groups. However, when patients with NUDT15 intermediate activity were analyzed, no fever occurred in the study group of 9 patients, while NF and fever occurred in 11 and 8 patients in the control group.

Conclusion: During maintenance therapy in Korean pediatric ALL patients, the individualized dosing of 6MP based on TPMT and NUDT15 genotypes significantly reduced treatment discontinuation. In particular, as a result of reducing the dose in patients with NUDT15 intermediate activity from 50 mg/m2/day to 30 mg/m2/day, febrile toxicity could be reduced compared to the historical controls. Through this study, we expect to provide appropriate pharmacogenomic dosing guidelines of 6MP for Korean ALL patients in the future.

Keyword: Acute lymphoblastic leukemia, Mercaptopurine, Pharmacogenetics, Korea, Guideline

OP04-3

Current treatment trends of infant leukemia in Korea based on a retrospective multicenter review: the Korean society of hematology, pediatric ALL working group

Seung Min Hahn[1], Hyery Kim[4], Kyung-Nam Koh[4], Ho Joon Im[4], Hee Young Joo[7], Keon Hee Yoo[7], Hong Hoe Koo[7], Kyung Taek Hong[2], Jung Yoon Choi[2], Jae Won Yoo[3], Jae Wook Lee[3], Nack-Gyun Chung[3], Bin Cho[3], Hee Jo Baek[5], Hoon Kook[5], Ju Kyung Hyun[6], Eu Jeen Yang[6], Young Tak Lim[6], Hyoung Jin Kang[2] and Chuhl Joo Lyu[1*]

[1] Pediatric Hematology and Oncology, Yonsei Cancer Center, Korea
[2] Pediatric Hematology and Oncology, Seoul National University Hospital, Korea
[3] Pediatric Hematology and Oncology, Catholic Medical Center, Korea
[4] Pediatric Hematology and Oncology, Asan Medical Center, Korea
[5] Pediatric Hematology and Oncology, Chonnam National University Hospital, Korea
[6] Pediatric Hematology and Oncology, Pusan National University Hospital, Korea
[7] Pediatric Hematology and Oncology, Samsung Medical Center, Korea

Background: Infant leukemia is a rare disease, accounting for about 2-5% of all childhood acute lymphoblastic leukemia (ALL), which shows distinct aspects compared with other acute leukemia. Clinically, its' aggressiveness shows frequent hyperleukocytosis, organomegaly and CNS involvement, biologically KMT2A gene rearrangements are mostly found, and infant age groups are most vulnerable patients therapeutically. Overall, prognosis outcome is relatively poor compared with leukemia in other pediatric age groups, resulting event free survival of ~50%, overall survival ~60% in recent international collaborative clinical trials. Because of its' rarity and unique characteristics, infant leukemia patients should be approached with risk stratification, exquisite treatment strategy, and delicate long-term follow up. Moreover, well designed prospective clinical trials could be recommended to increase outcome of the patients. In Korea, estimated infant leukemia new cases are 5~10/year. The Korean Society of Pediatric Hematology-Oncology (KSPHO) is recently planning a nationwide prospective clinical trial for infant leukemia. This retrospective review of Korean infant leukemia patients would be a cornerstone for a new start.

Method: On behalf of Pediatric ALL Working Party in the Korean Society of Hematology, we planned nationwide retrospective review of infant leukemia in Korea. Subjects who were diagnosed as ALL, undifferentiated leukemia or mixed phenotype acute leukemia with lymphoid predominance between January 1st, 2005 to June 30th, 2020 were enrolled. Enrolled subjects

must be under 1 years old at the time of leukemia diagnosis. Medical data was collected retrospectively from 7 major hospitals in Korea. (Asan medical center, Catholic medical center, Chonnam national university hospital, Pusan national university hospital, Samsung medical center, Seoul national university hospital, and Yonsei cancer center) Aim of the study is to describe current characteristics and treatment trends of infant leukemia in Korea, to find out prognostic factors in infant leukemia in Korean population, and finally to find out the role of hematopoietic stem cell transplantation (HSCT) in infant leukemia patients.

Results: Total 110 infant subjects were collected with median age of 183 days (range 1-363days) at diagnosis. 57 subjects (51.8%) were over 6 months old, and there were more females than males (57.3% vs. 42.7%). Median WBC count was 72,155/mm2 (range 770-1,009,000/mm2), 23.6% (n=26) subjects were diagnosed with more than 300,000 WBC counts at diagnosis. B-ALL composed 91.8% (n=101), there were a few T-ALL (n=5), undifferentiated (n=2), or mixed phenotype (n=2) cases. CNS involvement was found in 17.3% (n=19). KM2TA mutation was found in 75 cases (68.2%), and KMT2A-AFF1 was the most common type of mutation consisting of 52% (n-39) of KMT2A mutations. Treatment strategies varied from centers. Following high risk group ALL protocol with dose reduction method was most used (n=53, 48.2%) for infants, while 'COG' based protocol (n=28, 25.5%), 'Interfant trial' based protocol (n=26, 23.6%) were also commonly used. Post induction complete remission (CR) was achieved in 89.1% (n=98, with molecular CR in 41 cases), and among who entered consolidation (n=103), post consolidation remission was achieved in 83.7% (n=92, with molecular CR in 53 cases). HSCT was performed in 79 (71.8%) subjects. Radiotherapy (for either HSCT conditioning, cranio-spinal irradiation or testis) was used in 10 cases (9.1%). During median follow up duration of 3.66 years, there were 38 relapse cases (34.5%) and 46 deaths (41.8%). Treatment related mortality (TRM) consists of 60.9% of death cases (n=60.9%). Event (relapse or death) free survival (EFS) of the subjects was 41.8%, and overall survival (OS) of the patients was 48.0%. In Kalplan-meier survival analysis, transplanted patients and minimal residual disease (MRD) negative group after induction or consolidation showed significantly better survival rates. In univariate analysis, younger age at diagnosis and not achieving MRD after induction or consolidation seemed to impact higher mortality rate. However, in multivariable analysis, no variable was statistically meaningful to impact death.

Conclusion: Infant leukemia patients in Korea have shown lower survival rate and event free survival rate compared to other pediatric age group leukemia. Patients show higher TRM, and death in 50days after diagnosis was in 7, which takes 15.2% all expired cases. Treatment strategies were variable among the centers in the drug choice, and transplantation. HSCT and MRD status seemed important to patients however, there are limitations in interpretation. To improve OS and EFS of the patients, new nationwide prospective study for infant ALL should be prepared.

Keyword: Precursor cell lymphoblastic leukemia-lymphoma, Infant, hematoloietic stem cell transplantation

OP04-4

Prognostic impact of cytogenetic classification in adult all patients treated with intensive chemotherapy and allogeneic HCT -based post-remission therapy

Jae-Ho Yoon, Daehun Kwag, Jong-Hyuk Lee, Tong Yoon Kim, Joonyeop Lee, Gi June Min, Sung-Soo Park, Silvia Park, Sung-Eun Lee, Byung-Sik Cho, Ki-Seong Eom, Yoo-Jin Kim, Hee-Je Kim, Chang-Ki Min, Seok-Goo Cho, Jong Wook Lee and Seok Lee

Department of Hematology, Catholic Hematology Hospital and Leukemia Research Institute, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Cytogenetic risk-stratification at diagnosis has been one of the most useful tools for prognostic assessment in patients with acute lymphoblastic leukemia (ALL). Several stratification guidelines showed their ability to predict clinical outcomes, but the validation results in other cohorts have not been widely elucidated. First, we tried to validate several guidelines in our patients treated with intensive chemotherapy followed by post-remission therapy based on allogeneic hematopoietic cell transplantation (allo-HCT).

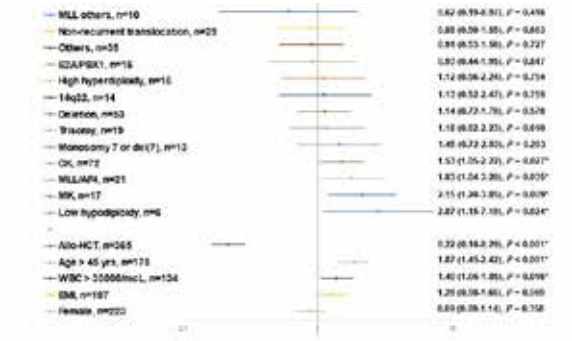
Method: From Jan 2009 to Dec 2020, 815 consecutive adult patients with ALL were treated with modified hyper-CVAD and high dose cytarabine plus mitoxantrone alternative chemotherapy. After 2-3 cycles of chemotherapy, we conducted allo-HCT for post-remission therapy in patients with available donor. In patients who had no donor or were unfit for allo-HCT, we finished treatment after 4 cycles of chemotherapy. For validation of cytogenetics, we excluded Philadelphia chromosome and used CIBMTR, modified MRC-ECOG, NCCN, NILG, and SWOG guidelines in 466 patients. Among them, the definition of complex karyotype (CK) was different especially in CIBMTR and NILG guidelines, which defined 3 or more abnormal cytogenetic aberrations rather than 5 or more. We also made our own classification according to the response to initial chemotherapy, relapse, and disease-free survival (DFS).

Results: In our data, MRC-ECOG and CIBMTR guidelines showed significant distinction between standard-risk and poor-risk karyotypes, while NCCN and SWOG showed lower distinctive power. We found CK with 3 or 4 aberrations was as poor as CK with 5 or more aberrations in terms of CR rate, relapse, and survival outcomes. We

applied CK with 3 or more aberrations to MRC-ECOG and got more significant distinctive power. Based on the CR rate and subsequent relapse, and poor DFS hazard ratio >1.4, we classified abnormal 7 (HR 1.45, p=0.293), CK≥3 (HR 1.53, p=0.027), MLL/AF4 (HR=1.83, p=0.035), monosomal karyotype (HR=2.15, p=0.009), and low hypodiploidy (HR=2.87, p=0.024) into the poor-risk group. All other karyotypes were classified into the standard-risk group. Estimated 5-year DFS of standard and poor-risk group was 47.2% and 29.0% (p < 0.001), and 5-year OS was 54.0% and 33.9% (p < 0.001), respectively. Among patients after allo-HCT in CR (n=356), CK≥3 (HR 1.59, p=0.087), abnormal 7 (HR 4.2, p=0.038), 14q32 (HR=2.66, p=0.086) and MLL/AF4 (HR=2.31, p=0.052) showed poor DFS.

Conclusion: Our data revealed poor DFS of CK with 3 or more aberrations, monosomal karyotype, MLL/AF4, abnormal 7 chromosome including monosomy 7 or del(7), and low hypodiploidy showing poor CR rate and frequent relapse. Along with the CIBMTR and MRC-ECOG guidelines, our own cytogenetic classification must be validated by another prospective cohort.

Keyword: Acute lymphoblastic leukemia, Karyotype, Cytogenetics, Allogeneic hematopoietic cell transplantation



CHH-ALL karyotype

Group	Karyotypes
Standard	**Normal karyotype** Aneuploid: High hyperdiploidy (51-65), Tetraploidy Recurrent translocations: E2A/PBX1, TEL/AML1 All other translocations All other MLL 14q32 abnormality All other karyotypes including trisomy, deletion
Poor	**Complex karyotype (≥ 3)** **Aneuploid: Low hypodiploidy (30 -39)** **Monosomal karyotype** **Chromosome 7 abnormalities: -7, Del 7** **Recurrent translocation: MLL/AF4**

OP04-5

DEFIFrance registry study: efficacy and safety of defibrotide for the treatment of severe/very severe VOD/SOS after hematopoietic cell transplantation

Mohamad Mohty[1], Didier Blaise[2], Régis Peffault de Latour[3], Marie Detrait[4], Hélène Labussière-Wallet[5], Delphine Lebon[6], Janet Pong[7], Kobby Asubonteng[8], Ibrahim Yakoub-Agha[9] and Jean-Hugues Dalle[10]

[1] Hôpital St Antoine, Sorbonne University, INSERM UMRs 938, Paris, France
[2] Institut Paoli-Calmettes, Aix Marseille Univ, CNRS, INSERM, CRCM, Marseille, France
[3] Hôpital Saint-Louis, Paris, France
[4] Service d'Hématologie, CHU de Nancy, Hôpitaux de Brabois, Nancy, France
[5] Service d'Hématologie, Hôpital Lyon Sud, Pierre Bénite, France
[6] CHU Amiens Picardie Hôpital, Amiens, France
[7] Jazz Pharmaceuticals, Oxford, UK
[8] Jazz Pharmaceuticals, Philadelphia, PA, USA
[9] CHU de Lille, Université Lille, INSERM U1286, Infinite, Lille, France
[10] Hôpital Robert-Debré, GHU APHP Nord and Université of Paris, Paris, France

Background: Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a life-threatening complication of hematopoietic cell transplantation (HCT) conditioning that may also develop after high-dose chemotherapy and may result in multiorgan failure (MOF). Defibrotide is approved for the treatment of severe hepatic VOD/SOS post-HCT in patients (pts) aged >1 month (mo) in the EU and the Republic of Korea. The DEFIFrance study collected real-world data on the efficacy and safety of defibrotide from HCT centers in France. This analysis presents final data on the primary study population: pts who received defibrotide treatment for severe/very severe VOD/SOS post-HCT.

Method: This post-marketing registry study collected retrospective and prospective real-world data on pts receiving defibrotide at 53 French HCT centers from July 2014 to March 2020. VOD/SOS diagnosis was at the investigator's discretion using standard criteria per local clinical practice. Disease severity was categorized using adult EBMT criteria in pts aged ≥18 years (y), and pts aged <18 y were retrospectively/prospectively categorized using pediatric EBMT criteria. The primary endpoints were Day 100 post-HCT survival and complete response (CR; total serum bilirubin <2 mg/dL and MOF resolution per the investigator) in pts with severe/very severe VOD/SOS. A secondary endpoint was the evaluation of treatment-emergent serious adverse events (SAEs) of interest: hemorrhage, coagulopathy, immunogenicity (allergy and hypersensitivity), septicemia, injection-site reaction, infection, and thromboembolic event, irrespective of relationship to treatment.

Results: Of 798 defibrotide-treated pts, 251 pts received defibrotide for severe/very severe VOD/SOS post-HCT (severe: 117 [47%]; very severe: 134 [53%]). Median age was 45 y (range: 0, 74) and 58 (23%) pts were <18 y of age. The most common primary diagnoses were AML (68 [27%]) and ALL (49 [20%]). Risk factors of interest were relapsed/refractory disease (137/251 [55%]), prior HCT (29/239 [12%]),

transaminase levels >2.5 ULN (43/250 [17%]), and prior treatment with gemtuzumab ozogamicin (17/251 [7%]). At diagnosis, 55/250 (22%) pts had anicteric VOD/SOS (bilirubin levels ≤2 mg/dL). Median (interquartile range) time from VOD/SOS diagnosis to defibrotide administration was 0 (0, 1) days.

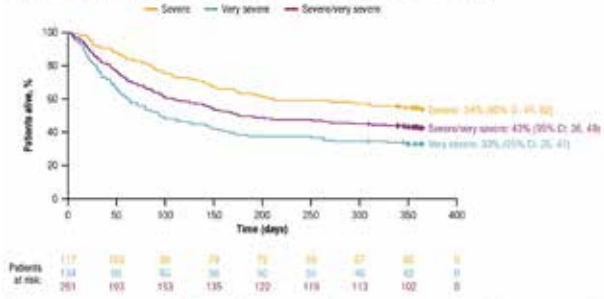
The Kaplan-Meier (KM)-estimated survival rates at Day 100, 6 mo, and 12 mo were higher for those with severe vs very severe disease (Figure). The KM-estimated CR rate by Day 100 in patients with severe/very severe VOD/SOS was 74% (95% CI: 66%, 81%); at Day 100, 137/251 (55%) pts were alive and in CR. A higher CR rate was observed by Day 100 in pts with severe (84% [95% CI: 74%, 92%]; n=117) vs very severe (63% [95% CI: 52%, 74%]; n=134) VOD/SOS.

Of 251 patients, treatment-emergent SAEs of interest occurred in 29%; the most common (≥2%) categories were infection (17%), hemorrhage (16%), and hypotension (2%). Mortality due to VOD/SOS at 12 mo was 15%.

Conclusion: The DEFIFrance study represents the largest collection of real-world data on post-registration use of defibrotide. The efficacy and safety observed in this study add to evidence from prior studies supporting the utility of defibrotide for treating pts with severe/very severe VOD/SOS post-HCT in the real world. Among pts receiving defibrotide for VOD/SOS post-HCT, outcomes were better in pts with severe vs very severe VOD/SOS, highlighting the importance of early VOD/SOS diagnosis and treatment, before pts reach the most severe stage of VOD/SOS.

Keyword: Clinical research, Biological therapies, Transplantation

Figure. KM-estimated 12-month post-HCT survival rate by VOD/SOS severity



	Severe/very severe VOD/SOS (n = 251)	Severe VOD/SOS (n = 117)	Very severe VOD/SOS (n = 134)
Day 100, % (95% CI)	61 (55, 67)	75 (66, 82)	49 (40, 57)
6 mo, % (95% CI)	50 (44, 56)	63 (54, 71)	38 (30, 46)
12 mo, % (95% CI)	43 (36, 49)	54 (44, 62)	33 (25, 41)

KM, Kaplan-Meier; HCT, hematopoietic cell transplantation; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; CI, confidence interval.

OP05-1

Causal role of iron status on anemia and on cardiometabolic outcomes among UK whites and Taiwanese Han Chinese using hemoglobin-genetic risk scores

Vanessa Joy Timoteo[1*], Kuang-Mao Chiang[2] and Wen-Harn Pan[1,2]

[1] National Yang Ming Chiao Tung University and Academia Sinica, Taiwan International Graduate Program in Molecular Medicine, Rep of China (Taiwan)

[2] Institute of Biomedical Sciences, Academia Sinica, Rep of China (Taiwan)

Background: Anemia due to iron deficiency remained to be a global public health problem, while a number of epidemiological studies have implicated elevated iron levels with higher risk and onset of cardiometabolic outcomes, presumably via the production of free radicals and oxidative stress. Genetic susceptibility and environmental factors were reported to cause both anemia and a number of cardiometabolic outcomes. However, there has been scarcity of data on the susceptibility genes of iron deficiency or excess, especially among non-European populations. It is also not completely clear whether variants of iron homeostasis genes causally influence the development of anemia and cardiometabolic syndrome (CMS). Therefore, our study elucidates the causal effects of iron deficiency and excess in predicting the risk for anemia and CMS, respectively. Hemoglobin (Hb) was chosen as a surrogate of iron status as it partially reflects the largest amount of functional iron in the body.

Method: We first conducted sex-specific two-stage genome-wide association studies of blood Hb concentration involving 60,518 Taiwanese Han Chinese (HC) of Taiwan Biobank and 269,451 European Whites of UK Biobank. Following an additive model in PLINK 1.9, multivariate linear regression was performed in all stages while adjusting for five-year age groups and genetic principal components as covariates. Correction for multiple tests was applied using a false discovery rate (FDR) adjustment. We then constructed ethnic-specific genetic risk scores (Hb-GRS) from the identified Hb-associated SNPs as instrumental variables for iron status. In our Mendelian randomization (MR) analyses, we conducted logistic regressions that adjusted for sex, age, and age-squared in order to investigate the causal associations between tertiles of Hb-GRS and various outcomes-of-interest.

Results: We identified consistent genome-wide Hb-association of SNPs (FDR-adjusted p <0.05) in TMPRSS6 (chr 22), ABO (chr 9), and PRKCE (chr 2) across sexes in both ethnic groups. Specific to the Taiwanese HC, the Hb-association with AXIN1, together with other loci near the chr 16 alpha-globin gene cluster, was found novel. On the other hand, majority of the Hb-associated SNPs among Europeans were identified along the chr 6 major histocompatibility complex region, which has established roles in immune system control. In our MR analyses, increasing Hb-GRS tertiles confer protection against anemia. We found evidence (p <0.05) to support causal as-

sociations between increasing tertiles of Hb-GRS and risks for CMS, hypertriglyceridemia, hypertension, diabetes mellitus, overweight and obesity, and hyperuricemia in both male and female Taiwanese HC groups. This corroborated the results of our observational association analyses. Our initial MR studies among European Whites similarly illustrated the causal role of elevated iron status on risks for self-reported hypertension, high diastolic blood pressure, and combined cases of hypertension.

Conclusion: Such findings confirm the causal role of elevated iron levels in the pathophysiology of metabolic dysfunctions in both ethnic groups investigated. Our future works will include additional MR studies among European Whites and the conduct of sensitivity analyses that will investigate whether the obtained MR estimates are being influenced by pleiotropic effects.

Keyword: Anemia, Cardiometabolic syndrome, Hemoglobin, Mendelian randomization study, Taiwanese Han Chinese, UK Whites

OP05-2

Favorable outcomes of familial-mismatched donor transplantation using post-transplant cylophosphamide (PTCy) for pediatric severe aplastic anemia

Jae Won Yoo, Seongkoo Kim, Jae Wook Lee, Pil-Sang Jang, Nack-Gyun Chung*, Dae-Chul Jeong and Bin Cho

Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: The optimal conditioning regimen for familial-mismatched hematopoietic stem cell transplantation (HSCT) remains unclear in pediatric severe aplastic anemia (SAA). In addition to conventional approach using a fludarabine, cyclophosphamide, and antithymocyte globulin (ATG) conditioning, recent studies have been reported encouraging outcomes with post-transplant cyclophosphamide (PTCy). Here, we compared the outcomes of familial-mismatched HSCT using two different conditioning regimens in our institution.

Method: We analyzed 31 pediatric patients diagnosed with SAA (≤ 18 years at diagnosis) who underwent familial-mismatched HSCT between Apr. 2011 and Nov. 2021. The study cohort was divided into 2 groups according to transplant period and conditioning regimen: "Group I" included 15 patients who underwent HSCT during late study period (2011-2018) and received ATG-based conditioning; "Group II" included 13 patients who underwent HSCT during recent study period (2019-2021) and received PTCy-based conditioning. Three patients who underwent αβ+ T-cell depleted HSCT were excluded from the analysis.

Results: The median age at diagnosis and at HSCT were 9.0 (range, 1-18) and 12.9 years (range, 1.8-24.3), respectively. More patients received immunosuppressive therapy prior to HSCT in Group I compared to Group II (53% vs. 23%, $P > 0.05$). The donors included 11 mothers, 11 fathers, and 9 siblings, and HLA mismatching at 1 or 2 loci (6/8 or 7/8) in 4 donors, and at 3 or 4 loci (5/8 or 6/8) in 27 donors. Only peripheral blood was used as a stem cell source. Neutrophil engraftment achieved in 13 patients with Group I and 12 patients with Group II at a median of 12 (range, 11-22) and 14 (range, 12-18) days, respectively. Three patients failed to achieve primary engraftment, one patient experienced graft rejection soon after engraftment, and one patient showed poor graft function with full donor chimerism. These 5 patients received a second familial-mismatched HSCT from same donors except one, all of them maintained sustained engraftment during study period. The cumulative incidences (CIs) of grade II to IV acute GVHD were 45.2% in Group I and 16.4% in Group II ($P = 0.06$); The CI of grade III to IV acute GHVD was 13.3% in Group I, and no patient experienced severe acute GVHD in Group II. The similar CIs of chronic GVHD were observed between two groups (Group I 15.6% vs. Group II 19.2%, $P = 0.78$). Although both groups showed a high CI rate of CMV reactivation (Group I 73.3% vs. Group II 61.5%, $P = 0.67$), there was no case of CMV disease in study cohort. The significantly low incidence of EBV reactivation was showed in Group II (8.3%) compared with Group I (73.3%) ($P < 0.001$). Two patients (one in each group) were treated for post-transplantation lymphoproliferative disease. With a median follow up of 90 months in Group I and 22 months in Group II, no differences were observed in the probabilities of failure-free survival (FFS) and overall survival (OS) between 2 groups (FFS: Group I 86.7% vs. Group II 83.9%, $P = 0.89$; OS: Group I 92.9% vs. Group II 100%, $P = 0.35$).

Conclusion: We present favorable outcomes of familial-mismatched HSCT using both ATG-based and PTCy-based conditioning in pediatric SAA. The incidence of grade II to IV and grade III to IV acute GVHD seemed decreased in patients with PTCy-based conditioning, and we need to validate our results by large cohort in the future study.

Keyword: Aplastic anemia, Idiopathic, Hematopoietic stem cell transplantation, Graft vs Host disease, Pediatrics

OP05-3

The long-term efficacy and safety of eculizumab in patients with paroxysmal

nocturnal hemoglobinuria; retrospective study on behalf of Korean society of hematology aplastic anemia working party

Jin Seok Kim[1], Jun-Ho Jang[2], Deog-Yeon Jo[3], Seo-Yeon Ahn[4], Sung-Soo Yoon[5], Je-Hwan Lee[6], Sung-Hyun Kim[7], Chul Won Choi[8], Ho-Jin Shin[9], Min-Kyoung Kim[10], Jae Hoon Lee[11], Yeung-Chul Mun[12], Jee Hyun Kong[13], Sujin Heo[15], Eun Hye Kim[15], Kyong Eun Kim[16], Min Joo Kwak[16], Yong Kyun Won[16] and Jong Wook Lee[14*]

[1] Divison of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Korea

[2] Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

[3] Department of Internal Medicine, Chungnam National University College of Medicine, Korea

[4] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Korea

[5] Division of Hematology/Medical Oncology, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Korea

[6] Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea

[7] Division of Hematology and Oncology, Department of Internal Medicine, Dong-A University Hospital, Dong-A University College of Medicine, Korea

[8] Department of Internal Medicine, Korea University Guro Hospital, Korea

[9] Department of Internal Medicine, Medical Research Institute, Pusan National University Hospital, Pusan National University School of Medicine, Korea

[10] Devision of Hematology-Oncology, Department of Medicine, Yeungnam University College of Medicine, Korea

[11] Division of Hematology and Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, Korea

[12] Department of Internal Medicine, Ewha Womans University, College of Medicine, Korea

[13] Department of Hematology Oncology, Division of Internal Medicine, Wonju Severance Christian Hospital, Yonsei College of Medicine, Korea

[14] Division of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

[15] Clinical research team, Handok, Inc., Korea

[16] Medical affairs, Handok, Inc., Korea

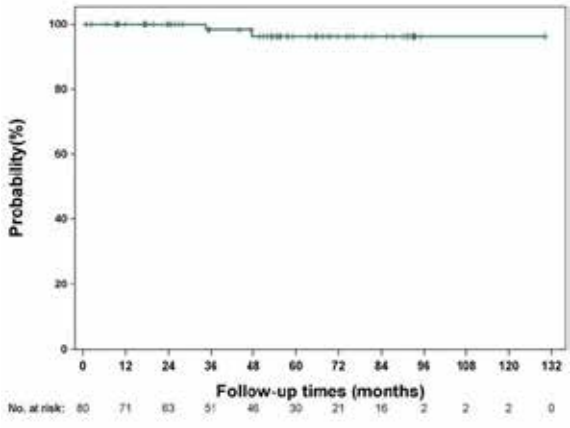
Background: Paroxysmal nocturnal hemoglobinuria (PNH) was regarded as a life-threatening disease. However, the overall survival of patients with PNH has become similar to those of general population after availability of eculizumab. Although eculizumab treatment dramatically improved the clinical outcome of patients with PNH in Korea, some of them may experience extravascular hemolysis (EVH), breakthrough hemolysis (BTH) or meningococcal infection while being on treatment. Thus, in this study, we aimed to evaluate the long-term effectiveness and safety of eculizumab in patients with PNH with high disease burden and severe PNH-related signs and symptoms in real-world practice.

Method: Korean Society of Hematology Aplastic Anemia Working Party collected data who initiated eculizumab treatment between December 1, 2009 and January 31, 2020 from 14 institutions. This analysis included baseline characteristics, treatment effectiveness, and safety in patients with PNH treated with eculizumab.

Results: Overall 80 patients (male, n=50) were enrolled. The median age at the initiation of eculizumab treatment was 52 years (range 18-88). The median time from PNH diagnosis to starting eculizumab was 68.5 months (range 2-456). The median LDH value at treatment initiation was 6.84 X upper limit of normal (ULN) (range 0.63-29.76) and median granulocyte clone size was 93.0% (range 15.4-100.0), indicative of high disease burden. The common PNH-related signs and symptoms for the rationale of eculizumab use by physicians were renal failure (n=36), followed by smooth muscle spasm (SMS, n=24), thromboembolism (TE, n=20), and pulmonary hypertension (PHT, n=15). Total treated patient-year (PY) was 338.58 PY and median treatment duration was 52.65 months (range 0.95-127.28). The survival was 96.16% overall and LDH levels (< x1.5 ULN) remained stable throughout the treatment period. Among 20 patients with TE, 14 achieved complete regression of TE during eculizumab treatment. Among 24 patients with SMS, 23 were symptom-free after eculizumab treatment. However, 11 out of 15 patients with PHT and 20 out of 36 patients with renal failure did not improve according to physician's judgement. Regarding clinical symptoms related to PNH, half of patients with fatigue (n=43◊22) reported significant symptom relief. Twenty-three patients experienced EVH by the physician's evaluation based on hemoglobin, reticulocyte, Coombs' test, and transfusion requirement leading to incidence rate of EVH per PY of 0.09. Nine of 23 EVH patients received therapeutic intervention such as steroids or transfusion. Fifteen patients experienced BTH. Incidence rate of BTH per PY was 0.06. Twenty-six patients discontinued eculizumab, of whom 19 patients discontinued due to participation in clinical trials. There was no case of discontinuation due to adverse event (AE) of eculizumab. Two deaths were reported within 3 months after eculizumab discontinuation (due to bladder cancer and fungal sepsis). No case of meningococcal infection was reported.

Conclusion: These data demonstrated that eculizumab showed sustained effectiveness with outstanding control of intravascular hemolysis-related manifestations during long-term treatment (338.58 PY) in patients with PNH with high disease burden and severe signs and symptoms. The incidence of EVH was 28.75% (approximately 1/3 of these patients required intervention) and BTH was 18.75%. Treatment adherence to eculizumab was excellent and there was no AE leading to drug discontinuation.

Keyword: Antibodies, Monoclonal, Humanized / therapeutic use, Eculizumab, Hemoglobinuria, Paroxysmal, Adult



OP05-4

Response to chemotherapy in patients with juvenile myelomonocytic leukemia in Korea: the Korean pediatric hematology-oncology group (KPHOG)

Eun Sang Yi[1,2], Seong Koo Kim[3], Bin Cho[3], Bo Kyung Kim[4], Hyung Jin Kang[4], Hee Jo Baek[5], Hoon Kook[5], Eu Jeen Yang[6], Won Kee Ahn[7], Seung Min Hahn[7], Sang Kyu Park[8], Eun Sun Yoo[9] and Keon Hee Yoo[2,10,11*]

[1] Department of Pediatrics, Korea University Guro Hospital, Korea University College of Medicine, Korea
[2] Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[3] Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine, The Catholic University, Korea
[4] Department of Pediatrics, Seoul National University College of Medicine, Seoul National University Children's Hospital, Korea
[5] Department of Pediatrics, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Korea
[6] Department of Pediatrics, Pusan National University School of Medicine, Pusan National University Children's Hospital, Korea
[7] Department of Pediatrics, Yonsei University College of Medicine, Severance Hospital, Korea
[8] Department of Pediatrics, Ulsan University Hospital, University of Ulsan College of Medicine, Korea
[9] Department of Pediatrics, Ewha Womans University College of Medicine, Ewha Womans University Seoul Hospital, Korea
[10] Department of Health Science and Technology, SAIHST, Sungkyunkwan University, Korea
[11] Stem Cell & Regenerative Medicine Institute, Samsung Medical Center, Korea

Background: Juvenile myelomonocytic leukemia (JMML) is a life-threatening myeloproliferative neoplasm, caused by mutations in the RAS signaling pathway. The effect of chemotherapy on survival remains unclear and response criteria are not well established.

Method: This multicenter study evaluated the response to chemotherapy according to chemotherapy type and survival outcomes according to response status in JMML patients diagnosed in Korea between 2000 and 2020. Patients' clinical information was collected from 8 institutions and stored in the Internet-based Clinical Research and Trial Management System (iCReaT). Responses were defined by two criteria: the criteria proposed by Chan et al (Chan criteria) and the simplified criteria of the international symposium criteria proposed at 2013 (sIS criteria).

Results: A total of 75 patients who received chemotherapy were included in this study. Patients were classified into 4 groups: group I (low dose cytarabine and etoposide-based chemotherapy, n=45), group II (low dose cytarabine-based chemotherapy without etoposide, n=22), group III (high dose cytarabine and fludarabine-based chemotherapy, n=4), group IV (others, n=4). Complete response (CR) rate was 54.3% (38/70) by Chan criteria and 36.6% (26/71) by sIS criteria at the end of chemotherapy. CR rate by Chan criteria was not different among groups: 45.2% (19/42), 65.0% (13/20), 75% (3/4), and 75% (3/4) in Group I, II, III, and IV, respectively. And CR rate by sIS criteria was also not different: 44.2% (19/43), 20.0% (4/20), 25% (1/4), and 50.0% (2/4) in Group I, II, III, and IV, respectively. Except for type 1 neurofibromatosis, which was associated with a higher CR rate by sIS criteria (100% vs. 33.8%), no other factors were associated with the CR rate by both criteria. Among patients who received allogeneic hematopoietic cell transplantation, it was observed that patients with CR by Chan criteria prior to transplantation had a better 5-year overall survival after transplantation than those who did not (73.6% vs. 52.8%). However, it was not different according to the sIS criteria response. The 5-year event-free survival did not differ according to the response results by both criteria.

Conclusion: In conclusion, response to chemotherapy may be associated with survival outcomes. Further studies are needed in the future to clarify standard chemotherapy, definition of response, and factors related to response.

Keyword: Juvenile myelomonocytic leukemia, Chemotherapy, Myeloproliferative neoplasm, Children, Hematopoietic stem cell transplantation, Response criteria

OP05-5

A multicenter, open-label, phase IV clinical study for efficacy and safety evaluation of anagrelide in patients with treatment-naïve, high-risk essential thrombocythemia as a primary treatment

Ja Min Byun[1], Dong-Yeop Shin[1*], Seulki Song[2], Sung-Soo Yoon[1], Seung-Hyun Nam[4], Ho Young Kim[3], Jinny Park[5], Yeung-Chul Mun[6], Sung Hwa Bae[7], Ho-Jin Shin[8], Sang Kyun Sohn[9], Yong Park[10], Young Rok Do[11] and Sang Hoon Han[12]

[1] Internal Medicine, Seoul National University Hospital, Korea
[2] Cancer Research Institute, Seoul National University Hospital, Korea
[3] Internal Medicine , Hallym University Sacred Heart Hospital, Korea
[4] Internal Medicine , Veterans Health Service Medical Center, Korea
[5] Internal Medicine , Gachon University Gil Medical Center, Korea
[6] Internal Medicine , Ewha Womans University School of Medicine, Korea
[7] Internal Medicine , Daegu Catholic University School of Medicine, Korea
[8] Internal Medicine, Pusan National University Hospital, Korea
[9] Internal Medicine , Kyungpook National University Hospital, Korea
[10] Internal Medicine , Korea University Anam Hospital, Korea
[11] Internal Medicine , Keimyung University Dongsan Hospital, Korea
[12] Internal Medicine , Jeju National University School of Medicine, Korea

Background: Essential thrombocythemia (ET) is a type of myeloproliferative neoplasm characterized by abnormal proliferation of megakaryocytes in the bone marrow leading to elevated platelet counts. Since ET patients are associated with almost normal survival, any survival effects of treatment is very difficult to prove. Thus, the goal of ET treatment is reduction of thrombotic and hemorrhagic complications, and the target platelet reduction to <400 x109/L. While cytoreductive therapy with or without low-dose aspirin is the mainstay of thrombosis risk reduction, the optimal choice of therapeutic agent is less clear. Several agents, including hydroxyurea, anagrelide, and interferon are in use for this purpose, but data directly comparing these agents are lacking. As such, there is a gap in preferred therapeutic agents among the continents: based on the ANAHYDRET study which showed non-inferiority of anagrelide to hydroxyurea, anagrelide is used as a first-line therapy for high risk ET patients in Korea. On the other hand, due to concerns about leukemogenesis observed in EXELS study and conflicting results of PT-1 trial data, anagrelide remains a second-line therapy in Europe. Anagrelide is an amidazoquinazolin, originally developed as an anticoagulation drug, which was shown to have a potent platelet reducing effect. It is the only platelet-specific cytoreductive drug known, having no inhibitory effects on red or white cell progenitor proliferation. It reduces platelet production by inhibiting megakaryocyte colony development, thus producing a left-shift in megakaryocyte maturation, reducing megakaryocyte size, and maturation. As discussion of anagrelide efficacy and safety is ongoing and a consensus has not been reached, we aimed to prospectively examine the efficacy and safety of anagrelide in cytoreduction therapy-naïve ET patients in Korea.

Method: Design overview This was a multi-center, prospective, observation study. The aim of the study was to examine the efficacy and safety of first-line anagrelide treatment in high risk Korean ET patients. The primary objective was the anagrelide response, defined as platelet reaching < 600 x 109/L, at week 8 with anagrelide monotherapy. The secondary objectives included (1) platelet normalization rates (platelet < 400 x 109/L) at week 8 and 12 months; (2) platelet reduction by more than 50% at week 8 and 12 months; (3) anagrelide tolerability and compliance at 12 months; (4) adverse events profile; and (5) somatic mutation profiles and anagrelide efficacy.

Study population Patients older than 18 years with ET diagnosed according to the 2008 WHO classification were screened. Those participants with high risk ET (age older than 60 years or a history of vascular complication) and cytoreductive treatment naïve were invited to participate in the study, regardless of mutational status. Patients with underlying medical conditions requiring active interventions, inadequate organ (cardiac, hepatic, renal, pancreatic) functions, pregnancy, concurrent malignancies, or taking phosphodiesterase III/IV drugs were excluded. The study was conducted according to Declaration of Helsinki and was approved by the institutional review board (IRB) of each hospital. Informed consent was taken from all participants.

Interventions From week 1 to week 8, anagrelide monotherapy was required. Patients were started on anagrelide 0.5mg twice a day and after 1 week dose escalation was allowed. From week 9, additional agents for cytoreduction was allowed as needed. Maximum anagrelide dose allowed was 10mg/day (2.5mg four times a day). Patients were followed up at week 1, week 4, week 8, 3 months, 6 months, 9 months, 12 months, 18 months and 24 months for lab testing and drug compliance monitoring.

Results: In the end, 70 patients (34 males and 36 females) were enrolled. The median age at ET diagnosis was 64 years (range 24 – 90), and time to study enrollment was median 13 days. Majority of the patients harbored JAK2V617F mutation (46/70, 65.7%) and there were 17 (24.3%) triple negative patients. Interestingly, 2 patients showed concurrent JAK2V617F mutation and MPL mutation. There was 1 patient who dropped out of the study at week 1 (consent withdrawal after discussion with family members). By week 8, 64/70 (91.4%) patients remained on anagrelide monotherapy. Among the 64 patients remaining on anagrelide, all but 1 had taken ≥80% of the prescribed medication. Response was evaluated in the 63 patients with good compliance to anagrelide: 50.8% of

the patients were able to achieve platelet < 600 x 109/L and 20.6% achieved platelet normalization with anagrelide monotherapy by week 8. By 12 months, 55/70 (78.6%) patients stayed on anagrelide and 54/55 patients showed good compliance to the drug. By 12 months, 40.7% patients showed platelet normalization and 44.4% experience more than 50% decrease in platelet counts. There were 14 patients who required additional hydroxyurea (HU) for cytoreduction. Median dose of needed HU was 500mg (range 250mg – 1500mg). Anagrelide treatment had minimal effects on white blood cell counts and henoglobin level. The median dose of anagrelide required was 2.5mg per day. There were 5 thromboembolic events and 6 bleeding events during the follow-up period. The most common side effects of anagrelide was headache (25/69), followed by edema and palpitation (15/70), itching or pruritis (14/70), diarrhea or loose stool (10/70) and abdominal pain (9/70) and generalized weakness or malaise (9/70). There were 7 patients who wished to discontinue anagrelide treatment due to adverse events. There were no acute leukemia transformation or myelofibrosis transformation during the follow-up.

Conclusion: First line anagrelide treatment for high risk ET is safe and efficacious regardless of mutational status.

Keyword: Essential thrombocythemia, Phase IV, Anagrelide

OP06-1

Prognostic role of the ratio of natural killer to regulatory T cells in multiple myeloma treating lenalidomide and dexamethasone

Sung-Soo Park, Ji-Young Lim, Jung Yeon Lee, Jae-Ho Yoon, Sung-Eun Lee, Ki-Seong Eom, Hee-Je Kim, Chang-Ki Min* and Seung Yeon Kim

Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, Catholic University of Korea, Korea

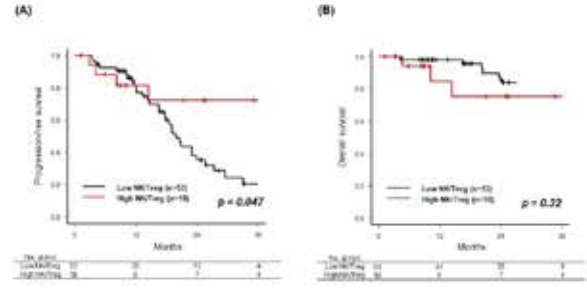
Background: Despite advances in treating multiple myeloma (MM), biomarker-driven personalized approach remains as unmet needs. A combination of lenalidomide and dexamethasone (RD) is a widely available chemotherapeutic option for newly diagnosed multiple myeloma (NDMM). We aimed to find a circulating immune cell-based biomarker to predict prognosis following RD in patients with NDMM.

Method: Clinical data and peripheral blood samples of consecutive 71 NDMM patients treated with RD were retrospectively analyzed. Peripheral blood samples were taken at the time of diagnosis. Immune cell populations including natural killer cells, T cells, and their subpopulations were identified by flow cytometry.

Results: The median age was 71.0 years (range, 55-85) at diagnosis. In univariable analysis, four variables including low expression (≤ 3rd quartile) of NK cells, high expression (> 1st quartile) of regulatory T cells (Treg), female sex, lambda light chain type had potential impacts associated with poor progression-free survival (PFS). Regarding the assembled biomarker of the ratio of NK cells to Treg cells (NK/Treg), median PFS of patients with low (< 1st quartile, n=18) NK/Treg was significantly inferior to that with high (≥ 1st quartile, n=53) NK/Treg (19.8 vs 57.27 months, p = 0.047). In multivariable analysis, low NK/Treg was significantly associated with poor PFS [hazard ratio of 2.877 (95% CI, 0.001-1.009, p=0.048), even after adjustment with other factors.

Conclusion: NK/Treg at time of diagnosis might be a useful immune cell-biomarker for clinical decision-making to choose RD in NDMM. Further investigations to increase NK/Treg could be important to improve outcomes in NDMM patients treated with RD.

Keyword: Biomarker, Multiple Myeloma, NK cell, Regulatory T cell, Immune, Lenalidomide



OP06-2

Rejuvenation of antigen-specific CD8+ T cells using induced pluripotent stem cell technology and specific regulatory pathways for T cell commitment

Jooeun Bae[1*], Shuichi Kitayama[1], Zach Herbert[1], Laurence Daheron[2], Keiji Kurata[1], Derin Keskin[3], Kenneth Livak[3], Shuqiang Li[3], Mehmet Samur[1], Nikhil Munshi[1], Shin Kaneko[4], Jerome Ritz[1] and Kenneth Anderson[1]

[1] Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, USA

[2] iPSC Core Facility, Harvard University, USA

[3] Broad Institute, Massachusetts Institute of Technology, USA

[4] Center for iPS Cell Research and Application, Kyoto University, Japan

Background: T cell regenerative medicine is a novel immunotherapeutic strategy for reprogramming of antigen-specific induced Pluripotent Stem Cells (iPSC) into rejuvenated CD8+ cytotoxic T lymphocytes (CTL). Here, we report a therapeutic strategy targeting B-Cell Maturation Antigen (BCMA) to overcome exhaustion of antigen-specific memory CTL and revitalize them into fully functional cognate antigen-specific T cells to target multiple myeloma (MM).

Method: IFN-g producing HLA-A2 heteroclitic BCMA72-80 (YLMFLLRKI)-specific CD8+ CTL were used to establish iPSC via transduction of reprogramming factors, OCT3/4, SOX2, KLF4 and c-MYC.

Results: The BCMA-specific iPSC demonstrated high pluripotency potential by differentiation into three key germ layers, as evidenced by distinct expression of stem cell markers (SSEA-4, TRA1-60), germ differentiation markers (SOX-17 on Endoderm, Brachyury on Mesoderm, and Pax-6 on Ectoderm) and alkaline phosphatase activity. Polarization during embryoid body formation from iPSC into mesoderm layer was evidenced by upregulation of transcriptional regulators (ABCA4, BMP10, CDH5, FOXF1, HAND1, PLVAP, SNAI2, TBX3). Next, embryoid body-derived hematopoietic progenitor cells (HPC; CD34+ CD43+/CD14- CD235a-) were sorted and induced to undergo T cell differentiation in the presence of Fc-DLL4 signaling and rectonectin. Our RNAseq analyses revealed specific regulatory pathways used by iPSC-derived HPC for their commitment to antigen-specific CD8+ T cells, which include upregulation of transcriptional regulators determining CD4/CD8 T cell differentiation ratio, memory CTL formation, NF-kappa-B/JNK pathway activation, and downregulation of regulators controlling B and T cell interactions or CD4+ Th cells and inhibitory receptor development. The T cells differentiated from HPC were fully mature CD8α+β+ T cells and predominantly CD45RO+ memory CTL with upregulation of activation (CD38) and costimulatory (CD28) molecules, while lacking the expression of various immune checkpoints (CTLA4, PD1, LAG3, Tim3). Functionally, the differentiated T cells demonstrated high (*$p < 0.05$) levels of cell proliferation (1,800-fold increase), anti-tumor cytotoxicity and Th1 cytokine (IFN-g, IL-2, TNF-a) production against primary MM patients' CD138+ tumor cells as well as MM cell lines in antigen-specific and HLA-A2 restricted manners. The functional activities were directed against parental BCMA72-80 (YLMFLLRKI) peptide via a distinct sole TCRa/TCRb clonotype.

Conclusion: These results highlight the processes and pathways mediating somatic T cell epigenetic reprogramming and differentiation into rejuvenated antigen-specific memory CD8+ T cells using iPSC-based regenerative medicine. With the proof-of-principle platform provided, we are in development of an immunotherapy to overcome T cell exhaustion and promote a highly effective long-term immunity to improve patient outcome in MM and other cancers.

Keyword: T cell Regenerative Medicine, induced Pluripotent Stem Cells

OP06-3

Busulfan and thiotepa as a conditioning regimen for autologous stem cell transplantation in multiple myeloma: KM-MWP-1801 study

Ga-Young Song[1], Sung-Hoon Jung[1], Jin Seok Kim[4], Hyeon Seok Eom[5], Joon Ho Moon[3], Ho-Young Yhim[6], Kihyun Kim[2], Chang-Ki Min[7] and Je-Jung Lee[1*]

[1] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital and Chonnam National University Medical School, Korea

[2] Division of Hematology-Oncology, Samsung Medical Center, Korea

[3] Department of Hematology-Oncology, Kyungpook National University Hospital, Korea

[4] Department of Hematology-Oncology, Severance Hospital, Yonsei University College of Medicine, Korea

[5] Department of Hematology, National Cancer Center, Korea

[6] Department of Hematology, Chonbuk National University Medical School, Korea

[7] Department of Hematology, Seoul St. Mary's Hematology Hospital, Catholic University of Korea, Korea

Background: Autologous stem cell transplantation (ASCT) remains the standard of care for patients with newly diagnosed multiple myeloma (MM), and currently the standard conditioning regimen for ASCT in MM is high-dose melphalan (HD-MEL; melphalan 200 mg/m2). Thiotepa is an active alkylating agent against MM, and this study retrospectively compared the efficacy and toxicity of busulfan and thiotepa (BuTT) and those of high-dose melphalan (HD-MEL) as conditioning regimen for ASCT in patients with MM.

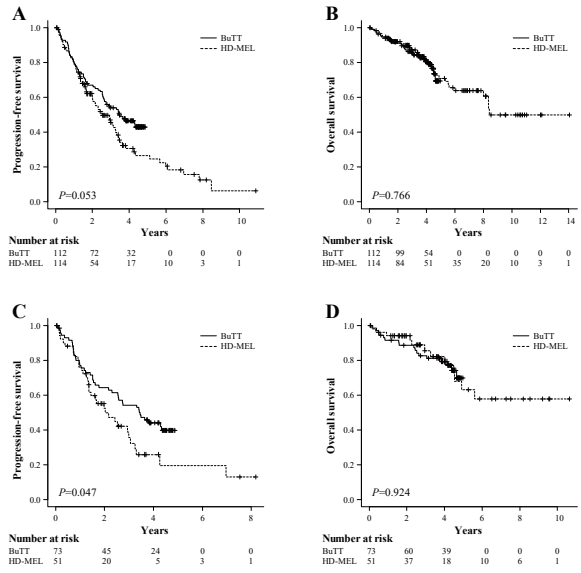
Method: This study retrospectively reviewed the record of patients who were diagnosed symptomatic MM between March 2008 to May 2020 from 7 institutions. Patients who received induction chemotherapy and performed the peripheral blood stem cell collection with appropriate stem cell counts (CD34+ cells ≥ 2 × 106/kg), and proceeded to ASCT with either BuTT or HD-MEL conditioning were included. BuTT conditioning regimen was composed of intravenous thiotepa 5 mg/kg once a day from days -7 to -6 followed by intravenous busulfan 3.2 mg/kg once a day from days -5 to -3. HD-MEL conditioning regimen was composed of melphalan 100 mg/m2 once a day from days -3 to -2. Response to treatment was assessed after induction chemotherapy before ASCT and 3 months after ASCT. Maintenance therapy was administered based on the policies of each participating center.

Results: One hundred and fourteen patients received BuTT conditioning and the same number of patients received HD-MEL. The baseline clinical characteristics of the patients were not significantly

different between two groups including high-risk chromosomal abnormalities and Revised-International Staging System (R-ISS). More patients in BuTT group received bortezomib-containing induction treatment (100.0% vs. 65.8%) and more patients in HD-MEL group received thalidomide maintenance after ASCT (28.1% vs. 50.0%). The ORR after ASCT was 94.7% in BuTT group and 97.4% in HD-MEL group (p = 0.333). The proportion of the patients who achieved more than very good partial response (VGPR) after ASCT was 91.7% in BuTT group and 93.3% in HD-MEL group (p = 0.391). After median follow-up of 47.6 months, median PFS was 41.5 months in BuTT group and 30.3 months in HD-MEL group (HR 0.706, 95% CI 0.497-1.004, p = 0.053, Figure 1A). OS was not different between two groups (not reached in BuTT group vs. 101.0 months in HD-MEL group, HR 1.092, 95% CI 0.610-1.956, p = 0.766, Figure 1B). Analysis including patients who did not proceed to maintenance or consolidation treatment after ASCT, PFS difference became more significant (41.5 months in BuTT group vs. 24.4 months in HD-MEL group, HR 0.621, 95% CI 0.388-0.993, p = 0.047, Figure 1C). OS was not different between two groups (not reached in BuTT group vs. not reached in HD-MEL group, HR 1.038, 95% CI 0.478-2.255, p = 0.924, Figure 1D). There was no significant difference in hematopoietic stem cell engraftment in both groups. BuTT group had fewer adverse events such as grade 3 or 4 stomatitis and diarrhea than HD-MEL group (stomatitis, 10.5% vs. 23.7%, p = 0.013; diarrhea, 10.5% vs. 25.4%, p = 0.005). There was no difference in occurrence of venous-occlusive disease (VOD) (2.6% in BuTT. Vs. 0.9% in HD-MEL, p = 0.622).

Conclusion: This study suggested that BuTT is an effective alternative conditioning regimen with reduced toxicity in patients with newly diagnosed MM, and further randomized controlled prospective trial is needed to confirm the efficacy of BuTT conditioning.

Keyword: Autologous stem cell transplantation, Multiple myeloma



OP06-4

Comparative analysis of single versus tandem autologous stem cell transplantation in patients with multiple myeloma in Korea: the KMM2102 study

Jongheon Jung[1], Je-Jung Lee[2], Sung-Hoon Jung[2], Young Rok Do[3], Ka-Won Kang[4], Jung Lim Lee[5], Sung-Soo Yoo[6], Chang-Ki Min[7], Hye Jin Kang[8], Ji Hyun Lee[9], Kihyun Kim[10] and Hyeon-Seok Eom[1*]

[1] Center for Hematologic Malignancy, National Cancer Center, Goyang, Korea
[2] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital/Chonnam National University Medical School, Hwasun, Jeollanamdo, Korea
[3] Department of Hemato-Oncology, Keimyung University, Dongsan Medical Center, Daegu, Korea
[4] Division of Hematology-Oncology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea
[5] Division of Hematology and Medical Oncology, Department of Internal Medicine, Daegu Fatima Hospital Cancer Center, Daegu, Korea
[6] Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[7] Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[8] Division of Hematology/Oncology, Department of Internal Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Korea
[9] Department of Internal Medicine, Dong-A University College of Medicine, Busan, Korea
[10] Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea

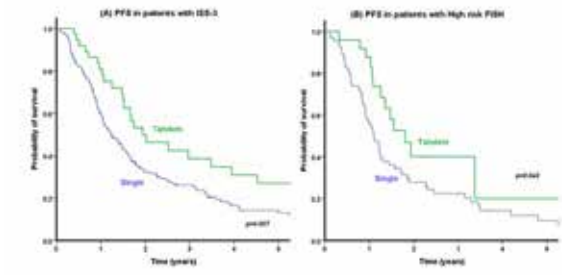
Background: Tandem autologous stem cell transplantation (ASCT) has been suggested to improve prognosis in patients with multiple myeloma (MM) in the late 1990s. It has presented clinical benefits in patients with high risk cytogenetics with extramedullary disease in a previous study. However, tandem ASCT did not result in improved outcomes in a previous meta-analysis. We performed this comparative analysis to investigate patients group who possibly obtain clinical benefit from tandem ASCT.

Method: In this retrospective study, we enrolled 117 patients who received tandem ASCT in 10 Korean institutions between 2005 and 2020. Control group consisted of 539 patients for whom single ASCT was performed in 3 institutions. Response status of pre- and post-ASCT were compared. Survival outcomes including overall survival (OS) and progression-free survival (PFS) were compared between tandem ASCT group and single ASCT group in overall and in subgroups. Multivariate Cox analysis was done after adjustment for conduct of maintenance therapy as post ASCT therapeutic strategies.

Results: Median follow up was 73.6 months for all patients. Median age at diagnosis was 54 years for tandem ASCT group and 57 years for single ASCT group. At diagnosis, tandem ASCT group revealed significantly higher rate of high risk FISH which was defined as 17p del, t(4;14), or t(14;16) compared to single ASCT group (33.8% vs. 27.8%, p=0.001). In tandem ASCT group, the rate of complete response (CR) or more improved from 29 (24.8%) after the 1st ASCT to 54 (46.2%) after the 2nd ASCT. Both PFS and OS did not show differences between tandem and single ASCT in whole patients (median 22.8 vs. 24.7 months for PFS; 76.2 vs. 80.6 months for OS). However, in patients with International Staging System (ISS) stage 3, tandem ASCT group (n=37) revealed significantly superior PFS compared to single ASCT group (n=163) (14.7 vs. 23.1 months, p=0.007) (Fig A). In subgroup analysis for high risk FISH, tandem ASCT group (n=24) presented significantly longer PFS than single ASCT group (n=319) (13.2 vs. 21.7 months, p=0.042) (Fig B). In analysis of patients who did not achieve CR after the 1st ASCT, tandem ASCT (n=88) was associated with significantly improved PFS than single ASCT (n=208) (12.6 vs. 20.3 months, p=0.003) (Fig C). In patients who showed very good partial response (VGPR) after the 1st ASCT, tandem ASCT (n=40) was significantly related to prolonged PFS compared to single ASCT (n=124) (11.8 vs. 18.6 months, p=0.008) (Fig D). After an adjustment for the conduct of maintenance therapy, patients with ISS stage 3 (HR 0.526, 95% CI 0.340-0.814, p=0.004), patients with high risk FISH (HR 0.540, 95% CI 0.295-0.990, p=0.046), and patients who did not achieve CR after the 1st ASCT (HR 0.569, 95% CI 0.429-0.756, p<0.001)– especially who presented VGPR (HR 0.545, 95% CI 0.631-0.822, p=0.004)– resulted in significantly improved PFS with tandem ASCT. However, tandem ASCT was not associated with significantly improved OS in an adjustment for maintenance therapy. No treatment-related mortality was reported with tandem ASCT.

Conclusion: In conclusion, tandem ASCT might be beneficial in high risk multiple myeloma patients defined as ISS-3 or high risk FISH. In addition, tandem ASCT showed possibility to improve clinical outcomes in patients who did not achieve CR, especially patients who presented VGPR after the 1st ASCT. Further study is warranted to enlighten the clinical role of tandem ASCT in patients with MM.

Keyword: Tandem, Autologous, Stem cell, Transplantation, Myeloma, High risk



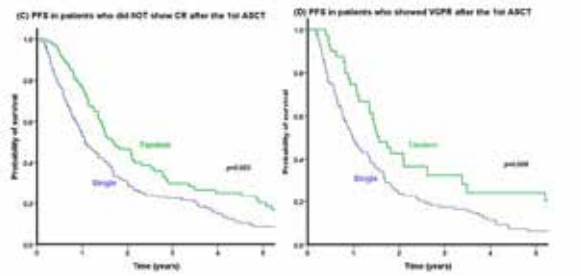


Fig. Kaplan-Meier curves of progression-free survival (A) in patients with International Staging System stage 3, (B) in patients with high risk FISH, (C) in patients who did not show complete response after the 1st autologous stem cell transplantation, and (D) in patients who showed very good partial response after the 1st autologous stem cell transplantation.

OP06-5

Subcutaneous daratumumab with bortezomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed light chain (AL) amyloidosis: 18-month analysis of the phase 3 andromeda study

Raymond L. Comenzo[1*], Giovanni Palladini[2], Efstathios Kastritis[3], Monique C. Minnema[4], Ashutosh D. Wechalekar[5], Arnaud Jaccard[6], Angela Dispenzieri[7], Hans C. Lee[8], Vaishali Sanchorawala[9], Simon D. Gibbs[10], Peter Mollee[11], Christopher P. Venner[12], Jin Lu[13], Stefan Schönland[14], Moshe Gatt[15], Kenshi Suzuki[16], Kihyun Kim[17], M. Teresa Cibeira[18], Meral Beksac[19], Edward Libby[20], Jason Valent[21], Vania Hungria[22], Sandy W. Wong[23], Michael Rosenzweig[24], Naresh Bumma[25], NamPhuong Tran[26], Xiang Qin[27], Sandra Y. Vasey[28], Samer Khaled[26], Jessica Vermeulen[29] and Giampaolo Merlini[2]

[1] Division of Hematology/Oncology, Tufts Medical Center, USA
[2] Department of Molecular Medicine, University of Pavia, Italy
[3] Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Greece
[4] Department of Hematology, University Medical Center Utrecht, Netherlands
[5] Division of Medicine, University College London, UK
[6] CRIBL Lab, Centre Hospitalier Universitaire and Reference Center for AL Amyloidosis, France
[7] Division of Hematology, Mayo Clinic, USA
[8] Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, USA
[9] Department of Medicine and Amyloidosis Center, Boston University School of Medicine and Boston Medical Center, USA
[10] Department of Haematology, Monash University Easter Health Clinical School, Australia

[11] Department of Haematology, Princess Alexandra Hospital and University of Queensland Medical School, Australia
[12] Department of Oncology, Cross Cancer Institute, University of Alberta, Canada
[13] Peking University People's Hospital, National Clinical Research Center for Hematologic Disease, China
[14] Medical Department V, Heidelberg University Hospital, Germany
[15] Hematology Department, Hadassah Hebrew University Medical Center, Israel
[16] Department of Hematology, Japanese Red Cross Medical Center, Japan
[17] Department of Medicine, Sungkyunkwan University School of Medicine, Korea
[18] Amyloidosis and Myeloma Unit, IDIBAPS, Spain
[19] Department of Hematology, Ankara University, Turkey
[20] Department of Medicine, University of Washington, USA
[21] Department of Hematology and Medical Oncology, Cleveland Clinic, USA
[22] Department of Hematology, Clinica São Germano, Brazil
[23] Department of Medicine, University of California San Francisco, USA
[24] Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, USA
[25] Division of Hematology, The Ohio State University Comprehensive Cancer Center, USA
[26] Department of Clinical Oncology, Janssen Research & Development, LLC, USA
[27] Department of Clinical Biostatistics, Janssen Research & Development, LLC, USA
[28] Department of Clinical Oncology, Janssen Research & Development, LLC, USA
[29] Department of Oncology, Janssen Research & Development, LLC, Netherlands

Background: Light chain (AL) amyloidosis is a plasma cell disease characterized by the deposition of insoluble amyloid fibrils into organs leading to organ dysfunction and death. The analysis at 6 and 12 months of the ANDROMEDA study showed that addition of subcutaneous (SC) daratumumab to standard of care combination of bortezomib, cyclophosphamide, and dexamethasone (VCd) was superior to VCd alone, with higher rates of hematologic complete response (CR) and an acceptable safety profile, leading to regulatory approval of daratumumab with VCd (D-VCd) for newly diagnosed AL amyloidosis in the US and EU. We present data from the 18-month analysis of the ANDROMEDA study.

Method: Patients with newly diagnosed AL amyloidosis were randomized (1:1) to D-VCd or VCd for 6 28-day cycles. Bortezomib (1.3 mg/m2), cyclophosphamide (300 mg/m2 up to 500 mg per week), and dexamethasone (20–40 mg) were administered weekly. SC daratumumab (1800 mg co-formulated with recombinant human hyaluronidase PH20 in 15 mL) was administered once weekly in cycles 1 and 2 and every 2 weeks in cycles 3 to 6. Patients in the D-VCd arm received only SC daratumumab after cycle 6, every 4 weeks (up to 24 cycles from first dose). Primary endpoint: overall (i.e., at any time) hematologic CR rate, defined as normalization of free light chain (FLC) levels and ratio (FLCr) and negative serum and urine immunofixation, confirmed at a subsequent visit; normalization of uninvolved FLC level and FLCr were not required if involved FLC was lower than the upper limit of normal. Secondary endpoints: major organ deterioration progression-free survival (PFS), organ response rate, time to hematologic response, overall survival (OS), and safety.

Results: 388 patients were randomized to receive D-VCd (N=195) or VCd alone (N=193). At the May 2021 clinical cutoff, the median duration of treatment for D-VCd and VCd was 21.3 and 5.3 months, respectively. In the D-VCd arm, 149 patients (77.2%) received daratumumab monotherapy after completing 6 cycles of D-VCd; 17 (11.4%) were still receiving treatment. The rates of deep hematological responses favored D-VCd treatment (Table). At a median follow-up of 25.8 months, the rate of hematologic CR was significantly higher in D-VCd vs VCd a (59.5% vs 19.2%; OR [95% confidence interval (CI)], 6.03 [3.80–9.58]; P<0.0001). More patients achieved a very good partial response or better (≥VGPR) (D-VCd vs VCd, 79.0% vs 50.3%; OR [95% CI], 3.74 [2.39–5.86]; P<0.0001). Among responders, the median time from randomization to ≥VGPR was shorter with D-VCd (0.56 months) vs VCd (0.82 months). Greater cardiac response rates were achieved with D-VCd compared with VCd at 18 months (53% vs 24%) when compared to the rates at 6 months (42% vs 22%). Renal response rates remained superior with D-VCd vs VCd alone at 18 months (58% vs 26% compared with 6 months [54% vs 27%]). 79 deaths occurred (D-VCd, N=34; VCd, N=45). In D-VCd, only 1 additional grade 3/4 treatment-emergent adverse event occurred over 18 vs 12 months (119 [61.7%] vs 118 [61.1%]) and no additional infusion-related reactions were reported. OS will be analyzed and major organ deterioration PFS will be updated after approximately 200 events have occurred.

Conclusion: Sustained clinical benefits of D-VCd vs VCd in terms of hematologic and organ responses were observed with longer follow-up, although it should be noted that many patients in the D-VCd arm received daratumumab monotherapy following 6 cycles of D-VCd, while patients in the VCd group stopped study treatment. The study continues to support the use of D-VCd over VCd alone in patients with newly diagnosed AL amyloidosis. Following its recent approval, D-VCd represents a new SOC for patients with AL amyloidosis.

Keyword: AL Amyloidosis, Bortezomib, Daratumumab, Dexamethasone, Cyclophosphamide

Table. Hematologic response rates by treatment group at any time

n (%)	D-VCd (N=195)	VCd (N=193)	Odds ratio (95% CI)	*P*-value
CR	116 (59.5)	37 (19.2)	6.03 (3.80, 9.58)	<0.0001
VGPR	38 (19.5)	60 (31.1)		
PR	25 (12.8)	52 (26.9)		
NR	8 (4.1)	37 (19.2)		
NE	8 (4.1)	7(3.6)		
≥VGPR	154 (79.0)	97 (50.3)	3.74 (2.39, 5.86)	<0.0001
ORR	179 (91.8)	149 (77.2)		

CI, confidence interval; CR, complete response; D-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; NE, not evaluable; NR, no response; ORR, overall response rate; PR, partial response; VCd, bortezomib, cyclophosphamide, and dexamethasone; VGPR, very good partial response.

OP07-1

2021 operation of the surveillance system of COVID-19 vaccination induced thrombosis with thrombocytopenia syndrome in Korea

Daehyun Chu[1], Seongsoo Jang[1*], Hyunji Kim[1], Sang-Hoon Na[2], Soo-Mee Bang[3], Won-Il Choi[4] and Youngkeun Ahn[5]

[1] Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea
[2] Department of Internal Medicine, Seoul National University Hospital, Korea
[3] Department of Internal Medicine, Seoul National University Bundang Hospital, Korea
[4] Department of Internal Medicine, Myongji Hospital, Korea
[5] Department of Internal Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Korea

Background: The COVID-19 vaccine is known to be an effective way to prevent and reduce the severity and death of COVID-19. Since the development of the COVID-19 vaccine was completed in a relatively short period of about a year and began to be used with rapid approval, the operation of an active monitoring system for unexpected side effects after vaccination has been strongly recommended. On April 7, 2021, the European Medicines Agency reported that a very rare side effect, thrombosis with thrombocytopenia, may occur in about 10 cases per million shots of ChAdOx1 nCov-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India), and there was consensus that it could also occur in another adenoviral vector vaccine like Ad26.COV2.S vaccine (Janssen, Johnson & Johnson). In Korea, the COVID-19 vaccination started on February 26, 2021, and in the early days, the AstraZeneca vaccine was the leading vaccine. So the centralized vaccine adverse reaction monitoring system has been performed using the anti-platelet factor 4 (PF4) antibody enzyme-linked immunosorbent assay (ELISA) and it is essential for diagnosing this rare side effect named thrombosis with thrombocytopenia syndrome (TTS).

Method: We reviewed and analyzed clinical and laboratory characteristics of 234 patients who were tested PF4 ELISA from May 26 to November 12, 2021, in Korea. Then, we calculated several parameters of diagnostic test accuracy for PF4 ELISA including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV).

Results: Fourteen cases (6.0%) showed positive and seven cases (3.0%) showed equivocal results. The most common symptoms were hemorrhagic petechiae (27.4%), headache (16.7%), dyspnea/chest pain (15.8%), abdominal pain (6.8%), lower extremity edema, and local neurological symptoms (each 6.4%). Symptoms appeared on average 14.4 days after vaccination. Thrombocytopenia (<150K/ul) was observed in 86.3% and severe thrombocytopenia (<50K/ul) was also observed in 29.5%. D-dimer increased in 85.5% of cases, and increased to more than four times the upper limit of reference range in 60.7% of cases. Thrombosis was present in 36.8% of cases, and venous thrombosis (25.2%) was more common than arterial thrombosis (11.5%). The most common locations of venous thrombosis were pulmonary embolism/deep vein thrombosis (25.2%), cerebral venous sinus thrombosis (3.4%), and visceral venous thrombosis (3.0%) in that order. Among arterial thrombosis, stroke (8.5%) was the most common. A total of three cases of TTS were confirmed, and the incidence rate of TTS in Korea was 0.27 cases per million, which was lower than in the Western countries. And they all occurred after the first dose of the AstraZeneca vaccine. In the PF4 ELISA results, the positive rate was 6.4%, and when the equivocal result was classified as "positive", the positive rate was 9.4%. According to the latter, the sensitivity and specificity of the test were 100% and 91.8%, respectively, with a PPV of 13.8% (95% CI: 9.29-19.52%) and a NPV of 100% (95% CI: 87.61-95.04%). If the PF4 ELISA is requested when TTS-related symptoms such as thrombocytopenia and thrombosis are present at the same time, the PPV rises to 37%.

Conclusion: PF4 ELISA presents relatively high diagnostic accuracy for TTS. However, a poor PPV is observed because of the low incidence rate of TTS. If the cases subject to the PF4 ELISA are narrowed down to TTS-suspected cases with TTS-related symptoms, the PPV increases. A more active PF4 ELISA test is required in patients with suspected TTS after COVID-19 vaccination considering a poor PPV of the test and low incidence rate of TTS in Korea.

Keyword: COVID-19, Vaccine, TTS, Anti-PF4 antibody, ELISA

OP07-2

Validation of Khorana score in cancer patients undergoing chemotherapy with east asian ethnicity

Junshik Hong[1*], Hyerim Ha[2], YeHee Ko[3] and Kwangsoo Kim[4]

[1] Department of Internal Medicine, Seoul National Universityi College of Medicine, Korea
[2] Department of Internal Medicine, Inha University Hospital, Korea
[3] Department of Applied Statistics, Yonsei University, Korea
[4] Transdisciplinary Department of Medicine & Advanced Technology, Seoul National University Hospital, Korea

Background: Khorana score has been widely used for the prediction of cancer-associated thrombosis (CAT) and recent pivotal phase III trials such as AVERT and CASSINI integrated Khorana score in the

inclusion criteria. However, most studies in development and use of Khorana score were conducted in Western cancer patients. Thus, we conducted a retrospective real-world analysis to validate Khorana score in Korean cancer patients who have East Asian Ethnicity.

Method: By using the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM), we collected de-identified data of the newly diagnosed cancer patients who underwent chemotherapy from January 2016 to June 2019 at Seoul National University Hospital (SNUH), Seoul, South Korea. Patients were eligible if they 1) had a new diagnosis code of cancer and 2) had initiated chemotherapy within 3 months after the first recoding of the cancer diagnosis. The patients undergoing chemotherapy were identified based on their prescription of chemotherapeutic agents and the procedural code for the first-time patient education for chemotherapy. Among the selected cancer patients, values of complete blood cell counts (CBC), body weight, and height on the very day of or the day closest to the chemotherapy initiation were obtained. A patient was counted as having a VTE if he or she had both newly-recorded diagnosis code of VTE and new record of anticoagulant medication code within 1 week after the emergence of VTE diagnosis code. Cumulative incidence of CAT was estimated at the time of 3, 6, and 12 months after the date of chemotherapy initiation.

Results: A total of 10,588 patients with cancer and chemotherapy were eligible and only 1.33% (141 patients) had a CAT at 6 months after the chemotherapy initiation, suggesting lower overall incidence of CAT in Asian population. Pancreas (4.9%) was the most common primary cancer site but CAT incidence rate in patients with stomach cancer was limited to 1.6%, reflecting different characteristics of the disease between the East and the West. The CAT incidences in patients with lung cancer (1.4%) and lymphoma (1.1%) were lower than expected, in line with a recent meta-analysis (Mulder at al.; Haematologica 2019), but CAT incidences in patients with liver (3.4%) and biliary (3.0%) cancer were higher than expected considering the Khorana scoring system.

Among 7,431 patients who had all data for the calculation of Khorana score, 5,549 patients (74.7%) had a BMI of < 25 kg/m 2, followed by 1,633 patients (15.4%) with a BMI of 25.0-29.9 kg/m 2. Only 39 patients (0.4%) had a BMI of 35 > kg/m 2, showing the difference of BMI distribution according to the ethnicity. Moreover, BMI was not associated with CAT development at all, whereas the 3 CBC parameters and the site of cancers were associated with CAT occurrence. In addition, patients who aged ≥ 65 years had significantly higher CAT risk compared to younger group. In a multivariate regression analysis (Table 1), age ≥ 65 years, leukocyte ≥ 11 x 10 3/μL, and sites of cancers were independently associated with the development of CAT. Hemoglobin < 10 g/dL and platelet ≥ 350 x 10 3/μL showed a tendency of association but failed to reach statistical significance.

When we classified the 7,431 patients according to the Khorana scoring system, 8.0% of the patients were considered as high risk group and their incidence of CAT at 6 months was 3.36% (Table 2), showing a smaller proportion of patients assigned to high risk group and their lower absolute risk of CAT compared to Western population.

Conclusion: In conclusion, Khorana scoring system was only partially validated in Korean cancer patients who underwent first-line chemotherapy: BMI was not but older age was a good predictor for the prediction of CAT occurrence. Weighing the risk of CAT according to the sites of cancers also needs some improvement. Further studies for better CAT risk stratification reflecting ethnic or regional differences are warranted.

Keyword: Cancer associated thrombosis, Khorana score, Venous thromboembolism

OP07-3

Acute transfusion reactions of pediatric blood transfusions at Chiang Mai university hospital

Rungrote Natesirinilkul[1*], Kaokiat Sumitrmor[1], Chatpong Suksaran[1], Pattheera Rungreungsarn[1], Methira Kamthong[1], Sarisa Parisayuth[1], Kanda Fanhchaksai[1,4], Sasinee Hantrakool[2] and Nipapan Leetrakool[3]

[1] Pediatrics, Faculty of Medicine, Chiang Mai University, Thailand
[2] Internal Medicine, Faculty of Medicine, Chiang Mai University, Thailand
[3] HLA Laboratory, Blood Bank Section, Faculty of Medicine, Chiang Mai University, Thailand
[4] Research Cluster of Thalassemia and Red Blood Cell Disorders, Faculty of Medicine, Chiang Mai University, Thailand

Background: Acute transfusion reactions (ATRs) are common complications which occur within 24 hours after blood transfusions. They are commonly found in pediatric patients who have hematologic or oncologic diseases and may cause serious adverse events or even death. There are several types of ATRs. However, the evidences of ATRs, particularly in Thai pediatric patients, are limited. The objectives of this study are to study the incidence of each ATR in Thai pediatric patients and to determine the association between the types of blood components and each ATR in Chiang Mai University (CMU) Hospital.

Method: A retrospective observational study was conducted at the CMU Hospital. All patients aged less than 21 years who received any blood component and developed ATRs between 1 January 2009 and 31 December 2020 were enrolled. All ATRs were classified into 7 groups including acute hemolytic transfusion reaction (AHTR), febrile non-hemolytic transfusion reaction (FNHTR), allergic reaction,

transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), anaphylaxis and other reaction according to the National Healthcare Safety Network (NHSM) Hemovigilance Module (HM) of United States of America (USA). The demographic data, underlying diseases, types of blood components and ATRs were collected. The statistical significance was accepted when P-value was ≤ 0.05.

Results: Among 245 ATRs, the total incidence of ATRs in pediatric population in 11 years of study was 2 per 1,000 transfusion. There was no significant variation of indicence of ATRs in 11 years of the study. Allergic reaction (49.0%), FNHTR (32.7%) and anaphylaxis (15.9%) were three of the most common ATRs in this study. TRALI was found only one event while no TACO was found in these pediatric population. Packed red cells (PRC) and leucocyte-depleted packed red cell (LD-PRC) were significantly associated with allergic reaction (P = 0.048 and 0.014, respectively). Platelet concentration (PC), Leucocyte-depleted pool platelet concentrate (LPPC) and single donor platelet (SDP) with platelet additive solution (PAS) were significantly associated with anaphylaxis (P = 0.015, 0.026 and 0.011, respectively). However, SDP with PAS was significantly decreased allergic reaction and anaphylaxis with odd ratio (OR) of 0.23 (95% confidence interval; CI 0.09-0.59) and 0.30 (95% CI 0.12-0.78), respectively. TRALI was found in a patient who received SDP.

Conclusion: The incidence of ATRs in pediatric population were not high in this study. Allergic reaction, FNHTR and anaphylaxis were the most common ATRs in these population. SDP with PAS may be the key to decrease common ATRs particularly allergy-related reaction in pediatric population.

Keyword: Acute transfusion reactions, Pediatrics, Thailand, Blood components

OP07-4

Risk factors of platelet transfusion refractoriness in patients with AA/MDS who receive allogeneic hematopoietic stem cell transplantation

Jaeik Oh[1], Dong-Yeop Shin[1,2,3*], Ja-Min Byun[1,3], Youngil Koh[1,2,3], Hyungsuk Kim[4], Junshik Hong[1,2,3], Inho Kim[1,3] and Sung-Soo Yoon[1,3]

[1] Department of Internal Medicine, Seoul National University Hospital, Korea

[2] Center for Medical Innovation, Biomedical Research Institute, Seoul National University Hospital, Korea

[3] Cancer Research Institute, Seoul National University College of Medicine, Korea

[4] Department of Laboratory Medicine, Seoul National University Hospital, Korea

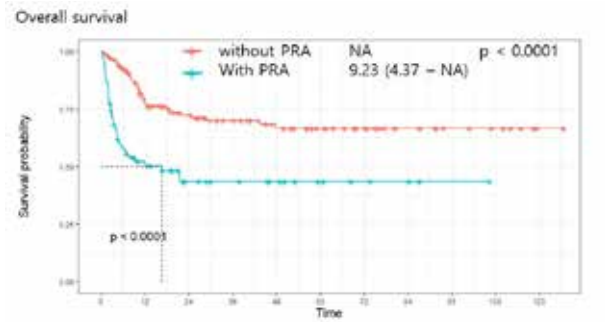
Background: Platelet transfusion refractoriness (PTR) is highly prevalent in patients with severe aplastic anemia (SAA) and myelodysplastic syndrome (MDS) who commonly receive a lot of transfusions. This study investigated risk factors of the occurrence and prognostic effects of PTR during allogeneic hematopoietic stem cell transplantation (HSCT) in patients with SAA/MDS

Method: Following patients' platelet count daily from the day patients received stem cells to discharge day, corrected count increment (CCI) was calculated based on platelet count after 14 hours from transfusion. Patients were considered as refractory to platelet transfusion when platelet counts were less than 10 x 10^9/L and when CCIs were less than 7.5 × 10^9/L on at least two sequential occasions.

Results: From 2011 to 2021, 235 MDS/SAA cases underwent allogenic HSCT were reviewed retrospectively. Of the 222 patients diagnosed with MDS or SAA, 89, 47 and 86 patients received allogenic HSCT from full matched siblings, full matched unrelated donors and mismatched donors respectively. Sixteen out of 59 (27.1%) patients with SAA had PTR and 54 out of 163 (33.1%) patients with MDS had PTR. Comparing patients according to the occurrence of PTR, septic shock, transfusion history of more than 10 red blood cell (RBC) units and number of transfused platelet unit were risk factors of PTR occurrence. On the other hand, SAA and matched gender between recipient and donors were favorable risk factors for PTR. Antithymocyte globulin usage and high body surface area also showed trends toward protective effects on PTR. Refractoriness to platelet transfusion not only affected patients' bleeding events, overall survival, and PLT & WBC recoveries, but also contributed to the occurrence of acute GVHD.

Conclusion: PTR is an important indicator of bleeding and survival outcomes. Occurrence of PTR should be closely monitored in patients with septic shock, gender mismatch between donor and recipient, and high requirement of blood transfusion after allogeneic HSCT.

Keyword: Platelet transfusion refractoriness, Allogeneic hemato-poietic stem cell transfusion, Aplastic anemia, Myelodysplastic syndrome, Acute graft versus host disease



OP07-5

Combining pharmacokinetics and comprehensive evaluation system to individualize the prophylaxis in pediatric patients with hemophilia A

Kun Huang, Runhui Wu*, Di Ai, Zhenping Chen, Yingzi Zhen and Gang Li

Hemotology Center, Beijing Children's Hospital, Capital Medical University, China

Background: Prophylaxis is the standard treatment for hemophilia A(HA). Due to the inter-individual variability of pharmacokinetics (PK), bleeding phenotype and joint vulnerability, individualized prophylactic protocol are vital to optimize the therapy of HA. Thus, this study was conducted to investigate the clinical outcomes of the new proposed PK-guided dosing strategy which combined the comprehensive evaluation system for escalation.

Method: Patients with severe HA and without FVIII inhibitor were enrolled. After a 72h washout period and a single-dose infusion of 50IU/kg of their routine used FVIII concentrate, each one received a PK test with a five-point design. The trough levels were calculated by WAPPS-Hemo. The bleeding rates (ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate) were estimated from six month before enrollment to the study exit. The ultrasound and HJHS were used to evaluate the patients' joints (both sides of ankles, knees and elbows) at every 12 months. The escalation criteria depended on joint bleeds, US scores and HJHS scores. Their quality of life was assessed by CHOKLAT sheets. The yearly FVIII consumption and infusions were calculated according to the prophylactic record of patients.

Results: Fifty-eight severe HA boys who had an observational period over 2 years were analyzed. Their age and body weight was 5.3(2.8,6.9) years and 21.5(16,25) kg respectively. At baseline, 34 of them had a trough level of <1IU/dL and seven target joints were detected according to previous definition. During the study period, 47 escalations were observed. Joint bleeds count the most proportion (48.3%, N=28). Significantly reduced ABR [0(0,6) vs. 4(0,8),P<0.0001] and AJBR[0(0,0.25) vs. 0(0,2),P<0.0001] was observed at study exit as well as the trend of decreased bleeding rates as the study progressed. Also, 85% (6/7) of the target joints vanished during the study. Statistical improvement of US scores(P=0.04) and HJHS scores(P=0.02) were also reported at study exit. The median annual weight adjusted FVIII consumption and infusions were 3500IU/kg/year and 156 times/year finally.

Conclusion: This PK-guided dosing strategy could reduce bleeding rates, eliminate target joints and improve impaired joints.

Keyword: Hemophilia A, Pediatric, Pharmacokinetics, Ultrasound, HJHS

		Baseline	0-6M	6-12M	12-18M	18-24M
ABR	Median (interquartile range)	4(0,8)	2(0,4)	2(0,4)	0(0,4)	0(0,2)
	Mean(range)	5.09(0-40)	3.02(0-14)	2.57(0-16)	1.76(0-8)	1.1(0-6)
	P value		<0.05	<0.01	<0.0001	<0.0001
AJBR	Median (interquartile range)	2(0,4)	0(0,2)	0(0,2)	0(0,2)	0(0,0.25)
	Mean(range)	2.68(0-26)	1.25(0-12)	1.13(0-12)	1.0(0-8)	0.67(0-6)
	P value		<0.05	<0.01	<0.001	<0.0001
ZBR	number (proportion)	16(27.6%)	28(48.3%)	29(50%)	35(60.3%)	40(69.0%)
ZJBR	number (proportion)	27(46.5%)	37(63.8%)	42(72.4%)	41(70.6%)	47(81.3%)

		Baseline	12M	24M
US scores	Median (interquartile range)	2(1,5)	2(1,5)	1.75(1,5)
	Mean(range)	4.04(0-22)	3.69(0-18)	3.39(0-18)
	P value		0.15	<0.05
HJHS scores	Median (interquartile range)	0.5(0,4.5)	0(0,3)	0(0,2.25)
	Mean(range)	2.5(0-9)	2.03(0-10)	1.55(0-10)
	P value		0.11	<0.05

POSTERS

BP01

Identification of cell type-specific effects of DNMT3A mutations involved in relapse of acute myeloid leukemia

Seo-Gyeong Bae[1], Jihwan Park[1*], Jae-Sook Ahn[2,3], Hyeoung-Joon Kim[2,3] and Mi Yeon Kim[2,3]

[1] School of Life Sciences, Gwangju Institute of Science and Technology (GIST), Korea

[2] Department of Internal Medicine, Chonnam National University Hwasun Hospital, Korea

[3] Genomic Research Center for Hematopoietic Diseases, Chonnam National University Hwasun Hospital, Korea

Background: Acute myeloid leukemia (AML) is a heterogeneous disease caused by distinctive mutations found in each patient and, as a result, each patient may have different cell type compositions. Since AML has a high frequency of relapse even if complete remission (CR) is achieved through treatment, the cause of relapse needs to be elucidated. DNMT3A mutation can persistently remain with a high variant allele frequency (VAF) in CR after treatment, and in some patients, DNMT3A mutations disappeared after induction therapy, showing a similar pattern to that of leukemic clones. To accurately analyze the complex cell composition in AML and identify the mutations of individual cells, it is necessary to sequence them at a single-cell level.

Method: We applied single-cell RNA sequencing (scRNA-seq) to bone marrow-derived mononuclear cells from six AML patients and three healthy donors. Sequential samples were obtained at the time of diagnosis (Dx) and CR for two non-relapsed patients and at Dx, CR, and relapse (Rel) for two relapsed patients to observe continuous transcriptional and mutational changes. We also used targeted sequencing to enhance the detection of DNMT3A mutations. We found 34 clusters, and cell type composition was compared based on the samples and disease stages. Gene set enrichment analysis was performed to identify signatures of leukemic stem cell (LSC) and DNMT3A mutant cell. Regulon network analysis was also performed to reveal activated master transcription factors of LSC compared to hematopoietic stem cell (HSC). To identify the clones that cause relapse, we analyzed copy number variation (CNV) at a single-cell level.

Results: By investigating cell type composition of each disease stage, we identified that LSCs are highly populated at both Dx and Rel while HSCs at Rel are lowly populated and HSCs at Dx are abnormal cells that do not express HSC markers and erythroid development-related genes. We found two transcription factors, FOXC1 and CEBPA, are overly expressed in LSC compared to normal HSC. By integrating scRNA-seq and targeted sequencing, we improved the detection of DNMT3A mutation, and revealed that DNMT3A mutant cells were enriched with AML-related gene sets, including relapse. Through CNV analysis, we identified that changes in DNMT3A mutant cells according to disease stage showed different patterns, and cell types including clones causing relapse were also different depending on the VAF of DNMT3A at CR: **i**) for a relapsed patient with low DNMT3A VAF at CR, DNMT3A mutation was mainly found in granulocyte-monocyte progenitor (GMP) at Dx and its mutation remained at CR. **ii**) for a relapsed patient with high DNMT3A VAF at CR, during CR, DNMT3A mutation was mainly found in lymphoid-primed multipotential progenitor (LMPP), where it was not originally discovered at Dx, and its mutation remained until Rel. Trajectory analysis revealed that, in both GMP and LMPP at CR proceeding towards LSC at Rel, the expression of cell proliferation and cell cycle-related genes decreased in the early stage of cell progression from CR to Rel, whereas the expression of cell-cell adhesion and negative regulation of apoptotic process increased towards the end of LSC.

Conclusion: Using scRNA-seq, we characterized the heterogeneity of HSC in AML and newly identified an abnormally behaved cell cluster, which can be used to accurately segregate heterogeneous HSC population. We also found that DNMT3A may play a key factor in the relapse of AML by identifying its transcriptome and mutations together at a single-cell level.

Keyword: Acute myeloid leukemia, Single cell RNA sequencing, DNMT3A, Mutation, Relapse

BP02

DNA methylation-based biomarkers for azacitidine resistance in myelodysplastic syndrome

Da Yeon Kim[1,2] and Eun Ju Kim[1,2*]

[1] Division of Radiation Biomedical Research, Korea Institute of Radiological and Medical Sciences, Korea

[2] Department of Radiological and Medico-Oncological Sciences, University of Science and Technology, Korea

Background: Myelodysplastic syndrome (MDS) is heterogeneous hematopoietic disorders that mainly involve cytogenetic changes and/or genetic mutations and exhibits a widespread gene hypermethylation in advanced stage. Patients with higher-risk MDS are typically treated with repeated cycles of the hypomethylating agents azacitidine. However, not all patients respond to these therapies, and less than 50% patients achieve hematologic improvement. In this study, we focused on the emerging role for epigenetic data in clinical management as a potential tool to aid in diagnostic and

therapeutic decision-making.

Method: First, we established an azacitidine-resistant F-36P cell line from the parent F-36P MDS cell line. Subsequently, we obtained expression profiles for azacitidine-resistant F-36P and F-36P cell, then we used biological and bioinformatics approaches to analyze candidate genes and pathways contributing to resistance to azacitidine.

Results: Sixty candidate genes encoding proteins involved in azacitidine-resistant-related pathways (eg, pathway in cancer, chronic myeloid leukemia, transcriptional misregulation in cancer, etc) were identified. Interestingly, twenty-four of the candidate genes showed differential methylation patterns in promoter regions that were inversely correlated with the azacitidine-resistant, suggesting that DNA methylation status may contribute to azacitidine-resistant.

Conclusion: Based on these results, we are pursuing development of a diagnostic gene chip for azacytidine-resistance in MDS patients, which may attract great interest to newly diagnosed MDS patients and MDS patients undergoing azacitidine treatment.

Keyword: Myelodysplastic syndrome, Azacitidine, Resistance, DNA methylation, Biomarkers

BP03

Integrated targeted RNA fusion analysis and deep sequencing highlights diverse primary and secondary clonal abnormalities in a cohort of paired diagnosis-relapse pediatric B-cell acute lymphoblastic leukemia cases

Rozy Thakur

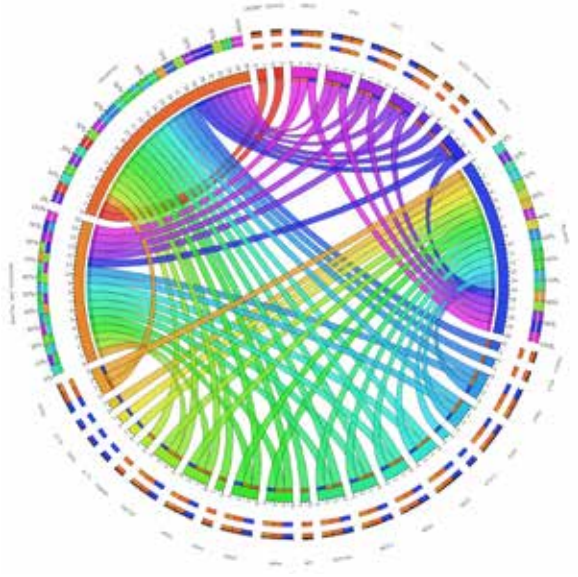
Pediatric Hematology-Oncology Lab-Advanced Pediatrics Centre, PGIMER, India

Background: B-ALL is the most common pediatric malignancy and despite improvements in standard of care, 15-20% cases relapse over a period of time. In this current study, we analyzed primary and secondary genetic events and clonal evolution architecture pattern in a cohort of paired B-ALL diagnosis and relapse samples to define and understand the mutational diversity and clonal pathways to disease relapse.

Method: A total of 22 B-ALL (11 paired) samples were included. FISH/RT-PCR, Targeted NGS based RNA fusion panel was used to note primary event. Cases negative for RT-PCR and fusion panel is tested for Ph like ALL by Genome expression profiling (GEP) by TaqMan array-based method. Secondary SNVs/INDELs and CNVs were characterized by deep sequencing using a custom 77 gene NGS panel. A major clone was defined with VAF >30% and minor <30%. Advanced bioinformatics analysis to define clonal patterns and pathways involved was performed.

Results: The age 3-11 years, M:F ratio 2.7:1. TLC at diagnosis 5.5-224 x109/L, 6 were NCI Intermediate & 5 standard risk, Day 8 ABC < 1 x 109/L in 10 cases, Day 35 MRD <0.01% in 7 and BM status was M1 in all. Relapse was very early (< 12 months) in 3 cases, early relapse (18-36 months) in 4 cases and late relapse (>36 months) in 4 cases. FISH/RT-PCR detected BCR-ABL1 in 2, ETV6-RUNX1 in 2 and hypodiploidy in 1 case. Fusion panel detected EBF1-PDGFR2a in 1 and KMT2A-MLLT1 in another case. 4 cases tested for Ph like ALL by genome expression profiling comes out to be negative. The secondary abnormalities included 67 SNVs/INDELs (9 recurrent) in 31 leukemia related driver genes as clonal (22/67-33%) or sub-clonal (45/67-67%) events. However, relapse enriched mutations were primarily noted in 14 genes -NR3C2, NT5C2, PMS2, MSH2, MSH6, TP53, NSD2, KMT2D, ETV6, KRAS, NRAS, TET2, UHRF1, TENM3 in 10/11 (91%) cases. A total of 45 CNV events were noted in 22 samples, of which, CDKN2A del was most common event noted in 10/22 (45%) cases. On clonal evolution analysis, 4 cases (36%) acquired a mutation under chemotherapy pressure, 3 (27%) shared major clones at diagnosis and relapse, 1 (9%) had a minor clone at diagnosis that evolved at relapse, 1 (9%) a mixed pattern, 1 (9%) had no major clone and 1 (9%) had? ancestral clonal origin.

Conclusion: The relapse enriched gene signature was noted in 14 genes related with epigenetic, mismatch repair, chemotherapy metabolism and cell signaling pathways. Clonal evolution highlighted higher percentages of our relapse cases (36%) evolving from a mutation under chemotherapy pressure compared to literature (25%).



BP04

A retrospective analysis of real-world outcomes of dose-adjusted epoch compared with CHOP based chemotherapy as frontline therapy for untreated PTCL

Sang-Bo Oh[1], Ho-Jin Shin[2*] and Do-Young Kim[2]

[1] Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Medical Research Institute, Pusan National University Yangsan Hospital, Yangsan, Korea

[2] Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Medical Research Institute, Pusan National University Hospital, Busan, Korea

Background: Patients with peripheral T-cell lymphomas (PTCL) have a globally poor prognosis and responses to currently recommended treatments which are often not durable. The standard CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) based chemotherapy (CHOP or the addition of etoposide to CHOP (CHOEP)) for PTCL has disappointing outcomes and the use of more intensive chemotherapy regimens has not resulted in favorable outcomes in patients with PTCL. Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) has been evaluated in prospective phase II studies in patients with previously untreated PTCL and may be considered as a first line approach for PTCL. We aimed to compare outcomes of CHOP based chemotherapy and DA-EPOCH in untreated PTCL patients in real world data.

Method: This multicenter retrospective study enrolled 99 consecutive patients with untreated PTCL at the Hematology division in Pusan National University Hospital and Pusan National University Yangsan Hospital from the January 2008 to September 2021. Clinical data were retrospectively collected from the medical records.

Results: We analyzed retrospectively 99 patients diagnosed with PTCL between 2008 and 2021. Median patient age was 62 years and 62% of patients were men. PTCL-NOS was the predominant histological finding (44 patients, 44.4%), followed by AITL (34 patients, 34.3%), ALK positive ALCL (10 patients, 10.1%), ALK negative ALCL (7 patients, 7.1%), MEITL (2 patients, 2.0%), and EATL (1 patient, 1.0%). The majority of the patients were stage III and IV. According to IPI criteria, 41% of patients were high-intermediate or high risk, and 41 patients were categorized as PIT group 3-4. The patients were divided into two treatment groups; patients who received treatment with CHOP-based chemotherapy (71 patients, 71.7%) and patients who received treatment with DA- EPOCH (26 patients, 26.3%). Among the patients treated with CHOP based regimen, 74% achieved CR and 6% achieved PR. Among the patients treated with DA-EPOCH regimen, 90.4% achieved CR and 4.8% achieved PR. With a median follow-up 28.7 (range 0.5-175) months, the estimated 2-year progression-free survival (PFS) and overall survival (OS) were 54.2 and 64.3% in CHOP based chemotherapy group and 64.2 and 72.6% in DA-EPOCH chemotherapy group, respectively. There were no significant differences in PFS and OS between patients treated with CHOP based and DA-EPOCH based combination chemotherapy. In this retrospective study, 15 patients with PTCL undergoing autologous stem cell transplantation (ASCT) in first CR. (6 patients among CHOP based chemotherapy group, 9 patients among DA-EPOCH chemotherapy group). At the median follow-up of 28.7 months, the median overall survival was not reached for the entire cohort of patients who underwent ASCT, whereas it was 114 months for those not receiving ASCT among CHOP based chemotherapy group, and 32.2 months for those not receiving ASCT among DA- EPOCH based chemotherapy group. The most common grade ≥3 adverse events were neutropenia (88.4%), thrombocytopenia (27%) and anemia (23%).

Conclusion: In conclusion, our results indicate that DA-EPOCH had a high response rate with manageable toxicity profile for untreated PTCL patients compared with CHOP based chemotherapy. DA-EPOCH may be considered as reasonable fist line approach for peripheral T-cell lymphoma patients.

Keyword: Peripheral T cell lymphoma, Dose-adjusted EPOCH, CHOP

Table and images

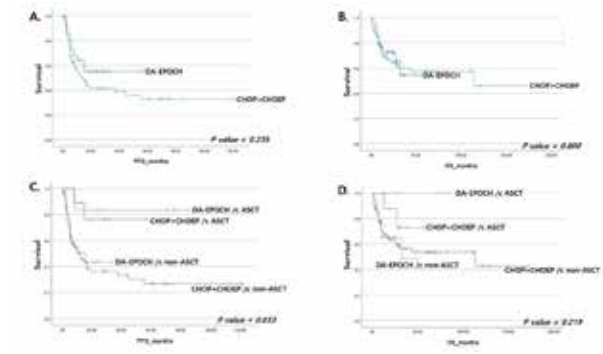


Figure 1. Kaplan-Meier estimates of progression-free (A) and overall survival (B) of patients with peripheral T-cell lymphomas (PTCL) receiving DA- EPOCH and CHOP based chemotherapy. Analysis of progression-free survival (C) and overall survival (D) for first complete remission patients with PTCL (autologous stem cell transplantation (ASCT) versus non-ASCT) by treatment group.

BP05

First-line treatment with either VMP or RD for transplant-ineligible patients with multiple myeloma: a pooled analysis of multicenter real-world data

Jung Yeon Lee[1], Young-Woo Jeon[2], Seung-Ah Yahng[3], Seung-Hwan Shin[4], Chang-Ki Min[1] and Sung-Soo Park[1*]

[1] Department of Hematology, Catholic Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea
[2] Department of Hematology, Yeoido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea
[3] Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea
[4] Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

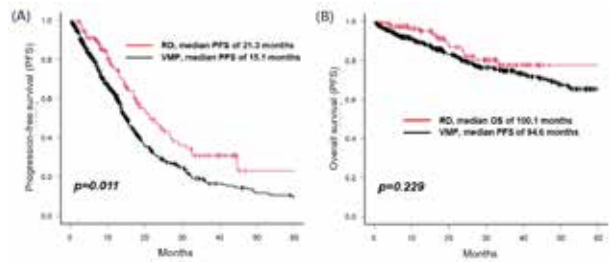
Background: Bortezomib, melphalan, and prednisone (VMP) and lenalidomide and low-dose dexamethasone (RD) regimens remain the standard treatment of transplant-ineligible patients for newly diagnosed multiple myeloma (MM) in Korea. To date, there are currently no direct head-to-head clinical trials comparing VMP versus RD as the first line treatment for MM. In this analysis, we retrospectively evaluated data with the aim of assessing the impact of each regimen on clinical outcomes as well as the characteristics associated with beneficial therapeutic choice in elderly untreated MM patients.

Method: A total of 559 transplant-ineligible MM patients treated with VMP or RD between 2010 and 2021 were analyzed. Cytogenetic analyses were performed using conventional cytogenetics and fluorescence in situ hybridization (FISH). According to the International Myeloma Working Group 2014 consensus criteria, high risk cytogenetics included deletion of 17p13, translocation of chromosome 4 and 14 and translocation of chromosome 14 and 16. Progression free survival (PFS) and overall survival (OS) was the primary and secondary end-points, respectively. Survival analyses were conducted by the Kaplan-Meier method, and the Cox proportional hazards regression model was used to estimate hazard ratios (HR) and 95% confidence intervals (CI). PFS and OS survival curves for VMP and RD were compared using the log-rank test.

Results: Of the total 559 patients, 443 (79.2%) were in the VMP and 116 (20.8%) in the RD. The sex ratio was 1.0 and elderly patients (age ≥75 years) were 160 (28.6%). Among the 365 patients whose genetic risk assessment was possible, 94 (16.8%) in high risk cytogenetics. The median duration of follow up for all was 32.4 months (95% CI, 29.2-35.3). The median PFS and OS was 16.1 months (95% CI, 14.6-17.7) and 100.1 months (95% CI, 85-not reached), respectively. In VMP, there were significantly higher percentage of International Staging System (ISS) III (35.9% vs. 18.1%, P <0.001) and elevated lactate dehydrogenase (LDH) (31.4% vs. 21.6%, P=0.035). The glomerular filtration rate (GFR) was significantly lower than RD (56.4 vs. 74.3 mL/min/1.73m2, P<0.001). Median age was significantly older in RD (70 vs. 72, years, P<0.001). The overall response rates (partial response or better) (VMP vs. RD: 86.2% vs. 91.4%) and complete response rate (VMP vs. RD: 28.4% vs. 25.9%) were similar. The PFS was significantly different in the two groups (VMP vs. RD: 15.1 vs. 21.3 months, P=0.011), while no significant difference in OS (VMP vs. RD: 94.6 vs. 100.1 months, P=0.229). A 2:1 matched cohort study was conducted by age (< 75 years), β2-microglobulin (β2-MG) (< 5.5 μg/mL) and LDH (within normal). Baseline creatinine was significant difference between VMP and RD (1.0 vs. 0.93 mL/min/1.73m2, P=0.006). The PFS (VMP vs. RD: 15.7 vs. 20.0 months, P=0.055) and OS (VMP vs. RD: 100.1 vs 111.0 months, P=0.848) tended to be longer in RD. In the subgroup analysis, RD regimen was more effective in age (< 75 years) (HR 0.61, 95% CI 0.42-0.87, P=0.005), standard risk cytogenetics (HR 0.59, 95% CI 0.40-0.87, P=0.010), ISS II (HR 0.55, 95% CI 0.39-0.85, P=0.004), β2-MG (< 5.5 μg/mL) (HR 0.62, 95% CI 0.45-0.86, P=0.003), normal LDH (HR 0.65, 95% CI 0.37-1.13, P=0.006) and GFR (≥ 30 mL/min/1.73m2) (HR 0.59, 95% CI 0.45-0.81, P < 0.001).

Conclusion: In light of this results, RD regimen as induction chemotherapy was effective in younger (< 75 years) and standard risk patients, while high risk cytogenetics and low GFR (< 30 mL/min/1.73m2) benefited more from VMP. The RD seems to be associated to better PFS in the long term.

Keyword: Multiple myeloma, Induction chemotherapy, Survival



BP06

Neutrophil– lymphocyte ratio and carotid plaque burden in patients with essential thrombocythemia and polycythemia vera

Seug Yun Yoon, Sun Young Jeong, Min-Young Lee, Kyoung-Ha Kim, Namsu Lee and Jong-Ho Won*

Division of Hematology & Medical Oncology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Seoul, Korea

Background: Philadelphia chromosome-negative MPNs are clonal disorders of hematopoietic stem cells including PV, ET, and primary myelofibrosis (PMF). The MPNs are inflammatory cancers, in which the malignant clone triggers inflammatory cytokines, which in a self-perpetuating vicious cycle sustain the inflammatory drive.

MPNs progression is in the biological continuum from the early cancer stages (ET/PV) to the advanced "burnt-out" myelofibrosis and impending leukemic transformation. The goals of treatment for ET and PV are prevention of thrombosis in addition to the control of general symptoms and monitoring the progression to leukemia. To date, drug therapy has not been shown to improve survival or prevent leukemic/fibrotic transformation in either ET or PV. The main goal of therapy in both ET and PV is to prevent thrombohemorrhagic complications. The NLR, a fast and simple method for assessing inflammatory status calculated as the ratio of absolute neutrophil count to absolute lymphocyte count, has been reported to be associated with subclinical atherosclerosis. Carotid Ultrasound is a safe and available noninvasive diagnostic tool that provides information about the carotid arteries' characteristics and may be used for early detection of coronary artery disease as well as cardiovascular and stroke event risk stratifications. To the best of our knowledge, there is limited studies regarding the assessment of NLR and carotid intima-thickness (cIMT) in patients with ET or PV. Therefore, we evaluated the NLR in patients with PV or ET and compared it with control participants. We also investigated the relationship between NLR and cIMT based on inflammatory activity.

Method : Study population

We performed a single center, retrospective study of patients with ET or PV who diagnosis according to WHO 2016 criteria, between January 2010 and September 2021. Patients diagnosed with PMF were not included. We selected control group as subjects who underwent carotid ultrasonography as the medical health checkup program at the Health Promotion Center of Soonchunhyang University Seoul Hospital during January 2016 to June 2018. We made propensity-score matching to minimize allocation bias and better represent the effects of MPN disease itself. All carotid ultrasonography of the MPN group in this study were performed at the time of diagnosis or during the follow-up period. This study was carried out in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Soonchunhyang University Hospital (IRB no.), which waived the requirement for informed consent due to the retrospective nature of the study.

Variables and definitions

The neutrophil-to-lymphocyte ratio was calculated on the basis of absolute peripheral granulocyte (as a proxy for the neutrophil count) (N; ×109/Liter) and lymphocyte (L; ×109/Liter) blood counts, using the formula: NLR = N/L. To see whether the distribution was influenced by any current infection, we further assessed the associations in individuals for whom a CRP (mg/dL) measurement was available. We considered individuals with an elevated CRP level (CRP>1 mg/dL) as having a potential infection and excluded them from the analysis. Diabetes mellitus was defined by the patient having been informed of this diagnosis by a physician prior to admission or was receiving hypoglycemic treatments (dietary, oral anti-diabetic agents, or insulin) or serum HbA1c levels >6.5%. Hypertension was defined by known elevation of blood pressure on at least two separate occasions according to the medical history or the use of anti-hypertensive medications in a patient with known controlled hypertension. Dyslipidemia was defined by medical history or the use of lipid-lowering medications in order to reduce lipids or fasting serum low-density lipoprotein (LDL) levels >160 mg/dl (2). Smoking status was ascertained by the medical history.

Carotid ultrasound examination

A high-resolution B-mode ultrasound (EPIQ 5C or IE 33 ultrasound systems; Philips, Andover, Massachusetts) equipped with a 11.0 MHz linear array transducer was used for carotid ultrasonography. Common carotid artery IMT (CCA-IMT) is measured from the level of the common carotid artery (1 cm proximal to the dilation of the carotid bulb) far wall in a region free of plaque. Carotid plaque was defined as local thickening of the IMT of >50% compared to the surrounding vessel wall, an IMT >1.5 mm, or local thickening >0.5 mm. If plaque was identified at that site, a different segment was chosen. For measurement of the IMT, the distance between the leading edges of the lumen-intima interface and the media-adventitia interface of the B-mode frame was taken. Software (Q-lab; Philips Medical Systems, Andover, MA, USA) that analysed the IMT automatically at 64 points within a segment of 10mm was adopted; the value given was the arithmetic mean IMT calculated. Mean CIMT was determined as the average of all measurements of both the left and right arteries. The extracranial carotid arteries were divided into three sectors on each side: the common carotid artery and its bulb, the internal carotid artery, and the external carotid artery. At least one plaque in any sector was scored 1 point, while the absence of plaques was scored as 0. Thus, the carotid plaque score ranged from 0 (absence of plaques) to 6 (plaques in all sectors) (3). All the measurements were performed on the same device by the same experienced sonographer (SM Yoon with 10 years of experience, RDCS; Registered Diagnostic Cardiac Sonographer holder).

Statistics

Categorical variables are reported as numbers (percentages) and were compared using the chi-square test or Fisher exact test. Continuous variables are reported as mean ± SD and were compared using Student's t-test. Pearson's correlation coefficients were calculated to determine the relationships between NLR and carotid plaque score. A propensity score was used to adjust for potential selection or predisposition bias. Age, sex, smoking status, diabetes, hypertension and dyslipidemia were selected to calculate the propensity score. On the basis of the propensity score, the patients were selected by 1:3 matching without replacement using a greedy algorithm and the nearest available pair matching methods. A caliper width of 0.1 SD of the logit of the estimated propensity score was used for matching. The covariate balance achieved by propensity score-matching was assessed by calculating the absolute standardized differences in covariates between the two groups. $p < .05$ was considered significant. All statistical analyses were performed using R version 3.6.1 and Rex version 3.0.3 (RexSoft Inc., Seoul, Korea).

Results : Study Population and clinical features

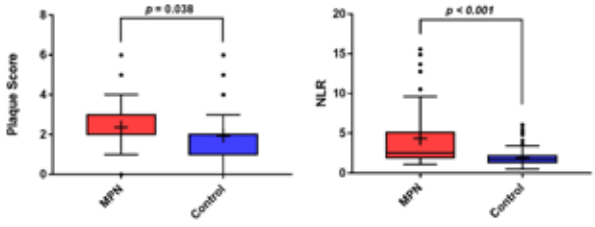
After 3:1 propensity-score matching, 140 of 4822 patients in the control group (2.9%) were successfully matched to 51 patients in the ET/PV group. The two groups were well-balanced in their baseline characteristics after matching. The mean ages of the patients with ET/PV and the control group were 63.65 ± 13.53 and 62.09 ± 10.89 years, respectively. There was no significant difference in age, sex and various cardiovascular risk factors between the groups. Total cholesterol, LDL and HDL cholesterol levels was higher among control group than ET/PV group. Median duration of the ET/PV disease was 3.74 (interquartile range 1.28, 8.44) years.

Comparison of carotid plaque burden and NLR between ET/PV and control groups

When comparing NLR, the number of excluded patients with a CRP exceeding 1mg/dL was five in ET/PV group and one in control group. The mean NLR was significantly higher in ET/PV group than in control group (4.77 ± 3.96 vs. 1.93 ± 1.03, $p < 0.001$). The carotid plaque score was also higher in ET/PV group than in control group (2.37 ± 1.47 vs. 1.94 ± 1.17, $p = 0.038$) (Figure 1), but no difference between groups in IMT. There was no difference between MPN disease (ET vs. PV) in the NLR, carotid plaque score and IMT.

Conclusion: Patients with PV/ET show a high NLR and carotid plaque burden, expression of potentially increased cardiovascular risk. These findings may be the basis for supporting the value of early initiation of preventive treatment such as statin for decrease CV risk in patients with MPN disease.

Keyword: Essential thrombocythemia, Polycythemia vera, Carotid plaque burden, Neutrophil-lymphocyte ratio



BP07

Detection of recurrent, rare gene fusions and correlation with clinical manifestations in acute leukemia by targeted RNA-sequencing

Seo Wan Kim

Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea

Background: Gene fusions can emerge from chromosomal rearrangements such as translocations, inversions and deletions and they are crucial for categorizing acute leukemia, selecting the appropriate treatment and predicting prognosis. Conventional methods for detecting gene fusions have drawbacks such as a risk of missing cryptic translocation due to low resolution, limited coverage by using pre-designed probes or primers targeting known aberrations and lacking multiplexity. Targeted RNA sequencing with AMP(Anchored Multiplex PCR) based cDNA library development has been introduced as an alternative option in current laboratories. Using AMP, amplifying sequences of interest without prior knowledge of the partner sequence is possible with universal primers complementary to the molecular barcoded adaptor and various gene-specific primers(GSPs). Here, we evaluate the diagnostic performance of targeted RNA sequencing in detecting known recurrent gene fusions and rare gene fusions by comparing results with conventional methods.

Method: Patients diagnosed or relapsed with acute leukemia in our center were included between August 2017 and December 2021. Four hundred forty-four samples at initial diagnosis and ten follow-up samples from nine relapsed patients were obtained. Total RNA was extracted from bone marrow aspirate using QIAamp RNA Blood Mini Kit (Qiagen, Hilden, Germany). The cDNA library was prepared by two rounds of low-cycle PCR with the Archer FusionPlex Pan-Heme kit (ArcherDX, Boulder, Colorado), using GSPs covering 199 target genes and universal primers. Final products were sequenced on the NextSeq 550Dx instrument (Illumina, San Diego, California). After sequencing, data were analyzed and interpreted by Archer Analysis Software (version 5.1, ArcherDX). Results were compared with the G-banding karyotyping, fluorescence in situ hybridization, and/or RT-PCR.

Results: 184 of the 454 samples tested positive for gene fusion, representing a positive rate of 40.53%, and 48 fusion genes were detected. Among fusions identified, 13 were recurrent translocations listed in the WHO classification, 25 were fusions previously reported, and 10 were novel fusions. Total 444 samples were included in the comparison analysis with conventional methods after excluding ten samples that could not be compared because no karyotyping, FISH, and RT-PCR findings were available. Positive and negative concordance rate was estimated as 91.5% and 82.8%, respectively. A substantial agreement between targeted RNA sequencing with conventional methods was observed (Kohen's kappa coefficient=0.691, p-value<0.001). In the group which was positive for targeted RNA sequencing but negative in conventional methods, cryptic translocation ETV6-RUNX1 with favorable prognosis was most common (10/52 samples). Also, in this group, KMT2A rearrangements with various partner genes were common (5/52 samples). Among results that were negative for targeted RNA sequencing but positive in conventional methods, inv(3)(q21.3q26.2) involving MECOM was most common (4/12 samples).

Conclusion: Targeted RNA sequencing showed a good agreement with conventional methods in detecting gene fusion in acute leu-

kemia patients with comparable turn-around time. Targeted RNA sequencing identifies more cases with cryptic translocations and gene fusions with multiple or novel partner genes than conventional methods. In conclusion, targeted RNA sequencing results and results of conventional methods should be interpreted as complementary to minimize false negatives in detecting gene fusions.

Keyword: Acute leukemia, Gene fusion detection, Next-generation Sequencing, Targeted RNA sequencing

BP08

Characterization of alpha beta double negative T cells in children with acquired aplastic anemia

Hui Chen

Hematologic Disease Laboratory, Beijing Children's Hospital, China

Background: Acquired aplastic anemia (aAA) is characterized by hematopoietic bone marrow failure and peripheral cytopenia. The pathophysiology is most associated with T cell mediated immune dysfunction. CD4+ helper and CD8+ cytotoxic T cells are classic subsets in T lymphocytes, which express both alpha and beta chains of the T cell receptor (TCR). However, a small subpopulation expressing gamma/delta (γδ) or alpha/beta (αβ) TCR, that lacks the CD4 and CD8 co-receptors in peripheral blood, was known as CD4-CD8- T cells. Especially, αβ double negative T (DNT) cells can have immune and inflammatory responses which contribute to various disorders. But the data on these DNT cells in aAA children are limited.

Method: We aimed to investigate alpha beta (αβ) DNT cells among 185 cases of newly diagnosed aAA children in Beijing Children's hospital from January 2018 to December 2020, and analyzed the percentages in different severity of aAA, hepatitis-associated aplastic anemia (HAAA) which is a variant of aAA followed acute viral hepatitis, autoimmune lymphoproliferative syndrome (ALPS), inherited bone marrow failure syndrome (IBMFS) and healthy donors (HD). Assessment of DNT cells was done using sensitive multi-color flow cytometry with FITC-conjugated anti-CD3, PerCP-conjugated anti-CD45, PE-Vio770-conjugated anti-CD4, APC-Vio770-conjugated anti-CD8, PE-conjugated anti-TCRγδ and APC-conjugated anti-TCRαβ. One-way ANOVA test was used for analysis among multiple unpaired groups. All analyses were performed using GraphPad Prism 5.0. The difference was considered significant when P value was less than 0.05.

Results: Flow cytometric immunophenotyping of aAA patients'peripheral blood showed that the percentage of αβ DNT cells were significantly higher compared to IBMFS (1.52% vs 0.76%, $p<0.05$) and HDs (1.52% vs 1.10%, $p<0.001$).And HAAA showed a marked increase of CD4-CD8- T cells as compared to MAA (15.94% vs 7.73%, $p<0.01$) , SAA/VSAA (15.94% vs 8.32%, $p<0.05$) , IBMFS (15.94% vs 7.96%, $p<0.05$) and HDs (15.94% vs 8.50%, $p<0.05$).

Conclusion: We demonstrated the percentage of αβ DNT cells are amplified in patients with aAA, and an elevated percentage of CD4-CD8- T cells was seen in HAAA. It suggests that these cells might play a role in the clinical course of aAA. However, further insights into the mechanism of DNT cells in aAA, could be used to predict disease progression and possibly remission.

Keyword: Double negative T cell, ALPS, IBMFS, Aplastic anemia, Children

BP09

Levels of heparin induced anti-PF4 antibodies and endogenous glycosaminoglycans and their relationship with inflammatory biomarkers in pulmonary embolism patients

Bulent Kantarcioglu[1*], Amir Darki[2], Fakiha Siddiqui[1], Debra Hoppensteadt[1], Joseph Lewis[1], Roland Krämer[3] and Jawed Fareed[1]

[1] Department of Pathology and Laboratory Medicine, Cardiovascular Research Institute, Health Sciences Division., Loyola University Chicago, USA

[2] Department of Internal Medicine, Division of Cardiovascular Disease., Loyola University Chicago, USA

[3] Institute of Inorganic Chemistry, Heidelberg University, Germany

Background: Venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism, is the third leading cause of cardiovascular death. Heparin induced thrombocytopenia is a life-threatening complication of exposure to heparins resulting from an autoantibody directed against endogenous platelet factor 4 leading to catastrophic venous and arterial thrombosis. The inflammatory cytokines are a well-known part of the coagulation and fibrinolytic processes. Increased levels of inflammatory cytokines have been shown in studies of venous thrombosis. Endothelial damage and shedding of endothelial glycocalyx have also been shown in certain thrombotic disease states, conferring that they have important functions in circulatory homeostasis. In this study, we sought to quantify the levels of heparin induced antibody (HIA) isotypes together with endogenous glycosaminoglycans (GAGs) in a patient cohort, comprised of PE, to determine their impact on pathophysi-

ology of VTE and HIT and observe whether there is a relationship in between and inflammatory marker subtypes.

Method: Patients 18 years or older were recruited to participate in this study through enrollment conducted in conjunction with an ongoing IRB approved project by the Pulmonary Embolism Response Team (PERT) registry. Whole blood samples were drawn from patients within 24 hours of confirmed diagnosis of acute PE and collected under an Institutional Review Board approved protocol. Samples processed for platelet- poor plasma and stored at -80C prior to analysis. The samples were tested for various biomarkers of thromboinflammation HIA isotypes of IgA, IgG, and IgM ELISA assay, endogenous GAGs with heparin red assay and inflammatory biomarkers with biochip assay. Circulating levels of each biomarker in PE patient plasma were compared to control plasma. $P < 0.05$ was considered statistically significant.

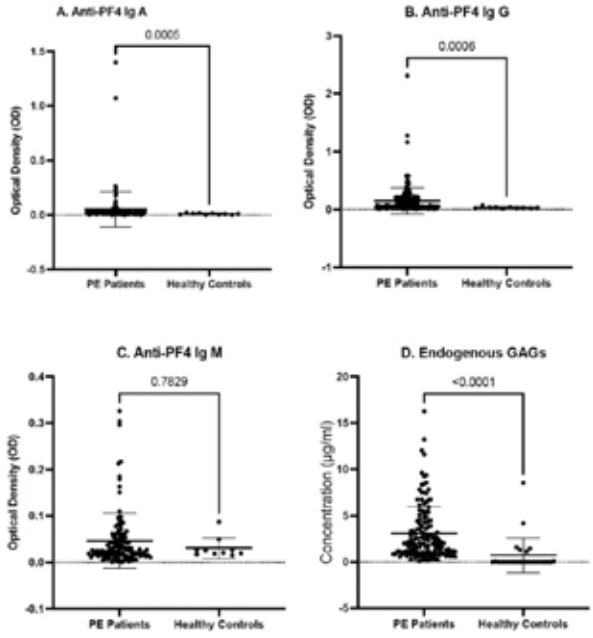
Results: The levels of anti-PF4 Ig A, Ig G and endogenous GAGs were significantly elevated in acute PE patients compared to normal healthy individuals ($P < 0.05$). The increase in anti-PF4 Ig M was not statistically significant (p: 0.78).

Anti PF4 Ig A were correlated with IL-2 (Spearman r: 0,294; p: <0,01), IL-6 (Spearman r: 0,251; p: 0,01) and TNFA (Spearman r: 0,212; p: 0.04). Anti PF4 Ig G were correlated with IL-6 (Spearman r: 0,291; p: <0,01) and d-dimer (Spearman r: 0.239; p: <0,01). Anti PF4 Ig M were correlated with IL-2 (Spearman r: 0,347; p: 0,001) and MCP-1 (Spearman r: -0,245; p: 0,02). The levels of endogenous GAGs were correlated with with TNF-α (Spearman r: 0,413; p: <0,001), IL-10 (Spearman r: 0,357; p: <0,01), IL-8 (Spearman r: 0,324; p: <0,01), IL-1β (Spearman r: 0,253; p: 0.03), IL-1α (Spearman r: 0,241; p: 0.04) and VEGF (Spearman r: - 0,257; p: 0.03).

The levels of anti-PF4 antibody isotypes. Anti-PF4 Ig G was correlated with anti-PF4 Ig A ($r= 0.438$, $p <0.001$) and anti-PF4 Ig M ($r= 0.242$, $p <0.01$) and anti-PF4 Ig A was correlated with anti-PF4 Ig M ($r= 0.424$, $p<0.001$). However, we did not observe any significant correlation between the levels of anti-PF4 antibody isotypes and endogenous GAGs.

Conclusion: In conclusion, the levels of HIA Ig A and Ig G isotypes and endogenous GAGs were significantly elevated in PE patients compared to normal healthy individuals showing significant correlations with inflammatory biomarkers. Our findings supports that the development of thrombosis is likely due to releasing of PF4 antigen from platelets and shedding of endogenous GAGS from the endothelial cells causing activation of endothelial cells, platelets, and leukocytes, resulting in inflammatory cytokine release and triggering of the coagulation system.

Keyword: Pulmonary embolism, Inflammatory biomarkers, Glycos-aminoglycans, Anti-PF4 antibodies



BP10

Differences in comorbidities by trajectory groups as a reference in identifying patients at risk for late mortality in childhood cancer survivors

Hyery Kim[1], Hae Reong Kim[2], Sunghan Kang[1], Kyung-Nam Koh[1], Ho Joon Im[1] and Yu Rang Park[2*]

[1] Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea

[2] Biomedical Systems Informatics, Yonsei University College of Medicine, Korea

Background: Childhood cancer causes significant long-term morbidity and mortality. Tracking the long-term morbidities and assessing the risks for mortality are needed for childhood cancer survivors. This study analyzed comorbidities by trajectory groups for late mortality in childhood cancer survivors of >10 years, based on data collected from the nationwide claims database of the entire Korean population.

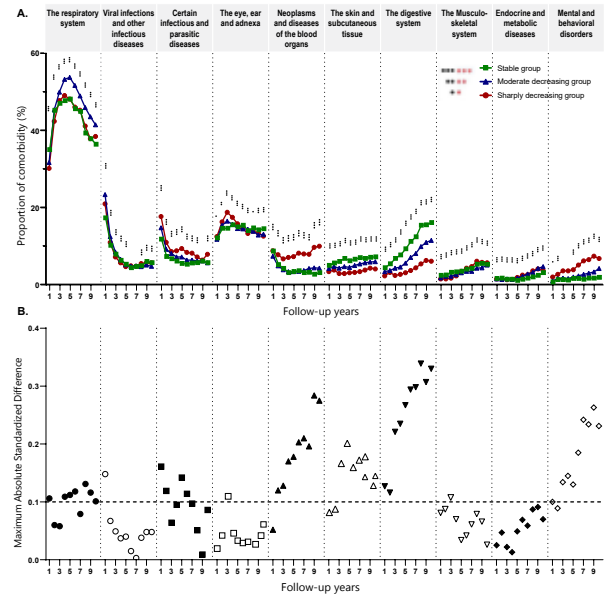
Method: Data were collected from the National Health Insurance Service. Patients who first received a cancer diagnosis under the age of 20 years between 2003 and 2017 were included. The onset of cancer diagnosis was defined as the time of the earliest diagnosis when any cancer-related medical treatment was prescribed within

one month. For group-based trajectory analysis, the total numbers of the entire claimed diagnostic codes per year were used as an input variable.

Results: This study included 8,119 patients who were diagnosed and treated for cancer before the age of 20 between 2003 and 2017. Trajectory groups were classified into three, with increasing annual changes in the number of diagnoses from group 1 to group 3. There were significant differences in the patterns of most of the comorbidity and survival rates between the trajectory groups. Figure shows the proportions of each diagnosis to the total yearly numbers of the top 10 comorbidities. There were three major trends in the annual incidences—early surge and decreasing, midterm surge, and continuously decreasing and growing proportion. Infection-related disorders (e.g., certain infections and parasite disease, viral infections and other infectious diseases) continuously decreased from the starting point. The proportion of diseases in the eye, ear, adnexa, or respiratory system showed a midterm surge at around 3–5 years, although respiratory disorders were the most common comorbidities at all times. In contrast, endocrine or metabolic, mental or behavioral, digestive, musculoskeletal, or skin-related disorders showed increasing trends during 10 years. The proportions of comorbidities were statistically different between 3 groups at most follow-up periods in the top 10 comorbidities. Specifically, mental and behavioral disorders predominantly increased in group 3 within the 10 years. Furthermore, neoplasms or diseases of the blood organs (D00–D89) showed a unique trend in group 3 by decreasing in the first 4–5 years and abruptly increasing thereafter. When evaluated by the absolute standardized difference (ASD), the judgment was more conservative than the chi-square test result (Figure). The ASD of the mental and behavioral disorder, the neoplasms and diseases of the blood organs, the skin and subcutaneous tissue, and the digestive system showed increasing trends higher than the threshold of 0.1 by follow-up year, which demonstrated overt differences of the incidence of comorbidities between each groups. In summary, the mental and behavioral disorders and neoplasms and diseases of the blood organs predominantly increased in group 3, but the skin and subcutaneous tissue and the digestive system diseases increased in group 1. Overall survival was the highest in group 1 and the lowest in group 3 ($P < .001$). Multivariate analysis was performed after adjusting for sex, onset age, treatment exposure duration, and the number of treatment prescriptions. Trajectory grouping showed the highest hazard ratios (HRs). Group 3 had an HR of 2.545 (95% CI, 1.402–4.621; $P = .002$) compared with group 1. The most common diagnosis at the time of death was CNS tumors.

Conclusion: Our study demonstrated that the comorbidity patterns significantly differed according to the trajectory group for late mortality, indicating the potential of utilizing comorbidities as a reference in identifying patients at risk for late mortality among childhood cancer survivors.

Keyword: Survival, Child, Cancer survivor, Morbidity, Mortality, Survival



PP01-01

RUNX1 mutation in children with acute myeloid leukemia of a single-center

Hong Bo He, Hu Yong Zheng and Chao Gao

Hematology Center, Beijing Children's Hospital, China

Background: Acute myeloid leukemia (AML) is a highly heterogeneous clonal disease, accounting for about 30% of children's acute leukemia. With the application of MICM classification, risk stratification and multi drug combined intensive therapy in children with AML, the remission rate of primary chemotherapy reached 70%, but the prognosis of patients was not significantly improved, the prognosis was poor, the long-term survival time was short, and the recurrence rate and mortality were high. At present, chromosome karyotype and gene mutation type are mainly used as risk stratification indicators to guide clinical treatment. Runx related transcription factor 1 (Runx1) is a key regulator of hematopoietic function. It participates in the formation of hematopoietic stem cells and affects the self-renewal of hematopoietic stem cells and the differentiation of cell lineage through chromosome translocation and somatic mutation, so as to participate in the occurrence and development of AML.

Method: Bone marrow samples of 87 newly diagnosed children with AML treated in Beijing Children's Hospital Affiliated to Capital Medical University from 2005 to 2014 were collected. Bone marrow genomic DNA was extracted, the target gene fragment was amplified by polymerase chain reaction, and the mutation of Runx1 gene was analyzed by gene sequencing. By comparing the clinical characteristics and prognosis of Runx1 mutant group and Runx1 wild-type group, to explore the correlation between Runx1 gene mutation and clinical characteristics and its impact on the prognosis of children.

Results: A total of 87 newly diagnosed children with AML were included, including 47 males and 40 females, aged 15.3 (0.7-16.0) years at the time of diagnosis. RUNX1 mutation accounted for 29% (26 / 87), and the most common mutation sites were exon 1, exon 6 and exon 7. The median follow-up time was 24 (0.5 ~ 129) months. 58 cases survived, 29 died and 21 relapsed. The age difference between RUNX1 mutation group and wild-type group was statistically significant ($P < 0.05$). The incidence of RUNX1 mutation in M2 and M4 was higher, but the difference was not statistically significant ($P > 0.05$). The complete remission rate after the first course of treatment and the complete remission rate after the second course of treatment in RUNX1 mutation group were lower than those in wild-type group ($P < 0.05$), but there was no significant difference in gender, leukocyte count at initial diagnosis, the incidence of fusion gene, FLT3 mutation rate and bone marrow morphological typing between the two groups ($P > 0.05$). Kaplan Meier method was used for survival analysis, and logistic regression test was used to compare the difference of survival time. The results showed that there was no significant difference in 8-year survival rates of EFS and OS between RUNX1 gene mutation group and wild-type group ($P > 0.05$).

Conclusion: RUNX1 gene mutation is common in high-age children. The remission rates of the first course and the second course of treatment in children with RUNX1 mutant AML were low, but there was no significant difference in the overall survival and event free survival.

Keyword: RUNX1 gene mutation, Children, Acute myeloid leukemia, prognosis

PP01-02

Establishment of a panel of biomarkers for immunophenotyping in acute leukemia

Amar Ranjan, Harshita Dubey* and Pranay Tanwar

Lab Oncology Unit, AIIMS, New Delhi, India

Background: Identification of surface antigen expression (CD markers) is one of the most sensitive methods for the classification of acute leukemia (AL). Immunophenotyping (IPT) by Flowcytometry is a powerful tool to identify cell membrane antigens required for the diagnosis and post-therapeutic evaluation of measurable residual disease. No standard panel has been established yet. We propose a panel for worldwide acceptance as described below.

Method: After clinical suspicion of AL, peripheral blood (PB, if >10% blasts) or bone marrow aspirate (BMA) is used for IPT. We process samples to be run for a screening (initial) panel of 5 markers composed of MPO (Acute Myeloid Leukemia, AML), cCD79a (B - Acute Lyphoid Leukemia, B-ALL), cCD3 (T-ALL), CD34 (immaturity marker) & CD 45 (gating). Fluorochromes used are FITC (Fluorescein isothiocyanate), PE (phycoerythrene), PB (Pacific Blue), PE (Phycoerthyrin Cyanin) 5.5 & Kroma A (KO) respectively. A total of 112 cases were studied. After the exclusion of 10 samples, which were not run for all above mentioned five markers, we studied 102 cases. The initial diagnosis on the screening panel was compared with the final diagnosis on the basis of morphology, cytochemistry, and extended immunophenotyping panel. The sensitivity and specificity of the screening panel were evaluated.

Results: Out of 102, being male 70 and female 32), 49 cases of

AML (45 AML and 4 APML) and 53 cases of ALL (46 B-ALL and 07 T-ALL) were found. In AML, expression of MPO was positive in 34/45 (75.5%), cCD79a negative in 45/45 (100%), and cCD3 negative in (45/45) 100% of cases. 11/45 (24.4%) AML cases showed negative MPO, which were M4 or M5 types. It needed an extended panel for confirmation of diagnosis. 1/ 44, the case showed aberrant expression of CD19, which also needed extended panel for exclusion of MPAL. This case on bone marrow aspirate showed 50% CD45 dim+ blasts which were CD34+, CD117+, CD13+, CD33+, CMPO+(dim), CD38+, CD19+, HLA - DR+, CD56+, and negative for cCD79a, CD7, cCD3, sCD3, CD16, CD123, CD11b, CD36, CD64, CD4 and CD14. Thus totals 12/45 (26.6%) cases of AML needed extended panel. In APML, expression of MPO was positive in 4/4 (100%) cases, while cCD3 and CD79a were negative in all cases. In B- ALL, expression of CD79a was positive in 46/46 (100%) cases while MPO was negative in 46/46 (100%), and cCD3 negative in 46/46 (100%) cases. In T-ALL, expression of cCD3 was positive in 7/7 (100%) cases while cCD79a was negative in 7/7(100%) and MPO was negative in 7/7 (100%).

DISCUSSION:Except in AML, we got 100% accuracy in the diagnosis of BALL, TALL & APML cases. In AML, the correct diagnosis was made in 75.5% of cases. Rest (24.5%) cases need an extended panel for confirmation of the diagnosis. This is due to the variable positivity of MPO in AML. Parikh BP et al 2016 have shown a similar panel with replacement of CD34 with TdT; also an immaturity marker, with an approximately similar result (1).

Conclusion: We can conclude that the said panel (MPO, cCD79a, cCD3, CD34 & CD 45) for screening of AL may be set as a standard panel of markers, although CD34 may be replaced by TdT which will be present in the acute form of leukemia only, not in chronic one (2). This is suitable for five-color flow cytometry, which is the minimal requirement for a hematology Laboratory. We recommend the establishment of the proposed CD markers as a standard panel for screening acute leukemia.

Keyword: Biomarkers, Immunophenotyping, Acute leukemia

Table1: Immunophenotyping of all cases of Acute leukemia, Positive (+), Negative (-)

Acute Leukemia	Total cases	Ccd79a		MPO		CD3		Accuracy (%)
	102	+	-	+	-	+	-	
B-ALL	46	46	0	0	46	0	46	100%
AML	45	0	45	34	11	0	45	75.5%
APML	04	0	04	04	0	0	04	100%
T-ALL	07	0	7	0	7	7	0	100%

Abbreviations:
MPO: Myeloperixidase
cCD: Cytoplasmic cluster of differentiation
APML: Acute promyelocytic leukemia

References:
1. Parikh BP, Patel SP, Raiya BN, Vora HH, Jetly DH. Applicability of a single 5 color cytoplasmic markers tube as primary panel for immunophenotyping of acute leukemia: A Gujarat Cancer and Research Institute experience. Indian journal of cancer. 2016 Jul 1; 53(3):349.
2. Basso G, Lanza F, Orfao A, Moretti S, Castoldi G. Clinical and biological significance of CD34 expression in acute leukemia. J Biol Regul Homeost Agents. 2001 Jan-Mar; 15(1):68-78.

PP01-03

The prognostic impact of reduced variant burden in elderly patients with acute myeloid leukemia treated with decitabine

Mihee Kim[1], Seo-Yeon Ahn[1], Sung-Hoon Jung[1], Ga-Young Song[1], TaeHyung Kim[3], Deok-Hwan Yang[1], Je-Jung Lee[1], Seung-Hyun Choi[2], MiYoen Kim[2], Hyeoung-Joon Kim[1,2], Dennis Dong Hwan Kim[4] and Jae-Sook Ahn[1,2*]

[1] Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea
[2] Genomic Research Center for Hematopoietic Diseases, Chonnam National University Hwasun Hospital, Korea
[3] Computer Science, University of Toronto, Canada
[4] Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Canada

Background: The prognosis of elderly patients with AML is poor with various causes including patient's medical comorbidity, performance status and disease biology. Even though genomic advance has improved the development of next-generation sequencing (NGS), it is unclear which genetic mutations are associated with the prognosis of elderly AML patients. The National Comprehensive Cancer Network (NCCN) guidelines recommend HMA with or without venetoclax for elderly AML patients who are not eligible for intensive chemotherapy and they have no actionable target of mutations. The HMAs are widely used in clinical practice, because HMAs have relatively well-tolerated with low hematologic toxicity. HMAs are particularly feasible for the treatment of AML in elderly patients with comorbidities, poor performance status and intolerance to combination with and unavailable for venetoclax. The aim of this retrospective cohort study is to determine prognostic impact of genetic mutation in elderly patients who received HMAs treatment. Additionally, this study aimed to investigate the role of NGS- based MRD monitoring in elderly patients with newly diagnosed AML.

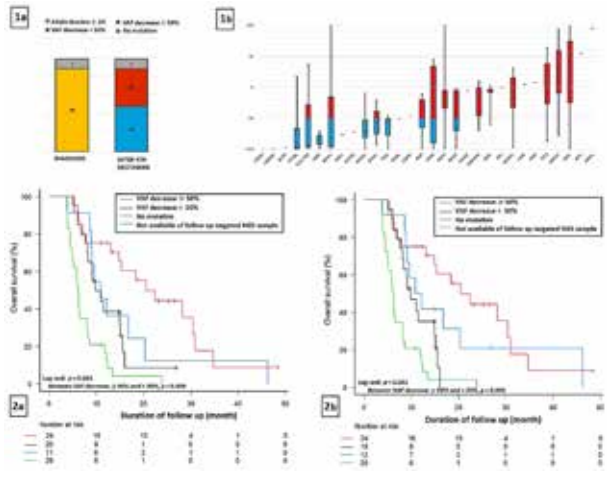
Method: Total 123 patients aged 65 years or older with AML were eligible. All patients received decitabine in standard doses (20 mg/m2 by a 1-h intravenous infusion for 5 consecutive days) every 4 weeks. NGS was performed in 123 samples collected from BM at initial diagnosis and 49 follow-up BM samples after 4th cycle of decitabine. To clarify the immortal timed bias, landmark analyses were performed with patients (n=84) who remained at least the median time to perform follow-up Bone marrow biopsy after 4th cycle of decitabine treatment.

Results: Through the genetic profiling including the targeted deep sequencing of 51 genes, TP53, TET2 gene mutations and complex karyotype at diagnosis showed significantly poor overall survival in

this cohort. We analyzed the VAF dynamics of 49 patients in follow up BM samples after 4th cycle of decitabine, and the optimal cut off value was Δ53.3%. 24 patients (54.5%, 24 of 44) showed more than 53.3% decrease of VAF after 4th cycle of decitabine (figure 1a). DMNT3A, TET2, IDH1, IDH2, and SETBP1 and SMC1A showed less than 50% of the decreases of VAF. Patients with DNA methylation genes showed significantly reduced VAF less than 50% (figure 1b). The survival outcome of patients who showed more than Δ53.3% reduction of initial VAF after 4th cycle of decitabine was significantly better than other group(Median OS of group with reduced VAF (ΔVAF ≥ 53.3%, n=24), 20.5 month; group with stable VAF (ΔVAF <53.3%, n=20), 9.8 month; no mutated group (n=11), 10.9 month; not available of follow up targeted NGS analysis (n=29), 6.2 month; $p < 0.001$, figure 2a). After the exclusion of DTA mutations, the survival outcome improved prognostic risk stratification power of NGS-based MRD assessment in AML (figure 2b).

Conclusion: Older adults with AML need to consider age, disease biology, and medical comorbidities. It is important to identify factors that are associated with good survival outcomes and that could make appropriate treatment decisions. The study suggested that Reduce VAF could be an indicator to predict long-term response of decitabine in elderly AML patients. In elderly AML patients with poor performance status, HMAs could be an alternative treatment, particularly in patients with reduced VAF. In elderly AML patients with stable VAF, however the residual disease burden is considered for the selection of combination treatment with novel agent before the disease progresses. In conclusion, ΔVAF could give information to decide whether to maintain decitabine treatment or combine novel agents to improve survival outcome.

Keyword: Acute myeloid leukemia, Elderly patient, Variant allelic frequency, Next-generation sequencing



PP01-04

Therapeutic effect of metformin on acute myeloid leukemia through targeting AMPK/ mTOR, cell cycle, apoptosis and autophagy

Juan liu and Wenyu shi*

Oncology and hematology, Affiliated Hospital of Nantong University, China

Background: Acute myeloid leukemia (AML) belongs to malignant hyperplastic disease which mainly treated with anthracycline-based chemotherapy currently. Considering the side effects of current regimens, especially cardiac toxicity, to find an effective treatment for AML remains a serious challenge. Accumulated evidence has proved that metformin (MET) possesses varieties of functions on resisting aging, cancers and cardiovascular diseases. However, more current studies focus on effects of metformin in solid tumors, and fewer reports on malignant hematologic diseases.In addition, since traditional anthracyclines have great toxic and side effects in the treatment of AML, this study was conducted to further clarify whether metformin can be used as an adjuvant in the treatment of AML and to increase the sensitivity of chemotherapy drugs to reduce the dosage and side effects.

Method: We show in this study that the Adenosine monophosphate-activated protein kinase (AMPK)/ mammalian target of rapamycin (mTOR) signaling pathway is functional in AML cell lines (Kasumi- 1, HL-60 and U937), resulting in an inhibition of protein synthesis and cell cycle arrest by metformin, also combined with activation of apoptosis linked with P53-BAX/BCL2-Caspase3 pathway, furthermore inhibit tumor growth. The inhibition of mTOR induces a dephosphorylation of the key translation regulators, 4E binding protein1 (4E-BP1) and S6 kinase (S6K), which inhibit the initiation step of mRNA translation. Furthermore, we demonstrated that the combination of metformin and daunorubicin (DNR) had an additive effect both in vitro and in vivo. Using siRNA-mediated knockdown of the α1 and α2 catalytic subunits of AMPK, we showed that metformin inhibited the growth of AML cells through an AMPK-dependent mechanism. Meanwhile, we also found that metformin can induce autophagy in AML cells by transmission electron microscopy (TEM) and observation of unc51-like autophagy-activa ting kinase- 1 (ULK1), BECN (Beclin1), microtubule-associated protein 1 light chain 3 (LC3) and P62 via Western Blotting (WB) and immunohistochemical data. Thus targeting these signaling ways by metformin may be a compelling ally in AML treatment.

Results: 1. AMPK activator metformin inhibited AML cell proliferation. Using MTT assay, we measured fifty percent of growth inhibition (IC50) respectively: Kasumi- 1 for 13.42 ± 0. 17mM HL-60 for

16.73±0.77Mm and U937 for 11.987±0.43mM. It turned out that metformin showed markedly growth inhibition in all AML cell lines in dose-dependent way. Considering of IC50 values, we examined the inhibitory effect of metformin on AML cells at 24h, 48h, 72h respectively using 10mM metformin, which showing noteworthy time-dependent response. We also applied soft agar clone formation assay and the results were shown. Metformin significantly inhibited the clonal proliferation of AML cell lines.

2. Metformin induced cell cycle arrest and promoted apoptosis in AML cells.
To further evaluate the mechanism of growth inhibition by metformin, the cell-cycle profile was analyzed by flow cytometry (FCM) after treatment with metformin at 10mM for 36h in AML cell lines. Metformin treatment groups presented the majority of cells in the G0/G1 phase of the cell cycle vs control groups respectively. Meanwhile, WB showed that the expression of CyclinD1 showed a significant dim trend in experimental groups. Meanwhile WB detected the relative expression of apoptosis-related proteins Caspase3, BAX and BCL2. We also found that the expression of P53 was also increased in the metformin-treated group. Results showed that metformin induced cell apoptosis in a dose-dependent manner and might be associated with P53 pathway.

3. Metformin induced the occurrence of autophagy in both AML cell lines and primary AML cells.
We examined the cell proliferation of primary AML cells after treatment with metformin and found that metformin also inhibited the proliferation of primary AML cells in dose and time-dependent manner. In addition, we explored the role of metformin in inhibiting AML cells through inducing autophagy both in AML cell lines and primary AML cells. We pictured Kasumi- 1, HL-60 and U937 cells, finding that metformin-treated group having more phagophores comparing with untreated ones vividly at 5000 times magnification through transmission electron microscope (TEM). Furthermore, we explored that metformin could both up-regulated the expression of autophagy-associated protein ULK1, Beclin1, LC3B and P62 was reduced accordingly by Western Blotting.

4. Metformin exerted the antitumoral effect in AML through an AMPK-dependent mechanism.
Western Blotting analysis suggested that metformin stimulated phosphorylation of AMPK. Meanwhile, metformin treatment resulted in attenuated activation of mTOR, as shown by the decreased phosphorylation of mTOR, p70S6K and increased expression of phosphorylated 4E-BP1, which was a critical translational pathway for protein synthesis. This indicated that the AMPK/mTOR pathway took great part in the anti-proliferative effect of metromin in AML. Next, we examined whether knockdown of the α1 and α2 catalytic subunits of AMPK would prevent the inhibitory effects of metformin. We used the AMPK siRNA to block AMPK expression in U937 cells showing us the electrotransfection efficiency was reliable and U937 cells knocked-down of AMPK failed to inhibit p-mTOR and curtailed the activation of AMPK by metformin in the control group. MTT and FCM were used to determine that knock-down of AMPK abrogated metformin-induced AML cell proliferation inhibition and cell cycle arrest respectively.

5. Effect of combined treatment of metformin and daunorubicin in vivo and in vitro.

All of the cell lines were simultaneously treated with metformin and anthracycline daunorubicin (DNR), a chemotherapeutic agent for AML. The data denoted additive interactions in all of the cell lines (Kasumi- 1, HL-60 and U937), even when metformin at a low-level concentration of 2.5mM. The xenograft mouse model was also used to verify the inhibitory effect of metformin or/and daunorubicin on the development of AML tumors in vivo. Both Met and DNR groups had a growth inhibition on AML tumor tissue, meanwhile the combination of the two drugs had a synergistic and super-positive effect. Compared with the control group, on the 9th day of treatment, the Met, DNR and Met +DNR groups had statistical significance ($P<0.01$). On the 15/ 17th day of treatment, Met +DNR vs DNR and Met +DNR vs Met were both statistically significant ($P<0.05$).

Conclusion: Metformin can exert anti-tumor effects in AML cell lines, primary AML cells and xenograft models, involving multiple mechanisms to cross-link each other, especially AMPK/mTOR pathway. Therefore, therapeutic metformin for AML is generally an effective, safe and inexpensive option for AML patients.

Keyword: Acute myeloid leukemia (AML), Metformin, AMPK-mTOR, Cell cycle, Apoptosis, Autophagy

PP01-05

Epigenetic regulation and synthetic lethal targeting of genetically deficient acute myeloid leukemia by siRNA loaded customized polymeric and superparamagnetic multifunctional nanoparticles

Anas Ahmad

Pharmacology, Chandigarh College of Pharmacy, India

Background: Acute myelogenous leukemia (AML) is a cancer of the blood and bone marrow and is one of the largest reasons for cancer-related morbidity and mortality on the global scale. Existing limitations of currently existing anticancer drugs have necessitated a continuous urge for novel and effective anti-tumor therapeutic

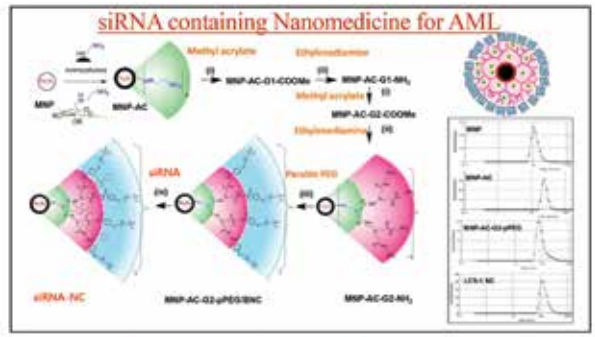
paradigms. Synthetic lethality is a selective and targeted approach where simultaneous mutations in two genes become lethal while independent mutations in either one remain viable. In the current approach, we employed synthetic lethal targeting and epigenetic regulation of AML cells by siRNA containing polymeric and magnetic nanomedicine which can selectively kill AML cells while leaving healthy cells unharmed. Various genes are associated with the advanced prognosis of AML, and customized multifunctional siRNA containing polymeric and metallic nanocarriers can be employed used for the protection of siRNAs from degradation and also to control epigenetic regulation-based AML therapy.

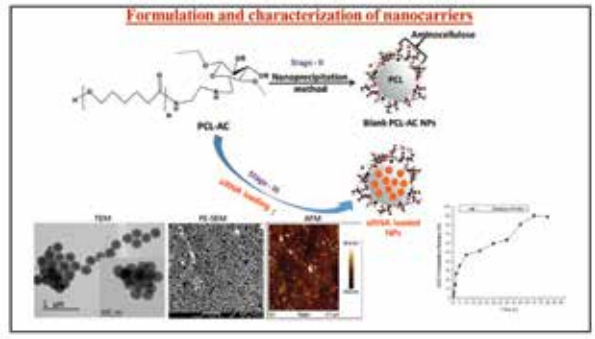
Method: Nanocarriers were formulated by nanoprecipitation and solvent evaporation method, characterized for particle size, zeta potential, polydispersity-index, shape, surface morphology siRNA loading, and other physicochemical properties. MTT-assay was done to assess the safety and efficacy of nanoparticles in HEK293, gene-proficient, and gene-deficient AML cell lines. Confocal microscopy and flow cytometry were done to see the cellular uptake and internalization of nanoparticles in AML cell lines. Immunofluorescence studies were carried to assess the mechanisms of cell death via persistent DNA double-strand breaks and caspase-mediated apoptosis.

Results: The particle size of magnetic and polymeric nanomedicine was around 100 and 200 nm, PDI of 0.2-0.3 while zeta potential of 20-30 mV. Smooth spherical shape and size were confirmed by TEM, SEM, and AFM microscope. It was noted that nanoparticles caused significant cell death in gene-deficient AML cells compared to gene-proficient cells. Cellular uptake and internalization of nanoparticles in tumor cells were well observed in confocal microscopy and flow cytometry in AML cells. The persistent DNA-double strand breaks were observed in the AML cell nucleus and green fluorescence also confirmed caspase-mediated apoptosis. In the case of superparamagnetic iron-oxide nanoparticles (SPIONS), magnetic field-mediated hyperthermia also enhanced the cancer cell killing effects.

Conclusion: Optimized magnetic and polymeric nanomedicines selectively targeted gene-deficient AML cells while sparing the gene-proficient cells unharmed. The nanoparticles also stabilized interaction between siRNA and polymeric components were used to protect the siRNA from RNase-mediated degradation. Furthermore, nanoparticles also enhanced the transfection efficiency in-vitro and exhibited selective toxicity toward AML cell lines through the higher internalization of nanocarriers in the cellular periphery via the caveolae-mediated endocytosis pathway. si-RNA-containing nanocarriers were found to be more effective in diminishing the tumor-targeted signaling compared to free siRNA and enhanced gene knockdown in AML cells. In summary, si-RNA-containing nanoparticles demonstrate superior RNAi therapeutics through caspase 3 activation.

Keyword: Nanomedicine, Acute myeloid leukemia, Targeted cancer therapy, Synthetic lethality, Polymeric nanoparticles





PP01-06

Investigation of genes and pathways associated with low platelet count in normal karyotype acute myeloid leukemia

Chang-Hun Park[1] and Jae Won Yun[2*]

[1] Department of Laboratory Medicine & Genetics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Korea

[2] Veterans Medical Research Institute, Veterans Health Service Medical Center, Korea

Background: Acute myeloid leukemia (AML) is related with the risk of bleeding due to the disease-related lack of platelets, and systemic coagulopathy. Generally platelets play a role in hemostasis, and leukemic blasts could alter platelet activation in vitro in previous report. Herein, we systemically investigated cellular pathways contributing to low platelet count in normal karyotype AML (NK-AML).

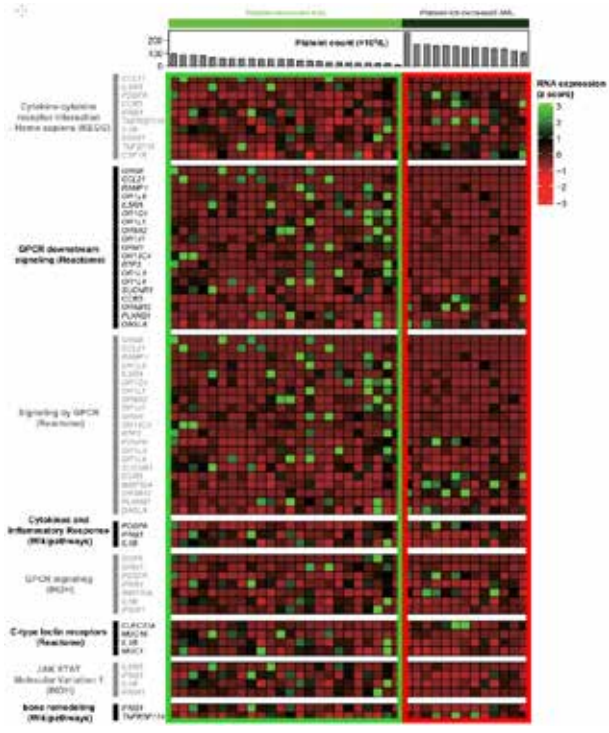
Method: Among 200 AML cases in GDAC database of The Cancer Genome Atlas, 37 NK-AML with no known driver mutations were selected in this study. Among them, AMLs with platelet count <100×109/L (N=24) were regarded as platelet-decreased AML (PD-AML) and the others (N=13) as control. Based on the RNA-seq ex-

pression data, differentially expressed gene (DEG) analysis was done. Next, pathway analysis and network analysis were performed using the result of DEG analysis.

Results: In DEG analysis, 175 genes were differentially expressed in PD-AML with normal karyotype. Among them, CHIH3 (p=0.0003), CSF1R (p=0.0007), HTR3E (p=0.0015), CILP2 (p=0.0023), and LOC64685 (p=0.0028) were most differentially expressed. In pathway analysis, GPCR-related signalings, Cytokine-cytokine receptor interaction, cytokines and inflammatory response, JAK STAT molecular variation 1, C-type lectin receptors, and bone remodeling signalings were significantly altered in PD-AML with normal karyotype. In network analysis, four key genes (IFNB1, IL1B, PDGFA, and IL5RA) that are involved in multiple pathways were putative biomarkers for decreased platelet status in NK-AML.

Conclusion: We identified the GPCR-related signalings which are altered in NK-AML with low platelet count, and these pathways were known to be related to platelet activation in other cancers. Key genes involved in multiple signaling pathways were considered as putative biomarkers which could represent the decreased platelet status and/or the bleeding tendency in NK-AML.

Keyword: RNA sequencing, Acute myeloid leukemia, Pathway analysis, Thrombocytopenia



PP01-07

Clinical and molecular significance of multilineage dysplasia in acute myeloid leukemia: a single-center experience

Hee Sue Park[2,4], Bo Ra Son[2,4] and Jihyun Kwon[1,3*]

[1] Internal Medicine, Chungbuk National University College of Medicine, Korea
[2] Laboratory Medicine, Chungbuk National University College of Medicine, Korea
[3] Internal Medicine, Chungbuk National University Hospital, Korea
[4] Laboratory Medicine, Chungbuk National University Hospital, Korea

Background: The clinical significance of multilineage dysplasia in acute myeloid leukemia (AML) has long been controversial. We investigated the clinical characteristics of dysplasia by retrospectively analyzing data from patients with AML. In addition, the gene mutation analysis results of these patients were compared with those of patients with myelodysplastic syndrome with excess blasts (MDS-EB).

Method: We collected information on the clinical characteristics, treatment response, and survival of 127 patients diagnosed with AML at Chungbuk National University Hospital from January 2015 to November 2021. The mutational status of 49 genes was analyzed using next-generation sequencing (NGS) of DNA obtained from the BM aspirates of these patients. Among them, NRAS, KRAS, FLT3, KIT, CBL, and PTPN11 were classified as RAS pathway-related genes. We also compared the genetic information of 34 MDS-EB1 or EB2 patients with those of AML patients with dysplasia.

Results: The median age of the enrolled patients was 70.4 years. Most of the cases were de novo AML, and nine cases were diagnosed as secondary AML. Thirty-seven patients (29.4%) had dysplasia in two or more lineages, and 38 patients (30.4%) had MDS-related cytogenetic abnormalities. Finally, 67 patients (53.2%) were classified as having AML with myelodysplasia-related changes (AML-MRC). Among the AML patients, there were significantly more patients aged 75 years or older with dysplasia than without (48.6% vs. 26.7%, P = 0.018); the blast percentages in the bone marrow and peripheral blood were also significantly lower in patients who had AML with dysplasia. Chromosomal analysis revealed that dysplastic changes were significantly associated with a higher frequency of monosomy and complex karyotypes. Forty percent of AML patients with dysplasia were treated with intensive induction chemotherapy, while 60% used decitabine as the first-line treatment. The overall response rates of intensive induction chemotherapy and decitabine treatment were 66.7% and 29.4%, respectively, and there was no significant difference in the response rate of patients who had AML without dysplasia.

In the patient group who received intensive induction chemotherapy, the time to recovery of the absolute neutrophil count (> 1,000/mm3) and hemoglobin level (> 10.0g/dL) were 35.8 and 33.3 days, respectively, which showed a longer trend compared to 30.9 and 29.7 days, respectively, in patients without dysplasia. The most commonly mutated gene in AML patients with dysplasia was TP53, followed by RUNX1 and FLT3. AML patients with dysplasia had a significantly higher frequency of TP53 (35.1% vs. 8.1%, P < 0.001) and SF3B1 (8.1% vs. 0%, P = 0.026) mutations than patients without dysplasia, whereas the mutation rate of RAS pathway-related genes including NRAS was significantly lower (21.6% vs. 44.2%, P = 0.025). The high frequency of TP53 and low frequency of NRAS were similar to that of patients with MDS-EB, while the significant frequencies of mutations in FLT3, DNA methylation-related genes, and NPM1 were characteristics shared with patients who had AML without dysplasia. In the survival analysis, dysplastic changes were not associated with overall survival. In the multivariate analysis using Cox regression, FLT3-ITD mutation, MDS-related cytogenetic abnormality, and (over 70 years) were identified as significant survival factors.

Conclusion: Although associated with adverse prognostic factors such as age, chromosomal type, and genetic mutation pattern, dysplastic changes in the bone marrow cells of patients have no prognostic significance in themselves. AML with dysplastic changes shares some genetic characteristics represented by MDS-EB and TP53 mutations, regardless of the history of MDS.

Keyword: Acute myeloid leukemia, Dysplasia, Mutation, Myelodysplastic syndrome

PP01-09

Stepwise combination of azacitidine and low-dose venetoclax in treatment-näive, critically ill elderly patient with acute myeloid leukemia: a case report

Truc Phan[1,3], Thanh Nguyen Huu[3], Nghi Tran Phuong[3], Trang Nguyen Le[2], Kelly Smith[1,3,4] and Yi Hyeon Gyu[1,3*]

[1] Oncology & Hematology Dept, Vinmec Times City International Hospital, Viet Nam
[2] Pharmacy Dept, Vinmec Times City International Hospital, Viet Nam
[3] College of Health Science, Vin University, Viet Nam
[4] Perelman School of Medicine, University of Pennsylvania, USA

Background: Acute myeloid leukemia (AML) is a subtype of acute leukemia that is the most common in adults, comprising 80% of cases.2 Although treatment with high-dose chemotherapy and/or consolidation with allogeneic stem cell transplantation shows promising results in younger and fit patients, this strategy is not available to frail elderly patients with poor performance status and major co-morbidities.3,7 Less intensive treatments including hypomethylating agents (HMA) such as azacitidine or decitabine and low-dose cytarabine (LDAC) have been commonly recommended to elderly AML patients, but complete remission is hard to achieve.7,12 Recently, venetoclax, a BH3-mimetic that blocks the anti-apoptotic B-cell lymphoma (Bcl-2) protein and leads malignant cells into the cellular apoptotic pathway, was introduced as a breakthrough therapy for AML and chronic lymphocytic leukemia (CLL).13 Two significant issues arising from the treatment of venetoclax include (1) the high risk of tumor lysis syndrome (TLS), in which stepwise ramp-up dosing is necessary; and (2) the high-cost treatment with a daily dose of 400 mg. Some reports describe the use of a lower dose of venetoclax with posaconazole since this anti-fungal medication increases plasma concentration of venetoclax by cytochrome P450 (CYP) 3A4 inhibition.14 In the following case, we take advantage of drug-drug interactions between venetoclax and posaconazole and demonstrate the safety and therapeutic efficacy of sequential azacitidine and low-dose venetoclax in an elderly patient with severe underlying diseases after only one cycle.

Method: A seventy five-year-old male with history of hypertension and prostate cancer was admitted to the emergency room with a persistent high fever and hypotension. The patient experienced fever and 20 kg of weight loss over 1 month. He was diagnosed with AML with minimal differentiation with 52% of blasts in the bone marrow with a normal karyotype without any detectable genetic abnormalities. The outside hospital decided to treat him with palliative care only but he visited our institution for a second opinion after his condition worsened. He presented with lethargy, a persistent high fever, cough with thick phlegm, mouth ulcers with white plaques, hypotension with a BP of 70/40 mmHg, and a poor performance status(ECOG PS = 4). Blood test results were notable for aa hemoglobin (Hb) level of 77 g/L, total white blood cell (WBC) count of 0.7x109/L with an absolute neutrophil count (ANC) of zero, platelet (PLT) count of 75x109/L, C-reactive protein of 144 mg/dL, Na+/K+ of 158/2.86 mmol/L, creatinine of 170 µmol/L, and 20% blasts in the peripheral blood blood. A CT scan showed left lower lobar pneumonia. We diagnosed him with septic shock, pneumonia, acute kidney injury with severe electrolyte disturbances and

acute myeloid leukemia. He was admitted to the intensive care unit for management Extended-spectrum β-lactamase producing Klebsiella pneumonia from sputum cultures and Capnocytophaga sputigena from blood cultures were isolated. After five days, the patient's infection, electrolyte imbalance and nutritional status were controlled in the ICU and he was then transferred to general ward. We started azacitidine 75 mg/m2 for 7 days with posaconazole oral suspension 600 mg per day. After 15 days of azacitidine, the platelet count began to recover (40x109/L), but immature cells were still present in the peripheral blood, and anemia and leukopenia were still severe (WBC 0.4x109/L, Hb 77 g/L). From day 16 of azacitidine, venetoclax was added with a dose of 100 mg on day 1, 200 mg on day 2, 300 mg on day 3, then 100 mg once daily. Posaconazole was withheld during this initiation and titration phase. From day 4, posaconazole was restarted and maintained with venetoclax 100 mg once a day. After 12 days of venetoclax, hematologic responses were achieved (hemoglobin 79 g/L without transfusion, WBC/ANC 1.0/0.5x109/L and PLT 230x109/L). A bone marrow biopsy showed no blast cells, substantial proliferation of erythroid precursors with dysplastic characteristics and normal differentiation of myeloid lineage and megakaryocytes with full maturation stages. He was then treated with G-CSF (filgrastim) 30 MIU subcutaneously.His leukocyte count recovered fully and remained stable on the last day of the first cycle. His studies demonstrated a complete response (CR) and he was discharged from the hospital. He then underwent a second cycle of outpatient treatment with azacitidine subcutaneously and venetoclax 100 mg in combination with posaconazole 600 mg per day and bicalutamide 50 mg once daily. At the time of submission of this article, the patient had completed his fourth cycles of this regimen and remained in CR without remarkable complications except for neutropenia requiring a dose adjustment posaconazole.

Results: B-cell lymphoma 2 (BCL-2) was incidentally discovered in t(14;18) translocation in follicular lymphoma and is believed to be an essential factor in lymphoid cells. Subsequent discoveries have shown that BCL-2 is a significant member of the multi-functional BCL-2 family, which plays a crucial role in supporting/inhibiting the formation of MOMP complexes on the mitochondrial membrane, leading to the release of cytochrome c into the cytoplasm, initiating the apoptosis cascade.13 Since then, researchers have focused more on the myeloid lineage, and venetoclax has shown optimal efficacy when it is combined with HMA or LDAC in increasing AML response rate up to 83%.9 Besides CLL/SLL, venetoclax was approved as the first-line therapy with azacitidine for elderly AML patients based on VIALE-A trial results.8 Venetoclax is better tolerated than high-dose chemotherapy.Furthermore, with its unique mechanism of leading malignant cells to programmed death, venetoclax has been known to overcome the disadvantage of unfavorable genetic alterations which are more frequently detected in elderly AML patients.11 Posaconazole is the preferred antifungal prophylaxis agent in AML. Like other azoles, posaconazole strongly inhibits the CYP isoenzyme 3A4 system.5 As a nearly indispensable component of adjuvant therapy for AML, posaconazole has the potential to interact strongly with drugs metabolized by the CYP3A system. Venetoclax is a typical illustration of this case. If these two drugs are used together, the concentration of venetoclax will increase 2-7 times fold.6 Based on this interaction, we can not only save a significant amount of venetoclax - an expensive drug with a cost that hinders access for many patients, especially in resource-limited countries like Vietnam -but also maintain concentrations within the desired therapeutic range. In our case, the patient had a 75% dose reduction (100 mg daily compared to the standard 400 mg daily dose) when co-administered with posaconazole oral suspension 600 mg daily as recommended by National Health Service England adjusted during the Covid-19 pandemic.1 When deciding to initiate AML treatment, the patient was in a very high-risk state with severe infections and kidney dysfunction. Considering the very high risk of complications and TLS with venetoclax at that time, we decided to choose a stepwise approach with using azacitidine 75 mg/m2 alone first and delaying venetoclax until the risk became tolerable, as mentioned by Brain A. Jonas et al.11 From day 16 of azacitidine, the patient's platelets showed signs of recovery (PLT 34x109/L), despite severe neutropenia and transfusion-dependent anemia and persistent blasts in peripheral blood. Early recovery of platelet count after HMA treatment is considered to be a consequence of azacitidine's effect on megakaryocyte differentiation and growth and is a predictor of a good response in the treatment of elderly AML.4 These signs were signals for us to introduce venetoclax into the patietnt's treatment because, at this point, the biochemical indicators showed a low risk of TLS. The patient achieved CR on day 12 of venetoclax, corresponding to day 28 of azacitidine, without significant complications. He was eligible to start cycle two without any delays.

Fortunately, we could achieve CR after only one cycle of azacitidine and venetoclax, showing the great potential of this treatment for very elderly AML patients, even those with poor performance status with complex underlying diseases. This case demonstrates the need of personalized treatment including (1) early initiation of targeted therapy regardless of infection status; (2) delayed introduction of venetoclax due to TLS and bone marrow suppression risks, and waiting for azacitidine effect; and(3) the cost-effectiveness of the use of low-dose venetoclax (100 mg) in combination with azoles.14 Early platelet reconstitution by azacitidine also can provide further information about HMA in its differentiation and prognostic effects.

Conclusion: For a long time, the treatment of AML has not made much progress, with anthracycline and high-dose cytarabine remaining the back-bone of therapy. Venetoclax appears to have changed the landscape remarkably, becoming the first-line combination with HMA for elderly AML patients who cannot tolerate high-dose chemotherapy. Physicians are still working on expanding the indications of this drug, and recent investigations showed a better outcome than intensive treatment for even young people during the Covid-19 pandemic.10 This clinical case is unique in several aspects. It demonstrates successful treatment of a frail and elderly patient with multiple comorbidities in a highly individualized manner with a stepwise combination of azacitidine and venetoclax

leading to an impressive CR after the first cycle.Further studies with HMA and venetoclax for AML patients to optimize the schedule, dose and response monitoring and assessment are required.

Keyword: AML, Venetoclax, Azacitidine, Elderly patients

PP01-10

Relevance of Wilms' tumor-1(WT-1) gene expression in AML patients among north Indian population

Harsh Goel[1], Anita Chopra[1], Amar Ranjan[1], Ganesh Kumar Viswanathan[2], Aditya Kumar Gupta[3], Jagdish Prasad Meena[3], Sameer Bakhshi[4], Maroof Ahmad Khan[5] and Pranay Tanwar[1*]

[1] Laboratory Oncology Unit, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

[2] Hematology, All India Institute of Medical Sciences, New Delhi, India

[3] Pediatric Oncology, All India Institute of Medical Sciences, New Delhi, India

[4] Medical Oncology, All India Institute of Medical Sciences, New Delhi, India

[5] Biostatistics, All India Institute of Medical Sciences, New Delhi, India

Background: Acute myeloid leukemia (AML) is a genetically heterogeneous disease which is the most prevalent acute leukemia in adults characterized by the accumulation of mutations in hematopoietic progenitor cells and different cytogenetic and molecular features. Wilms tumor-1 (WT-1) gene is an important regulator of malignant hematopoiesis and has been implicated in the pathogenesis of AML. In the present study, we investigated the expression levels of WT-1 gene in newly diagnosed AML.

Materials and Methods: Peripheral blood (PB) or bone marrow samples (BM) were collected at the time of diagnosis from 40 newly diagnosed AML patients and 15 non-malignant BM samples were recruited as controls. Using quantitative real-time polymerase chain reaction, we assess the expression of WT-1 gene and normalized it against the endogenous control gene beta-actin (ß-actin). Finally, we correlated the expression level of WT-1 gene to the state and course of the disease.

Results : A total of 40 AML patients consist of 29 males (72.5%) and 11 females (27.5%), out of this 31 (77.5%) patients show overexpression of WT-1 gene. Higher levels of WT-1 mRNA expression were found to be correlated with the FAB subtype M4, and cytogenetic adverse risk groups. Higher levels of WT-1 mRNA expression in blast cells of newly diagnosed AML patients are associated with resistance to therapy, shorter disease-free survival, shorter overall survival, and a greater incidence of disease relapse when compared to patients with low WT-1 mRNA expression.

Conclusion: WT1 gene overexpression positively associates with the leukemic burden in AML. Increased expression of WT1 gene detected in a high proportion of AML patients could be considered as a potential molecular marker for diagnosis, response to treatment, prognosis, and clinical progression of the diseases or MRD monitoring. Also the current finding will be used as an additional marker for risk stratification of AML patients and target for the development of novel therapeutic approaches.

Keyword: Gene Expression

PP01-11

Clinical outcomes in patients with relapsed/refractory acute myeloid leukemia treated with gilteritinib who received prior midostaurin or sorafenib

Alexander E Perl[1*], Jessica K Altman[2], Naoko Hosono[3], Pau Montesinos[4], Nikolai Podoltsev[5], Giovanni Martinelli[6], Catherine C Smith[7], Mark J Levis[8], Christoph Röllig[9], Marco Groß-Langenhoff[10], Nahla Hasabou[11], Qiaoyang Lu[11], Ramon V Tiu[11] and Joon Seong Park[12]

[1] Abramson Cancer Center, University of Pennsylvania, USA

[2] Robert H. Lurie Comprehensive Cancer Center , Northwestern University Feinberg School of Medicine, USA

[3] Department of Internal Medicine , University of Fukui, Japan

[4] Department of Hematology, Hospital Universitario y Politécnico La Fe, Spain

[5] Department of Hematology , Yale School of Medicine, USA

[6] Research Department, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRST IRCCS, Italy

[7] Department of Hematology , University of California-San Francisco, USA

[8] The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, USA

[9] Clinical Studies Department , Universitätsklinikum Carl Gustav Carus, Germany

[10] HEOR Department , Astellas Pharma GmbH, Germany

[11] Medical Department , Astellas Pharma US, USA

[12] Department of Hematology-Oncology, Ajou University Hospital, Korea

Background: Gilteritinib is a FLT3 inhibitor with demonstrated effi-

cacy and safety in patients with FLT3-mutated relapsed or refractory (R/R) AML. The phase 1/2 CHRYSALIS trial demonstrated the safety and antileukemic activity of gilteritinib in a FLT3-mutation–enriched R/R AML population (Perl AE, et al. Lancet Oncol. 2017). The phase 3 ADMIRAL trial demonstrated the superiority of gilteritinib to salvage chemotherapy (SC) in FLT3-mutated patients based on longer median overall survival (OS) with gilteritinib (9.3 vs 5.6 months; hazard ratio [HR]=0.64 [95% CI: 0.49, 0.83]; P<0.001) (Perl AE, et al. N Engl J Med. 2019). We assessed whether prior TKI therapy affected response and survival in these two trials.

Method: We retrospectively analyzed clinical outcomes in patients with R/R AML previously treated with TKIs midostaurin or sorafenib, before receiving 120- or 200-mg gilteritinib in the CHRYSALIS trial, or before receiving 120-mg gilteritinib in the ADMIRAL trial. Patients randomized to SC in the ADMIRAL trial were also assessed. Patients in the CHRYSALIS trial had received at least one line of prior AML therapy; patients in the ADMIRAL trial received only one line of prior AML therapy.

Results: Of the 145 FLT3-mutation–enriched patients who received 120- or 200-mg gilteritinib in the CHRYSALIS trial, 33 (23%; 120 mg, n=15; 200 mg, n=18) had received a prior TKI (all received sorafenib). Baseline characteristics among patients who received (n=33) or did not receive prior TKIs (n=112) were similar. Rates of composite complete remission (CRc) were similar in patients who received prior TKIs (42%; n=14/33) and in those who did not (43%; n=48/112). Among patients who received prior TKIs, rates of CRc were 53% (n=8/15) in the 120-mg dose group and 33% (n=6/18) in the 200-mg dose group; rates of CRc in patients who did not receive prior TKIs were similar across both the 120- and 200-mg dose groups (44% [n=18/41] and 42% [n=30/71], respectively). Among patients treated with prior TKIs across the 120- or 200-mg dose groups (n=33), most (73%; n=24) had received ≥3 lines of any prior AML therapy. In the phase 3 ADMIRAL trial, 31 of 247 (13%) R/R FLT3-mutated AML patients in the gilteritinib arm and 14 of 124 (11%) patients in the SC arm had received prior TKIs. Demographic and baseline characteristics were well balanced between treatment arms and were also similar between prior TKI–treated (n=45) and non-treated patients (n=326). In the gilteritinib arm, CRc rates were comparable in patients who received (48%; n=15/31) and did not receive prior TKIs (55%; n=119/216); lower CRc rates were observed in the SC arm in both TKI–treated and non-treated groups (21% [n=3/14] and 22% [n=24/110], respectively). Median OS in patients treated with prior TKIs, albeit not statistically significant, remained high in patients treated with gilteritinib compared with those treated with SC (6.5 vs 4.7 months, respectively; HR=0.671 [95% CI: 0.328, 1.376]) (Figure). In patients who did not receive prior TKIs, median OS was 9.6 months in the gilteritinib arm and 6.0 months in the SC arm (HR=0.625 [95% CI: 0.474, 0.824]) (Figure).

Conclusion: Patients with R/R AML who received prior TKIs (midostaurin or sorafenib) were able to achieve remission with gilteritinib. High response rates with gilteritinib were observed in heavily pre-treated FLT3-mutation–enriched patients in the CHRYSALIS trial who received prior TKIs. Higher response rates with gilteritinib than with SC were observed in prior TKI–treated patients with FLT3 mutations in the ADMIRAL trial.

Keyword: Acute myeloid leukemia, Tyrosine kinase inhibitor, FLT3 mutation

PP01-12

Prognostic implications of Wilms' tumor 1 (WT1) gene expression in newly diagnosed cases of primary acute myeloid leukemia

Pranay Tanwar[1*], Harsh Goel[1], Anita Chopra[1], Aditya Kumar Gupta[3], Jagdish Prasad Meena[3], Sameer Bakhshi[2] and Amar Ranjan[1]

[1] Laboratory Oncology, Dr. BRA-IRCH, AIIMS, New Delhi, India
[2] Medical Oncology, Dr BRA-IRCH, AIIMS, New Delhi, India
[3] Pediatrics, AIIMS, New Delhi, India

Background: Acute myeloid leukemia (AML) is a heterogeneous disorder of the hematopoietic system characterized by abnormal differentiation and uncontrolled proliferation of undifferentiated myeloid progenitor cells in the bone marrow. The Wilms tumor 1 (WT-1) gene is involved in normal and malignant hematopoiesis, it encodes a zinc-finger transcription factor that can either activate or repress genes to regulate cell growth, apoptosis, and differentiation. In this study, we investigated the prognostic role of WT-1 gene expression levels in AML in combination with flow cytometry counts.

Method: Peripheral blood samples (PB) and Bone marrow (BM) specimens were collected from 54 newly diagnosed cases of AML. WT-1 gene expression level were assessed at the time of diagnosis, after completion of induction therapy and relapse cases by performing real-time polymerase chain reaction (RT-PCR). Flow cytometric immune-phenotyping study was also performed using a panel of monoclonal antibodies specific for AML.

Results: Of the 54 subjects studied, 41 were male and 13 females. In relation to the age, we found a higher number of cases in adult patients. RT-PCR analysis demonstrated that the expression of WT-1 in the initial and relapse group was significant higher than that in the complete remission (CR) group (P<0.001). In all AML patients, WT-1 expression levels were inversely correlated with normal hematopoiesis, negatively correlates with platelet count and hemoglobin level, and positively associated with blast and flow cytometer counts (per-

centage of granulocytes and percentage of CD34+ cells) in AML. Flow cytometric immune-phenotyping study demonstrated CD34, CD45, CD117, CD38, CD13, CD33, CD56 were expressed as positive in most cases, while cCD79a CD19, CD7, cCD3, CD16, CD123, CD-11bwerenegatively observed. Patients with increased WT-1 levels are associated with poor outcomes because of higher incidence of relapse and resistance to standard chemotherapy

Conclusion: WT1-mRNA levels have been proposed as a diagnostic and prognostic marker of AML. The combined usage of MFC and WT-1 monitoring contributed to an improved detection rate of relapse, and may be used to monitor MRD, assess the treatment efficacy, prognosis, and predict the risk of recurrence in leukemia patients

Keyword: AML, WT1, Gene expression, Biomarker

PP01-13

Arsenic trioxide-based regimen versus autologous hematopoietic stem cell transplantation as post-remission therapy in relapsed acute promyelocytic leukemia

Gi June Min, Byung-Sik Cho*, Daehun Kwag, Tong Yoon Kim, Jong Hyuk Lee, Joonyeop Lee, Sung-Soo Park, Silvia Park, Jae-Ho Yoon, Sung-Eun Lee, Ki-Seong Eom, Yoo-Jin Kim, Seok Lee, Chang-Ki Min, Seok-Goo Cho, Jong Wook Lee and Hee-Je Kim

Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea

Background: Arsenic trioxide (ATO) is the standard induction treatment option for relapsed acute promyelocytic leukemia (APL). However, the consensus for post-remission therapy is still lacking. Furthermore, limited studies have compared autologous hematopoietic stem cell transplantation (HSCT) versus consolidation without HSCT in relapsed APL patients.

Method: To address the issue about optimal post-remission treatment options, 31 relapsed APL patients, who achieved molecular complete second remission (mCR2) after reinduction between 2000 and 2019 at the Seoul St. Mary's Hospital, were included in this retrospective analysis. The median age of the patients was 39 years (range, 18-72 years), and there was a slight male predominance (58.1%) at diagnosis. At first relapse, the median CR1 duration was 18.0 months (range 6.0–49.0 months), and 22.6% of them presented early relapse within 12 months after CR1. Nineteen patients in the ATO-based post-remission group without HSCT were treated with various doses of ATO 0.15mg/kg/day (median 50 days, range 20–96 days). Twelve patients underwent autologous HSCT; three received two cycles of anthracycline-based IC consolidation with peripheral blood stem cell (PBSC) collection before transplant, and the remaining nine underwent two cycles of 25 days ATO consolidation and PBSC collection by additional anthracycline-based IC or intermediate-dose cytarabine induced mobilization. There was no other significant difference in demographic characteristics, Sanz risk at diagnosis and relapse, CR1 duration, early relapse rate, or the type of relapse between the two groups.

Results: There were no significant differences in overall survival (64.9% (95% confidence interval (CI), 37.6–82.6) vs. 75.0%, (95% CI, 40.8–91.2) p=0.850), disease-free survival (44.1% (95% CI, 20.9–65.2) vs. 50.0% (95% CI, 20.8–73.6), p=0.978), cumulative incidence of relapse (50.7% (95% CI, 24.8–71.8) vs. 41.7% (95% CI, 13.9–67.9), p=0.878), and non-relapse mortality (5.3% (95% CI, 0.3–22.0) vs. 10.0% (95% CI, 0.5–37.4), p=0.707) between both groups. In the ATO-based post-remission group (n=19), one patient died during the second cycle of ATO consolidation due to sudden cardiac arrest. Nine patients achieved mCR2, and the remaining nine experienced a second relapse. Of these nine patients, five underwent allogeneic HSCT after salvage therapy, and four of these five patients are alive without relapse. One patient died because of CMV pneumonia during maintaining mCR3 status after allogeneic HSCT. However, four patients did not undergo HSCT due to either death by infectious complications during consolidation treatment or disease progression after patients' refusal of HSCT. In the autologous HSCT treatment group (n=12), one patient died because of pneumonia septic shock during the transplantation, six patients achieved mCR2, and the remaining five experienced a second relapse. Among these five patients, two received salvage allogeneic HSCT and are alive without relapse, and the other three received only ATO, of whom one died from infection during ATO consolidation, and two are alive without relapse.

Conclusion: The ATO-based post-remission treatment group showed similar second relapse rates and overall survival as the autologous HSCT group in relapsed APL patients who achieved mCR2. Indeed, about a half of the patients who received limited doses of ATO as post-remission therapy had long-term, event-free survival even without transplantation. Given that allogeneic HSCT could serve as an effective salvage treatment, our data highlight the necessity of prospective, controlled, multicenter studies to identify optimal post-remission treatment in mCR2 of relapsed APL patients

Keyword: Acute promyelocytic leukemia, Relapse, Arsenic trioxide, Stem cell transplantation, Postremission therapy,

PP01-14

Diagnosis of acute promyelocytic leukemia with 3D microscope: toward an objective diagnosis

Hyunji Kim[1], Seongsoo Jang[1*], Daehyun Chu[1], Miyoung Kim[1], Young-Uk Cho[1], Sang-Hyun Hwang[1], Chan-Jeoung Park[1] and YongKeun Park[2]

[1] Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

[2] Department of Biological Sciences, KAIST, Daejeon, Korea

Background: Optical diffraction tomography (ODT) is a microscope that analyzes live-cells by applying the refractive index (RI), which is inherent optical index of the substance. ODT provides three-dimensional live cell images as well as numerical information for several parameters such as morphological parameters (volume, surface area, projected area, and sphericity), physical parameters (mean RI and threshold RI), and biochemical parameters (concentration and dry mass). ODT analyzes live cells without pretreatment, which is useful in situations that require immediate therapeutic intervention. In this study, we aim to identify the ODT profiles of various leukemic blats and compare their differences between acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL) and lymphocytes. In particular, we would like to determine whether it is possible to differentiate acute promyelocytic leukemia (APL) blasts that require immediate therapeutic intervention from among myeloblasts.

Method: We analyzed leukemic blasts by ODT using residual peripheral blood and bone marrow samples from tests performed at Asan Medical Center in Seoul from May 2021 to September 2021. The ODT profiles of all the collected data were classified as AML, ALL, and lymphocytes and the statistical significance between the groups was compared. The collected ODT data of myeloblasts were divided into a learning group (data from March 2021 to August 2021) and a validation group (data from September 2021) according to the sample collection date. The APL blast differential diagnostic equation obtained by discriminant analysis of the learning group was verifies through the validation group.

Results: The study included 2,198 cells data from a total of 66 samples; AML of 1,111 cells in 39 samples, ALL of 1,087 cells in 27 samples, and lymphocytes of 81 cells in 4 samples. In AML and ALL, the p-value for all ODT parameters except the threshold RI was less than 0.05, which was statistically significant; volume (AML, 475.9±199.9; ALL, 257±87.0, p<0.001), surface area (360.2±107.6; 236.3±54.8, p<0.001), projected area (84.2±29.3; 53.5±15.0, p<0.001), dry mass (80.4±30.0; 44.2±12.7, p<0.001), and sphericity (0.81±0.03; 0.82±00.03, p<0.001). ALL and lymphocytes also showed less than 0.001 differences in p-values for volume, surface area, projected area, and dry mass. In the analysis for APL blast differentiation, the learning group was 755 cells in 25 samples (including APL data of 91 cells in 3 samples), and the validation group was 356 sample in 14 samples. The ODT profile of myeloblasts were summarized in figure. The APL blasts differential diagnostic equation was D=16.899×sphericity-0.28×volume+0.145×projected area+0.071×dry mass+98.775×mean RI-153.307. In the validation of the equation by the validation group, sensitivity 65.9%, specificity 87.0%, accuracy 84.6% were confirmed, and the negative predictive value was 95.1%. One sample of APL included in the validation group was predicted to be APL with 65.9% probability. The other myeloblasts in 13 samples were determined not to be APL except for 2 samples undetermined that 50% probability of non-APL.

Conclusion: In addition to the differentiation of AML and ALL and normal lymphocytes, ODT-based APL numerical diagnosis may enable objective cell differentiation. The difference in numerical information between cells can help determine immediately whether to transfer from a primary and secondary hospital without a hematologist to a tertiary hospital.

Keyword: Optical diffraction tomography, Acute promyelocytic leukemia, Live cell image, Numerical information

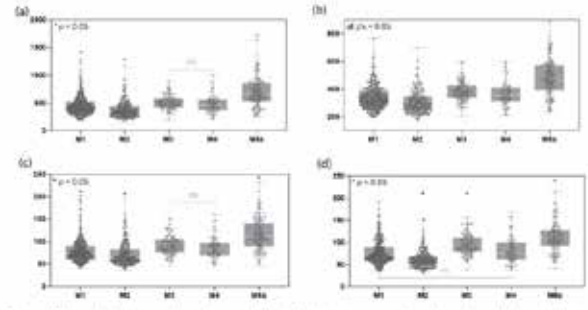


Figure. Numerical information from optical diffraction tomography of various leukemic blasts according to FAB classification; (a)volume, (b)surface area, (c)projected area, and (d) dry mass. When compared between groups, all p-values were less than 0.05, except for the ns shown in the figure. Dots represent each data. The median of box marks the mid-point of the data. The whiskers at the bottom and top represent the minimum and maximum range of data.
Abbreviation: ns, not significant.

PP01-15

Efficacy of cytarabine, daunorubicin plus etoposide as induction regimen for pediatric acute myeloid leukemia

Huong-Giang Nguyen-Tran[1*], Tuan Nguyen[1] and Nghia Huynh[2]

[1] Hematology, Cho Ray Hospital, Viet Nam

[2] Hematology, Ho Chi Minh University of Medicine and Pharmacy, Viet Nam

Background: Pediatric acute myeloid leukemia (AML) confers a poor prognosis. The survival rates for paediatric AML patients have greatly improved over the past several decades. The standard induction regimen is a seven-day continuous infusion of cytarabine plus a three-day of anthracycline (A7D3). In addition, Cytarabine, Daunorubicin plus Etoposide (ADE) regimen is another option, in which Etoposide is included, but the benefit of this additional agent has not yet been proven. We carried out this study to evaluate the efficacy of ADE as induction regimen for pediatric acute myeloid leukemia at Ho Chi Minh Blood Transfusion Hematology from 2010 to 2019.

Method: In this descriptive case series study, we retrospectively reviewed the medical records with the clinical and biological characteristics at the time of diagnosis, chemotherapy regimen toxicities, remission and outcome of all pediatric non-acute promyelocytic leukemia AML patients treated with ADE induction regimen, which included cytarabine 100 mg/m2 every 12 hours for 10 days, daunorubicin 50 mg/m2 for 3 days and etoposide 100 mg/m2 for 5 days, at Ho Chi Minh Blood Transfusion Hematology Hospital from 2010 to 2019.

Results: From 2010 to 2019, 35 eligible children with non-acute promyelocytic leukemia AML were included in our study. The median age was 10 (10-15) years, the male/female ratio was 2.97/1. The common clinical symptoms were anemia (97.1%), thrombocytopenia (85.6%), fever (54.3%), hepatomegaly (71.4%), splenomegaly (40%), central nervous system involvement (11.4%), orbital sarcoma (8.6%). The most common FAB morphologies were M2 and M4. AML with favorable cytogenetics accounted for 40% (n=14), with intermediate cytogenetics accounted for 40% (n=14), with adverse cytogenetics accounted for 20% (n=7). The early mortality rate in induction was 2.9% (n=1). Mean length of hospital stay in the induction phase was 48.29±6.387 days. Neutropenia fever was the leading complications, accounted for 100% patients. After the 1st induction, 80% (n=28) patients achieved complete remission (CR) and after the 2nd induction, 91.4% (n=32) patients achieved CR. The rates of OS, EFS, RFS, RD after 3 years were similar to those after 10 years (51.2%, 41.8%, 43.2%, 57.7%, respectively). The median time of relapse was 9 (1-22) months. Medullary relapse accounted for 90%, isolated extramedullary relapse accounted for 10%. There was no statistically significant difference in the effect of age, FAB classification, extramedullary manifestation and time from diagnosis to treatment on the patient outcome. However, the white blood cell count (WBC) at diagnosis was a poor prognostic factor. Patients with WBC < 50,000/microL at the time of diagnosis had better OS (61.2% vs 25%, p=0.032). Core-binding factor (CBF) was a favorable prognostic factor, contributing to an increase in OS rate (77.1% vs 33.9%, p=0.053). CR and negative measurable residual disease (MRD) after induction were strong predictors of patient outcome (OS, EFS, RFS, RD) p<0.003.

Conclusion: ADE is an effective induction regimen of pediatric non-acute promyelocytic leukemia AML with acceptable toxicities. Complete remission and negative measurable residual disease after induction are strong predictors of patient outcome (OS, EFS, RFS, RD).

Keyword: Paediatric acute myeloid leukemia, ADE, A7D3 regimen

PP01-16

Genetic characteristics according to subgroup of acute myeloid leukemia with myelodysplasia-related changes

Silvia Park[1], Dain Kang[2], Byung-Sik Cho[1], Hee-Je Kim[1], Yeojae Kim[2], Jong Mi Lee[3], Ari Ahn[3], Yonggoo Kim[3] and Myungshin Kim[3*]

[1] Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

[2] Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

[3] Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea

Background: Current diagnosis of acute myeloid leukemia (AML) is largely dependent on genetic aberrations.In the 2016 WHO classification, gene mutations were included in the category of recurrent genetic aberrations such as NPM1 and double CEBPA mutations. Nonetheless, some AML categories are diagnosed based on bone marrow (BM) morphology and other associated findings. One of the aforementioned categories is AML with myelodysplasia-related changes (AML-MRC), which is diagnosed in patients who have previous history or specific cytogenetic or morphological properties. The diagnosis remains difficult even for an experienced hematopathologist. In recent years, next-generation sequencing (NGS) has been widely used in clinics and has established the genetic characteristics and their significance in each disease category. In this study, we analyzed the genetic aberrations in AML-MRC using an RNA-based NGS panel assay and detected gene fusions, mutations, and expressions. We compared the genetic profiles among AML-MRC subgroups and endeavored to determine characteristic genetic mutations according to subgroup and to elucidate their clinical significance.

Method: We evaluated all 45 consecutive patients who were diagnosed with AML-MRC at Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea from 2013 to 2018. Patients were classified into the following three subgroups: 1) patients with

history of prior myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasm (AML-MRC-H), 2) patients with MDS-defining cytogenetic abnormalities (AML-MRC-C), and 3) patients with >50% dysplasia in at least two lineages (AML-MRC-M). Anchored multiplex PCR-based enrichment RNA-sequencing libraries were performed to identify gene fusions, mutations and expression using the ArcherDx FusionPlex Myeloid assay for Illumina. TP53 and FLT3-internal tandem duplication mutations were separately analyzed using Sanger sequencing and fragment analysis.

Results: We detected a total of 86 genetic aberrations in 39 patients (87%); 4 gene fusions of KMT2A-SEPT9, KMT2A-ELL, NUP98-NSD1, and RUNX1-USP42, and 82 somatic mutations in 20 genes. When combined with cytogenetics, all AML-MRC cases had at least one genetic aberration. The most frequent mutation was present in TP53 (n=11, 24%), followed by ASXL1 (n=9, 20%), IDH2 (n=9, 20%), SRSF2 (n=7, 16%), CEBPA (n=5, 11%), PTPN11 (n=5, 11%), FLT3 (n=5, 11%), IDH1 (n=4, 9%), and RUNX1 (n=4, 9%). All TP53 mutations were observed in AML-MRC-C (P=0.002), specifically in patients with complex karyotype (P<0.001). On the other hand, ASXL1 and SRSF2 mutations were more commonly detected in AML-MRC-M compared to AML-MRC-C (P=0.032 and 0.024, respectively) and were frequently co-mutated (55%, 6/11, P <0.001). IDH1/IDH2 (n=13, 29%) were commonly mutated in AML-MRC and could have more significance as a risk factor or susceptibility marker for target therapy. Among all patients, the overall survival (OS) was significantly different by AML-MRC group; the estimated OS was 13.7, 5.4, and 8.8 months in the AML-MRC-M, -C, and -H groups (P=0.013), respectively. This significant survival difference was identically observed when the analysis was performed for patients receiving any treatment (P=0.028) or only those who had undergone intensive chemotherapy (P=0.036). When analyzed within the AML-MRC-C group, the TP53 mutation predicted a shorter OS not only in all patients (P=0.006), but also in those receiving any treatment (P=0.010) in the univariate analysis for OS. In multivariate analysis for OS, the AML-MRC subgroup had an independent prognostic value. In addition, AML-MRC-C compared to AML-MRC-M showed a significantly worse outcome, with threefold higher hazard ratio for death (P=0.003)

Conclusion: AML-MRC is composed of heterogenous cases with different risk categories and genetic characteristics. Most AML-MRC patients had genetic aberrations including gene fusions and mutations as well as cytogenetic changes. In terms of genetic mutations, AML-MRC showed characteristics according to subtype, and each had its own significance. The TP53 mutation was closely associated with AML-MRC-C and extremely poor outcome in AML-MRC. ASXL1 and SRSF2 mutations were associated with AML-MRC-M and could be used as surrogate markers to diagnose AML-MRC. Mutations in IDH1/IDH2, CEBPA, PTPN11, FLT3, and RUNX1 were not limited to any AML-MRC subgroup and could be more significant as risk factors or susceptible markers for target therapy in not only AML-MRC, but also other AML categories.

Keyword: Acute myeloid leukemia, Myelodysplasia-related changes, Next-generation sequencing, Anchored multiplex PCR,

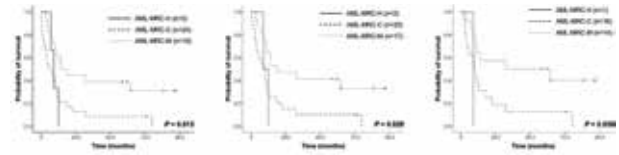


Figure 1. Overall survival of all patients according to acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) subtype (a) in all patients, (b) among treated patients and (c) among patients underwent intensive chemotherapy. AML-MRC-H, patients with history of prior myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasm ; AML-MRC-C, patients with MDS-defining cytogenetic abnormalities; and AML-MRC-M, patients with >50% dysplasia in at least two lineages.

PP01-17

Clinical significance of masked systemic mastocytosis with associated hematological neoplasm in AML with RUNX1::RUNX1T1

Beom Joon Kim[1], Jee Soo Lee[2], Moon-Woo Seong[2], Soo Hyun Seo[1], Jinho Paik[4], Sang A Kim[3], Ji Yun Lee[3], Jeong Ok Lee[3], Soo Mee Bang[3], Yoon Hwan Chang[2] and Sang Mee Hwang[1*]

[1] Laboratory Medicine, Seoul National University Bundang Hospital, Korea
[2] Laboratory Medicine, Seoul National University Hospital, Korea
[3] Internal Medicine, Seoul National University Bundang Hospital, Korea
[4] Pathology, Seoul National University Bundang Hospital, Korea

Background: Systemic mastocytosis (SM) is a rare, heterogenous malignant disease of mast cell (MC) proliferation, characterized by abnormal MC infiltration that accumulate in one or more organ systems. Systemic mastocytosis with associated hematological neoplasm (SM-AHN) presents unique, special challenges in the diagnosis because of concurrently existing distinct hematological malignancy including myelodysplastic syndrome, myeloproliferative neoplasm and acute myeloid leukemia (AML). As the presence of KIT D816V mutation is a minor criteria for the diagnosis of SM-AHN, patients diagnosed as AML with RUNX1::RUNX1T1 known to have KIT mutations in 25% of the patients, may have concurrent SM-AHN. Although masked SM-AHN with AML cases have been previously reported, the immunohistochemical (IHC) staining of CD117 and CD25 for the differential diagnosis are not routinely included in work up of SM-AHN in AML with RUNX1::RUNX1T1. In this study, the clinical significance of SM-AHN in AML with RUNX1::RUNX1T1 were assessed with emphasis on the IHC and KIT mutation detection after therapy.

Method: From December 2014 to April 2020, the presence of SM-AHN was assessed in patients diagnosed with AML with RUNX-1::RUNX1T1. SM-AHN was diagnosed according to the WHO criteria. We have assessed whether the bone marrow (BM) at diagnosis of AML showed presence of atypical mast cell collection with CD117 and CD25 IHC and compared the results to the post induction sample in SM-AHN. To evaluate the KIT D816V mutation burden in different sources of sample at diagnosis and during follow up, droplet digital PCR (ddPCR) was performed with BM aspirate, BM smear slide and formalin-fixed paraffin-embedded BM section, separately. The clinical characteristics and overall survival (OS) were compared in patients with and without SM-AHN. Additional somatic mutations were assessed in SM-AHN patients.

Results: Twenty-three patients were diagnosed with AML with RUNX1::RUNX1T1 during the study period, and four (17.4%) of these patients were diagnosed with SM-AHN. No significant differences were observed in the clinical characteristics of the two groups, except for the presence of KIT mutations (P = 0.040). Patients with or without SM-AHN did not show a significant difference in OS by Kaplan Meier analysis (P = 0.565). Patients with SM-AHN at diagnosis of AML, did not show evident mast cell collections on hematoxylin-eosin slide. Retrospectively analyzed, CD117 IHC showed positivity in mast cell collections at diagnosis in two patients but in the other two patients, mast cell collection was not evident with IHC of CD117, with diffuse dim positivity of CD117 on blasts at diagnosis of AML. Aberrancy of masts cells with CD25 at diagnosis was only evident in one case. However, IHC staining on the BM after induction therapy revealed mast cell collections in all patients with CD117 positivity and CD25 aberrancy in mast cells. The mutant burden of KIT D816V decreased as the blast count decreased and the allele burden was similar with BM smear slide, aspirate, and tissue section. However, KIT D816V mutations persisted post induction. Two patients with SM-AHN had targeted sequencing results and showed additional mutations in RUNX1 (n = 2), FLT3 (n = 1), TP53 (n = 1), and NRAS (n = 1).

Conclusion: Presence of concomitant SM-AHN was found in 17.4% of AML with RUNX1::RUNX1T1. The clinical characteristics and the overall survival were not significantly different for those with or without SM-AHN. The study results showed the importance of IHC staining for CD117 and CD25 after the induction chemotherapy to screen for SM-AHN, in patients with AML with RUNX1::RUNX1T1, especially in those with KIT mutations. Persistent KIT D816V mutations were detected with ddPCR in BM after induction with BM samples of various sources, which needs to be considered when analyzing and assessing molecular results in SM-AHN with AML with RUNX-1::RUNX1T1.

Keyword: Systemic mastocytosis with associated hematological neoplasm, Acute myeloid leukemia with RUNX1::RUNX1T1, Immunohistochemistr, KIT mutation, Droplet digital PCR

PP01-18

Incidence of therapy-related myeloid neoplasms and their risk factors for the selection of patients with an increased risk: a Korean nationwide study

Hyerim Ha[1,2], Hyo Jeong Kim[3], Ju Hyun Park[3], Na Rae Lee[3] and Junshik Hong[1*]

[1] Department of Internal Medicine, Seoul National Universityi College of Medicine, Korea

[2] Department of Internal Medicine, Inha University Hospital, Korea

[3] National Evidence-based Healthcare Collaborating Agency (NECA), Korea

Background: Therapy-related myeloid neoplasms (t-MNs) are myeloid malignancies caused after cytotoxic treatment such as chemotherapy (CT) or radiotherapy (RT) for preceding diseases, mostly cancers. Recent studies showed that preceding somatic or inherited genetic alternation can predispose t-MNs. Therefore, t-NMs can be a condensed model for exploring dynamic changes in pre-leukemic stages of MDS and AML. To specify groups of cancer patients who are suitable for a future prospective cohort for the investigation of t-MNs pathogenesis by serial collection of samples with clinical information, we investigated recent incidences and risk of t-MNs after contemporary chemotherapy (CT) or radiation (RT) in Korean adult cancer patients.

Method: By merging to Korean nationwide healthcare big data, CT and/or RT-treated adult cancer patients from 24 different sites diagnosed between 2009 to 2013 were selected as a denominator. The selected patients were followed up to the date of t-MN development or December 2019. The risk of developing t-MNs was estimated using standardized incidence ratio (SIR) with Poisson-based 95% confidence intervals. The expected incidence was calculated in each 5-year interval of ages and sex group from the NHIS database of whole Korean population during 2010 to 2019.

Results: Among the 245,343 patients, 555 (0.18%) patients were diagnosed with t-MNs with a median latency of 5.37 person-years with a SIR of 3.40 (95% CI 3.13-3.70). Bone cancer, soft tissue cancer, malignant lymphoma, and plasma cell tumor had an SIR of > 10. A significantly higher SIR was noted within the first 5 years after the treatment initiation of preceding cancer (SIR 17.4, 95% CI 15.71-19.09). Afterward, SIR decreased back to almost the risk of general population (SIR 1.17, 95% CI 1.02-1.32). Patients who received both CT and RT showed the highest SIR (4.64, 95% CI 4.08-5.20), followed by those who received CT only (SIR 3.30, 95% CI 2.89-3.70; Table 2). In contrast, RT alone did not show a higher risk of developing t-MNs compared to general Korean population (SIR1.16, 95% CI 0.76–1.56). Exposure to leukemogenic agents increased the risk of t-MNs devel-

opment. On the other hand, among patients who received monoclonal antibodies or tyrosine kinase inhibitors but lacked cytotoxic chemotherapeutic agents, higher risk of developing t-MNs was not reported.

Conclusion: Based on the results of our work, it would be a valuable approach if we carefully select particular groups of patients who are expected to have a substantially high-risk of developing t-MNs, for example patients with bone and soft tissue cancers with chemotherapy or those with lymphoid malignancies or solid tumors who are inevitable to receive intensive CT with more than single leukemogenic agents with the addition of RT. If we establish and maintain a prospective cohort to conduct serial collection of laboratory samples and clinical information from those patients, we could gain useful insights on the prevention or preemptive treatment of therapy-related and possibly even non-therapy-related myeloid malignancies at preleukemic stage. In addition, those high risk patients could be suitable subjects of clinical trials investigating the effectiveness of certain chemoprevention for t-MNs.

Keyword: Therapy-related myeloid neoplasms, Acute myeloid leukemia, Myelodysplastic syndorme, Second cancer

PP01-19

Induction of differentiation in acute myeloid leukemic stem cells by a natural compound: Esculetin

Ankit Mathur and Daman Saluja*

Dr. B.R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi, India

Background: Acute Myeloid Leukemia (AML) is a heterogeneous condition in which genetic/epigenetic alterations results in a block of differentiation (maturation arrest) that allows myeloid leukemic cells to continue to proliferate and/or prevents the terminal differentiation and apoptosis. The intra-tumoural heterogeneity in AML is partially attributed to clonal evolution of accumulated immature blast cells endowed with cancer stem cell properties. We have previously demonstrated anti-proliferative, anti-leukemic, and anti-oxidative effects of natural compound (Esculetin) on AML/ pancreatic cancer cells. The current study supports the rationale of using esculetin to induce differentiation in AML blast/stem cells.

Method: The differentiation potential of esculetin was accessed on two in vitro cellular models using acute myeloid leukemia cells (Kasumi-1) with t(8;21/AML-ETO) translocation as well as human colon carcinoma cells line (HCT116) with p53 and p73 knockdowns.

Results: Morphological alterations associated with neutrophilic differentiation as well as corresponding acquisition of myeloid lineage markers indicate terminal differentiation potential of esculetin in leukemic blast/stem cells. The study highlights the possibility that the cells that escaped the early apoptosis program were stimulated to undergo differentiation upon esculetin treatment. Interestingly, esculetin remarkably altered the genes associated with stem cell proliferation/maintenance as well as planner cell polarity. These results suggest that esculetin abolish the leukemic stem cell (LSC) properties by induction of differentiation as well as suppression of the stem cell maintenance. Esculetin was also found to be associated with reversion of cancer stem cell marker expressions consistent with the reduction in functional cancer stem cell properties viz. colonogenic potential/ sphere forming capacity in leukemic cells. Considering the differentiation potential of esculetin in immature leukemic blast/LSC population, we extended our study to ascertain putative corresponding role of esculetin on the solid tumour cancer stem cells. Esculetin was found to attenuate the aggressive mesenchymal features and migration of colon carcinoma cells by reversing EMT phenotypes. Esculetin also showed potential to revert the Cancer Stem Cell (CSC) marker expressions consistent with reduced functional CSC properties and suppression of Wnt associated genes in colon cancer as well as leukemic cells.

Conclusion: We demonstrate that esculetin terminally differentiate the AML LSCs into neutrophils. The study may provide significant therapeutic innervations of esculetin as a differentiating agent in both solid cancers as well as in leukemia.

Keyword: Acute myeloid leukemia, Leukemic stem cells, Differentiation, Blast cells, Natural compound, Esculetin

PP01-20

Acute promyelocytic leukemia with cryptic IRF2BP2-RARA rearrangement in a patient with germline DDX41 mutation: the first case in Korea

Jae Joon Lee[1], Hyun-Young Kim[1], Jun Ho Jang[2], Sun-Hee Kim[1] and Hee-Jin Kim[1*]

[1] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

[2] Department of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Background: Acute promyelocytic leukemia (APL) is characterized by the accumulation of promyelocytes. Most patients with APL are developed by all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) sensitive PML-RARA rearrangement, however some patients have various rearrangement that are rarely found, including various RARA rearrangement. Here, we report a case of variant APL with ATRA sensitive IRF2BP2-RARA rearrangement in a patient with Germline DDX41 mutation.

Method: An 81-year-old man was followed up for spinal stenosis. Multiple metastatic lesions of L3 vertebra were found on spine magnetic resonance imaging (MRI), and myeloid sarcoma was diagnosed on vertebral biopsy. Complete blood cell count (CBC) showed white blood cells (WBC), 3.40x109/L; hemoglobin, 11.9 g/dL; and platelets, 144x109/L, and no myeloid precursor cells were observed on peripheral blood (PB) smear. Bone marrow (BM) study showed hypercellular marrow (80% of cellularity) with significant proliferation of myeloid cells. Most of myeloid cells were mature granulocytes with heavy granules, and abnormal promyelocytes were not evident. Chromosome study showed normal karyotype and multiplex reverse transcriptase-polymerase chain (RT-PCR) assay using HemaVision were also negative. Therefore, at that time, no definite diagnosis was made on BM study. However, follow-up CBC after a month showed WBC, 18.01x109/L; hemoglobin, 10.2 g/dL; platelets, 46x109/L, and 15% of abnormal promyelocytes containing auer rods were observed, and BM study was performed again.

Results: BM study showed 100% of cellularity with significantly increased abnormal promyelocytes. Flow cytometry showed the immunophenotypes of CD13pos, CD33pos, CD34neg, CD64pos, CD117pos, and HLA-DRneg , which was typical finding for APL. Chromosome study showed 45,X,-Y[10]/46,XY[10], and fluorescence in situ hybridization (FISH) for PML/RARA and RARA rearrangement were all negative. Multiplex RT-PCR were also negative. Finally, variant APL was suggested based on the morphologic and immunophenotypic findings. However, since it was not identified from a molecular level, the patient started treatment with decitabine and venetoclax. Next-generation RNA-sequencing was then performed, and IRF2BP2-RARA rearrangement with distinct breakpoints within IRF2BP2 exon 2 and RARA intron 2 were identified. This fusion transcript was confirmed by subsequent RT-PCR and direct sequencing, and currently, this patient is receiving ATRA treatment. Additionally, next-generation sequencing of the first BM specimen revealed a heterozygous pathogenic DDX41 mutation (NM_016222.2:c.19G>T, p.Glu7*), which was confirmed as a germline mutation using PB specimen in complete remission.

Conclusion: To our knowledge, this is the first case of APL with IRF2BP2-RARA in Korea. To date, six cases of IRF2BP2-RARA rearrangement have been reported worldwide and known to be sensitive to ATRA. Since ATRA sensitivity differs depending on the accompanying genetic feature in patients with suspected variant APL, it is important for diagnosis and treatment to confirm the accompanying genetic features, and a thorough evaluation is required.

Keyword: Acute promyelocytic leukemia, IRF2BP2-RARA, Myeloid sarcoma, DDX41

PP01-21

Therapy-related myeloid neoplasm with inv(11)(p15q22)/NUP98-DDX10 rearrangement: the first case in Korea

Noorie Kang[1], Jae Joon Lee[1], Hyun-Young Kim[1], Chul Won Jung[2], Sun-Hee Kim[1] and Hee-Jin Kim[1*]

[1] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[2] Department of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Inv(11)(p15q22) rearrangement is a rare genetic aberration reported in de-novo or more frequently in therapy-related myeloid neoplasms (t-MNs). It creates the fusion of the nucleoporin gene (NUP98) on 11p15.5 and the DEAD-box helicase 10(DDX10) gene on 11q22.3. Here we report a case of an adult Korean patient diagnosed as having t-MNs with inv(11)(p15q22)/NUP98-DDX10 rearrangement.

Method: The patient was a 51-year-old woman and underwent bone marrow (BM) study due to persistent pancytopenia. On the day of the BM study, her complete blood cell counts (CBC) were as follows: hemoglobin, 10.0 g/dL; white blood cells, 2.47 x109/L (absolute neutrophil count, 1.46x109/L); platelets, 56x109/L, and differential count was segmented neutrophils, 59%; lymphocytes, 17%; monocytes, 24%. Cytogenetic and molecular genetic studies were conducted for evaluation of hematologic malignancy. A review of her past medical history revealed treatment for epithelial ovarian cancer from February 2018. Following the initial surgical intervention, she received multiple courses of chemotherapy along with radiotherapy due to the recurrent relapses of disease: carboplatin and bevacizumab from March to July 2018, doxorubicin and carboplatin from October 2019 to April 2020, nivolumab from January to February 2021, and radiation therapy in April 2021.

Results: The BM study showed normocellular marrow (30% cellularity) with relatively increased plasma cells, which were polyclonal in nature by flow cytometry. There was no definite evidence of dysplastic features in either peripheral blood cells or bone marrow precursors. Cytogenetic study revealed chromosome 11 with pericentric inversion with break and reunion at p15 and q22 bands in 14 out of 20 metaphases. Reverse transcription-PCR and direct

sequencing revealed the NUP98 exon 14-DDX10 exon 7 gene rearrangement (type II). In combination with the past treatment history for ovarian cancer, she was finally diagnosed with t-MN.

Conclusion: To our knowledge, this is the first case of t-MN with inv(11)(p15q22)/NUP98-DDX10 in Korea. Although there was no morphologically definite evidence of myeloid neoplasms on BM study, molecular genetic test revealed NUP98-DDX10 rearrangement. This case indicates the importance of meticulous clinical correlation and genetic investigation for the diagnosis of t-MN. Data from more cases are needed for the elucidation of clinical and therapeutic implications of inv(11)(p15q22)/NUP98-DDX10.

Keyword: Therapy-related myeloid neoplasms, NUP98-DDX10, inv(11)(p15q22)

PP01-22

Gene expression profiling of VASH1 and its prognostic role in acute myeloid leukemia

Avanish Kumar Pandey[1], Sarita Kumari[1], Jay Singh[1], Mohit Arora[3], M Shadab Ali[4], Jayanth Kumar Palanichamy[3], Sameer Bakhshi[2], Atul Sharma[2], Mercilena Benjamin[1], Neha Thukral[1] and Anita Chopra[1*]

[1] Laboratory Oncology Unit, Dr. BRA-IRCH, AIIMS, NEW DELHI, India
[2] Department of Medical Oncology, AIIMS, NEW DELHI, India
[3] Department of Biochemistry, AIIMS, NEW DELHI, India
[4] Department of Pulmonary, AIIMS, NEW DELHI, India

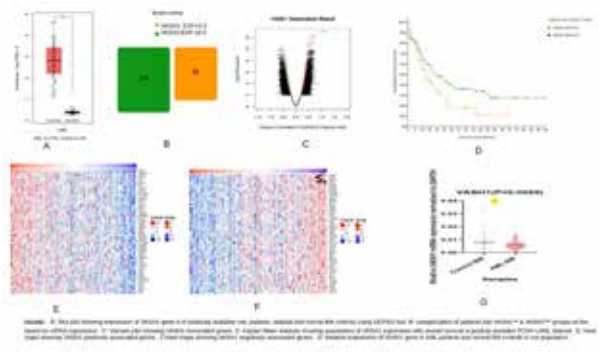
Background: Acute myeloid leukemia (AML) is a common hematological malignancy which is associated with significant morbidity and mortality due to bone marrow (BM) failure and treatment resistance. The prognosis of AML is extremely poor. Thus, understanding the mechanisms regulating the pathobiology of AML is important for better assessment of risk and developing novel effective therapies for the disease. Vasohibin-1 (VASH1), is induced by fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor in endothelial cells and act as negative regulator of angiogenesis. Some studies supported the expression of VASH1 in several cancers having poor prognosis. However, there is no study available on the prognosis of VASH1 in AML. In this study, we explored the mRNA expression of VASH1 in publicly available AML datasets and further determined its prognostic significance. We also estimated the mRNA expression levels of VASH1 genes in our adult AML patients.

Method: We have investigated VASH1 mRNA expression in publicly available TCGA-LAML dataset (n=173) using cBioPortal and GEPIA2 tools. Patients were divided into high and low mRNA expression groups based on z-score (VASH1:exp>0.3: high expression group, VASH1:exp<0.3: low expression group). LinkedOmics database and cBioPortal were used to screen out the positively and negatively correlated genes with VASH1. Volcano plots and heat maps were generated to represent VASH1 associated genes. Gene Set Enrichment Analysis (GSEA) was used for functional enrichment analysis. VASH1 and its associated genes were subjected to Kyoto Encyclopedia of Genes and Genome (KEGG) and Gene Ontology functional analysis to predict the enriched signaling pathway in the TCGA-AML dataset. Kaplan Meier plot along with log-rank test was used for overall survival analysis of 173 adult AML patients in publicly available TCGA-LAML through cBioPortal. To validate the transcriptional level of VASH1 expression in our population, a total of 100 BM samples of newly diagnosed AML patients were collected. Total RNA was isolated and quantitative real-time PCR was performed for determining mRNA expression levels of VASH1 in AML patients and non-diseased controls (n=16). Mann-WhitneyU-test was used for comparing VASH1 mRNA expression levels between normal and bone marrow samples of AML patients. P-value < 0.05 was considered statistically significant.

Results: We observed a higher level in the VASH1 mRNA in AML patients as compared to normal (P<0.05) in the publicly available TCGA-LAML dataset. Based on the z-score of mRNA expression, 104 patients were found to be in the low expression group while 69 patients were in the high expression group. Volcano plot and heat maps showed that a total of 4,848 were significantly associated with VASH1 (P<0.05 & FDR< 0.05) which consists of 2,315 positively and 2,533 negatively correlated genes. Pathway analysis revealed that the clustered genes were involved in cancers, myeloid leukocyte activation and migration, T-cell activation, response to tumor necrosis factor, leukocyte cell-cell adhesion and cell cycle regulation. Kaplan Meier plot showed VASH1high was associated with worse overall survival compared to VASH1low (P=0.0089). We also found underexpression of VASH1 mRNA in AML patients as compared to normal samples (P<0.05). Association of VASH1 mRNA expression with patient's clicopathological feature and survival needs to be further investigated.

Conclusion: This is the first study that shows the aberrant expression and prognostication of VASH1 in AML. Higher expression of VASH1 in AML patients is associated with poor prognosis. Exact mechanism of action of VASH1 in AML needs to be studied further for better understanding its role in AML patients prognosis, and to define novel approaches for therapy that may improve patient outcomes.

Keyword: VASH1, Acute myeloid leukemia, Angiogenesis, Gene expression, Overall survival



most comprised, followed by frameshift mutations (n=80, 22.4%), nonsense mutations (n=36, 10.1%), and inframe insertions (n=5, 1.4%). In 84.1% (132/157) of patients, at least one variant was identified: 94.0% in AML, 68.6% in MDS, 87.2% in MPN. Prognostically significant somatic mutations were found in 50.4% (n=180) of cases. And 64.7% (n=231) of patients had variants with therapeutic impact.

Conclusion: NGS panel assay for MN can provide clinically actionable variants relevant to diagnosis, prognosis, and therapeutic decisions according to the current standards. These can guide clinicians manage the disease in daily practice.

Keyword: Next-generation sequencing, Myeloid neoplasms, Diagnosis, Prognosis, Treatment

PP01-23

Clinical usefulness of next-generation sequencing panel for myeloid neoplasms

A-Jin Lee, Sang-Gyung Kim*, Chang-Ho Jeon and Eun-Hyung Yoo

Department of laboratory medicine, Daegu Catholic University School of Medicine, Korea

Background: Next-generation sequencing (NGS) has enabled to detect the wide range of genes relevant to myeloid neoplasms (MN) and clarify the disease entity. In this study, we assessed the clinical usefulness of targeted NGS panel in the clinical setting regarding MN.

Method: A total of 157 patient test results were obtained. NGS was performed using the OncomineTM Myeloid Research Assay (OMA, Thermo Fisher Scientific) on Ion S5 XL sequencers. Targeted panel cover 40 DNA genes recurrently mutated in MN including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN). A bioinformatics pipeline was Oncomine Myeloid Research 530 (w3.0-4.2). Sequencing data were analyzed using Torrent Suite, Torrent Variant Caller, Ion Reporter (v.5.10.-5.18.). Genetic variants including single nucleotide variants (SNV), small insertions or deletions (INDELs) were detected. Detected variants are classified to Tier I, Tier II, Tier III, and Tier IV based on the 2017 guideline recommendations by AMP/ASCO/CAP. Variants of Tier I to III were regarded as clinical significant.

Results: The assay showed an average base coverage depth of 4,089, with 97.99% of on-target reads, 97.04% of mean uniformity of amplicon coverage, 97.30% of amplicons with no strand bias and 86.89% of amplicons reading end-to-end passed quality control criteria. Patients were comprised of AML (n=67, 42.7%), MDS (n=51, 32.5%), and MPN (n=39, 24.8%). A total of 357 variants were detected (39.5% INDELs and 60.5% SNVs). Missense mutations (n=216, 60.5%) were

PP01-24

Differences of genetic alteration between pediatric and adult acute myeloid leukemia detected by panel-based next generation sequencing

Jae Won Yoo[1], Tong Yoon Kim[2], Jong Mi Lee[3], Ari Ahn[3], Seongkoo Kim[1], Silvia Park[2], Jae Wook Lee[1], Myungshin Kim[3], Yonggoo Kim[3], Byung-Sik Cho[2], Hee-Je Kim[2], Nack-Gyun Chung[1] and Bin Cho[1*]

[1] Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Korea

[2] Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[3] Laboratory medicine, Seoul St. Mary's Hospital College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Although using next generation sequencing (NGS) technique to reveal potentially targetable mutation in adult acute myeloid leukemia (AML) has been emerged, the relevance of those findings to pediatric patients remains unclear. However, there are comparatively fewer reports focusing on analyzing the genetic differences between pediatric and adult AML. Here, we present the mutational frequencies in pediatric AML and the distinct results of age-related genetic alterations.

Method: We analyzed 819 patients (752 adults and 67 pediatrics) with non-M3 AML using panel-based NGS which including 68 leukemia-related genes in our institution between Jul. 2017 and Sep. 2021. Chromosomal and molecular abnormalities such as RUNX1-RUNX1T1, CBFB-MYH11, KMT2A fusion, and FLT3-ITD, which did not include within panel, were excluded from analysis. The patients

were classified into five age-specific groups as follow: infant (< 1 year, n = 8), children (1-14 years, n = 45), adolescent and young adult (AYA) (15-39 years, n = 189), adult (40-60 years, n = 301), and elderly (> 60 years, n = 276).

Results: A total of 678 patients (82.7%) harbored 1,514 genetic mutations (without RUNX1-RUNX1T1, CBFB-MYH11, KMT2A fusion, and FLT3-ITD) in study cohort; 59 (88%) pediatric and 619 (82%) adult patients harbored 105 and 1,409 mutations, respectively. Among pediatric AMLs, the most frequently mutated gene was KIT (13.3%), followed by CEBPA (12.3%), NRAS (10.4%), KRAS (7.4%), PTPN11 (6.6%), WT1 (6.6%), and NPM1 (5.7%) in order. Among adult AMLs, the most frequently mutated gene was NPM1 (9.4%), followed by DNMT3A (8.4%), NRAS (6.6%), CEBPA (6.1%), TET2 (5.6%), RUNX1 (5.4%), and IDH2 (5.2%) in order. Mutations in KIT and N/KRAS were two most frequent genes in children with core binding factor AML. Among normal karyotype AML, a high prevalence of mutated CEBPA (50%) and NPM1 (38%) genes were detected in pediatric and adult patients, respectively. The landscape of somatic variants in pediatric AML was markedly different from adult AML. We found that KIT (P < 10-3), NRAS (P < 10-2), JAK3 (P < 10-3), CEBPA double mutation (P < 10-3), PTPN11 (P = 0.028), and GATA2 (P = 0.021) were mutated significantly more frequent in pediatric AMLs, whereas NPM1 (P < 10-3), DNMT3A (P < 10-3), TET2 (P < 10-3), and IDH1/2 (P < 10-3) were more frequent in adult AMLs.

Conclusion: The frequencies of genetic alteration were significantly different between pediatric and adult AML. Our data set will serve as a foundation for development of age-specific mutational landscape of AML in nation-wide survey.

Keyword: Myeloid, Acute, High-Throughput nucleotide sequencing, Gene frequency, Pediatrics

PP01-25

Allogeneic hematopoietic cell transplantation overcomes adverse prognosis in patients with low allelic ratio FLT3-ITD in NPM1 mutated AML

Ga-Young Song[1], TaeHyung Kim[2,3], Seo-Yeon Ahn[1], Sung-Hoon Jung[1], Mihee Kim[1], Deok-Hwan Yang[1], Je-Jung Lee[1], Seung Hyun Choi[4], Mi Yeon Kim[4], Chul Won Jung[5], Jun-Ho Jang[5], Hee Je Kim[6], Joon Ho Moon[7], Sang Kyun Sohn[7], Jong-Ho Won[8], Seong-Kyu Park[8], Sung-Hyun Kim[9], Zhaolei Zhang[2,3,10], Jae-Sook Ahn[1,4], Dennis Dong Hwan Kim[11] and Hyeoung-Joon Kim[1,4*]

[1] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital and Chonnam National University Medical School, Korea

[2] Department of Computer Science, University of Toronto, Canada

[3] The Donnelly Centre for Cellular and Biomolecular Research, , University of Toronto, Canada

[4] Genomic Research Center for Hematopoietic Diseases, , Chonnam National University Hwasun Hospital, Korea

[5] Division of Hematology-Oncology, Samsung Medical Center, Korea

[6] Department of Hematology, The Catholic University of Korea, Korea

[7] Department of Hematology-Oncology, Kyungpook National University Hospital, Korea

[8] Department of Hematology-Oncology, Soon Chun Hyang University Hospital, Korea

[9] Department of Hematology-Oncology, Dong-A University College of Medicine, Korea

[10] Department of Molecular Genetics, University of Toronto, Canada

[11] Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Canada

Background: The European LeukemiaNet (ELN) guideline classifies AML with low allele ratio (AR) fms-like kinase 3-internal tandem duplication (FLT3-ITD) and nucleophosmin member 1 (NPM1) mutation as having a favorable prognosis. Allogeneic hematopoietic cell transplantation (HCT) is not recommended in patients with AML with this mutation profile in the first complete remission. However, questions have been raised about whether the patients with FLT3-ITD with low AR and NPM1 mutation have an actually favorable prognosis. So, this study was designed to determine the clinical impact of low allelic ratio FLT3-ITD in NPM1 mutated AML and whether the patients with low AR FLT3-ITD and NPM1 mutations would benefit from receiving allogeneic HCT.

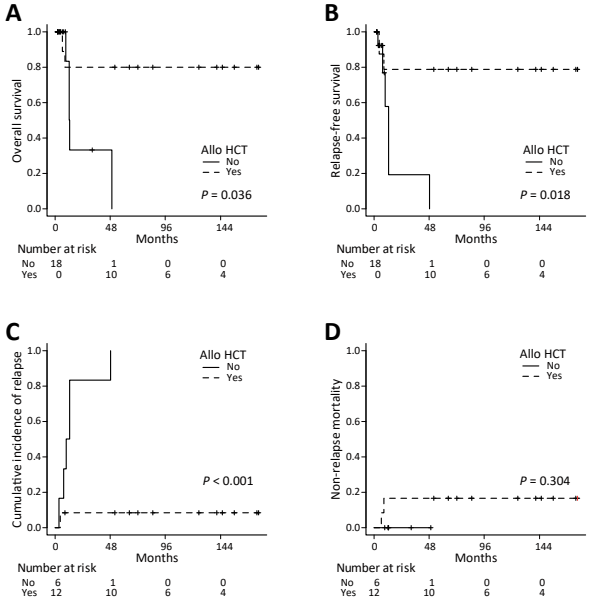
Method: Totally, 624 patients diagnosed with AML and received intensive induction therapy from November 1996 to May 2019 were screened for the study. The patients were selected from the cohorts of previous studies. Patients received consolidation chemotherapy with or without allogeneic HCT, depending on the availability of a matched donor, and genetic factors were not considered in choosing allogeneic HCT. Cryopreserved bone marrow or peripheral blood samples obtained at diagnosis were archived. Genetic profiling included the targeted deep sequencing of 45 genes. About the AR of FLT3-ITD, low AR (ARlow) was defined AR<0.5, and high AR (ARhigh) was defined AR≥0.5.

Results: Among the 624 patients, 93 patients (14.9%) had a mutated FLT3-ITD. Forty-eight patients (7.7%) were ARhigh FLT3-ITD and 45 patients (7.2%) were ARlow FLT3-ITD. According to the ELN 2017 risk stratification criteria, 99 patients (15.9%) were assessed to adverse risk group, 276 patients (44.2%) were intermediate risk group, and 249 patients (39.9%) were favorable risk group. Among the favorable risk group patients, 24 patients had ARlow FLT3-ITD. In order to analyze the prognostic impact of ARlow FLT3-ITD, we

compared overall survival (OS), relapse-free survival (RFS), cumulative incidence of relapse (CIR) and cumulative incidence of non-relapse mortality (NRM) in patients who have intermediate cytogenetics risk and did not received allogeneic HCT. OS and RFS were inferior in patients with ARlow FLT3-ITD than the patients without FLT3-ITD (5yr OS 0.0% vs. 25.0%; 5yr RFS 0.0% vs. 22.8%) (OS, HR 2.009, 95% CI 0.939-4.296, p=0.066; RFS, HR 2.848, 95% CI 1.178-6.883, p=0.015). CIR was higher in patients with ARlow FLT3-ITD than the patients without FLT3-ITD (5yr CIR 100.0% vs. 36.9%) (HR 4.073, 95% CI 1.983-8.368, p=0.001). There was no difference in cumulative incidence of NRM between the patients with ARlow FLT3-ITD and FLT3-ITD wild-type (5yr NRM 22.2% vs. 20.5%) (HR 1.122, 95% CI 0.251-5.025, p=0.880). Then we analyzed the clinical outcome according to allogeneic HCT in the patients with ARlow FLT3-ITD and NPM1 in patients with intermediate risk cytogenetics using Mantel byar test. Twelve patients who received allogeneic HCT showed significantly superior OS, RFS and lower CIR than 6 patients who received only chemotherapy consolidation (5yr OS 75.0% vs. 0.0%; 5yr RFS 75.0% vs. 0.0%; 5yr CIR 8.3% vs. 100.0%) (OS, HR 0.157, 95% CI 0.028-0.888, p=0.036; RFS, HR 0.126, 95% CI 0.023-0.697, p=0.018; CIR, HR 0.045, 95% CI 0.005-0.422, p<0.001). All 6 patients who received chemotherapy consolidation experienced relapse, but only 2 of the 12 patients who received allogeneic HCT relapsed. Cumulative incidence of NRM was not statistically different (5yr NRM 16.7% vs. 0.0%) (p=0.304) (Figure 1).

Conclusion: AML patients with mutated NPM1 and ARlow FLT3-ITD have a worse prognosis than patients with mutated NPM1 and FLT3-ITD wild-type, and the adverse prognosis of ARlow FLT3-ITD could be overcome by allogeneic HCT.

Keyword: FLT3-ITD, Acute myeloid leukemia



PP01-27

Treatment outcomes of venetoclax and hypomethylating agents for newly diagnosed acute myeloid leukemia

Eun-Ji Choi, Je-Hwan Lee*, Han-Seung Park, Jung-Hee Lee and Kyoo-Hyung Lee

Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea

Background: Elderly or unfit patients with acute myeloid leukemia (AML) generally show poor survival outcomes owing to high rates of antecedent hematologic disorders, multiple comorbidities, and adverse cytogenetic-molecular features. Venetoclax in combination with azacitidine or low-dose cytarabine showed superior response rates and overall survival compared to a single agent azacitidine or low-dose cytarabine in each phase 3 randomized trial. Venetoclax-based regimens were recently approved for the treatment of newly diagnosed AML and are currently being actively used. In this study, we aimed to evaluate the treatment outcomes, tolerability, and survival of the newly diagnosed elderly or unfit AML patients who were treated with venetoclax and HMA as a first-line treatment.

Method: We retrospectively analyzed 39 AML patients treated with venetoclax and HMA as a first-line treatment at Asan Medical Center between September 2019 and October 2021. The endpoints of this study include the rates of composite complete remission (CR, and CR with incomplete hematologic recovery [CRi]), overall response (CR, CRi, partial remission, and morphologic leukemia-free state [MLFS]), and overall survival (OS).

Results: Thirty-five patients received venetoclax and decitabine, and four received venetocalx and azacitidine. The median age at diagnosis was 66 years (range, 23–85), and more male patients (82.1%) were enrolled. Nineteen patients (48.8%) had secondary AML, and 26 (66.7%) had adverse risk. Nine (23.1%) patients were exposed to HMA previously for MDS, and 8 (20.5%) had undergone allogeneic hematopoietic cell transplantation (HCT) before a diagnosis of AML. At the data cut-off, 14 patients continued the treatment, and 25 discontinued because of no response (n=10), proceeding to HCT (n=7), toxicity or death (n=6), or intolerability (n=2). Patients received median 3 (range, 1–11) courses of treatment, and the median interval between treatment courses was 34.5 (range, 24–62) days. Among 31 assessable patients, best responses were CR (n=2), CRi (n=8), MLFS (n=12), and PR (n=1), and 8 patients showed no response. The composite CR rate was 25.6%, and the overall response rate was 59.0%. Median time to CR and overall response was 2.3 months (range, 0.7–5.1) and 2.4 months (range, 0.7–6.0), respectively. All patients experienced grade 3–4 hematologic adverse events during cycle 1. The rates of hematologic adverse events substantially decreased with subsequent treatment cycles (66.7% in cycle 2 and

48.7% in cycle 3). The median OS was 15.1 months. Previous exposure of HMA (P =0.007), history of allogeneic HCT (P=0.009), and adverse risk (P=0.041) were associated with inferior OS. There was no difference in OS between the patients receiving decitabine and azacitidine.

Conclusion: Venetoclax combined with HMA showed clinically meaningful response rate and survival outcomes in elderly or unfit AML patients, including secondary AML. Although the hematologic adverse events occurred in most patients, the toxicities were manageable and steadily decreased during subsequent treatment cycles.

Keyword: Acute Myeloid leukemia, Venetoclax, Hypomethylating agent

PP01-28

Cannabidiol exhibits anti-leukemic and anti-inflammatory activities through regulation of the NF-κB signaling pathway in human leukemia monocytic cell line

Krai Daowtak[1,2], Thitiya Luetragoon[2], Kanchana Usuwanthim[2] and Ruttiros Khonkarn[3*]

[1] Unit of Hematology and Clinical Microscopy, Department of Medical Technology, Unit of Hematology and Clinical Microscopy, Department of Medical Technology, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand

[2] Cellular and Molecular Immunology Research Unit , Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand

[3] Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, 50200, Thailand

Background: Cannabidiol, the non-psychoactive cannabinoid, possess promising medical and pharmacological activities. This study aimed to examine the anti-leukemic and anti-inflammatory activity of cannabidiol on human monocytic cell line, THP-1.

Method: Post-treatment with CBD, cellular viability and apoptosis were assessed in human leukemia monocytic cell line, THP-1, using MTT and apoptotic assay, respectively. THP-1 derived macrophage was stimulated by Lipopolysaccharide to assess the pro-inflammatory cytokines production by Bioplex-sandwich immune assay. Additionally, the cell lysates from cell treated with CBD were examined for its anti-inflammatory activity and the NF-κB signaling pathway using western blot analysis.

Results: Expose of THP-1 and THP-1 derived macrophage to cannabidiol led to reducing in cell viability and inducing in apoptosis. CBD attenuated both LPS-induced cytokine release and NF-κB activity similar to dexamethasone. CBD effectively inhibited the expression of inflammatory mediators, including IL-1B, IL-6 and cyclooxygenase-2. CBD significantly attenuated LPS-induced NF-κB activity via inhibiting phosphorylation of IκB-α and reduce expression of the nuclear factor (NF)-κB p65, suppressing its nuclear translocation.

Conclusion: Our study demonstrated that cannabidiol possess anti-cancer and anti-inflammatory activities through regulation of the NF-κB signaling pathway. It appears that CBD has potential as a promising drug for inflammatory diseases and leukemia treatment.

Keyword: Cannabidiol, NF-κB, Leukemia, Inflammation, THP-1

PP01-30

Risk of serious infections with the use of immunomodulatory drugs in multiple myeloma patients

Md Sarfaraj Hussain

Pharmacology and Toxicology, Lord Buddha Koshi Pharmacy College, Biajanathpur, Saharsa (Bihar), India

Background: In the treatment of multiple myeloma, immunomodulatory medications such as thalidomide, pomalidomide, and others are frequently used to suppress the immune system. The epidemiological evidence revealed a wide range of findings that were connected to an increased risk of serious illnesses. The evidence from trials supplied little data, which resulted in challenges in evaluating drug-based infections in the context of multiple myeloma therapy, as previously stated. To gain a better understanding of the relationship between immunomodulatory medication use and the risk of infection.

Method: Literature search was done in databases including Medline, Embase, Cochrane central and in major conference proceedings. Search term used were "immunomodulatory drugs AND infections AND multiple meyeloma." Qualities of studies were assessed using Newcastle-Ottawa scale. Immunomdulators reporting serious infections rate among multiple myeloma patients were qualified for the analysis. All analyses were performed using Review Manager version 5.5 (RevMan v5.4).

Results: This meta-analysis was based on 3824 patients from all the

included studies with a mean age range from 54 years to 75 years from pooled analysis of 51 eligible studies. Included studies reported infection incidence from 2.59% to 27.66%. Due to the significant heterogeneity, the random effect model was applied. Pooled incidence of serious infection due to immunomodulatory agents was 9.87% (95% CI: 7.30% - 11.10%). The pooled incidence of serious infection among pomalidomide users with relapsed and refractory cases was 13.90% (95% CI: 7.30% - 16.01%). Thalidomide user has a higher incidence in multiple myeloma patients (Fig.2) on induction therapy 8.70% (95% CI: 6.50% - 10.90%). Where the pooled incidence was lower in maintenance therapy in thalidomide user 2.90% (95% CI: 0– 7.60%).

Conclusion: Patients with multiple myeloma who were taking immunomodulatory medication had a higher risk of infection, according to the findings. The importance of preventive management is essential for patients.

Keyword: Multiple myeloma, Thalidomide, Pomalidomide, Infections, Immunomodulatory drugs

PP01-31

An evaluation of the efficacy and safety of lenalidomide as monotherapy and as part of a combination regimen in the treatment of acute myeloid leukaemia

Md. Sarfaraj Hussain

Pharmacology and Toxicology, Lord Buddha Koshi Pharmacy College, Biajanathpur, Saharsa (Bihar), India

Background: acute myeloid leukaemia (AML), is a type of cancer that affects the blood-forming cells of the bone marrow. Several epidemiological studies have been published in the last several years evaluating the efficacy of lenalidomide in AML, with varying conclusions about the drug's efficacy in this setting. The goal of this meta-analysis is to better understand the pooled effect of lenalidomide as monotherapy and multitherapy in patients with acute myeloid leukaemia (AML).

Method: Electronic databases like PubMed, Embase, and Cochrane central were searched from inception to November 2018. Potential articles were retrieved by two independent reviewers. Primary outcomes of this study were achievement of overall response rate, complete remission and overall survival. Safety outcomes were considered under secondary outcomes. Heterogeneity was defined based on Cochrane chi-square test and I2 values, based on this value random effect or fixed effect model was applied. Quality assessment of the study was done using Newcastle-Ottawa scale. All the statistical analysis was done using Review Manager (RevMan) version 5.4.

Results: A total of 18 studies qualified for the final inclusion in the meta-analysis after the screening of 497 articles. This meta-analysis is comprised of 507 patients of whom 49.72% were female. The pooled overall response for AML patients treated with monotherapy was 27% (95% CI: 18% to 34%), while the overall response was higher 39% (95% CI: 32% to 47%) and 33% (95% CI: 27% to 43%) for combination therapy [(Lenalidomide + Cytarabine) and (Lenalidomide + Azacitidine)]. Likewise, pooled complete response for AML patients treated with monotherapy was 14% (95% CI: 9% to 22%), while the complete response was higher 24% (95% CI: 19% to 34%) and 34% (95% CI: 21% to 49%) for combination therapy [(Lenalidomide + Azacitidine) and (Lenalidomide + Cytarabine)]. The overall survival was 2 to 8.4 months for lenalidomide monotherapy. Myelosuppression was the most common adverse event reported in patients receiving lenalidomide followed by thrombocytopenia.

Conclusion: In patients with acute myeloid leukaemia, lenalidomide was found to be effective; however, combined therapy was proven to be more effective than monotherapy. In addition, the safety profile was found to be good.

Keyword: Acute myeloid leukemia, Cancer, Epidemiology, Lenalidomide, Hematology, Meta-analysis

PP01-32

Early bone marrow assessment after 3+7 induction chemotherapy is predictable of outcome in AML with intermediate or adverse cytogenetics

Daehun Kwag [1,2], Byung-Sik Cho [1,2], Tong Yoon Kim[1,2], Jong Hyuk Lee[1,2], Joonyeop Lee[1,2], Gi-June Min[1,2], Sung-Soo Park[1,2], Silvia Park[1,2], Young-Woo Jeon[3], Seung-Hwan Shin[4], Seung-Ah Yahng[5], Jae-Ho Yoon[1,2], Sung-Eun Lee[1,2], Ki-Seong Eom[1,2], Yoo-Jin Kim[1,2], Seok Lee[1,2], Chang-Ki Min[1,2], Seok-Goo Cho[1], Jong Wook Lee[1] and Hee-Je Kim[1,2*]

[1] Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[2] Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

[3] Department of Hematology, Yeouido St. Mary's Hospital, College of

Medicine, The Catholic University of Korea, Seoul, Korea
[4] Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[5] Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Although many new therapeutic agents have been introduced in the field of AML, the most important induction regimen of AML patients for whom intensive chemotherapy is available is still 7+3 chemotherapy based on cytarabine and anthracycline. Currently, major guidelines recommend to exam bone marrow (BM) aspirate and biopsy in 14-21 days after the initiation of induction to determine whether to proceed with intensification chemotherapy. However, there is no solid evidence that these timings are most optimal. If the evaluation at an earlier time point is significant for prognostic prediction, a new treatment strategy of early intensification could be considered. In this regard, we investigated if the intramedullary blast rate evaluated on the 7th day after the start of 7+3 chemotherapy (D7 BM blast) was useful in predicting the treatment response of induction chemotherapy.

Method: We conducted a retrospective study through the data collected from a single institution. We collected the data of patients who were newly diagnosed AML from February 2002 to February 2021, received induction chemotherapy by 7+3, had a D7 BM examination, and received no intensification chemotherapy. A total of 665 patients were enrolled by these criteria. In these patients, we analyzed the prognostic significance of the D7 BM blast in the induction treatment response (complete remission or complete remission with incomplete hematologic recovery (CR/CRi)). Also, we analyzed whether the predictive significance of the D7 BM blast varies by the patient's cytogenetics, categorizing patients using Medical Research Council classification (MRC risk). After that, we checked the diagnostic ability of the D7 BM blast by the receiver operating characteristic (ROC) curve for treatment response prediction. To find an appropriate D7 BM blast cut-off value, the value that maximizes Youden's index was investigated.

Results: Among 665 AML patients who underwent 7+3 without intensification, the proportion of patients who acquired CR/CRi after single induction was 68.3%. A significant decrease in the CR/CRi rate was observed in the intermediate/adverse MRC group according to the increase of the D7 BM blast (tests for the trends in the intermediate and adverse group, p<0.001 and p=0.008, respectively; Figure 1). In univariable/multivariable (using covariates of age, sex, etiology, and MRC risk) logistic regression models, the D7 BM blast showed a significant correlation with the CR/CRi rate in the intermediate/adverse cytogenetic group (Table 1). To evaluate the usability of the D7 BM blast as a practical tool, the ROC curve for the treatment response prediction was plotted (Figure 2) and the D7 BM blast was significantly predictable only in the adverse MRC risk group (area under the curve (AUC): 0.7007, Mann-Whitney test statistics p=0.002). The D7 blast cut-off in the adverse MRC risk group which maximizes Youden's index was 4-4.9%, near to 5%, which is the cut-off used to evaluate the treatment response. The sensitivity and specificity for treatment response prediction according to D7 BM blast <5% or not were 82.8% and 61.1%, respectively.

Conclusion: We conducted a retrospective study through the data collected from a single institution. We collected the data of patients who were newly diagnosed AML from February 2002 to February 2021, received induction chemotherapy by 7+3, had a D7 BM examination, and received no intensification chemotherapy. A total of 665 patients were enrolled by these criteria. In these patients, we analyzed the prognostic significance of the D7 BM blast in the induction treatment response (complete remission or complete remission with incomplete hematologic recovery (CR/CRi)). Also, we analyzed whether the predictive significance of the D7 BM blast varies by the patient's cytogenetics, categorizing patients using Medical Research Council classification (MRC risk). After that, we checked the diagnostic ability of the D7 BM blast by the receiver operating characteristic (ROC) curve for treatment response prediction. To find an appropriate D7 BM blast cut-off value, the value that maximizes Youden's index was investigated.

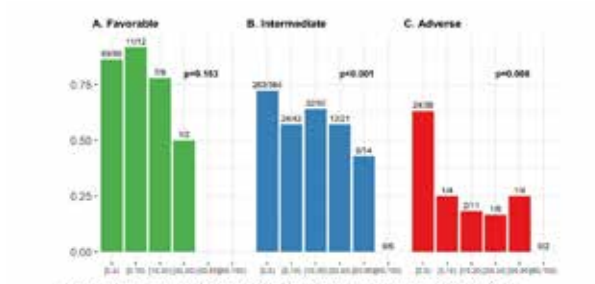


Figure 1. Induction response according to the day 7 BM blast rates, categorized by MRC risk

MRC risk	Odds ratio for CR/CRi (per D7 blast 5%) (95% CI)			
	Univariable	p	Multivariable	p
Favorable	0.79 (0.56-1.14)	0.165	0.80 (0.57-1.15)	0.187
Intermediate	0.88 (0.83-0.94)	<0.001	0.89 (0.83-0.94)	<0.001
Adverse	0.81 (0.64-0.94)	0.024	0.81 (0.64-0.95)	0.025

Table 1. Logistic regression for induction response by day 7 BM blast rates

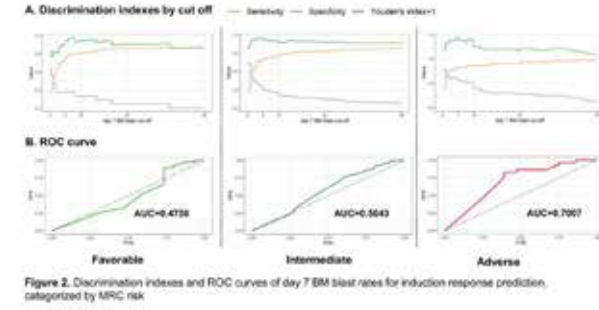


Figure 2. Discrimination indexes and ROC curves of day 7 BM blast rates for induction response prediction, categorized by MRC risk

PP01-33

Decetabine plus venetoclax versus decetabine alone for older adults with newly diagnosed acute myeloid leukemia

Daehun Kwag [1,2], Tong Yoon Kim[1,2], Jong Hyuk Lee[1,2], Joonyeop Lee[1,2], Gi-June Min[1,2], Sung-Soo Park[1,2], Silvia Park[1,2], Young-Woo Jeon[3], Seung-Hwan Shin[4], Seung-Ah Yahng[5], Jae-Ho Yoon[1,2], Sung-Eun Lee[1,2], Ki-Seong Eom[1,2], Yoo-Jin Kim[1,2], Seok Lee[1,2], Hee-Je Kim[1,2], Chang-Ki Min[1,2], Seok-Goo Cho[1], Jong Wook Lee[1] and Byung-Sik Cho [1,2*]

[1] Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[2] Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

[3] Department of Hematology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[4] Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[5] Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

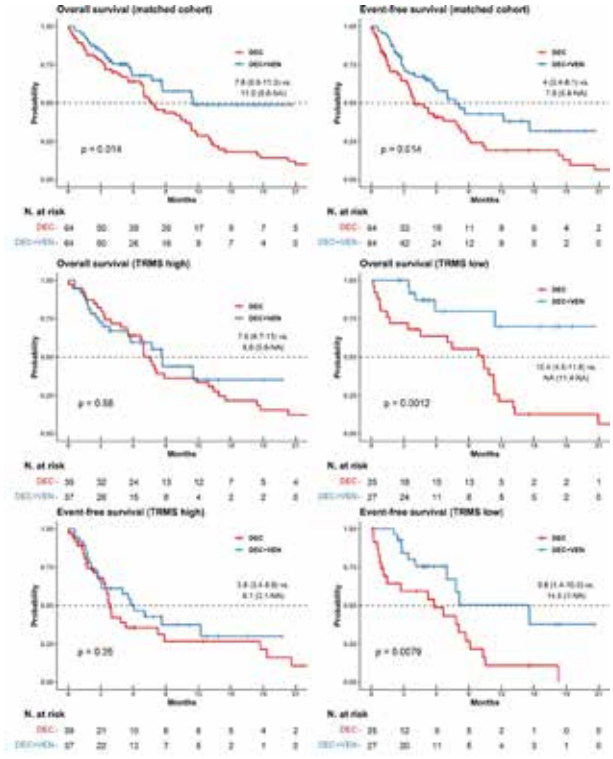
Background: Venetoclax, a BCL-2 inhibitor, has been recently introduced to the field of acute myeloid leukemia (AML), and due to its efficacy and low toxicity, it was quickly established as one of the major therapeutic agents for AML. In particular, low toxicity is attractive to older adults who are at risk of treatment-related toxicity. Therefore, venetoclax is popularly used as for older adults with newly diagnosed AML in combination with hypomethylating agents such as decitabine and azacitidine. Previously, the superiority of venetoclax with seven-day of azacitidine therapy to azacitidine monotherapy was demonstrated in a large-scale clinical trial. In terms of decitabine, it was reported that venetoclax with 10-day decitabine treatment showed better outcomes than those of intensive chemotherapy in elderly patients. Various clinical experiences have been published, but so far, no real-world data is comparing the venetoclax plus five-day decitabine regimen. In this regard, we compared the patient outcomes between venetoclax with decitabine five-day treatment with decitabine monotherapy, by propensity score-matched cohort.

Method: We retrospectively collected data from October 2011 to October 2021, of elderly (≥ 65 years) patients who received venetoclax plus decitabine five days (DEC+VEC) or decitabine alone five days (DEC) as a frontline treatment for AML. Venetoclax has been available since March 2020 in Catholic Hematology Hospital. Given the significant different treatment strategy for older adults with newly diagnosed AML between before and after the introduction of venetoclax, we constructed a matched cohort through propensity score matching. European leukemiaNet (ELN) risk stratification (2010 version) and treatment-related mortality score (TRMS) of patients were used to calculate the propensity score. TRMS is a validated tool for AML patients to predict death within 28 days and consists of performance status, age, platelet count, albumin, secondary AML, WBC count, peripheral blood blast percentage, and creatinine as variables. We extracted patients from the DEC group by one-to-one propensity score matching with the DEC+VEN group, using the nearest neighbor method. In the matched cohort, we compared overall survival (OS), event-free survival (EFS, event of disease progression, relapse, death, regimen change due to lack of response or intolerance), the cumulative incidence of events, and treatment response.

Results: In our cohort, the number of the DEC+VEN or DEC group was 64 or 208, respectively. Sixty-four patients in the DEC group were picked out by propensity score matching. In the matched cohort, baseline characteristics were similar, with nearly identical distributions of TRMS and ELN 2010 risk. In the survival of the matched cohort, the median OS of the DEC+VEN group was 11.5 months (95% confidence interval (CI): 8.6-Not available(NA)), which was significantly higher than that of the DEC group, 7.8 months (6.9-11.3) (P=0.013). The EFS of the DEC+VEN group was 7.8 months (5.8-NA), which was also significantly longer than that of the DEC group (4.0 months (3.4-8.1)) (P=0.014). Of note, the superiority of survival outcomes of DEC+VEN group was significantly different according to TRMS. When the patients were divided into TRM high-risk and TRM low-risk groups based on TRMS cut-off (13.1) presented in previous studies, the DEC+VEN group showed superior survival than the DEC group in the TRM low-risk group (median OS months: Not reached median (11.4-NA) versus(vs).10.4 (4.5-11.8), P=0.001; Median EFS months: 14.6 (7-NA) vs. 5.8 (1.4-10.3), P= 0.008). However, in the high TRM risk group, there was no significant difference in OS (median 8.6(5.6-NA) vs. 7.6(6.7-13) months, P=0.580) and EFS (median 6.1 (3.1-NA) vs. 3.8 (3.4-8.9) months, P=0.350) between the DEC+VEN group and the DEC group. When estimating the cumulative incidence estimates, the DEC group showed a similar Non-relapse/progression mortality (NRM) regardless of the TRM risk (cumulative incidence of NRM in DEC group during follow up: 28.1% (14.7-49.5), 22.6% (10.1-46.2) in TRMS high, TRMS low group, respectively. P=0.775). However, in the DEC+VEN group, the NRM rate in patients with high TRM risk was worse than that in patients with low TRM risk (31.7% (17.9-52.1) vs. 8.7% (2.2-30.4), P=0.061). In treatment response, leukemia-free state (CR, CRi, MLFS) at best response state was significantly better in DEC+VEN group (68.8% vs. 20.3%, P<0.001), and time to reach the best response was significantly faster (median 1.2 months (0.9-2.6) vs. 3.7 months (1.9-5.5), P<0.001)

Conclusion: In older adults with newly diagnosed AML, five days of decitabine with venetoclax showed better and faster treatment response than decitabine monotherapy, resulting in longer OS and EFS. However, in patients at high TRM risk, this survival benefit diminished. While venetoclax-based therapy has been accepted as

a popular treatment regimen for elderly patients due to its low toxicity compared to its efficacy, the risk of death was still substantial in patients at high TRM risk. A comprehensive assessment might be needed when initiating venetoclax-based treatment. This should be validated in multicenter prospective studies.



PP01-34

Real-world experience of gilteritinib in relapsed/refractory FLT3 mutated acute myeloid leukemia

Jong Hyuk Lee, Daehun Kwag, Joonyeop Lee, Tong Yoon Kim, Gi-June Min, Sung-Soo Park, Silvia Park, Jae-Ho Yoon, Sung-Eun Lee, Byung-Sik Cho, Ki-Seong Eom, Yoo-Jin Kim, Seok Lee, Chang-Ki Min, Seok-Goo Cho, Jong Wook Lee, and Hee-Je Kim*

Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: FLT3 mutation in acute myeloid leukemia (AML) is associated with poor treatment response and survival outcomes. Recently, a novel FLT3 inhibitor gilteritinib (GIL) was approved to treat relapsed/refractory(R/R) FLT3mut AML. However, real-world data of gilteritinib treatment are limited, especially in Korean patients.

Method: In this retrospective, single center study, we analyzed characteristics and outcomes of adult patients (age > 18) with R/R FLT-3mut AML who received salvage GIL monotherapy from November 2020 to November 2021 at Seoul St. Mary's Hospital. Baseline patient and disease characteristics were acquired prior to GIL initiation. Regardless of response to GIL, subsequent allogeneic stem cell transplant (SCT) was intended for fit patients. For those proceeding to SCT, GIL was stopped before transplant conditioning.

Response evaluation was done after each 28-day cycle. All response definition (complete remission[CR], CR with incomplete platelet recovery[CRp], CR with incomplete hematologic recovery[CRi], composite CR[CRc], CR with partial hematologic recovery[CRh], partial remission[PR], no response[NR]) was adopted from the ADMIRAL study for efficacy assessment. We excluded patients not evaluable for response for outcome analyses.

Results: A total of 21 R/R FLT3mut AML patients were treated with GIL. The median (range) age was 49 years (23-73) and 17 (81.0%) were females. Prior to GIL treatment, 10 (47.6%) patients had been treated with other FLT3 inhibitors, 5 (23.8%) experienced venetoclax and 7 (33.3%) had relapsed after allogeneic SCT. All patients had FLT3-ITD mutation, with median (range) allelic ratio (AR) and insertion length of 0.470 (0.032-9.615) and 56 (28-119) base pairs (bp), respectively. Concurrent NPM1 mutation was observed in 10 (47.6%) patients.

GIL was administered for a median (range) of 81 days (14-124) and 19 patients were evaluable for response. Early (≤1 cycle) discontinuation of treatment occurred in 2 patients, 1 due to aggravated pretreatment condition (ileus) and 1 due to high drug cost. Overall response (CRc) rate was 63.2% (12/19, 3 (15.8%) CRh and 9 (47.4%), CRi as the best response). There was no patient with CR or PR. Initial and best responses were achieved after a median (range) of 1.0 (1-4) and 1.8 cycles (1-4), respectively. 14 patients (73.7%), 9 (47.4%) in CRc, proceeded to SCT.

Since most patients underwent SCT after GIL, we did not censor SCT for survival analysis. For a median (range) follow-up period for survivors of 7.5 months (1.9-12.5), median overall survival (OS) was 11.6 months with 6-month OS of 81.6% (95% CI 52.8-93.7).

Chi-square test results showed that all analyzed factors, i.e., sex, prior FLT3 inhibitor, venetoclax use, SCT, disease status, FLT3-ITD AR/insertion length, pretreatment leukemic burden, NPM1 mutation status, did not predict GIL response.

Two patients experienced CTCAE Grade 3 hyperbilirubinemia during GIL treatment but were able to resume treatment after temporary discontinuation. We did not experience deaths related to GIL nor post-treatment SCT: all patients died in active disease state (7) or due to pre-GIL medical condition (1).

Conclusion: Salvage gilteritinib treatment for R/R FLT3mut AML in real-world experience show comparable response rates and safety as published 3-phase clinical trial. Further analysis of FLT3-ITD insertion site and other parameters may find patients who benefit most from this drug. Extended follow-up after SCT may provide advanced strategies to help patients survive R/R FLT3mut AML which otherwise has devastating prognosis.

Keyword: Acute myeloid leukemia, Relapsed/refractory, FLT3 inhibitor, Gilteritinib, Allogeneic stem cell transplantation

PP02-01

Genetic mutations associated with blood count abnormalities in myeloid neoplasms

Chantana Polprasert[1*], Pimjai Niparuck[2], Thanawat Rattanathammethee[3], Suporn Chuncharunee[2], Sirorat Kobbuaklee[1], Amornchai Suksusut[1], Theerin Lanamtieng[4], Sunisa Kongkiatkamon[1], Panisinee Lawasut[1], Thiti Asawapanumas[1], Kitsada Wudhikarn[1], Udomsak Bunworasate[1] and Ponlapat Rojnuckarin[1]

[1] Department of Medicine, Chulalongkorn University, Thailand
[2] Department of Medicine, Mahidol University, Thailand
[3] Department of Medicine, Chiangmai University, Thailand
[4] Department of Medicine, Khon kaen University, Thailand

Background: Myelodysplastic syndromes (MDS) predominantly present with varying degrees of cytopenia, while myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN) exhibit proliferative features. Genetic defects underlying different complete blood count (CBC) alterations remain to be defined. We aimed to evaluate somatic mutations and impacts on abnormal blood counts in MDS and MDS/MPN.

Method: MDS and MDS/MPN patients from four medical centers in Thailand were subjected to targeted next generation sequencing. Clinical variables were correlated with genetic abnormalities and clinical outcomes.

Results: A total of 168 patients with myeloid neoplasms were recruited (92 cases of low-risk MDS, 57 cases of high-risk MDS and 19 cases of MDS/MPN). Patients with high-risk MDS presented with more severe neutropenia compared to low-risk MDS and MDS/MPN with 50% showing absolute neutrophil counts (ANC) lower than 1x109/L and 17.5% of cases below 0.5x109/L. MDS/MPN harbored a greater number of mutations than high-risk MDS and low-risk MDS (3 vs. 2 vs. 1, p<0.001) and more mutations than other groups (94% vs. 89.5% vs. 56.5%, p<0.001). Patients with SF3B1 mutations showed lower hemoglobin levels compared to wild-type (7.9 vs. 8.4 g/dL, p=0.02), but were associated with normal platelet counts (286x109/L vs. 93x109/L; p<0.001). Patients with U2AF1 mutations were associated with more severe leukopenia compared to wild-type (3 x109/L vs. 4.18 x109/L; p=0.02). Patients with KRAS and CBL mutations were associated with monocytosis (p<0.001 and p=0.001). Multivariate analysis revealed high-risk MDS, MDS/MPN, severe neutropenia (ANC<0.5x109/L), ASXL1 and SETBP1 mutations were associated with inferior survival outcomes.

Conclusion: Certain mutations are related to more severe anemia, lower white blood cell count or monocytosis in Asian MDS and MDS/MPN patients.

Keyword: Myelodysplastic syndromes, Myelodysplastic syndromes/myeloproliferative neoplasms, cytopenia, gene mutation, monocytosis

PP02-02

Increased apoptotic activity in patients with lower risk myelodysplastic syndrome

Songyi Park[1], Dong-Yeop Shin[1,2,3*], Hee Sue Park[4], Soo Young Moon[5], Sung-Soo Yoon[1,3] and Dong-Soon Lee[3,6]

[1] Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Hospital, Korea
[2] Biomedical Research Institute, Seoul National University Hospital, Korea
[3] Cancer Research Institute, Seoul National University College of Medicine, Korea
[4] Department of Laboratory Medicine, Chungbuk National University Hospital, Korea
[5] Department of Laboratory Medicine, Pusan National University Hospital, Korea
[6] Department of Laboratory Medicine, Korea Cancer Center Hospital, Korea

Background: Myelodysplasic syndrome (MDS) is a heterogeneous hematopoietic disorder which is related to cellular proliferative and apoptotic activity. We hypothesized that Ki-67 and cleaved caspase-3 representative of proliferation and apoptosis could be prognostic markers in MDS patients

Method: This study is a retrospective study using bone marrow (BM)

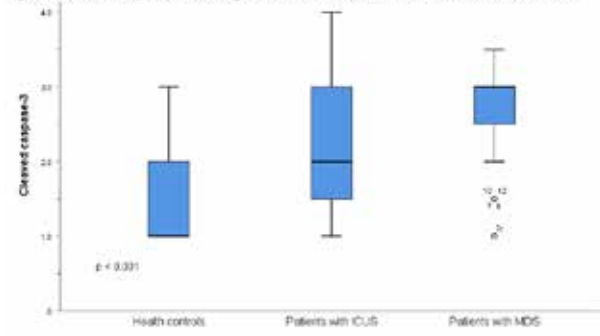
samples from patients with MDS. We included 118 76 MDS patients who were diagnosed between 2004 and 2014 at Seoul National University Hospital. We compared proliferative and apoptotic activities assessed by immunohistochemical (IHC) staining of cleaved caspase-3, ki-67 and telomere length measured by fluorescence in situ hybridization technique in patients with MDS, idiopathic cytopenia of undetermined significance (ICUS) and health controls (HC). And we also analyzed difference of degree of staining of cleaved caspase-3 and ki-67 according to MDS risk scoring system

Results: The mean value of cleaved caspase-3 by IHC was highest in MDS patients, followed by ICUS patients and HCs (2.70, 95% CI: 2.56-2.85 vs. 2.19, 95% CI: 1.85-2.54 vs. 1.45, 95% CI: 1.17-1.73, $p < 0.001$) (Figure 1). Similarly, the mean ki-67 grade was also the highest in MDS patients, followed by ICUS patients and HCs (1.72, 95% CI: 1.55-1.90 vs. 1.58, 95% CI: 1.30-1.86 vs 1.72, 95% CI: 0.95-1.16, $p = 0.001$). Interestingly, among MDS patients, higher cleaved caspase-3 grade was significantly associated with a lower IPSS-R score ($p = 0.020$), while Ki-67 was not.

Conclusion: Our results suggest that pathophysiology of lower risk MDS and higher risk MDS might be different, which dyshematopoiesis due to activated apoptosis of hematopoietic cells mainly occurs in lower risk MDS, while leukemogenic process is accumulated in higher risk MDS. Cleaved caspase-3 grade in BM biopsy could be a prognostic marker in patients with MDS

Keyword: Apoptosis, Caspase-3, Myelodysplastic syndrome

Figure 1. Cleaved caspase-3 according to health controls, patients with ICUS, patients with MDS



PP02-03

DDX41 -mutated myeloid neoplasms with propensity for higher-risk myelodysplastic syndrome and distinct bone marrow features depending on mutation type

Youn Ji Hong[1], Young-Uk Cho[1*], Miyoung Kim[1], Seongsoo Jang[1], Chan-Jeoung Park[1], Eul-Ju Seo[1], Eun-Ji Choi[2], Je-Hwan Lee[2] and Kyoo-Hyung Lee[2]

[1] Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea

[2] Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea

Background: The revised World Health Organization (WHO) classification of hematologic tumors introduced a new category of myeloid neoplasms with germline DDX41 mutation. DDX41 germline mutations have been described in approximately 1-5% of myeloid neoplasms and were characterized by male preponderance, frequent preexisting cytopenia, additional somatic DDX41 mutations, and relatively good outcome. While the prior studies have focused primarily on the clinical features and mutation profiles in these cases, there is little detailed information on pathologic findings in patients with DDX41 mutations. Thus, we have investigated to characterize the detailed morphologic and pathologic features of DDX41-mutated myeloid neoplasms.

Method: Internal next-generation sequencing database of patients with myeloid neoplasms was queried to locate cases with DDX41 mutations. We reviewed the corresponding clinical, morphologic, pathologic and genetic findings of these cases.

Results: DDX41 mutations were detected in 82 (8.0%) of consecutive 1,020 patients, including 48 (14.8%) of 325 myelodysplastic syndrome (MDS) cases, 28 (5.6%) of 500 acute myeloid leukemia cases, 5 (3.5%) of 142 myeloproliferative neoplasm (MPN) cases, and 1 (1.9%) of 53 myelodysplastic/myeloproliferative neoplasm (MDS/MPN) cases. Probable germline DDX41 mutations were identified in 70 (85.4%) of 82 DDX41-mutated cases, including 45 in MDS, 19 in AML, 5 in MPN, and 1 in MDS/MPN. Of these germline DDX41 mutations, the most common type was p.Y259C (24.3%), followed by p.A500fs (18.6%), p.V152G (17.1%), p.E7* (8.6%), p.D139G (4.3%), p.E3K, p.D27N, p.H274R (2.9% for each), and the remaining 13 ones (1.4% for each). Germline DDX41 mutations was accompanied by somatic DDX41 mutations in only 50 cases (71.4%), including 40 in MDS and 10 in AML. Interestingly, p.Y259C and p.V152G were identified exclusively in patients with MDS, whereas other types were detected across all entities. Overall, the most common concurrent mutation was in ASXL1 (15.9%), followed by mutations in DNMT3A (12.2%), EZH2 (11.0%), SRSF2 (9.8%), TET2, TP53 (8.5% for each), CBL, JAK2 and NF1 (7.3% for each). Cases of DDX41-mutated MDS were largely confined to category of excess blasts (75.0%) and higher-risk MDS (74.5%), whereas cases of DDX41-mutated AML were heterogeneous in terms of WHO-defined categorization. In subgroup analysis of MDS, the frequency of hypoplastic MDS was 31.9%. Cases with germline DDX41 p.Y259C showed lower myeloid:erythroid ratio ($P = 0.002$), higher frequency of bone marrow eosinophilia ($P = 0.02$), lower frequency of significant dysgranulopoiesis ($P = 0.022$), and a trend for higher rate of MDS with excess blasts 1 ($P = 0.057$)

compared with those harboring p.V152G.

Conclusion: Our study demonstrated that germline DDX41 mutation has a considerable frequency in our population and a certain type of mutation could be associated with specific bone marrow pathology. This indicates that meticulous microscopic examination might have a role in the prediction of a specific genetic alteration, particularly in patients with MDS. Our observations can be a trigger for unveiling hidden pathogenesis of DDX41-mutated myeloid neoplasms.

Keyword: DDX41, Myelodysplastic syndrome, Bone marrow feature, Mutation type

PP02-04

R-loop induced DNA damage and clinical features of DDX41- mutated Korean MDS

Silvia Park[1], Won Chan Hwang[2], Kiboem Park[2], Jong Mi Lee[3], Myungshin Kim[3], Hongtae Kim[2] and Yoo-Jin Kim[1*]

[1] Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[2] Department of Biological Sciences, Ulsan National Institute of Science and Technology, Ulsan, Korea

[3] Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Inherited hematologic malignancies are increasingly identified. DEAD-box helicase 41 (DDX41) is one of the genes that is associated with familial myelodysplastic syndrome (MDS) and its variants have known to account for 1-5% of MDS cases. Currently, multiple DDX41 variants of either germline or somatic mutations have been revealed with substantial ethnic differences. However, the role of these mutations in MDS pathogenesis have yet to be understood.

Method: Between Jul 2017 and Apr 2021, genomic data from 333 adult patients (age ≥ 18 years) with MDS at Seoul St. Mary's hospital was obtained by targeted next-generation sequencing (NGS) using bone marrow samples. We selected the patients with pathogenic DDX41 mutations, where we captured specific features of Korean MDS patients, and compared their clinical characteristics with rest of patients. DDX41 has recently been shown to have many biological functions including DNA damage response pathway. To characterize further functional activities of DDX41, we generated DDX41 knout-out (KO) and DDX41 R525H knock-in (KI) K562 cells and performed western blotting for DNA damage response and immunostaining of r-H2AX and S9.6 for detection of DNA damage foci coupled with altered R-loop signals.

Results: Among a total of 333 patients, we identified 42 patients (12.6%) with DDX41 mutations. Excluding 5 patients with DDX41 variant of undetermined significance (VUS) (n=3, germline variants only; n=2, somatic variants only), 37 MDS patients (11.1%) were identified as having likely pathogenic DDX41 variants. Of the germline mutations, p.Y259C (n=15, 40.5%) and p.V152gG (n=9, 24.3%) were the most common. The distinct common mutated sites in germline mutation along with its strikingly high incidence, DDX41 mutations in Korean MSD patients were quite distinguished from those of Western and other Asian countries. In case of somatic mutations, p.R525H comprised the most (n=11, 37.9%). Overall, 16 of these 37 patients (43.2%) had concurrent genetic mutations other than DDX41 and co-mutations in DNMT3A (n=4, 25.0%) and ASXL1 (n=3, 18.8%) were relatively common. When compared to DDX41 non-mutated group, patients with pathogenic DDX41 variants showed significant association with older age at diagnosis, male sex, excess blast subtype, normal karyotype, lower risk by IPSS-R, lower absolute neutrophil count, and higher BM blast percentage. As a proposed mechanism of DDX41 in development of MDS, such as an alternative splicing or ribosome biogenesis, we tested a R-loop induced DNA damage response pathway by comparing DDX41 KO or DDX41 R525H KI K562 cells to wild type controls. We discovered that the phosphorylation of ATR and CHK1 are increased in DDX41 KO or R525H knock-in KI K562 cells. Next, we tested whether DDX41 functions in homologous repair (HR) as R-loop repaired proteins do. Using a DR-GFP based HR reporter assay, we found that HR efficiency was significantly decreased in DDX41 KO or DDX41 R525H KI K562 cells. Further, we demonstrated that DDX41 KO induced DNA damage through R-Loop accumulation. Finally, we confirmed that this finding is repeated in DDX41 R525H KI cell line, where R-loop accumulation, R-loop-mediated genome instability, and replication delay were observed.

Conclusion: The features of DDX41 mutations in Korean MDS patients was quite different as compared to those from other countries in its higher frequency and the distinguished common sites involved. We postulate that mutated DDX41 involves MDS pathogenesis through increased DNA damage by R-loop accumulation.

Keyword: Korean myelodysplastic syndrome, DDX41 mutation, DNA damage, R-loop

PP02-05

Survival analysis of post-transplant MDS according to relapse and treatment pattern

Joonyeop Lee[1], Gi-June Min[1], Sung-Soo Park[1], Silvia Park[1], Seung-Ah Yahng[2], Young-Woo Jeon[3], Seung-Hwan Shin[4], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Seok Lee[1], Hee-Je Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Jong Wook Lee[1] and Yoo-Jin Kim[1*]

[1] Department of Hematology, Leukemia Research Institute, Seoul St. Mary's Hematology Hospital, College of Medicine, Korea

[2] Department of hemato-oncology, Incheon St Mary's Hospital, College of Medicine, Korea

[3] Department of Hematology, Yeouido St. Mary's Hematology Hospital, College of Medicine, Korea

[4] Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, Korea

Background: Allogeneic stem cell transplantation (SCT) is the only curative treatment strategy for myelodysplastic syndrome (MDS), but relapse remains the major cause of transplantation failure. As survival of the patients having morphological or hematological relapse (HemRel) is dreadful, earlier intervention at lower level relapse should be pursued but there is no standard guideline for these approaches. This study aimed to analyze the influences of treatment options at different level of relapse upon survival of the relapsed MDS.

Method: Adult patients (age ≥18 years) who received first allogeneic SCT for MDS and related neoplasms between May 2009 and July 2020 at the Catholic Hematology Hospital were screened for relapse and all consecutive relapsed patients were enrolled. Initial relapse type was HemRel in 87 patients and pre-HemRel in 62 patient including 28 case of imminent relapse (ImmRel: loss of full donor chimerism accompanied with cytopenias which was not associated with other possible causes), 17 cases of WT1 relapse (WT1Rel: WT1 transcript level > 250 copies/104 ABL), and 17 cases of cytogenetic relapse (CyRel: reappearance of patient-specific cytogenetic aberrations) according to the definition of our previous report (Ther Adv Hematol 2021,12: 12:20406207211043748). Following withdrawal of immunosuppressant (ISW), whenever it was still given, therapeutic options were chosen according to the type of relapse and the availability of DLI. In case of HemRel or CyRel, chemotherapy followed by DLI was considered, while for ImmRel and WT1Rel, treatment with DLI was first considered. Overall survival after relapse was analyzed according to the relapse patterns and treatment options.

Results: A total of 149 consecutive patients were enrolled and the median age at the time of allogeneic SCT was 49 years (range 20 – 69). 92 patients (62%) were male and median time to relapse was 5.3 months (range 0.4 – 121.2). Prior to relapse, 22 patients (19%) experienced progression to secondary acute myeloid leukemia (sAML). At the median follow-up of 48.6 (range 13.9-145.7) months after relapse, 4-year overall survival (OS) rate was 27% in all patients. 4-year OS was statistically different according to the type of initial type of relapse (HemRel 15% vs. pre-HemRel 44%, p<0.001). Further survival analysis according to the subtypes of pre-HemRel showed that 4-year OS was statistically different (ImmRel 54% vs. WT1Rel 62% vs. CyRel 8%, p=0.039). In ImmRel and WT1Rel groups, DLI rather than ISW alone had a trend of higher 4 year survival (68% vs. 46%, p=0.089). For CyRel patients, OS was significantly lower than ImmRel or WT1Rel as above, and 14 (82%) of 17 CyRel patients progressed to HemReL. A total of 114 patients, including 27 patients progressed from pre-HemRel, experienced HemRel and their 4-year OS was 14%. Treatment options were categorized as best supportive care (BSC) group, cytoreductive therapy (CRT) group including hypomethylating agent, intensive chemotherapy and radiation therapy, and immunotherapy (IT) group including DLI and secondary allogeneic SCT with or without CRT. Survival analysis of HemRel patients regarding treatment patterns demonstrated that IT group showed statistically significant longer 4-year OS than CRT group or BSC group (27% vs. 6% vs. 0%, p<0.001). The type of treatment was independent factor for OS and remained significant in multivariate analysis which showed that relapse interval from SCT, IPSS-R at SCT, sAML at SCT, and bone marrow blast percentage at relapse were additional predictive factors.

Conclusion: These results showed that the survival after post-SCT relapse was associated with level of relapse and therapeutic option with active IT showed better results across all type of relapse except CyRel. Predictive factors for survival which was identified in this study could be used to make a treatment strategy for post-HemRel patients. This study also showed the importance of conventional chimerism and cytogenetic assays and their roles in the era of NGS-based MRD monitoring should be evaluated further.

Keyword: Hematopoietic stem cell transplantation, Relapse, DLI, Immunotherapy

PP02-06

Treatment outcomes of secondary acute myeloid leukemia from myelodysplastic syndrome, according to previous treatment history

Daehun Kwag[1], Tong Yoon Kim[1], Jong Hyuk Lee[1], Joon yeop

Lee[1], Gi June Min[1], Sung Soo Park[1], Silvia Park[1], Seung-Ah Yahng[2], Seung-Hwan Shin[3], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung Sik Cho[1,4], Ki-Seong Eom[1,4], Seok Lee[1,4], Hee-Je Kim[1,4], Chang-Ki Min[1,4], Jong Wook Lee[1] and Yoo-Jin Kim[1,4*]

[1] Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea.

[2] Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea

[3] Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[4] Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Myelodysplastic syndrome (MDS) is a bone marrow disease with key features of the clonal proliferation of hematopoietic stem cells, myelodysplasia, ineffective hematopoiesis, and it has a potency of progression to secondary acute myeloid leukemia(sAML). Secondary AML evolution from MDS occurs in approximately 30% of MDS patients and comprises the most of sAML which is preceded by a hematological disorder. Among various types of AML, treated sAML is known to have a worst prognosis. Based on these backgrounds and scarcity of large-scale information, we enrolled all consecutive cases having sAML evolving form MDS (sAML/MDS) and analyzed the clinical outcomes, focusing on the previous treatment history.

Method: We retrospectively analyzed data of 259 consecutive patients fulfilling the enrollment criteria for 2AML/MDS between 2008 and 2021 at Seoul St.Mary's Hematology Hospital. We categorized the 2AML/MDS patients into two categories; patients who had no history of previous disease modifying treatment for MDS (natural AML), and those who had previously been treated for MDS (post-treatment AML). Post-treatment AML patients were further classified into two groups; patients who received only HMA or cytarabine-based chemotherapy before AML progression (post-chemotherapy AML), and patients who relapsed after hematopoietic stem cell transplantation (post-HSCT AML). We evaluated the treatment response, toxicities, and survival in overall cases and in each subgroup.

Results: 259 patients were classified in 85 natural AML patients and 174 post-treatment AML patients (124 post-chemotherapy AML and 50 post-HSCT AML). When comparing the natural AML group and the post-treatment AML group, the post-treatment AML group were slightly older than the natural AML group at the time of secondary AML diagnosis (median age of years; 58.9 versus(vs). 55.1, P=0.044), had longer interval from MDS to AML (median 12.9 months vs. 5.1 months, P<0.001). and showed higher proportion of higher-risk MDS at the time of MDS diagnosis (77.6% vs. 56.5%, P=0.002). 77 (29.7%) of 259 patients underwent induction chemotherapy after AML diagnosis, and 93 (35.9%) underwent HSCT. In the natural AML patients, 33 (33.8%) and 39 (45.9%) were proceeded with induction chemotherapy and HSCT, and the respective numbers in the post-treatment AML group were 44 (25.3%) and 53 (30.5%). The median number of induction chemotherapy cycles was 1 (Interquartile range: 1-2), and the majority of patients received a 7+3 combination of cytarabine and anthracycline. Among patients who underwent HSCT after sAML diagnosis, the median time from AML diagnosis to transplantation was 3.4 (2.3-4.8) months.

The final response (CR, CRi, and mCR) rate of induction chemotherapy was 45.5% in whole patients. There was no significant difference in response rate between the natural AML group and the post-treatment AML group (48.5% vs. 43.2%, P=0.817). When the patients were further classified, the post-HSCT AML patients showed a lower response, but it was not found to be statistically significant (response rate in natural, post-chemotherapy, post-BMT AML group: 48.5%, 48.4% and 30.8%, respectively. P=0.361). In survival, the median OS from diagnosis of sAML for all patients was 6.2 (95% confidence interval: 5.2-7.7) months. There was a significant difference in OS by the group, in the order of the natural; 8.6 (6.1-11.4) months, post-chemotherapy; 5.8 (4.2-8.0) months, and post-BMT; 4.1 (2.5-7.7) months (P=0.029). When analyzing the OS before HSCT by censoring at the HSCT date, the median OS of patients who did not undergo induction treatment was 4.4 (3.5-6.4) months and 10.6 (6.1-20.1) months in those who received induction chemotherapy; the natural AML group showed a slight superiority, but no statistical significance was found no matter induction chemotherapy was taken or not (median OS months of the natural, post-chemotherapy, post-HSCT group: 7.5 (4.1-10.0), 4.2 (3.4-6.8), 2.8 (2.2-6.4), P=0.368 in no induction group; 10.2 (6.1-not available(NA)), 10.6 (5.7-NA), 5.5 (4.8-NA), P=0.460 in induction group, respectively). In patients who were able to proceed with HSCT, median OS was 13.8 (6.7-29.2) months and EFS was 11.0 (6.5-18.3) months. HSCT outcomes also tended to be better in the natural group compared to the post-chemotherapy or post-HSCT groups, but there was no statistical significance (median OS months from HSCT: 24.4 (6.5-NA), 13.8 (5.8-29.2), 11.7 (5.6-NA), P=0.265; median EFS, 18.3 (6.5-NA), 10.4 (3.0-20.6), 8.2 (3.5-NA), P=0.242 in the natural, post-chemotherapy, post-HSCT respective groups)

Conclusion: In conclusion, we confirmed again that overall survival of these sAML/MDS patients was very dismal and patients who had no history of previous disease modifying treatment had superior survival compared to those who had previously been treated for MDS. By identifying the factors contributing better response and survival, optimal treatment strategies could be made for these cohort having great unmet needs.

Keyword: Myelodysplastic syndrome, Secondary AML, Chemotherapy, Hematopoietic stem cell transplantation, Survival

PP03-01

Clinical application of next-generation sequencing -based monitoring of minimal residual disease in childhood acute lymphoblastic leukemia

Mai Huirong* and Li Qin

Department of Hematology and Oncology, Shenzhen Children's Hospital, China

Background: To explore the feasibility of next-generation sequencing (NGS) in detecting minimal residual disease (MRD) in childhood acute lymphoblastic leukemia (ALL) based on immunoglobulin (IGH, IGK, IGL) and T cell receptor (TRG, TRB), and analyze the risk factors of positive NGS-MRD at the end of induction chemotherapy.

Method: Bone marrow samples were collected before treatment, day 19, at the end of induction and end of consolidation chemotherapy with pediatric ALL admitted to Shenzhen Children's Hospital from 1st February 2020 to 31st January 2021. MRD was detected by NGS, multiparametric flow cytometry (MFC), and real-time quantitative PCR (RQ-PCR), respectively. We analyzed the correlation between NGS and traditional techniques of MFC and RQ-PCR. Risk factors of positive NGS-MRD at the end of B-ALL induction chemotherapy were analyzed with clinical data before treatment

Results: A total of 236 bone marrow samples were collected from 64 children with ALL (58 B-ALL and 6 T-ALL). The traceable clonal index sequence was detected in 51 (87.9%) cases of B-ALL and all cases of T-ALL by NGS before treatment as a baseline. Positive MRD was detected in 57.5% (77/134) of B-ALL and 80% (12/15) of T-ALL by NGS after chemotherapy, which was higher than those by MFC and RT-qPCR. In B-ALL patients, MRD results detected by NGS were consistent with MFC（r=0.708, P<0.001）and RQ-PCR（r=0.618, P<0.001）. At end of induction, NGS-MRD of 40.4% B-ALL was >0.01% and multivariate analysis indicated that ≥2 clonal rearrangement sequences before treatment was an independent affecting factor of negative NGS-MRD.

Conclusion: NGS is more sensitive than those of MFC and RT-qPCR for MRD measurement. B-ALL children with ≥2 clonal rearrangements detected by NGS before treatment are difficult to switch to negative MRD after chemotherapy.

Keyword: Acute lymphoblastic leukemia, Children, Minimal residual disease, Next-generation sequencing

PP03-03

Pediatric leukemia: a systematic review of oral manifestations, post-treatment complications & oro-dental management

Dr. Vaibhav Gupta* and Dr. Poonam Goel

National Institute of Pathology, India

Background: Leukemia constitutes approximately 30% of all childhood cancers and acute lymphoblastic leukaemia (ALL) is the most common type of malignancy encountered in children. ALL accounts for about 75% of childhood leukemias with its peak incidence at 4 years of age. Acute myeloid leukemia (AML), highly aggressive malignancy, represents 25% of pediatric leukemia. Early signs of leukemia usually manifest in oral cavity due to infiltration of leukemic cells or due to associated decline in normal marrow elements. Aim of the review is to highlight the oral presentations of leukemia among children along with oral care practices for patients during HSCT and dental complications after the treatment of leukemia along with its management.

Method: PubMed, EBSCO, COCHRANE and Google Scholar articles were searched for articles published during last 25 years i.e. between 1996 and 2021 with keywords "pediatric cancer," "leukemia and dental effects," "ALL or AML and oral health," "pediatric cancer and dental effects," "pediatric leukemia treatment and dental complications," and "pediatric dentistry and leukemia" Inclusion of articles was performed by a single examiner who initially read the abstracts and then read full articles for the selected abstracts. The data, including information on authorship, year of publication, study site, study design, purpose, sampling technique, sample size, ethnical background, age, oral symptoms and main results, were listed. A total of 127 articles were identified by the search; relevance was determined by examining the title and abstract of the articles. Total 36 original research studies met the inclusion criteria and 19 studies scored more than 14 points on STROBE checklist and included in the study for analysis. The data was tabulated into excel format which included type of study, objective, sampling technique, sample size, ethical background, age group, method of oral symptoms and required dental treatment.

Results: The most common oral symptoms in pediatric individuals reported in the literature were petechiae, spontaneous bleeding, mucosal alteration, ulcerations, gingival enlargement, mucosal necrosis. The orofacial abnormalities in leukemic children includes enamel hypoplasia, arrested teeth development, tooth anomalies and tooth maturity disturbance, embarking significant impact on aesthetic and cause functional and occlusal disturbances. In addition to mucosal pallor, higher caries prevalence, herpetic opportunistic infections and candidiasis, temporomandibular joint arthritis, and osteolytic lesions in the mandible may arise. Other oral

signs such as palatal pigmentation, tooth pain and mobility, hemorrhagic bullae on the tongue, cracked lips, parotid swelling, and chin numbness were less commonly reported. The prevalence of dental caries, gingivitis, oral mucositis, xerostomia, and candidiasis among leukemic subjects is higher than healthy children. The oral microbial structure of leukemic patients receiving chemotherapy is different from that of healthy children. Oral microbiota of leukemic groups showed less alpha diversity and significant differences in the composition of the oral microbiome compared to healthy controls. Adverse effects of oncological treatments are unavoidable and can impact oral health status, thus significantly affecting the quality of life of survivors. Treatment affects dental age maturity of involved patients with agenesis, microdontia, tapering roots and short roots. Periodontal debridement (scaling and root planing) with antibiotics prophylaxis and daily rinsing with 0.1–0.2% chlorhexidine gluconate is recommended to minimize oral complications during remission-induction chemotherapy. Certain complications of chemotherapy and radiotherapy such as hemorrhage, xerostomia, mucositis, and recurrent herpetic infection should be identified, and the treatment plan to be modified. Use of antifungal prophylaxis, such as posaconazole/ nystatin formulations in high-risk patients and Palifermin, low level infra-red laser therapy as well as Honey and mixture of Honey in the treatment of mucositis, Acyclovir for Herpes, artificial saliva & sugar- free chewing gum for treatment of xerostomia.

Conclusion: Oral complications affect activities like eating and speaking. These lesions may interfere with cancer treatment, causing more serious infections or even sepsis. These findings may be of clinical importance in developing better strategies for personalized preventive management of oral diseases among children with leukemia. The presence of an active dental surgeon on the multidisciplinary oncology team is therefore indispensable, as they can assist in the prevention, early diagnosis, and treatment of oral manifestations. A dental surgeon can prevent lesions from escalating, thereby improving the patient's quality of life during treatment. Parents need to be educated about the benefits of optimal oral hygiene for their children and the need to seek immediate care for mouth pain and lesions.

Keyword: ALL, Pediatric leukemia, Dental complications, Oral Hygiene, AML, Pediatric cancer

PP03-04

IKZF1 plus profile and outcome analysis in a cohort of paediatric B-cell acute lymphoblastic leukaemia cases

Prateek Bhatia[1*], Minu Singh1, Pragna Hc[1], Rozy Thakur[1], Amita Trehan[1] and Neelam Varma[2]

[1] Peditaric Hematology-Oncology Unit, Department of Pediatrics, Pgimer Chandigarh, India

[2] Hematology, Pgimer Chandigarh, India

Background: KZF1 deletion occurs in 15% of paediatric B-ALL and has been shown in some studies to be associated with an increased risk of relapse and poor outcome. However, in a recent study by Stanulla et al, presence of IKZF1 Plus profile has been shown to be associated with worse minimal residual disease (MRD), poor prednisolone response (PPR) and high cumulative incidence of relapse. This profile is defined by presence of IKZF1 deletion plus additional deletion in CDKN2A/2B, PAX5, or PAR1 region and with absent ERG deletion.

Method: In current study we retrospectively prospectively analysed our cohort of paediatric B-ALL for the frequency of IKZF1 Plus profile and noted its correlation with treatment outcome. A total of 178 paediatric B-ALL cases (118 prospective B-ALL and 60 B-cell other retrospective cohort negative for recurrent translocations and hyperdiploidy) were analysed for IKZF1 Plus profile using MLPA based probes and reagents from P-335 and P-202 kits using patient and control DNA extracted from blood. The MLPA data was analysed using coffalyzer software and dosage quotient (DQ) ratios were calculated to define copy number alterations. The data was then correlated with outcome parameters and survival curves were derived.

Results: Mean age in study was 5.3 years and mean TLC at presentation 82000/ul. 48/175 (27%) had a positive MRD and 11/176(6.2%) were in remission failure post induction. 63/118 (54%) were positive for recurrent translocations and or hyperdiploidy. As per final risk categorisation post genetics and MRD, 78/178(44%) were high risk, 58(33%) intermediate and 41(23%) standard risk. 40/178 (22%) had an IKZF1 del, out of which 27 (67%) had an IKZF1 Plus profile. Based on CNV risk group classification, 31 (17%) had high risk CNV profile, 57 (32%) intermediate risk and 90 (51%) good risk profile. RFS, EFS at 4 years for IKZF1 Del group was statistically poor as compared to non-IKZF1 del group (58% vs. 78%, p=0.046; 38% vs. 60%, p=0.0103); however no difference for OS was noted. RFS, EFS at 4 years was even worse for IKZF1 Plus group as compared to non-IKZF1 Plus group (50% vs. 70%, p=0.026; 36% vs. 58%, p=0.0103).

Conclusion: Overall frequency of IKZF1 Plus profile in our data was 15%. IKZF1 Del as well as IKZF1 Plus profile recognition is important since these cases tend to have a poor RFS and EFS. However long-term prognostic impact in combination with underlying cytogenetic sub-groups and MRD is needed to better risk stratify B-ALL cases. Current study is one of the first large paediatric series from our sub-continent to highlight impact of IKZF1 Plus profile on outcome.

Keyword: B-ALL, MLPA, RFS, EFS

PP03-06

Genetic variation and relationship of homo sapiens t(4;11)(q21;q23) translocation breakpoint sequence, MLL-AF4 gene fusion, in acute lymphoblastic leukemia

Ramlah Ramlah

Biology, Universitas Sulawesi Barat, Indonesia

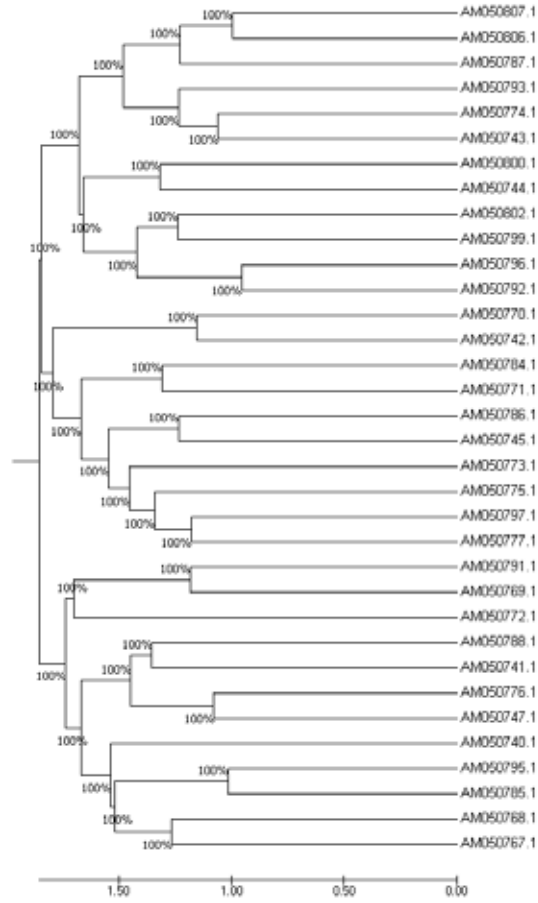
Background: Genetic variation is an important force in evolution as it allows natural selection to increase or decrease frequency of alleles already in the population. Genetic disease is mostly caused by familiarity in the genetic code. DNA arrays capable of simultaneously measuring expression of thousands of genes in clinical specimens from affected and normal individuals have the potential to provide information about superior characteristics gene from organism. Genes can be used as markers for cell recruitment and activation molecules. This study aims to evaluate the genetic variation and relationship of homo sapiens t(4;11)(q21;q23) translocation breakpoint sequence, MLL-AF4 gene fusion, in acute lymphoblastic leukemia.

Method: Data obtained from 34 nucleotide sequences of homo sapiens t(4;11)(q21;q23) translocation breakpoint sequence, MLL-AF4 gene fusion, in acute lymphoblastic leukemia on secondary data form on https://www.ncbi.nlm.nih.gov/ and selected articles journal evaluated by searching in PubMed, EMBASE, and the Cochrane Library database that have been carried out in the last 5 years (2017-2021). The phylogeny analysis of variations and relationships of DNA sequences was inferred using the UPGMA method and the evolutionary distances were computed using the Maximum Composite Likelihood method using MEGA7 software.

Results: Based on the analysis of variations and relationships, it is known that on the dendogram (Figure 1.), 34 sequences were divided into 3 main groups, namely group A consisting of 12 specimens, group B consisting of 10 specimens, and group C consisting of 12 specimens. The optimal tree with the sum of branch length = 47.96786873 is shown. The tree is drawn to scale, with branch lengths (next to the branches) in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The lowest genetic distance value was owned by AM050792.1 - AM050796.1 of 1.908, while the highest was owned by AM050770.1 - AM050795.1 of 5,440. This grouping is based on the existence of a similar genetic makeup equation with a high bootstrap value indicating the degree of kinship between specimens and the strength of the philogenous trees. Specimens that are in the same sub-groups show a degree of close kinship. On the other hand, specimens from different sub-groupss display distant kinship. Grouping was achieved on the basis of differences in expression levels across individual specimens.

Conclusion: It can be concluded that the variation and relationship of homo sapiens t(4;11)(q21;q23) translocation breakpoint sequence, MLL-AF4 gene fusion, in acute lymphoblastic leukemia sequence have highly variation. The highest of genetic distance was owned by AM050770.1 - AM050795.1 of 5,440. Information about kinship can be used as an informative source to assembly of superior genes in living of human cells.

Keyword: Genetic variation, Relationship, Homo sapiens, Translocation breakpoint, MLL-AF4 gene fusion, Acute lymphoblastic Leukemia



PP03-07

Prognostic utility of key copy number alterations in T cell acute lymphoblastic leukemia

Sarita Kumari[2,5], Md Shadab Ali[1], Jay Singh[2], Mohit Arora[3], Deepak Verma[2], Dr. Sameer Bakhshi[4], Jayanth Kumar Palanichamy[3], Atul sharma[4], Inder Singh[6] and Anita Chopra[2*]

[1] Department of Pulmonary, Critical Care and Sleep Medicine, All India institute of medical Sciences, India
[2] Lab oncology unit BRA.IRCH, All India institute of medical Science, India
[3] Department of Biochemistry, All India institute of medical science, India
[4] Department of medical Oncology, All India institute of medical science, India
[5] Department of Biotechnology, Gautam Buddha University, India
[6] Department of Neurology, All India institute of medical sciences, India

Background: T-ALL is an aggressive malignancy that accounts for 10%–15% of pediatric and 25% of adult ALL cases. Management of T-ALL is clinically challenging as relapse is common and fatal. Therefore, it is necessary to develop biomarkers for efficient identification of high-risk patients and to design novel therapies. T-ALL is a highly heterogeneous disease, and molecular features such as mutation patterns, DNA copy number, cytogenetics, epigenetics, and gene expression vary widely among individuals. While extensive heterogeneity in molecular alterations in T-ALL makes it challenging for researchers and clinicians to effectively utilize molecular features in clinics, nevertheless, some major subgroups have been identified and efforts are underway for clinical implementation. Distinct subtypes of T-ALL have been identified based on immunophenotype, which can also be determined using gene expression profiling (GEP). Several molecular subgroups of T-ALL have also been defined based on differential overexpression of transcription factors such as HOX11, LYL1, TAL1, LMO1, LMO2, and TLX3. Further, a variety of genomics and proteomics approaches have been utilized to develop markers for efficient risk stratification, amongst which, the role of aberrant DNA copy number profile in ALL has been widely recognized. The aim of this study was to determine the frequency of common copy number alterations (CNAs) in T-ALL and their association with clinicopathological features, such as response to therapy and patient survival.

Method: This study included a total of 128 T-ALL patients (115 males and 13 females comprising 98 pediatrics and 30 adults; median age 12 years; range 1-65 years). Multiparameter flow cytometry was used for immunophenotyping of the T-ALL patients. Bone marrow (BM)/peripheral blood (PB) samples were collected in an EDTA vial and processed using the stain-lyse-wash. DNA was extracted from BM/PB/ and the SALSA MLPA Probemix P383-A2 T-ALL was used to detect CNAs in T-ALL. The probe mix consists of 56 probes, which amplifies 130 to 504 nucleotide size products covering 13 chromosomal positions, including STIL::TAL1, LEF1, CASP8AP2, MYB, EZH2, MLLT3, MTAP, CDKN2A/2B, NUP214::ABL1, PTEN, LMO1, LMO2, NF1/SUZ12, PTPN2, and PHF6. Clinical characteristics of T-ALL patients were collected such as hemoglobin, total leukocyte count (TLC), platelet counts, PB blast %, BM blast %, immunophenotypic profile, day 8 blast count, MRD status, cytogenetics, central nervous system (CNS) disease. Fisher's exact test for categorical and nonparametric Mann-Whitney U test for continuous variable was used to investigate the association between clinical variables and CNA status. Correlations among the alteration in genes were measured by Spearman's Rho (ρ). Survival records of all the patients who took therapy were collected for the analysis of event-free survival (EFS), relapse free survival (RFS), and overall survival (OS). Kaplan-Meier survival analysis was performed to estimate survival functions and the two-sided log-rank test was used to compare differences in survival curves. Cox proportional hazard models were constructed to estimate the hazard ratio (HR) for OS, EFS, RFS and used for univariate and multivariate analyses.

Results: The highest frequency of deletion was observed in CDKN2A (59.38%), followed by CDKN2B (46.88%), LMO1 (37.5%), and MTAP (28.12%). Genes with the highest duplication events were PTPN2 (22.66%), PHF6 (14.06%), and MYB (14.06%). A total of 89.06% patients exhibited CNAs. STIL::TAL1, NUP214::ABL1, and LMO2::RAG2 fusions were observed in 5.47%, 3.12%, and 0.78% of patients, respectively. Deletion of CDKN2A, CDKN2B, and PTPN2 genes was mainly seen in pediatric patients, while CNA of NF1 and SUZ12 was observed more frequently in adults. In pediatric patients, alterations in CDKN2B, CASP8AP2, and AHI1 were associated with poor prognosis, while SUZ12 and NF1 CNAs were associated with favorable prognosis. In adult patients, ABL1 CNA emerged as an independent indicator of poor prognosis.

Conclusion: The observed molecular heterogeneity in T-ALL may provide the basis for variations observed in clinical response in T-ALL and MLPA based CNA detection may help in risk stratification of these patients and designing of effective personalized therapy.

Keyword: T-ALL, Leukemia, MLPA, Copy number alterations, CDKN2B

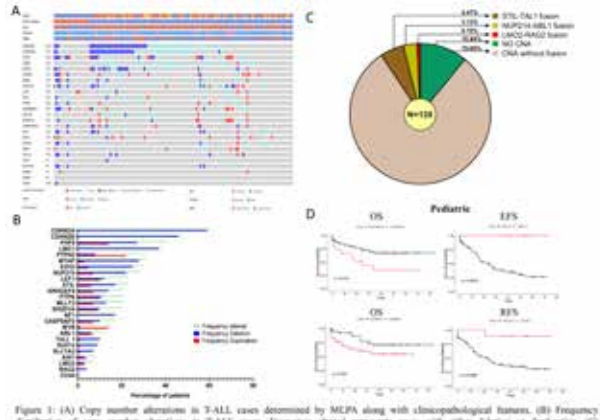


Figure 1: (A) Copy number alterations in T-ALL cases determined by MLPA along with clinicopathological features. (B) Frequency distribution of copy number alterations in T-ALL cases. Frequency altered represents cases with either deletion or duplication. (C) Interchromosomal gene fusion events in study cohort. (D) Kaplan-Meier survival analysis for association of OS, EFS and RFS with alterations of CASP8AP2, CDKN2B, and SUZ12 in pediatric T-ALL patients.

PP03-08

Segmentation of red blood cell image based on cell morphology to detect iron deficiency anemia

Elfiany Elfiany*, Rosmani Bahtiar and Bannure Bannure

Computational Science, Universitas Muhammadiyah Bulukumba, Indonesia

Background: Red blood cells are an essential component of the human body, which normally are biconcave, have no nucleus, and function as oxygen carriers. Normal or not the status of red blood cells can be seen from the morphology of the cells in the process of blood analysis for disease detection. One of the diseases characterized by morphological changes is iron deficiency anemia, which is anemia which is classified as microcytic anemia. The process of manual detection of iron deficiency anemia by examining peripheral blood images using a microscope in the laboratory can take quite a long time without real size and limitations. This study segmented red blood cell images to help diagnose iron-deficiency anemia based on morphological characteristics of shape and size to overcome these obstacles.

Method: This study applies a segmentation method using canny edge detection and morphological operations to separate cells categorized as macrocytic for feature extraction. Feature extraction resulted in three classifications of red blood cells according to the actual shape and size, namely normal cells, microcytic cells, and pencil cells. The detection process to assist the diagnostic process is determined by comparing the number of cells resulting from feature extraction with the IF determination algorithm and AND operator.

Results: The results showed that segmentation based on morphology can be applied to detect iron deficiency anemia by extracting cell features. The characteristics of the extracted cells were normal cells, microcytic cells, and pencil cells. This is evidenced by the success of the research results for disease determination which reached 88% for the sensitivity value, 86% for the specificity value, and 87% for the accuracy value.

Conclusion: t is concluded that the segmentation based on morphology can be applied. The application is to detect iron deficiency anemia based on feature extraction cells, namely normal cells, microcytic cells, and cells. This is evidenced by the success of research for disease determination which reached 87% for the accuracy value.

Keyword: Segmentation, Red blood cell image, Cell morphology, Deficiency anemia

PP03-09

Delineating CRLF2 positivity and its clinical significance in pediatric B-cell acute lymphoblastic leukemia

Jay Singh[1], Mercillena Benjamin[1], Avanish Kumar Pandey[1], Sarita Kumari[1], Mohit Arora[3], Gunjan Sharma[3], Md. Shadab Ali[8], Deepak Verma[7], Sameer Bakhshi[2], Rachna Seth[4], Amitabh Singh[6], Jayanth Kumar Palanichamy[3], Inder Kumar Singh[5] and Anita Chopra[1*]

[1] Laboratory Oncology unit, Dr. BRAIRCH, AIIMS, New Delhi, India
[2] Department of Medical Oncology, AIIMS, New Delhi, India
[3] Department of Biochemistry, AIIMS, New Delhi, India
[4] Department of Pediatrics, AIIMS, New Delhi, India
[5] Department of Neurology, AIIMS, New Delhi, India
[6] Department of Pediatrics, VMMC & Safdarjung Hospital, New Delhi, India
[7] Department of Oncology, School of Medicine, SKCCC, Johns Hopkins University, Baltimore, USA
[8] Department of Pulmonary, AIIMS, New Delhi, India

Background: Cytokine Receptor-Like Factor 2 (CRLF2) positive B-cell acute lymphoblastic leukemia (B-ALL) is one of the subtypes of high-risk B-ALL featuring aberrant overexpression of CRLF2 protein on the surface of the leukemic blasts. Despite the fact that B-ALL has high survival rates, roughly 20% of pediatric patients face chemoresistance and relapse which leads to high mortality. CRLF2 gene encodes thymic stromal lymphopoietin receptor (TSLPR) which forms a heterodimer with the IL7R α-chain and activates the JAK-STAT pathway, which is involved in B cell development and differentiation. Two cryptic translocations, P2RY8::CRLF2 and CRLF2::IGH along with mutation in CRLF2, IL7R and JAK2 genes lead to dysregulated expression of CRLF2. Molecular mechanisms related to CRLF2 overexpression have been widely studied but there is still paucity in understanding its clinical significance because of its multipronged downstream signaling pathways. In this study, we studied the CRLF2 expression in pediatric B-ALL patients and determined its association with presence of fusion transcripts, mutation of CRLF2, IL7R and JAK2 genes and copy number alterations. We also investigated its clinical significance and extrapolated our results with previously established datasets.

Method: A total of 128 B-ALL cases (males, n=87 and females, n=41) were prospectively enrolled in this study. CRLF2 surface expression was measured in bone marrow(BM) or peripheral blood (PB) samples at diagnosis by flowcytometry using anti-TSLPR antibody. Copy number variation(CNV) of commonly altered genes(IKZF1,CDKN2A/2B,JAK2,PAX5, ETV6, RB1, genes located in PAR1 region) in B-ALL were assessed using DNA isolated from BM/PB by Multiplex ligation-dependent probe amplification (MLPA). Presence of P2RY8::CRLF2 fusion and mutation in JAK2, CRLF2 and IL7R gene

was investigated in CRLF2 positive cases using PCR followed by Sanger sequencing. The difference in Gene expression profile (GEP) between P2RY8::CRLF2 fusion and CRLF2::IGH fusion group was explored using publicly available St. Jude dataset of ALL. RNA-Sequencing was done in CRLF2 positive cases (n=4) to find out the novel CRLF2 lesions. Association of clinicopathological parameters and CNV alteration status of commonly altered genes with CRLF2 positivity was studied by chi-square/Fisher's exact test. Association of CRLF2 positivity with event free survival (EFS) and overall survival (OS) was analyzed using Kaplan-Meier survival analysis and log rank test.

Results: CRLF2 expression was positive in 7.8% (n=10) of B-ALL cases. The median age of the patients was 6 years (range 1-18 years). In our cohort, CRLF2 positivity did not exhibit association with sentinel cytogenetic subtypes(BCR::ABL1, ETV6::RUNX1, TCF3::PBX1, MLL rearranged) and other clinical characteristics such as age, sex, TLC and NCI risk. CNV analysis revealed PAX5(36.7%) was mostly altered, followed by CDKN2A/2B(25%) andIKZF1(18%). Interestingly, PAX5 alteration was associated with CRLF2 positivity (p=0.006). Further, among CRLF2 positive cases, IL3RA and P2RY8 duplications were significantly associated to heterogenous low expressed (p=0.05) group when compared with the homogenous dim expression. Furthermore, P2RY8::CRLF2 fusion was present only in one CRLF2 positive case. Mutation analysis revealed no alteration in the CRLF2 gene, whereas IL7R(c818 C>T) and JAK2(c.2481_82 GG>CC, c.2484 ins T) was found to be altered in 3 and 2 cases, respectively. RNA-seq data revealed VWA2::CRLF2, TRA::CRLF2 and CSF2RA::CRLF2 fusions in CRLF2 positive cases. Analysis of St. Jude's B-ALL data suggested that P2RY8::CRLF2 fusion differs from CRLF2::IGH fusion in terms of upregulated molecular pathways(KRAS signalling, epithelial mesenchymal transition, NOTCH signaling, glycolysis and angiogenesis). Although there was no association of CRLF2 positivity with BM remission and MRD, however, survival analysis revealed CRLF2 positive patients exhibited poor EFS (p=0.002).

Conclusion: Varied expression patterns of CRLF2are suggestive of the presence of subclones in CRLF2 positive samples. P2RY8::CRLF2 fusion is not predominant in our pediatric B-ALL population. PAX5 association with CRLF2 positivity needs to be investigated further, given its association with poor patient prognosis.The difference in GEP of P2RY8::CRLF2 from CRLF2::IGH indicates heterogenous nature of CRLF2 positivity. Examining CRLF2 positivity status and its prognostic impact in B-ALL patients in a larger cohort is needed for its therapeutic implication.

Keyword: B-ALL, CRLF2, P2RY8::CRLF2, CNV, PAX5, Survival

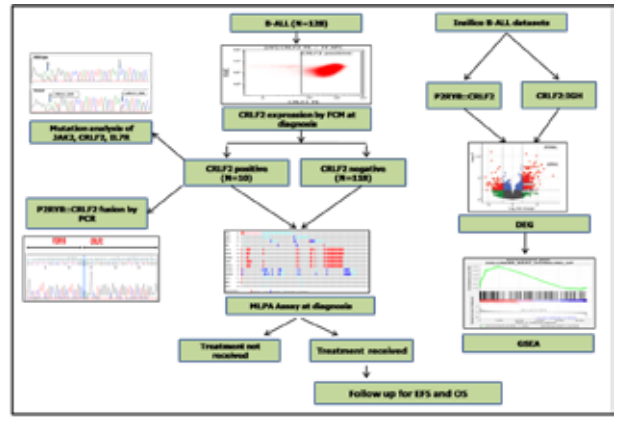


Figure: Flow chart showing the overview of the study

PP03-10

High-throughput drug sensitivity analysis strategy and salvage autologous CD19 CAR-T therapy in second marrow relapse of acute lymphoblastic leukemia with NT5C2 mutation

Xue Tang

Department of Hematology and Oncology, Shenzhen Children's Hospital, China

Background: The five-year survival rate of pediatric acute lymphoblastic leukemia (ALL) has reached ninety percent in twentieth century, however, recurrence is one of the main causes of treatment failure. Recently, chimeric antigen receptor (CAR)-T cell immunotherapy was shown to have success in control of relapsed/refractory B-cell malignancies. Although, lymphocyte-depleting chemotherapy (usually concluding fludarabine and cyclophosphamide) have been used in CAR T-cell therapy, reduction in the tumor load before infusion is still a challenge. Herein, we present a girl who experienced a second bone marrow relapse of ALL survived through salvage autologous CD19 CAR-T therapy followed by an allogeneic hematopoietic stem cell transplantation.

Method : Case presentation:
A 17-year and-3-month-old girl was diagnosed with B-ALL when she was 12 years old. At initial diagnosis (March 7, 2016). She had no evidence of central nervous system (CNS) involvement and her cerebrospinal fluid (CSF) test was negative. She was treated with intermediate risk (IR) of CCLG-2008 ALL protocol in the University of

Hong Kong-Shenzhen Hospital and achieved complete remission (CR) on day 33 evaluation. Four years after the first diagnosis of ALL, she was admitted with chief complain of fatigue and poor appetite. There were 80% blasts in peripheral blood and bone marrow. Flow cytometry indicated B-cell ALL. The diagnosis of late relapse of first solely bone marrow was established. HKPHOSGALL Relapsed 2007 protocol was introduced from July 29, 2020 in the University of Hong Kong-Shenzhen Hospital. Minimal residual disease (MRD) by flow cytometry was negative after receiving R2 and R1 courses of chemotherapy indicating second remission of ALL..After 24 months, while receiving maintenance, the patient was admitted to our hospital with cheaf complain of ecchymosis on lower limbs and her complete blood count (CBC) showed that platelet was 30×109/L. Bone marrow aspiration was performed and it showed 97%blastsindicating second bone marrow relapse. Whole transcriptome sequencing (RNA-seq) and high-throughput drug sensitivity test were performed at the same time to reveal the underlining mechanism of relapse. The resistant gene of NT5C2 was detected. Unfortunately, the blasts were not controlled with blasts increasing from 49.3% to 96% in bone marrow.we immediately collected peripheral lymphocytes for the modification of CAR-T cells. In the meantime, we received the results of drug susceptibility testing in vitro. It showed that carfilzomib was the only drug confirmed moderately sensitive for her, while the other cytotoxic drugs and adjuvant drugs were insensitive.

High-throughput Drug Sensitivity Analysis strategy

Bone marrow mononuclear cells were isolated by the Ficoll-Paque method. The cells were resuspended in DMEM supplemented with 15% FBS, 50-μM β mercaptoethanol, penicillin/streptomycin, and human cytokines (Peprotech, USA), including SCF (100 ng/mL), IL-3 (10 ng/mL), IL-6 (20 ng/mL), TPO (10 ng/mL), and FLT3L (10 ng/mL), and then plated on conflfluent irradiated stromal cells.Drugs were tested at appropriate concentrations equivalent to those used clinically. Cell viability was measured after 72 h using the CellTiter-Glo assay. All compounds are purchased from MedChem Express (Shanghai, China).

CART-cell clinical trial

This clinical trial was approved by the Ethics Committee of the Shenzhen Children's Hospital, China (202000103), and has been registered at www.clinicaltrials.gov (ClinicalTrials.gov, #NCT04033302. Registered 28 September 2014,https://www.clinicaltrials.gov/ct2/show/NCT04033302).

CD19 CAR-T-cell preparation

For the preparation of clinical-grade CAR-T cells, Shenzhen Genoimmune Medical Institute has established a standard operation protocol following the regulatory guideline for cell and gene therapy products. T cells from patients are genetically modified with a fourthgeneration CAR lentiviral vector (4SCAR) to recognize CD19 expression on the surface of cancer cells.

2.4 CAR detection by real time quantitative PCR(qPCR)

The presence of anti-CD19 CAR T-cells in the peripheral blood was determined using qPCR, based on both SYBR and Taqman probe methods, as described previously. Genomic DNA was harvested from blood cells using a Promega genomic DNA purification kit (Promega Corp. Madison, WI, USA). The qPCR data were collected using a MX3000P (Stratagene, Agilent Technologies, Santa Clara, CA, USA).

Results: The patient received cyclophosphamide and fludarabine on day -5 to -3 prior to CAR-T cells infusion. Considering the high tumor load, 20 mg/m2 carfilzomib on day -7 to -6 prior to CART infusion was also given according to the result of high-throughput drug sensitivity, and dexamethasone was taken to exerting a synergistic effect with it.One day before infusion, the patient's bone marrow smears showed 84% immature lymphocytes and flow cytometry MRD was 68.6%, but tumor burden of peripheral blood was significantly reduced.Autologous anti-CD19 CAR-T cells from the patient were infused at 8.5x106 cells per kg of body weight on day 0. The patient began to have a fever on day 2 (38.4**℃**) and agranulocytosis (0.02×109/L). Grade 1 CRS was diagnosed after infusion CAR-T cells. Anti-CD19 CAR transgene copy numbers in peripheral blood were determined by qPCR, which showed effective expansion. On day 28, no immature cell was found in bone marrow smear and MRD detected by flow cytometry was negative. NT5C2 also turned negative. These results indicated the patient achieved deeper molecular remission.

Conclusion: only a very small group of patients with second ALL relapse has a realistic chance for cure with still chemosensitive leukemia and tolerability of remission induction treatment followed by HSCT. Thus, patients with a second or multiple ALL relapse are ideal candidates for CAR-T cell immunotherapy then bridging to HSCT combined with high throughput drug sensitivity to modify the lymphodepleting chemotherapy protocol based on fludarabine and cyclophosphamide.

Keyword: Acute lymphoblastic leukemia, Relapse, High-throughput drug sensitivity, CAR-T, NT5C2 mutation

PP03-11

Circular RNA (CircRNA) transcriptomic signature in T-cell acute lymphoblastic leukemia (T-ALL)

M Shadab Ali[1], Deepak Verma[2], Jay Singh[1], Sarita Kumari[1], Avanish K Pandey[1], Mercilena Benjamin[1] and Anita Chopra[1*]

[1] Lab Oncology Unit, Dr. BRAIRCH, All India Institute of Medical Sciences, New Delhi, India

[2] Department of Oncology, School of Medicine, SKCCC, Johns Hopkins University, Baltimore MD, USA

Background: T-cell acute lymphoblastic leukemia (T-ALL) is a hematological malignancy that results from oncogenic transformation of T-cell precursors. Immunophenotypically, T-ALLs are classified into mature, cortical, and immature (pro- and pre-T) subtypes. Unlike B-cell ALL, T-ALL cannot be risk-stratified based on immunophenotype and cytogenetics. Thus, there is always a need of finding new markers for the disease that would indicate the likelihood of poor response to chemotherapy and to find new therapeutic targets. Circular RNA (circRNAs) is a non-coding RNA that has a wide range of biological functions including miRNA sponging, transcriptional activation, interactions with RNA-binding proteins, and translation into novel peptides not encoded by their linear counterparts. A progressively growing number of studies suggest that circRNAs play a key role in cancers. It is found to have the oncogenic function as well as prognostic significance in various malignancies including acute myeloid leukemia. In this study, we have used whole transcriptome sequencing to identify the landscape of CircRNAs in T-ALL patients and further determined subtype-specific CircRNA signatures.

Method: This prospective study included bone marrow (BM) / peripheral blood (PB) samples of newly diagnosed T-ALL patients (n=35) comprising of 26 children and 9 adults. Immunophenotyping was done on BM/PB samples using CD3, CD7, CD45, CD5, CD8, CD1a, CD13, CD33, CD117, HLA-DR, CD34, CD65 and CD11b antibodies. Whole transcriptomic sequencing was performed using the RNA extracted from the samples. CircRNA were detected using two pipelines "Find_Circ" and "CIRI". Transcriptome data of pooled RNA samples from 5 normal human thymus were used as control for the analysis. Validation of the CircRNA specific for each three T-ALL subtypes (immature; n=3, cortical; n=3, mature; n=1) was done by designing the divergent primers. The RNA samples were subjected to RNAse R treatment followed by PCR amplification with the designed primers and gel electrophoresis. CircRNA junction was identified by Sanger sequencing.

Results: Immunophenotypically, T-ALL cases were categorized into mature (n=5), cortical (n=17) and immature (n=13) groups. The median age of the patients was 14 (range 1-55 years). Using Find_Circ and CIRI, we identified a total of 330 differentially expressed CircRNA in our T-ALL cases compared to control thymus that were common in both the pipelines. Among them, a total of 20 CircRNAs were present in immature group exclusively, while 16 CircRNAs were found in the cortical group, and 294 in mature T-ALL group. All of the identified CircRNAs founds were novel. Validation of these findings were confirmed by the presence of size-specific bands on gel electrophoresis. Sanger sequencing of the purified PCR products further validated the presence of circular RNA junction where 25 base pairs from head and tail position were found to be linked together in our samples.

Conclusion: In conclusion, this study provides evidence of dysregulation of CircRNA in T-ALL with variation in different groups with distinct signatures. Upregulated transcripts of these CircRNA are still not characterized and its functional annotation is not yet known. The network analysis of these circular RNA with miRNA and mRNA is important as this interaction influence the gene expression in disease development and could well be used to explore their influence on associated genes and proteins. Given the importance of these CircRNA, elucidating the functional role of these molecules would be of great importance and could provide a prognostic significance and potential therapeutic target.

Keyword: T-ALL, Transcriptome, NGS, Circular RNA

PP03-17

A real world experience of clinical characteristics & treatment outcome of T-ALL: the Ampang experience

Siew Lian Chong*, Kim Wah Ho, Tee Chuan Ong, Veena Selvaratnam and Sen Mui Tan

Department of Haematology, Ampang Hospital, Dr, Malaysia

Background: T-cell acute lymphoblastic leukaemia (T-ALL) is a bone marrow malignancy. It accounts for around 20% of all ALL instances and is more common in adults than in children, though the frequency decreases as people get older. Hyperleukocytosis with extramedullary lymph node and organ involvement, as well as frequent central nervous system infiltration and the appearance of a mediastinal mass emerging from the thymus, can be seen in the clinical presentation.

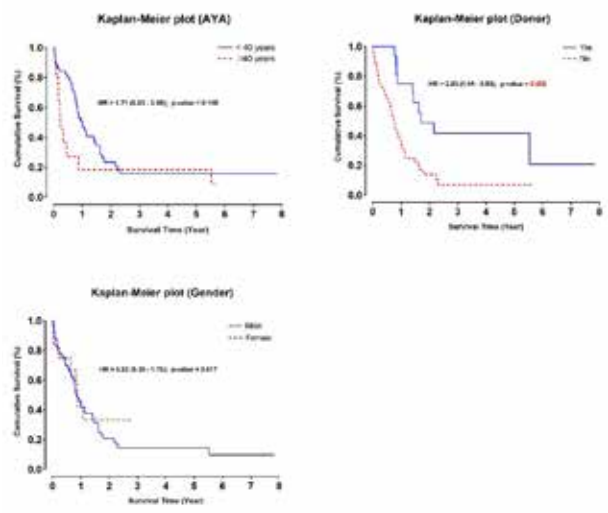
Method: This is a 8-year retrospective analysis of adult patients diagnosed with T-ALL between 2014 to 2021 in Ampang Hospital, Selangor.

Results: A total of 62 patients with T-ALL identified with male to female ratio around 4:1. The median age for patients was 28 years-old (range 14-77 years). Patients were mainly Malay (64.5%), followed by Chinese (17.7%) and Indian (12.9%), with a remaining 4.8% of other racial origins. Among them, 82.3% (n=51) were in adolescents and young adult (AYA, age of 12 to 39 years of age), and 17.7%(n=11) were elderly group for age of 40 and above. Overall survival (OS) for 1 years, 3 years and 8 years for (AYA) group were 46.8%, 15.6% and 15.6%, for elderly group OS were 18.2%, 18.2% and 9.1%; OS for groups underwent stem cell transplantation (SCT) with available donor 75.1%, 41.7% and 20.8%, for those do not have available donor and not underwent SCT 32.1%; 6.9% and 6.9%; OS for male 41.7%, 14.6% and 9.7%, for female 41.7%, 33.3% and 33.3%. There

was no significant association between age and gender. The risk of dying is about 3 times higher for those who did not underwent SCT (hazard ratio=2.92, 95%CI: 1.44-5.93, p=0.002) compared to those who had SCT.

Conclusion: We noticed that in our cohort, the survival outcomes in patients undergoing SCT plays a central role. However risk stratification and therapy intensification based on early treatment response abrogate the unfavorable prognosis of T-ALL. Future studies should focus precisely identifying poor risk features, such as disease genomic, MRD measurements, improving unrelated donor matching and developing post-SCT humoral and cellular therapy approaches.

Keyword: T-cell acute lymphoblastic leukaemia, T-ALL, OS T-ALL, OSTALL



PP03-18

Role of SOX4 and KRAS activation in relapsed pediatric B-cell acute lymphoblastic leukemia

Jae Wook Lee*, Jae Won Yoo, Seongkoo Kim, Pil-Sang Jang, Nack-Gyun Chung and Bin Cho

Division Hematology/Oncology, Department of Pediatrics, The Catholic University of Korea, Korea

Background: Relapsed acute lymphoblastic leukemia (ALL) is one of the most common pediatric cancers. Despite the discovery of several relapse-specific genetic mutations, the overall mechanism of relapse remains unclear. In this study, we undertook whole transcriptome sequencing (RNA-seq) in 3 precursor B (Pre-B) ALL children at relapse to determine major changes in gene expression at ALL relapse.

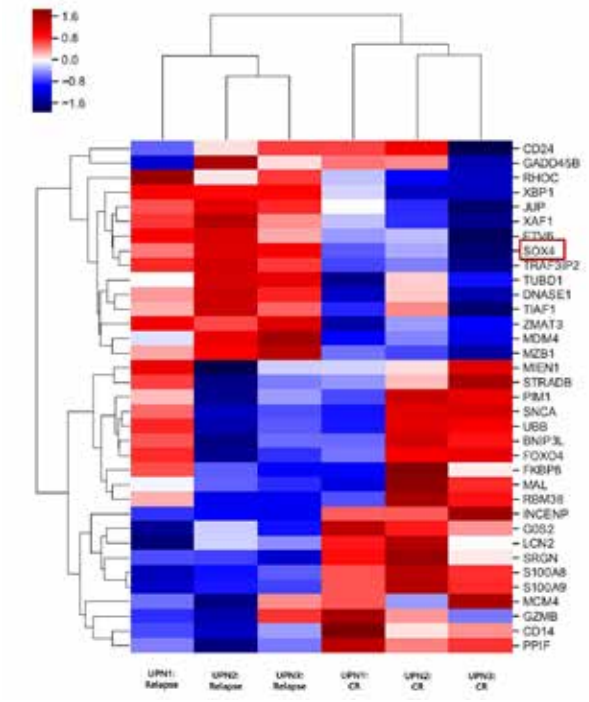
Method: RNA-seq was done in paired relapse-complete remission (CR) bone marrow (BM) specimens in 3 Pre-B ALL patients. BM study showed mostly leukemic blasts in the relapse samples. RNA quality was assessed prior to high-throughput sequencing, which was performed as paired-end sequencing using NovaSeq 6000 (Illumina, Inc., USA). Analysis focused on differential expression of genes involved in the cell cycle or cell death, followed by broader analysis of gene set enrichment at relapse compared to CR.

Results: Of 2,185 genes related to either the cell cycle or cell death, 35 genes showed significant changes in gene expression (≥ 2 fold change and ≥ 4 normalized data (log2)) in all 3 patients at relapse. Hierarchical clustering showed that the 3 relapse specimens grouped together for the 35 genes, indicating that the gene expression profile at relapse was similar for these patients, and differed from that found at CR. Of the genes involved in cell cycle regulation, SRY-Box Transcription Factor 4 (SOX4) gene showed the highest expression at relapse compared to CR status in all 3 patients, while Inner Centromere Protein (INCENP) gene and Minichromosome Maintenance Complex Component 4 (MCM4) gene uniformly showed lower expression at relapse. On STRING analysis, SOX4 showed significant protein-protein interaction with CD24 and JUP (interaction score 0.41 and 0.65 respectively). More broadly, gene set enrichment analysis showed significant enrichment of genes altered by oncogenic expression of KRAS in all 3 patients at relapse compared to CR.

Conclusion: This pilot study indicates a potential key role of SOX4 within the framework of KRAS activation in relapsed pediatric Pre-B ALL. SOX4 has previously been implicated in leukemogenesis through PI3K/AKT signaling. Further study is necessary to clarify the interactions between SOX4 and KRAS activation in relapsed ALL.

Keyword: Acute lymphoblastic leukemia, Relapse, Children, RNA-seq, SOX4, KRAS

Fig. 1 Heatmap showing hierarchical clustering of normalized expression of 35 cell cycle or cell death related genes with significant change in gene expression at relapse compared to CR for all 3 patients



PP03-19

Clinical and genetic characteristics of IGH aberrations detected by FISH analysis in childhood B-lymphoblastic leukemia

Sung Hee Min[1], Young Uk Cho[1], Seongsoo Jang[1], Chan Jeoung Park[1], Ho Joon IM[2], Kyoung-Nam Koh[2], Hyery Kim[2] and Eul Ju Seo[1*]

[1] Department of Laboratory Medicine, Asan Medical center, University of Ulsan College of Medicine, Korea

[2] Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

Background: Immunoglobulin heavy chain gene (IGH) has been known to play an important role in the pathogenesis of B-cell neoplasms, including B-lymphoblastic leukemia (B-ALL). In addition to IGH translocation, aberrations of IGH have been observed with various patterns in IGH break-apart FISH for B-cell neoplasms. In this study, we investigated patterns and characteristics of IGH aberrations with IGH break-apart FISH and evaluated the usefulness of IGH break-apart FISH as a screening tool for the relapse and persistence of blasts.

Method: Total 153 pediatric patients (78 males and 65 females) with B-ALL were examined at the time of diagnosis. The median age was 96 months (range 0-204). All patients underwent chromosomal analysis, FISH (IGH, CDKN2A, KMT2A and ETV6/RUNX1), and multiplex RT-PCR (Hemavision) for detection of genetic abnormalities and immunophenotyping for subclassification. We used IGH break-apart FISH probe (Vysis) with green signal of IGH variable region (IGHV) and red signal of IGH constant region (IGHC). RT-PCR and IGH FISH were performed for residual detection during the follow-up.

Results: IGH aberrations on FISH were detected in 76 patients (49.7%). There were 34 patients (22.2%) of IGH gain, 4 patients (2.6%) of IGH translocation, 15 patients (9.8%) of IGHV deletion, and 17 patients (11.1%) of IGHV partial deletion, 6 patients (3.9%) patients of IGHC deletion. Thirty-two cases of IGH gain (94.1%) showed high hyperdiploidy. Cases of IGH translocation showed 14q32 translocations or normal karyotype in chromosomal analysis. Most cases of IGHV deletion/partial deletion and IGHC deletion had recurrent genetic abnormalities in multiplex RT-PCR or chromosomal analysis, except KMT2A rearrangement. KMT2A rearrangement was significantly detected in normal IGH signal pattern ($P<0.05$). All patients with IGH aberrations were classified as common cell ALL or pre-B cell ALL, which were late-stage progenitor B cells. During the follow-up period, results of IGH FISH were consistent with RT-PCR.

Conclusion: We observed a high frequency of IGH aberrations in childhood B-ALL by FISH analysis and each pattern showed distinctive genetic characteristics. Most IGH aberrations are expected to exist exclusively in KMT2A rearrangement, and had the immunophenotypes of late stage B-ALL IGH translocations showed primary chromosomal event, while IGHV deletion/partial deletions and IGHC deletions were considered as secondary genetic changes. Since IGH aberrations occur in half of the childhood B-ALL, the IGH break-apart FISH can be used as a useful follow-up test.

Keyword: B-lymphoblastic leukemia, FISH, IGH, Pediatrics

PP03-20

Analysis of cerebrospinal fluid for malignant cells

Saransh Verma, Amar Ranjan*, Harshita Dubey and Pranay Tanwar

Laboratory Oncology Unit, All India Institute of medical Sciences, New Delhi, India

Background: Metastasis of cancers to the central nervous system (CNS) portends an unfavorable prognosis for the patients. It becomes essential to diagnose and treat cerebrospinal fluid(CSF) metastasis as soon as possible to reduce morbidity and mortality for the patient. The vast majority of cancers to metastasize to the brain are the cancers of the lung followed by breast cancers, melanomas and lymphomas.

Method: We analyzed 142 CSF samples collected as part of the routine care of the patients in a tertiary care oncology hospital in New Delhi , India in between Oct 2020 to Oct 2021. Males were 98/142 (69%) and females were 44/ 142 (31%). Routinely we conduct CSF analysis in all the diagnosed cases of B-ALL and in all the cases of malignancy showing features of neurological involvement.

Results: We excluded 4/ 142 samples due to traumatic puncture and inconclusive results. We found 14/142 (10%) samples to be positive for malignant cells. We had 11 cases male and 3 cases female. Age group was between 2 years to 26 years. We got 10/14 (71.4 %) cases of B-ALL (B cell acute lymphoblastic leukemia), 2/14 (14.3 %) cases of etinoblastoma(RB) and single sample came out to be positive for T-ALL and embryonic rhabdomyosarcoma each.

Conclusion: CNS involvement in cases of ALL IS 3-5% at initial diagnosis and 30-40% in cases of relapse. Leukemic infiltration of CNS is a well established prognostic factor in patients with ALL; it is predictive of a worse outcome and a higher rate of relapse. It is essential to accurately diagnose blast infiltration and subsequently adapt therapy to treat the condition.

PP03-21

Evaluation of genetic alterations in HBB gene and unravel the biochemical parameters among the sickle cell anaemia (SCA) patients

Krishnaswamy Rangaswamy[1*], Harysh Winster[1], Md.Younus Pasha[1], Dhivya Venkatesan[1], Balachandar Vellingiri[1] and Arul Narayanasamy[2]

[1] Department of Human Genetics & Molecular Bilogy, Bharathiar University, India

[2] Department of Zoology, Bharathiar University, India

Background: Sickle cell anaemia (SCA) is a hereditary illness caused by a mutation in both copies of the HBB gene in a person. A component of haemoglobin, the oxygen-carrying protein in red blood cells, is encoded by this gene. Haemoglobin molecules cling together as a result of the mutation, resulting in sickle-shaped red blood cells. The SCA is defined by the presence of dense, sickled cells, which induce blood cell haemolysis, anaemia, painful episodes, organ damage, and, in some cases, death. The aim of the present study was to perform the mutational screening of the HBB gene and unravel the biochemical levels in SCA patients.

Method: Totally 12 samples were selected including 6 SCA patients and 6 controls. The samples were provided asked to detailly fill in the questionnaire and questioned about family history using pedigree analysis. Institutional ethical clearance and informed consent forms were obtained. After the collection of blood samples, biochemical parameters were analysed using an HPLC assay. Further, the genomic DNA was isolated from blood samples followed by PCR and sequencing were utilized for common and rare sickle anaemia gene testing.

Results: The DNA sequence analysis showed a higher degree of HBB gene point mutation among the SCA patients when compared to their controls. Among the biochemical parameters the electrolytes, hepatic enzymes and alkaline phosphatase were elevated and statistically significant ($p<0.05$).

Conclusion: In conclusion, we suggest that further research should be conducted utilising modern molecular tools in genetic research as well as to conduct more biochemical assays to determine the specific reasons for genetic variance and to identify the biochemical profile in SCA from Tamil Nadu's tribal population.

Keyword: Sickle cell anaemia, HBB gene, Biochemical analysis, Tribes, Tamil Nadu

PP03-22

The outcome of blinatumomab in relapsed or refractory pediatric B-ALL: single center experience

Hyun Jin Park[1,2,3], Kyung Taek Hong[1,2,3], Jung Yoon Choi[1,2,3], Hong Yul An[1,2,3], Bo Kyung Kim[1,2,3] and Hyoung Jin Kang[1,2,3*]

[1] Department of Pediatrics, Seoul National University College of Medicine, Korea

[2] Seoul National University Cancer Research Institute, Korea

[3] Wide River Institute of Immunology, Korea

Background: Although more than 85% of newly diagnosed pediatric acute B-lymphoblastic leukemia (B-ALL) can survive without re-

lapse, outcome of relapsed/refractory (r/r) B-ALL is still poor. Blinatumomab, a CD19/CD3 bispecific monoclonal antibody, has showed to improve survival rate from patients with r/r B-ALL to patients with positive minimal residual disease (MRD). In Korea, blinatumomab was approved to be used as third line therapy, or second line therapy after fatal complication from intensive chemotherapy. However, there is a lack of Korean reports on real world data of blinatumomab in children. Herein, we report treatment outcome and response predictor of blinatumomab in pediatric r/r B-ALL in a single tertiary center.

Method: We retrospectively analyzed 19 pediatric patients with r/r B-ALL who received blinatumomab in Seoul National University Children's Hospital from 2017 to 2021. Indications for treatment were hematological relapse (n = 16), induction failure (n = 2), and MRD positivity (n = 1). Patients weighing less than 45 kg were given 5 mcg/body surface area (BSA) daily in the first week, and increased to 15 mcg/BSA daily in the next 3 weeks. Patients weighing 45 kg or above were given 9 mcg/BSA daily in the first week, and increased to 28 mcg/BSA daily in the next 3 weeks.

Results: The median age at diagnosis was 8.0-year-old (range 0.4 – 18.2). The median duration from diagnosis to administration of blinatumomab was 25 months (range 1 - 89). Two patients (2/19, 10.5%) were diagnosed with Pre-B ALL and others (17/19, 89.5%) were common B-ALL. Six patients (6/19, 31.6%) were classified as National Cancer Institute (NCI) standard risk at initial diagnosis and the remained patients (13/19, 68.4%) were NCI high risk, of which five patients (26.3%) showed very high risk feature; two of Philadelphia chromosome-positive ALL, one of infant ALL with MLL rearrangement, and two of induction failure. Nine patients (9/19, 47.4%) had previously received an allogenic hematopoietic stem cell transplantation (allo-HSCT) before blinatumomab treatment. Eleven patients including one with MRD positivity (11/19, 57.9%) achieved complete remission (CR) after blinatumomab treatment. Among 11 patients with CR, 8 patients (8/19, 42.1%) received allo-HSCT after median 2 cycles of blinatumomab (range 1-3). Six patients (6/19, 31.6%) sustained leukemia-free status for median 26.5 months (range 13.3 - 51.6). Five patients discontinued treatment during the first cycle of Blinatumomab due to disease progression. The median overall survival and progression-free survival were 13.8 months (95% CI 12.5 - 15.1) and 3.7 months (95% CI 0.5 - 6.9), respectively. There was neither treatment-related mortality nor permanent discontinuation due to grade 4 toxicity during blinatumomab treatment. One patient (5.3%) experienced a single event of seizure. Grade 1, 2, and 3 of cytokine release syndrome occurred in each 12 (63.2%), 4 (21.1%), and 3 (15.8%) patients. Comparing complete remission (n=11) and non-response (n=8) groups, bone marrow blast burden (p = 0.529), absolute lymphocyte count (p = 0.499) and CD3 positive T cell count (p = 0.983) were not significantly different. In subgroup analysis, previous HSCT, initial risk group, time to relapse (<36 months or ≥36 months), and the number of previous salvage treatment did not show significant difference in the ratio of treatment response.

Conclusion: Blinatumomab showed feasible outcome and tolerable toxicity in pediatric patients with r/r B-ALL. Due to the small number of cases, it was not possible to find determinants to predict the treatment response in this study. Nevertheless, some heavily pretreated patients achieved long-term survival through blinatumomab. Further nationwide studies to identify host and disease factors of blinatumomab treatment response are needed to establish optimal indication of blinatumomab in Korea.

Keyword: Acute B-lymphoblastic leukemia, Blinatumomab, Salvage chemotherapy, Pediatric

PP03-24

Comparison of mutational spectrum of IDH2, NRAS and TP53 genes in B-cell precursor lymphoblastic leukemia and acute myeloid leukemia

Hee Sue Park[1,2], Bo Ra Son[1,2] and Jihyun Kwon[3*]

[1] Laboratory Medicine, Chungbuk National University Hospital, Korea
[2] Laboratory Medicine, Chungbuk National University, College of Medicine, Korea
[3] Internal Medicine, Chungbuk National University, College of Medicine, Korea

Background: Sequential acquisitions of genetic mutations occur during leukemic evolution. Clonal hematopoietic stem cells contain not only leukemia-specific mutations but also pre-leukemic mutations. Pre-leukemic stem cells (pre-LSC) have the potential to differentiate into either myeloid or lymphoid. In particular, mutations in DMT3A, TET2, IDH1/2, FLT3 genes are known to be representative in pre-LSC. In this study, we retrospectively analyzed mutational spectrum detected in both B-cell precursor lymphoblastic leukemia (BCP) and acute myeloid leukemia (AML).

Method: Genetic NGS panel tests were performed on 144 AML patients and 21 BCP patients. Total 16 genes previous reported in both diseases were included BRAF, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, JAK2, JAK3, KRAS, NRAS, PTPN11, RUNX1, STAT3, TP53, and WT1.

Results: Mutations of IDH1 was detected in 2 (9.5%) of BCP and 9 (6.3%) of AML. TP53 mutations were more frequently detected in 3 patients (14.2%) in BCP and 20 patients (13.8%) in AML. NRAS mutations also frequently detected in 4 patients (19.0%) in BCP and 16 patients (11.1%) in AML. In the case of IDH1, missense mutations

in the P132 region were detected the most in both BCP and AML, and this was the case in 10 patients. In the case of BCP, it was a mutation IDH1 that occurred alone, but in the case of AML, additional mutations in other genes were detected. In the case of TP53, a broad spectrum was shown, and in AML, two TP53 mutations were detected occasionally as 8/20 (40%), but it was not observed in BCP. NRAS mutations was also detected at P12, P13, and P61, which correspond to hotspots, and mutations at P61 were detected in 7/16 (43.8%) in the case of AML, but not detected in BCP.

Conclusion: In the case of IDH1 and NRAS, the mutation spectrum was similarly observed in AML and BCP. In the case of TP53, it showed a somewhat dispersed form as it showed a broad mutation spectrum, but the number of mutations was higher in AML. Depending on the location of the genetic mutations, alteration of biological function induces variable clinical prognostic significance. And these genetic results give candidates for targeted therapy, so additional studies are needed.

Keyword: Acute myeloid leukemia, B-cell precursor lymphoblastic leukemia, IDH1, NRAS, TP53

PP03-25

Efficacy and safety of decitabine in the management of acute myeloid leukemia

Mohammad Asad Hussain

Health Outcomes Research, Jamia Millia Islamia, India

Background: Acute myeloid leukemia (AML) is a cancer of white blood cells and is most common in the elderly population. Recently decitabine was approved by the European Medicine Agency (EMA). Several epidemiological studies showed the efficacy and safety of decitabine in treating elderly AML patients. This meta-analysis was designed to understand the overall efficacy and safety of decitabine in the management of AML

Method: An extensive literature search was performed in PubMed, and Embase database to retrieve all the real-world evidence assessing the safety and efficacy of decitabine in the management of AML. The literature search, quality assessment, and data extraction were performed independently and double checked. Study quality was assessed using the Newcastle-Ottawa scale. The primary outcome was to compute the overall response and complete remission rate. Safety analysis was the secondary outcome of interest. Various subgroup analyses were performed. All the statistical analysis was performed using Review Manager version 5.4 software.

Results: The study was based on 798 patients with a median age of 74 years and 56.8% were male. Significant heterogeneity (I2 >50%) was observed so, a random effect model was applied instead of the fixed-effect model. Pooled completed remission rate, and overall response rate was 27% (95%CI: 19% – 36%) and 37% (95% CI: 28% - 47%). Subgroup analysis revealed that the overall response rate was higher [53% (95% CI: 37%–70%)] for 10 days 4 weeks treatment regimen versus 5-days 4 weeks treatment regimen [29% (95% CI: 22%–37%)]. Similarly, the overall survival rate was higher for 10 days 4 weeks treatment regimen [11.30 months (95% CI: 8.26–14.34)] versus the 5-days 4 weeks treatment regimen [6.40 months (95% CI: 4.24–8.56)]. Thrombocytopenia was the most common adverse event.

Conclusion: Decitabine was found to be an effective drug for the management of AML. The safety profile of decitabine was also found to be satisfactory. However, to make the evidence more robust a well-designed and sufficiently powered randomized controlled trial is required.

Keyword: Acute myeloid leukemia, Decitabine, Overall survival, Meta-analysis

PP03-26

Anti-leukemic effect of umbelliferone β-D-galactopyranoside against DMBA induced leukemic rat model: possible mechanism of action

Vikas Kumar[1*] and F Anwar[2]

[1] Pharmaceutical Sciences, SHUATS, India
[2] Biochemistry, King Abdulaziz University, Saudi Arabia

Background: Leukemia is a malignant disease of blood forming tissue inducing the over-production of large number of immature blood cells that enter the peripheral blood. Leukemia considered as the 9th most common cancer in men and 12th in women. Available treatment for leukemiaare chemotherapy, allogeneic cell transplantation and radiation therapy with side effects. Due to side effect linked with the treatment, medicinal herbs treatment having the more attraction to treat the leukemia. The current study was to scrutinize the anti-leukemic effect of Umbelliferone β-D-galactopyranoside(UFG) against 7, 12-dimethyl benza[a]anthracene (DMBA) induced leukemia in rats and explores the underlying mechanism.

Method: DMBA was used for the induction of leukemia in experi-

mental rats. The rats were divided into different groups and body weight, haematological parameters, DNA fragmentation and cell cycle regulatory parameter were also estimated. RT-PCR was used for the estimation of mRNA expression of sphingosine-1-phosphate receptor-1.

Results: UFG treated rats showed the up-regulation body weight as compared to other groups. Moreover, UFG reduced the blasts (67.8%) in leukemic rats. Its also altered the hemotological parameters such as RBC (69.8%), WBC (54.5%), lymphocytes (47.6%), neutrophils (48.9%), monocytes (44.7%), esnophills (48.7%), monocytes (64.5%) and basophils (43.5%), respectively. UFG treated rats showed the increased level of p21 and p53 and reduced level of cyclins D1 and E. RT-PCR showed the up-regulated of mRNA expression of sphingosine-1-phosphate receptor-1 (48.4%) of umbelliferone treated group rats as compared to other groups.

Conclusion: The current study, showed the anti-leukemic effect of UFGand highlights the possibility of its use in leukemia to minimize the side effect of the usual therapy.

Keyword: Leukemia, DMBA, Medicinal herbs, Cytotoxicity

PP03-27

A comparative study on digital dermatoglyphic patterns among adolescent with acute lymphoblastic leukemia in Guyana

Ameet Kumar Jha

Department of Preclinical Sciences, Texila American University, Nepal

Background: Dermatoglyphic patterns are the epidermal ridges seen on the surface of the palm, sole & digits which play an important role in predicting the various medical disorders. Recent association of the dermatoglyphic traits and specific chromosomal aberrations has established a predicting tool and a diagnostic aid. Acute lymphoblastic leukemia (ALL) is a malignancy of the lymphoid line of blood cells which in most cases are of unknown origin and is highly prevalent in the current perspective. The early diagnosis of such a fatal disorder is beneficial to undertake preventive measures and hence reduce the mortality rate. Fingerprints develop in the embryonic stage at the same time as the angiogenesis and hematopoiesis from mesodermal tissue, therefore insults to the embryo that may cause leukemic changes in the hemopoietic cells may also result in aberrant palmar crease patterns. This research aims to study the association between acute lymphoblastic leukemia (ALL) and dermatoglyphic trait to assess the value of dermatoglyphics as a screening tool to detect leukemia in high-risk groups. The study also reviews systematically and appraises available literature that evaluates an association of different dermatoglyphic variables with hematological disorders.

Method: A case-controlled study was conducted at the Georgetown Public Hospital Corporation(GPHC), a tertiary care hospital under the Ministry of Public Health, Georgetown, Guyana in 2019. The adolescent suffering from acute lymphoblastic leukemia was included in the study. Fingerprints of the affected adolescent were analyzed in both hands and compared with the fingerprint patterns of age and sex-matched controls. An intense systematic literature search was also conducted using keywords 'Dermatoglyphics', 'Adolescent', 'Acute Lymphoblastic Leukemia' from PUBMED, Medline, Google Scholar, EBSCO, HINARI, etc. The review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Qualitative dermatoglyphics patterns like whorls, loops, arches, and quantitative parameters like angles(atd, dat, adt), absolute finger ridge count (AFRC), total finger ridge count (TFRC), and a-b ridge count were studied.

Results: This research signifies an association between dermatoglyphic features and ALL. The mean ab–ridge count, and the mean atd angle were observed to be higher in cases while the mean dat angle was found to be lower in cases than controls. An increase in the frequency of whorls and a decreased frequency of loops in adolescents suffering from ALL were noted. Quantitative analysis: Mean pattern intensity index (PII) was found to be significantly higher in cases than controls.

Conclusion: The findings of the present study suggest a possible trend and an association of dermatoglyphic features with adolescents suffering from ALL. Such studies can be useful in forensic cases where the linkage of dermatoglyphic features with certain diseases is to be established. Fingerprint studies provide a simple, inexpensive, anatomical, and non-invasive means of determining the diseases with genetic linkage and can be employed as a method of screening the acute lymphoblastic leukemia of the high-risk population on early detection, thus reducing morbidity and mortality.

Keyword: Acute lymphoblastic Leukemia, Dermatoglyphics, Adolescents, Guyana

PP04-01

A single-center report on treatment outcomes of patients with CML treated with TKIs with a survey of health-related quality of life

Hee Jeong Cho, Jung Min Lee, Ju-Hyung Kim, Dong Won Baek, Joon Ho Moon and Sang-Kyun Sohn*

Department of Hematology/Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Korea

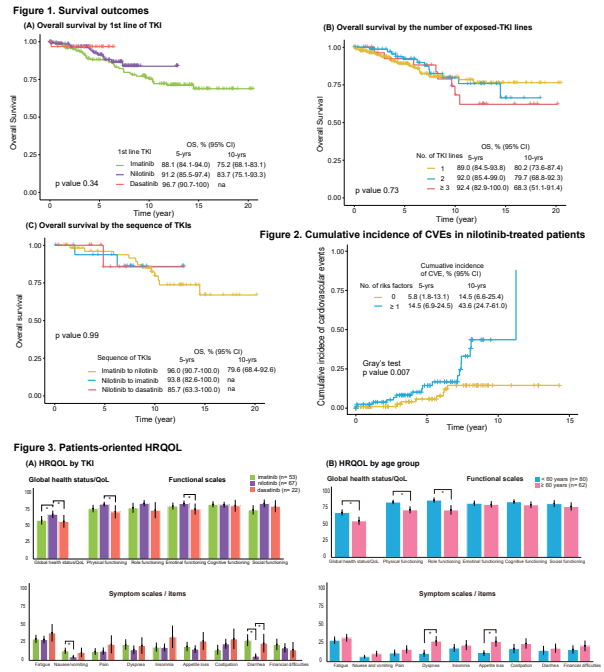
Background: An attempt to suspend treatment with tyrosine kinase inhibitors (TKIs) in patients with chronic myeloid leukemia (CML) who sustained deep molecular response was found to be feasible. However, half of the patients experienced molecular relapse after TKI suspension. Hence, lifelong treatment with TKIs is still inevitable. In this study, we reviewed patients' long-term management of CML in a single center and analyzed survival outcomes and safety issues associated with treatment with TKIs. We also investigated health-related quality of life (HRQOL) of patients treated with TKIs.

Method: Medical records of patients diagnosed with CML at Kyungpook National University Hospital, South Korea, from 2000 to 2021 were reviewed. All patients exposed to at least one type of TKI were included in this study. The EORTC QLQ-C30 questionnaire was used to assess patient-oriented HRQOL.

Results: Among 345 patients with CML, 188 (54.5%), 125 (36.2%), and 32 (9.3%) initiated imatinib, nilotinib, and dasatinib, respectively, as first-line therapy. During the follow-up period, 113 (60.1%), 58 (46.4%), and 14 (43.8%) of patients treated with imatinib, nilotinib, and dasatinib, respectively, discontinued first-line therapy; the occurrence of adverse events was the primary cause of TKI discontinuation (18.1% imatinib, 14.4% in nilotinib, and 28.1% in dasatinib), followed by progression/refractory. The estimated 5-year overall survival rate did not differ according to the type of first-line TKI (p=0.34, 88.1% vs. 91.2% vs. 96.7% in imatinib vs. nilotinib vs. dasatinib). Overall, 106 patients (30.7%) were exposed to two or more lines of TKIs during the follow-up period. There were no survival differences according to the number of TKI lines the patients were exposed to (p= 0.73), and the sequences of TKIs used (p= 0.99). Among 182 nilotinib-treated patients regardless the order of treatment lines, 25 (13.7%) experienced cardiovascular events (CVEs). The cumulative incidence of CVEs increased as the duration of nilotinib administration increased. Notably, patients with at least one cardiovascular (CV) risk factor, including hypertension, diabetes, dyslipidemia, smoking, and previous CV history, showed a higher risk of CVEs than those without CV risk factors. At 10 years of treatment with nilotinib, 43.6% of patients with CV risk factors were expected to have CVEs versus 14.5% of patients without CV risk factors. Dasatinib-associated pleural effusion (PE) was noted in 25 (32.1%) of all 78 dasatinib-treated patients. Ten patients (12.8%) discontinued dasatinib because of PE intolerance. Overall, 142 patients responded to a questionnaire regarding HRQOL. Patients treated with nilotinib had overall better HRQOL outcomes. Statistical significance was verified for global health status/QOL, physical functioning, emotional functioning, nausea/vomiting, and diarrhea. When analyzed by age group, patients aged <60 years reported better HRQOL scores for all items.

Conclusion: Overall survival outcomes did not differ according to the choice of first-line TKI, number of TKI lines that patients were exposed to, and sequence of TKIs used. Nilotinib was identified as the most favorable in patient-oriented HRQOL; however, safety issues regarding CVEs should be cautiously monitored in patients with CV risk factors if lifelong treatment is inevitable.

Keyword: Chronic myeloid leukemia, Tyrosine kinase inhibitors, Safety, Health-related quality of life



PP04-03

Long-term outcomes of tyrosine kinase inhibitor discontinuation in chronic myeloid leukemia patients in real-world clinical practice

Chang-Hoon Lee[1], So-Yeon Jeon[1], Ho-Young Yhim[1], Jeong-A Kim[2] and Jae-Yong Kwak[1*]

[1] Department of Internal Medicine, Jeonbuk National University Hospital, Korea

[2] Hemato-oncology, St. Vincent Hospital, The Catholic University, Korea

Background: After tyrosine kinase inhibitors (TKI) were introduced to chronic myeloid leukemia (CML) treatment, CML has become a well-controlled and life-long disease. In addition, as the duration of TKI administration increases, the demand for TKI discontinuation is also increasing. Although several studies on TKI discontinuation have already been conducted, most of them were prospective and company-sponsored. We aimed to investigate the long term outcomes of TKI discontinuation based on the patient's needs and the physician's judgment rather than a clinical trial.

Method: We collected chronic phase CML patients who discontinued TKI after achieving undetectable minimal residual disease (UMRD) between January 2009 and December 2021. We excluded patients treated with other treatment before frontline TKI therapy or received allogenic stem-cell transplantation after TKI therapy.

Results: Twenty eight patients (17 female, 11 male) was included. Twenty seven patients (96.4%) were treated with imatinib and 1 patient (3.6%) was treated with dasatinib. After TKI discontinuation, 50% of the patients lost UMRD after median 7 months. Among them, UMRD was persisted in 3 (10.7%) and 2 (7.1) at 8 and 10 years, respectively. Molecular relapse was confirmed in 23 patients. One patient who had received dasatinib was administered with ponatinib, three patients who had received imatinib were switched to dasatinib, and sixteen patients were re-administered with imatinib. Median time to achieve UMRD after second administration of TKI was 5.8 months (range 0.9~17.0). Two patients who lost UMRD after 2018 remain in major molecular response (MMR) and are followed without TKI re-administration. Second TKI discontinuation was attempted in six patients and UMRD persisted in 3 patients at 3 years and 1 patient at 8 years, respectively. We analyzed the prognostic factors related to molecular relapse-free survival, but there was no statistical significance.

Conclusion: These findings suggest that TKI discontinuation in patient who achieved UMRD after TKI treatment is safe and results in favorable long-term outcomes, as well. Considering that there was no statistical significance between the prognostic factors and the duration of molecular relapse-free survival, we suggest TKI discontinuation can be considered even in high-risk patients who achieve long-term UMRD.

Keyword: Chronic myeloid leukemia, Tyrosine kinase inhibitor discontinuation

Clinical characteristics	Total (n=28)	
UMRD status after 1st discontinuation of TKI		
UMRD ≥ 4 years	6 (21.4 %)	
UMRD ≥ 8 years	3 (10.7 %)	
UMRD ≥ 10 years	2 (7.1 %)	
Time to UMRD after 2nd administration of TKI	5.8 (0.9~17)	
UMRD status after 2nd discontinuation of TKI		
UMRD (≥ 3 years)	3	
UMRD (≥ 8 years)	1	
Variables	Duration of UMRD	P value
Age at TKI discontinuation		
< 51.5	32.3 (±10.3)	0.480
≥ 51.5	21.6 (±10.8)	
Sex		
Male	40.1(±15.1)	0.213
Female	18.4 (±7.0)	
Sokal score at diagnosis		
Low to intermediate	35.1 (±10.3)	0.093
High	12.4 (±7.9)	
Duration of TKI before TKI discontinuation (Median 70.3 months; range 26.6-171.0)		
< 70.3 (months)	23.6 (±8.1)	0.659
≥ 70.3 (months)	17.2 (±12.7)	
Time to UMRD (Median 16.8 months; range 4.1-72.9)		
< 16.8 (months)	45.7 (±13.2)	0.081
≥ 16.8 (months)	15.3 (±9.9)	
Duration of UMRD before TKI discontinuation (Median 44.2 months; range 8.0-122.0)		
< 44.2 (months)	22.5 (±8.3)	0.554
≥ 44.2 (months)	31.5 (±12.5)	

PP04-05

Clinical and hematological profile of chronic myeloid leukemia in sub-Himalayan region

Rajeev Sandal, Pravesh Dhiman*, Manish Gupta, Sunil Sharma, Vikas Fotedar, Sidharth Vats and Purnima Thakur

Department of radiotherapy and oncology, Indira Gandhi Medical College, India

Background: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the fusion of BCR and ABL1 gene forming fusion gene. It leads to dysregulated and uncontrolled proliferation of granulocytes. We studied the clinical and hematological parameters of patients with chronic myeloid leukemia who presented at the tertiary cancer center, Indira Gandhi Medical College Shimla Himachal Pradesh (IGMC, Shimla).

Method: We retrospectively analyzed data of patients with newly diagnosed chronic myeloid leukemia who were registered in regional cancer center IGMC Shimla from 2014 to 2019. Demographic data including age, place, gender, occupation and socioeconomic status of patients were recorded. Detailed history including duration of symptoms, any bleeding manifestations, and baseline spleen size (below costal margin) was analyzed. The baseline investigations included complete blood counts, biochemistries, and bone marrow examination. CML was diagnosed by morphology and demonstration of the Philadelphia chromosome, or by the demonstration of the BCR-ABL transcript. EUTOS score was calculated for every patient. All patients in the chronic phase were started on tablet imatinib 400 mg once daily after confirmation of diagnosis. Adverse events during therapy were also analyzed.

Results: Out of fifty-one (n=51) patients, thirty-seven were male and fourteen were female (M: F, 2.6:1). The median age of the studied population was 44.5 years (range 15-68 years) and 45.1 % of patients (n= 37) were between the age of 31 years to 60 years. 15.7% and 11.8 % of patients were less than thirty and more than 60 years of age respectively. 49 % of patients (n=25) presented with abdomen discomfort or left upper quadrant pain. Two patients (3.9%) were asymptomatic at the time of diagnosis. Other presenting symptoms were fatigue (19.6%, n=10), shortness of breath (17.6 %, n=9) and lymphadenopathy (3.9 %, n=2). Splenomegaly was seen in 76.5% of studies population (n=39) at the time of presentation. The median spleen size was 8 cm below the left costal margin (range 0 - 15 cm). Median Hb was 10.5 g/dl (range, 6.3-15.2g/dl) and median TLC was 81450/ul (range, 34000-332000/ul) of studies cohort. 76.5 % of patients (n=39) were in the chronic phase at the time of diagnosis. 15.7% (n=8) and 7.8% (n=4) of patients were accelerated and blast phase at time presentation.

Conclusion: We concluded that most of the patients were younger age group in our cohort. Abdomen discomfort was the most common presenting symptom. Massive splenomegaly was the most common physical finding on examination. Most of the patients presented with anemia along with high TLC. Three fourth of patients were in the chronic phase at the time of presentation.

PP04-06

Discontinuation of tyrosine kinase inhibitors based on BCR-ABL1 monitoring by digital droplet PCR in pediatric chronic myeloid leukemia

Seongkoo Kim [1], Yeojae Kim [2], Jong Mi Lee[2,3], Ari Ahn[2,3], Jae Won Yoo[1], Jae Wook Lee[1], Bin Cho[1], Nack-Gyun Chung[1], Yonggoo Kim[2,3], Myungshin Kim[2,3]

[1] Division Hematology/Oncology, Department of Pediatrics, The Catholic University of Korea, Seoul, Korea

[2] Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

[3] Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea

Background: Tyrosine kinase inhibitors (TKIs) are the cornerstone of successful clinical management of chronic myeloid leukemia (CML) patients. Since the introduction of TKIs to the treatment strategy in CML, the prognosis has considerably improved not only in adult patients but also in children. However, lifelong treatment for children treated with TKI may influence their growth and development. For these reasons, clinical trials have explored the feasibility of TKI discontinuation in children with a sufficient TKI response. The international guidelines propose discontinuation of TKI in selected patients throughout the careful monitoring of molecular responses (MR) of each patient using highly sensitive methods with at least BCR-ABL1 MR 4.5 and ≤0.0032% on International Scale (IS). In this study, we quantified BCR-ABL1 using reverse transcription quantitative polymerase chain reaction (RT-qPCR) and digital droplet PCR (ddPCR) and investigated whether they could be used to determine TKI discontinuation for pediatric CML patients in clinical setting.

Method: Forty-two pediatric CML patients were enrolled. Among the consecutive cohorts, 31 patients were in chronic phase (74%), 6 in accelerated phase (14%) and 5 in blast phase (12%) at diagnosis. Patients were treated with first-line TKIs including imatinib (n=27, 64%) and dasatinib (n=12, 29%). Three patients started with imatinib were switched into dasatinib. Analytical performance of ddPCR by QXDx™ BCR-ABL %IS Kit (Bio-Rad Laboratories, USA) was evaluated using certified reference materials (CRM) for BCR-ABL1 and clinical sample preparations. In addition, BCR-ABL1 and ABL1 transcript copy numbers were quantified in a total of 104 samples using RT-qPCR and ddPCR and the results were compared. Seven patients met the criteria for TKI stopping and were attempted to discontinue TKI. After discontinuation, BCR-ABL1 was carefully monitoring using both RT-qPCR and ddPCR.

Results: ddPCR showed excellent analytical performance of sensitivity with 0.001% IS and linearity with $R^2 > 0.99$ in log scale, range from 0.01 to 10%. In clinical samples, ddPCR results of BCR-ABL1 (% IS) were well correlated with those from RT-qPCR ($R^2 = 0.9435$). Interestingly, we found 39 samples with ddPCR positive but RT-qPCR negative result. In contrast, only 2 samples were negative in ddPCR but positive in RT-qPCR. Among 37 samples which were both ddPCR and RT-qPCR positive results, 29 samples showed higher ddPCR levels than RT-qPCR, while 8 samples did higher RT-qPCR levels than ddPCR. Among patients with TKI discontinuation, we observed complete MR and major MR in two and three patients, respectively. Two patients experienced loss of MMR, restart TKI and achieved

MMR and CMR afterward.

Conclusion: Results from this study demonstrated that ddPCR was highly sensitive and appropriate method to monitor BCR-ABL1 with less than 4.0 MR compared to RT-dPCR. ddPCR also could be useful to determine TKI discontinuation and to monitor BCR-ABL1 after TKI discontinuation in pediatric CML patients.

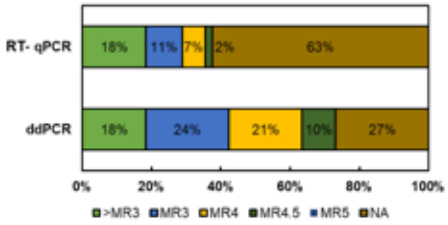


Figure 1. Distribution of molecular response (MR) classes by reverse transcription quantitative polymerase chain reaction (RT-qPCR) and digital droplet PCR (ddPCR).

PP05-01

Productivity of 18F-FDG-PET/CT diagnostic tool in the management of pediatric lymphoblastic lymphoma

Ahmed Abdelsalam

Pediatric Hematology/Oncology, Children's Cancer Hospital Egypt (CCHE 57357)., Pediatric Hematology/Oncology Consultant, Egypt

Background: Lymphoblastic lymphoma (LL) comprises approximately 20% of childhood non-Hodgkin lymphoma (NHL). 18F-FDG-PET/CT is emerging as a potential noninvasive diagnostic modality for lymphoma including NHL. However, few studies had investigated the role of 18F-FDG-PET/CT in pediatric LL patients

Method: A prospective study enrolled on biopsy proven newly diagnosed pediatric LL patients presenting in Children
Cancer Hospital Egypt (CCHE) during the period from October 2016 to October 2018. 18F-FDG-PET/CT was done initially before therapy and after induction of chemotherapy in all patients. The patients were followed until end of April 2020 (mean23.5 months).

Results: Eighteen patients were included (14 males and 4 females; median age, 13 years), 11 had T-cell (61.1%) while 7 had B-cell Lymphoblastic Lymphoma (38.9%). All lymphoma involvement lesions (n=43) were FDG avid and the intensity of nodal FDG uptake was variable. Two patients (11%) had bone marrow (BM) involvement by < 25% blast cells with corresponding positive BM focal uptake in 18F-FDG-PET/CT (SUVmax= 4 and 4.5). There was non-significant correlation between SUVmax of involved lesions and both tumor Size (p= 0.161) and LDH level (p= 0.172). Evaluation post induction phase, CT detected 8 residual lesions in 8 patients (44.4%), while 18F-FDG-PET/CT detected only 3 Deauville-positive residual lesions in 3 patients (16.6%). No intensification of therapy was done in all post-induction positive patients. Repeated 18F-FDG-PET/CT at week 18 for post-induction patients, revealed cleared all Deauville positive residual lesions. On the other hand, repeated CT at week 18 detected regression but still residual in 4/8 (50%) post-induction CT lesions with clearance of the rest (50%). We found the specificity of post-induction 18F-FDGPET/CT was 81% while the negative predictive value was 87% compared to 50% and 80% for post-induction CT respectively.

Conclusion: In initial staging, 18F-FDG-PET/CT is a useful tool for disease extent evaluation of pediatric LL. Moreover, it could provide a diagnostic hint for BM involvement. 18F-FDG-PET/CT done after induction therapy has a good negative predictive value with higher specificity than CT alone but it not an indication for treatment intensification due to false positive results.

Keyword: 18F-FDG-PET/CT; CCHE.; Pediatric lymphoblastic lymphoma.

Pt.	Response to induction				Evaluation at Week 18		Relapse/Progression	Follow up duration (months)	Fate
	CT and BMB	FDG-PET	IRC	Deauville Score	FDG-PET	CT			
1	CR	Negative	CR	0	–	–	No	37	A
2	PR	Positive	PR	4	Negative	Positive	No	15	A
3	CR	Negative	CR	0	–	–	No	30	A
4	CR	Negative	CR	0	–	–	No	21	D
5	PR	Positive	PR	4	Negative	Negative	No	29	A
6	CR	Negative	CR	0	–	–	No	18	D
7	PR	Negative	CRu	0	–	Positive	No	25	D
8	CR	Negative	CR	0	–	–	No	24	A
9	PR	Negative	CRu	0	–	Negative	No	17	A
10	CR	Negative	CR	0	–	–	No	18	A
11	CR	Negative	CR	0	–	–	No	18	A
12	CR	Negative	CR	0	–	–	No	16	A
13	PR	Negative	CRu	2	–	Positive	No	24	A
14	PR	Negative	CRu	2	–	Negative	No	28	A
15	CR	Negative	CR	0	–	–	No	31	A
16	PR	Positive	PR	4	Negative	Positive	No	31	A
17	PR	Negative	CRu	0	–	Negative	No	17	A
18	CR	Negative	CR	0	–	–	No	24	A

CT: Computed Tomography; FDG-PET: Fluorodeoxyglucose Positron Emission Tomography; BMB: Bone Marrow Biopsy; IRC: International Response Criteria; CR: Complete Remission; PR: Partial Response; CRu: Complete Remission Uncertain; A: Alive; D: Dead

PP05-03

A case of primary effusion lymphoma

Dawpadee Dharmasena*, Sanka Vijayabandara and Champika Bodinayake

Teaching Hospital, Karapitiya, Galle, Sri Lanka

Background: Primary effusion lymphoma (PEL) is a B-cell lymphoma, presenting with a malignant effusion without a tumor mass. It was formerly known as body cavity–based lymphoma, as it affects serous body cavities; pleural, pericardial, peritoneal and results in recurrent lymphomatous effusions. By definition no discrete, contiguous lymphomatous mass associated with the effusion. PEL most commonly arises in patients with underlying immunodeficiency, such as AIDS. It is usually associated with Kaposi's sarcoma and Human Herpes Virus-8 infection (HHV-8). The condition can exist in the absence of HHV-8 and HIV, though this is rare. These are mostly elderly individuals. The advanced age of these individuals may represent a source of immunodeficiency. We report a case of primary effusion lymphoma in a HIV negative individual who was on long term steroids for Addison's disease.

Method: Case Report

Results: A 75 year old male, with Addison's disease, admitted with anorexia, generalized malaise for one month and low grade fever, dyspnoea on moderate exertion, intermittent stabbing type central chest pain for one week duration. Addison's disease was diagnosed one year back and, he had been on oral hydrocortisone and fluodrocortisone with good drug compliance. Examination revealed thin built, hyperpigmented patient without pallor or icterus. There was no lymphadenopathy anywhere. He was tachycardic (PR-108b.p.m) and blood pressure was 110/60 mmHg without postural drop. Jugular venous pressure was elevated and heart sounds were muffled. There was dull percussion note and absent breath sounds over left lower chest. No organomegaly or ascites was found on abdominal examination. Initial investigations revealed, an ECG with small QRS complexes without electrical alterans or ischaemic changes, a large globular cardiac silhouette on chest radiograph. 2D Echocardiogram showed large pericardial effusion measuring 23mm causing right atrial collapse. Complete blood count and blood picture were normal whereas inflammatory markers were elevated with ESR of 72mm and CRP of 26mg/L. Renal and liver functions were normal. Pericardiocentesis was carried out and 550cc haemorrhagic fluid aspirated. Pericardial fluid full analysis showed lymphocytic exudate (Protein: 35g/l, Glucose: 102mg/dl, Polymorphs 02/cumm, Lymphocytes 05/cumm , Red cells 2465/cumm) and few malignant cells with possible differential diagnoses for morphology being large cell lymphoma (NHL) or Germinoma (Mediastinal seminoma). Further investigations with contrast enhanced CT Chest Abdomen and Pelvis revealed pericardial effusion; however, no enlarged lymph nodes, intrabdominal organomegaly or other malignancy were identified. A pericardial biopsy was performed along with immune staining which revealed high grade Non-Hodgkin's lymphoma (large B cell lymphoma) arising primarily as an effusion from pericardium. Then, the patient was referred to oncology for further management.

Conclusion: The significance in this case of primary effusion lymphoma is, our patient was HIV negative and diagnosed Addison's disease on steroid replacement. Anyway advanced age and being on steroids for long duration could be the risk factors. There are reported cases of lymphomas (Non-Hodgkin's lymphoma) in Addison's disease patients who were on long term corticosteroids, and considered that steroid-induced abnormal immune state as the pathological basis for their unusual complications.

Keyword: Primary effusion lymphoma, Pericardial effusion

PP05-04

Bone marrow infiltration in non-hodgkin lymphoma: 18F-FDG PET/CT versus bone marrow aspiration biopsy

Manas Kumar Sahoo[1*], Smeeta G[2], Bhawna Jha[3] and Nagender Sharma[4]

[1] Nuclear Medicine, Medanta-the Medicity, Gurgaon, Senior Consultant, India

[2] Laboratory Oncology, All India Institute of Medical Sciences, New Delhi, Assistant Professor, India

[3] Hematopathology, Medanta-the Medicity, Gurgaon, Senior Consultant, India

[4] Medical & HematoOncology, Medanta-the Medicity, Gurgaon, Consultant, India

Background: Evaluation of bone marrow infiltration (BMI) plays a crucial role in the staging as well as prognosis of lymphoma. Bone marrow aspiration/biopsy (BMAB) is considered to be the gold standard modality for evaluation of BMI. BMAB is also helpful in detecting unsuspected lymphoma; however, it has few limitations such as inadequate sampling or focal marrow involvement. 18F-fluoro-2-deoxy-D-glucose positron emission tomography /computed tomography (18F-FDG PET/CT) has been proved to be an excellent non-invasive diagnostic tool for whole body assessment including BMI in lymphoma staging work up. However, in the era of PET/CT, BMB is an alternative or complementary or superior to PET/CT is still a topic of debate and is still under investigation. Herein, we compare the utility of BMAB and 18F-FDG PET/CT in detection of BMI in patients with Non-Hodgkin lymphoma (NHL) and highlights the limitations as well as advantages of both the modalities.

Method: This was a retrospective study of patients with histologically confirmed NHL, who underwent pre-treatment FDG PET/CT and BMB for staging which was performed simultaneously (time interval in both the procedure < 30days). All information was collected from the Hospital Information System (HIS) where all information pertaining to each patient is meticulously available since the time of registration.

Results: Total 362 patients of histology proven NHL (age range: 02-86 yrs), who underwent bone marrow biopsy and PET/CT for staging were evaluated. Male: female ratio was 2:1 (M= 240; F=122). Out of 362, 318 were B-cell and 44 cases were T cell NHL. B-NHL group included diffuse large B cell lymphoma(211), marginal zone lymphoma (25), follicular lymphoma(24), mantle cell lymphoma (20), T cell rich B cell lymphoma (17), Burkitt's lymphoma (12), lymphoblastic lymphoma(4), small cell lymphoma (4) and MALT lymphoma (1) patients.

Out of 318 B cell NHL patients, 137 (43.6%) patients showed BMI either by PET/CT or BMAB, 109 by PET/CT, 110 cases by BMAB and 81 cases by both the modalities. Out of 44 T cell NHL patients, 23 (52%) patients showed BMI either by PET/CT or BMAB, 19 by PET/CT, 12 by BMAB and 8 cases by both the modalities. PPV & NPV of PET/CT is higher than BMAB in T-cell NHL (82% & 84% vs 52% & 65) with p value <0.001 but in B-cell NHL group, PPV &NPV of both the modalities are similar (79 % & 86% vs 80% & 87%). However in low-grade B-NHL, PPV & NPV of BMAB is higher than PET/CT. Splenomegaly, anaemia and high LDH values were more common in BMI cases than non-involved cases ($p<0.05$). Difference in median TLC and platelet count in bone marrow involved and not involved group were not found to be statistically significant.

Conclusion: 18F-PET/CT is a valuable diagnostic tool for detection of focal BMI in non-Hodgkin lymphoma patients. In case of High Grade -NHL, BMAB may be avoided in PET/CT negative and focal/multifocal positive cases and should be performed in case of diffuse/focal low borderline marrow uptake in PET/CT. However, in Low Grade-NHL, BMAB should be mandatory as PET/CT shows lower accuracy in detecting BMI. In lymphoma patients associated severe anaemia PET/CT poses an evaluation challenge due to high marrow uptake and BMAB should always be performed. Additionally, in synchronous malignancy involving bone marrow, BMAB can detect marrow involvement which PET/CT cannot differentiate.

Keyword: 18F-PET/CT, Bone Marrow aspiration biopsy, Non-Hodgkin lymphoma

PP05-05

Diabetic foot ulcer as a manifestation of T-cell lymphoma: a case report

Jumria Tandi Panggalo[1] and Riswan Arisandi[2]

[1] Resident Internal Medicine, Internal Medicine Department, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia

[2] Division of Hematology and Oncology, Internal Medicine Department, Faculty Of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia

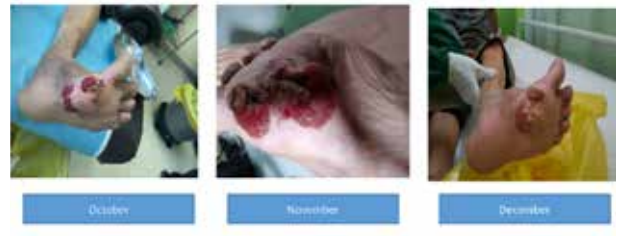
Background: Many studies reported Diabetic Foot Ulcers (DFUs) as an early manifestation of skin malignancy. It is not easy to distinguish between diabetic chronic ulcers and skin malignancies such as squamocellular or spinocellular carcinoma and melanoma. These malignancies has been reported as differential diagnosis for non-healing DFU. Cutaneus T-cell lymphoma (CTCL) is one of rare cases in heterogeneous group of lymphoma. This case reported diabetic foot ulcer as an early manifestation of T-Cell Lymphoma. Objective: To report a case of diabetic foot ulcer with T-Cell Lymphoma

Method: A 54-year-old man initially presented with left diabetic foot ulcer. Patient had large red-colored ulcer plantar, intensively vascularized and partially covered with hyperkeratosis ulcer that easily bled. After 4 weeks optimal standard treatment, due to deteriorating wound, reassessment is conducted and skin incisional biopsy was performed, the result was lymphoma maligna. Immunohistochemistry examination revealed strong positive sign of CD45 and CD3 marker. Patient was treated with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) and will receive consolidation external radiation therapy.

Results: Foot complications is increasing in Diabetes Mellitus and is associated with high morbidity and mortality. Foot ulcers present in more than 5% in diabetic patients and the cumulative incidence in lifetime is 25%. Higher prevalence of lymphoma maligna related to diabetes is reported. Misdiagnosing cutaneus lymphoma in plantar foot ulcers cases is common in diabetic patient due to diabetic neuropathy. If the wound doesn't show desirable improvement after 4 weeks optimal standard treatment, reassesment for malignancy should be done. Tissue biopsy is important to narrow down diagnosis in wound case with atypical or uncommon characteristic. This case elucidates the fact that foot ulcer in diabetic patients can be the early manifestation of T cell lymphoma.

Conclusion: This case reported diabetic foot ulcer as an early manifestation of T-Cell Lymphoma, also reiterates the importance of comprehensive foot examination.

Keyword: Diabetic foot ulcer, T-cell lymphoma, Diabetes mellitus



PP05-06

Flow cytometry V/S BM aspirate V/S BM biopsy as a screening tool for detection of marrow involvement by lymphoma: study at a tertiary cancer hospital

Garima jain[1*], Chandan kumar[2], Pranay Tanwar[2] and Amar Ranjan[2]

[1] Pathology, National Institute of Pathology-ICMR, India

[2] Laboratory Oncology, AIIMS, New Delhi, India

Background: The most common extra nodal site of involvement in lymphoid malignancies is Bone Marrow. However, the frequency of its involvement varies among different lymphoma subtypes. (1). Routine staging in Non-Hodgkin's Lymphomas thus includes evaluation of bone marrow involvement as this serves important information affecting both prognosis and treatment. (2) Bone marrow biopsies are also routinely performed in post treatment assessment of Non-Hodgkin Lymphoma. Flow cytometric immunophenotypic analysis is long known essential technique for the diagnosis and classification of many hematologic disorders. Besides leukemia, FCM also has a key role in staging of Non-Hodgkin's Lymphoma by assessing bone marrow for involvement or by detecting relapse. FCM on peripheral blood smear also serves as an excellent screening tool for detecting leukemic presentation of lymphoma and thus guide in prognostication, risk stratification and treatment plan. The utility of flow cytometric analysis in routine staging of NHL has been evaluated by previous studies (4), however sufficient data and standardization protocols are lacking.

Method: 159 flow cytometry samples of bone marrow aspirates/ PBS, and 427 BMA slides were received for staging or diagnosis of lymphoma over a period of 1 year between 1st February 2018 to 28 February 2019 at Laboratory Oncology Unit, Dr B.R.A.I.R.C.H, AIIMS, New Delhi.

Results: BMA morphology V/S FCM -66 bone marrow aspirate flow was run and results were concordant with morphological assessment in 87.8 % (58/66 cases). Results between morphological assessment of bone marrow aspirate and flow cytometry were discordant in 12.1% (8/66). PBS morphology V/S FCM 88 PB samples were evaluated by flow cytometry and results were concordant with morphological assessment of peripheral blood in 97.8 % (86/88) cases. Discordance was seen in 2 cases BMBx v/s FCM Among 66 FCM samples results were concordant in 56 /66 (84.84%) and discordant in 15.15%. 8 cases were picked up on FCM and were negative on BMBx whereas in 2 cases FCM was unable to pick up cells.BMA v/s BMBx Results were disconcordant in 87/372 (23.3%) with 17 cases being positive on aspirate and negative on biopsy and 72 cases positive on biopsy and negative on BMA.

Conclusion: We would like to conclude that flow cytometry, BMA and BMB are all useful methods for assessing bone marrow in NHL staging with each complementing the other. Although BMA and FC are not a substitute for BMB, they do play an important and complementary role in detecting a small portion of lymphoma cells in small subsets of patient as FC enables more specific gating of abnormal populations

Keyword: Lymphoma, Flow cytometry, Bone marrow aspirate, Staging

PP05-07

A retrospective analysis of the efficacy of low-dose metronomic cyclophosphamide for treatment in patients with low grade non-hodgkin lymphoma

Boram Han, Bum Jun Kim, Ho Young Kim, Dae Young Zang and Hyo Jung Kim*

Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University Medical Center, Korea

Background: Low-dose metronomic cyclophosphamide chemotherapy is an emerging strategy offering a potentially less toxic yet effective treatment modality. We evaluated the efficacy and safety of low-dose metronomic cyclophosphamide in patients with low grade non-Hodgkin lymphoma (NHL) by retrospectively reviewing the data.

Method: The patients received oral cyclophosphamide (50 mg per day) and/or oral methotrexate (2.5 mg twice weekly) until disease progression or unacceptable toxicity was noted.

Results: Of the 36 patients, 17 (47.2%) were male, median age was 66.4 years (range, 37-91 years), and subtypes of NHL were mucosa associated lymphoid tissue lymphoma (55.6%), small lymphocytic lymphoma (13.9%), follicular lymphoma (11.1%), mantle cell lymphoma (8.3%), nodal marginal zone lymphoma (4.5%), splenic marginal zone lymphoma (2.8%), and lymphoplasmacytic lymphoma (2.8%). The stage I, II, III, IV were 38.9%, 13.9%, 11.1%, 36.1%, respectively and 55.6% of patients received this regimen as the first-line treatment, mainly due to frailty, refusal to standard chemotherapy. The overall best response rate (ORR) was 73.5% (12 complete responses, CRs and 13 partial responses, PRs), with 29.1 months of the median duration of response and the disease control rate was 88.2%. The median treatment duration was 8.8 months (range, 0.1-38.4 months); the median progression-free survival

(PFS) was 43.5 months, and the median overall survival (OS) was not yet reached. Especially, the ORR in patients who were treated with metronomic cyclophosphamide as the first line treatment and as more than the second line treatment were 78.9% (10 CRs, 5 PRs) and 66.6% (2 CRs, 9 PRs), respectively. The median PFS were not reached in the first line cyclophosphamide treatment group and 26.5 months (range, 5.7-47.2 months) in the other group (p=0.110), and similarly, the median OS were not reached and 64.4 months (0-135.7 months) (p=0.058), respectively. The regimen was generally well tolerated, with small numbers of grade 3-4 toxicities; neutropenia (2%), anemia (3%), thrombocytopenia (3%), fatigue (4%), and anorexia (1%).

Conclusion: We concluded that low-dose metronomic cyclophosphamide represents efficacious and well-tolerated treatment for low-grade NHL patients.

Keyword: Low-grade non-Hodgkin lymphoma, Metronomic chemotherapy, Cyclophosphamide

PP05-08

The endothelial activation and stress index (EASIX) score is an independent prognostic factor in patients with diffuse large B cell lymphoma

Sungwoo Park[1], Gyeong-Won Lee[1*] and Seil Go[2]

[1] Division of Hematology and Oncology, Department of Internal Medicine, Gyeong-Sang National University Hospital, Gyeongsang National University School of Medicine, Korea

[2] Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Institute of Health Sciences, College of Medicine, Gyeongsang National University, Korea

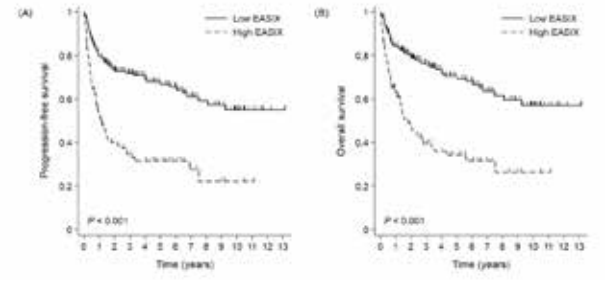
Background: The endothelial Activation and Stress Index (EASIX) score has been reported to predict overall survival (OS) in hematologic cancers. However, it has not been validated as a prognostic marker for diffuse large B cell lymphoma (DLBCL) to date.

Method: Between Jan 07, 2004 and March 05, 2020, the record of 265 patients with DLBCL in the Republic of Korea were retrospectively reviewed. The EASIX was calculated using complete blood count differential data. Serum lactate dehydrogenase (LDH), creatinine, and platelet count at diagnosis were measured in all included patients. EASIX scores were calculated using the formula-LDH (U/L) × Creatinine (mg/dL) / platelet count (109/L).

Results: The median age of patients was 64 years. The optimal EASIX cut-off value according to receiver operating characteristic analysis of overall survival (OS) was 1.33. All patients were treated with cyclophosphamide, doxorubicin, vincristine and prednisone combined with rituximab. The 1 year OS and PFS rate was lower in the high EASIX group compared to the low EASIX group, respectively (63.8 % vs 84.4 %; $p < 0.001$ and 54.0 % vs 79.6 %; $p < 0.001$, respectively). A high EASIX was an independent poor prognostic factor for OS and PFS (hazard ratio 1.61, 95% CI 1.077–2.395; $p = 0.020$ and hazard ratio 1.621, 95% CI 1.066–2.464; $p = 0.024$).

Conclusion: The EASIX is a readily available and cheaply obtained parameter in clinical studies, and shows considerable potential as a new prognostic marker for patients with newly diagnosed DLBCL.

Keyword: Diffuse large B cell lymphoma, Endothelial activation and stress index, Prognostic factor



PP05-09

CC-95251, a novel anti- SIRPα antibody, enhances phagocytosis of non-hodgkin lymphoma (NHL) cells when combined with rituximab

Henry Chan[1*], Christina Trout[2], David Mikolon[1], Preston Adams[1], Roberto Guzman[3], Gustavo Fenalti[4], Konstantinos Mavrommatis[5], Mahan Abbasian[6], Lawrence Dearth[1], Brian Fox[7], Pallavur Sivakumar[8] and Kandasamy Hariharan[1]

[1] Discovery Biotherapeutics, Bristol Myers Squibb, USA

[2] Formerly Research and Early Development Alliances, Bristol Myers Squibb, USA

[3] Exploratory Toxicology, Bristol Myers Squibb, USA

[4] Department of Crystallography, Bristol Myers Squibb, USA

[5] Computational Genomics, Bristol Myers Squibb, USA

[6] Formerly Discovery Biotherapeutics, Bristol Myers Squibb, USA

[7] Informatics and Predictive Sciences, Bristol Myers Squibb, USA

[8] Immuno-oncology and Cell Therapy Discovery, Bristol Myers Squibb, USA

Background: Signal regulatory protein-α (SIRPα) on macrophages (MPs) binds to CD47, a cell-surface ligand overexpressed in various types of NHL, and induces an anti-phagocytic signal enabling tumor cells to evade immune response. MP antitumor activity can be restored by simultaneously blocking the CD47–SIRPα signaling axis and inducing a pro-phagocytic signal with the use of rituximab (ritux). We report on CC-95251 and its preclinical activity in combination with ritux in CD20+ diffuse large B-cell lymphoma (DLBCL) cell lines.

Method: Approximately 10^{10} human IgG antibodies were screened using a yeast display platform, and the top candidates were characterized by Bio-Layer Interferometry (BLI) for SIRPα polymorphic variant binding. Surface plasmon resonance assays were performed to measure the ability of CC-95251 to block the CD47–SIRPα axis. SIRPα–CC-95251 Fab complex crystal structure was examined to define its epitope and structural basis for CD47–SIRPα disruption. Antitumor effects of CC-95251 + ritux were studied in co-culture phagocytosis assays of MPs and CD20+ DLBCL cell lines. CC-95251 binding to monocytes was confirmed through flow cytometry of peripheral blood mononuclear cells from healthy donors and cynomolgus monkeys. Pharmacokinetics and hematologic effects were analyzed in cynomolgus monkeys after treatment with CC-95251.

Results: CC-95251 was selected as the lead monoclonal antibody, with high binding affinity across the 6 most prevalent SIRPα human haplotypes. CC-95251 potently blocked CD47–SIRPα binding in a dose-dependent manner, with 100 nM inhibiting CD47 binding almost completely. Co-crystallization modeling showed that CC-95251 engages SIRPα in a region overlapping the CD47 binding site. Robust MP infiltration and CD47–SIRPα expression confirmed DLBCL as a suitable tumor type for CC-95251 treatment. Co-cultures of donor MPs and several DLBCL cell lines showed that CC-95251 monotherapy had overall limited effects on phagocytic MP levels. When combined with ritux, the levels of phagocytic MPs were markedly increased in a CC-95251 dose-dependent manner, demonstrating an enhanced antitumor effect of the combination in DLBCL cell lines. CC-95251 bound mainly to cells of myeloid origin, with little to no binding to cells of lymphoid origin. Toxicology studies in cynomolgus monkeys showed safe IV delivery of CC-95251 at therapeutic doses, with no evidence of white blood cell, monocyte, lymphocyte, or red blood cell depletion.

Conclusion: CC-95251 blocks CD47–SIRPα binding and enhances MP phagocytic activity against DLBCL cell lines in co-culture models when combined with ritux. These results support the clinical evaluation of CC-95251 + ritux for NHL. A phase 1 study of CC-95251 for the treatment of hematologic malignancies is underway (NCT03783403).

Keyword: Molecular pharmacology, Lymphomas

PP05-10

First clinical study of the anti- SIRPα antibody CC-95251 combined with rituximab in patients with relapsed/refractory (R/R) non-hodgkin lymphoma (NHL)

Paolo Strati[1*], Eliza Hawkes[2], Nilanjan Ghosh[3], Joseph Tuscano[4], Quincy Chu[5], Mary Ann Anderson[6], Amar Patel[7], Michael R. Burgess[7], Kristen Hege[7], Sapna Chhagan[7], Sarandeep Boyanapalli[8], Tracey Day[7], Frank Shen[9], Jin-Seok Kim[10] and Amitkumar Mehta[11]

[1] MD Anderson Cancer Center, The University of Texas, USA
[2] Austin Health, Austin Hospital, Australia
[3] Lymphoma Program, Levine Cancer Institute, USA
[4] Hematology and Oncology, University of California, Davis, USA
[5] Oncology, Cross Cancer Institute, Canada
[6] Clinical Haematology, Peter MacCallum Cancer Centre, Australia
[7] Early Clinical Development, Hematology/Oncology & Cell Therapy, Bristol Myers Squibb, USA
[8] Clinical Pharmacology and Pharmacometrics, Bristol Myers Squibb, USA
[9] Biostatistics, Bristol Myers Squibb, USA
[10] Severance Hospital, Yonsei University, Korea
[11] Comprehensive Cancer Center, University of Alabama at Birmingham, USA

Background: Blocking the CD47–signal regulatory protein-alpha (SIRPα) anti-phagocytic signal enables macrophage-mediated phagocytosis of tumor cells. Agents targeting CD47 combined with rituximab (ritux) have demonstrated promising clinical activity in R/R NHL; however, the broad expression of CD47 leads to on-target, off-tumor toxicities, including hemolytic anemia. CC-95251 is a novel, fully human immunoglobulin G1 antibody (Ab) that binds to SIRPα on macrophages to potently block the CD47–SIRPα interaction. Here we report interim results from a phase 1 study evaluating CC-95251 + ritux in patients (pts) with R/R NHL.

Method: Primary objectives of this multicenter, open-label, phase 1, dose-escalation and -expansion study are to evaluate the safety and tolerability of escalating doses of CC-95251 + ritux and to define the maximum tolerated dose (MTD) and/or recommended phase 2 dose for the combination in pts with CD20+ R/R NHL (NCT03783403). Pts were treated in 28-day cycles (C) with CC-95251 administered via IV at 3, 10, or 20 mg/kg every week (QW) and with ritux 375 mg/m^2 on days (D) 1, 8, 15, and 22 of C1, D1 of C2–5, and D1 of every other cycle C6–24 until disease progression or unacceptable toxicity.

Results: As of 5 Aug 2021, 17 pts had received ≥ 1 dose of CC-95251 + ritux. Median age was 67 (range 30–84) years. Pts had received a

median of 3 (range 1–7) prior systemic therapies, with 100% of pts having a prior history of anti-CD20 Ab exposure. Enrolled tumor types included R/R diffuse large B-cell lymphoma in 13 (77%) pts, follicular lymphoma in 2 (12%), and mantle cell lymphoma and marginal zone lymphoma in 1 (6%) pt each. Twelve (71%) pts had disease refractory to any prior line of therapy (LOT), including 10 (59%) refractory to any anti-CD20 Ab-containing regimen, and 9 (53%) to their last LOT.

Pts received a median of 4 (range 1–14) cycles of CC-95251. Median duration of treatment was 16.4 (range 2.1–53.1) weeks. There was 1 CC-95251 dose reduction, and 6 (35%) pts experienced ≥ 1 treatment-emergent adverse event (TEAE) leading to CC-95251 dose interruption. MTD has not been reached. Most common TEAEs of any grade (Gr)/Gr ≥ 3 included neutropenia (71%/59%) and infection (59%/29%). Treatment-related AEs Gr ≥ 3 included neutropenia (53%) and infection (12%); no treatment-related anemia or deaths were reported. Overall response rate in the efficacy evaluable population was 56% (9/16), with 4 (25%) pts achieving a complete response (CR). Of 9 pts refractory to any prior anti-CD20 Ab-containing regimen, 2 pts achieved a CR and 2 pts had stable disease. Median time to response was 7.9 weeks. Duration of response ranged from 7.4–28.1 weeks with a CR ongoing in 1 pt.

In this dose escalation, CC-95251 demonstrated dose-proportional increases in exposure at doses > 3 mg/kg QW and full receptor occupancy at doses ≥ 3 mg/kg.

Conclusion: CC-95251 + ritux demonstrated a manageable safety profile and promising efficacy in pts with heavily pretreated CD20+ R/R NHL. The study is enrolling in the dose-expansion phase.

Keyword: Non-hodgkin lymphoma, Antibody therapy, Clinical trials, Immunotherapy

PP05-11

The clinical outcome of rituximab biosimilars versus rituximab originator with CHOP as first-line treatment for patients with DLBCL

Amitawan Maneenut and Kannadit Prayongratana*

Hematology unit, Department of medicine, Phramongkutklao hospital, Thailand

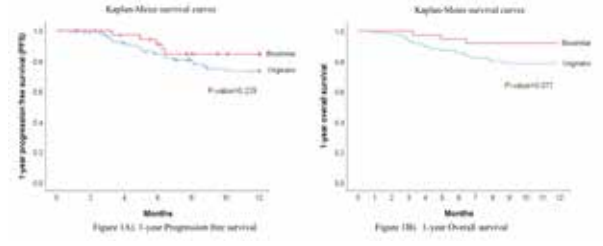
Background: Studies in patients with diffuse large B-cell lymphoma (DLBCL) have shown that rituximab biosimilars (Truxima®, Reddituxima®,Rixathon®) have equivalent or non-inferior efficacy and safety to rituximab originator (Mabthera®). We aimed to evaluated real-world efficacy and safety of rituximab biosimilars compared with originator rituximab in patients with newly-diagnosed DLBCL in Phramongkutklao hospital

Method: To evaluate efficacy and safety of rituximab biosimilars compared with rituximab originator in patients with newly-diagnosed DLBCL. We conducted a retrospective medical chart review of patients with newly-diagnosed DLBCL who received rituximab biosimilars or rituximab originator with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as first-line therapy, with 12 months follow-up after day 1, cycle 1. Primary outcome was overall response rate at the end of treatment compare between rituximab biosimilars and rituximab originator with CHOP. Secondary outcome included comparison of 1-year progression free survival, 1-year overall survival, and adverse events were evaluated for safety outcome between groups.

Results: A total 121 newly-diagnosed DLBCL patients were patients received rituximab with standard CHOP as first-line treatment. Patients received originator rituximab (n=84) and received rituximab biosimilars (n=37). There were no significant differences between rituximab originator and biosimilars groups in overall response rate (94% vs 94.6%, respectively; p = 0.905) or complete response rate (61.9% vs 62.2%, respectively; p= 0.993). Kaplan–Meier survival curves also showed no significant differences in 1-year progression-free survival (Figure 1A) and 1-year overall survival between groups (Figure 1B) (log-rank p=0.229 and p=0.077, respectively). Safety profiles were comparable between treatment groups.

Conclusion: Rituximab biosimilars was equivalent to rituximab originator in terms of efficacy and safety and was well tolerated in newly-diagnosed DLBCL, given the lowered financial barrier, to improve the overall prognosis for DLBCL patients.

Keyword: Diffuse large B-cell lymphoma, Rituximab, Biosimilar, Originator, Real-world efficacy



PP05-12

Bone marrow involvement in Korean patients with various lymphoma types: a 21-year large single-center study

Min-Sun Kim[1], Miyoung Kim[2*], Young-Uk Cho[2], Sang-Hyun Hwang[2], Seongsoo Jang[2], Han-Seung Park[3], Jung-Hee Lee[3], Dok Hyun Yoon[4], Cheolwon Suh[4], Hyery Kim[5], Kyung-Nam Koh[5], Ho Joon Im[5], Jooryung Huh[6] and Chan-Jeoung Park[2]

[1] Laboratory Medicine, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, Korea
[2] Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[3] Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[4] Oncology, Asan Medical Center, University of Ulsan College of Medicine, Korea
[5] Division of Pediatric Hematology/Oncology, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea
[6] Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: We investigated the distribution of lymphoma subtypes and the frequencies of their bone marrow (BM) involvement in a large number of patients of Korean ethnicity at a single center.

Method: In total, 75,005 BM examination reports from 26,664 consecutive patients treated at Asan Medical Center during 2000-2020 were reviewed. The frequency of referrals for BM examination and the rate of BM involvement per disease subtype were analyzed in patients undergoing initial staging of pathologically diagnosed lymphoma in non-BM anatomical sites. BM involvement was primarily determined by morphological assessment and immunohistochemical analysis.

Results: In total, 23,184 BM samples from 5,722 patients were examined for lymphoma involvement (B-lineage, 4,588 [80.18%]; T- or NK-lineage, 785 [13.72%]; Hodgkin's disease, 330 [5.77%]; and post-transplantation lymphoproliferative disorders, 19 [0.33%]). Initially, BM involvement was observed in 1,470 patients (25.69%), including B-lineage in 1,209 (26.35%), T- or NK-lineage in 216 (27.52%), Hodgkin's disease in 42 (12.73%), and post-transplantation lymphoproliferative disorders in 3 (15.79%). Frequently requested subtypes and rates of B-lineage lymphoma BM involvement at the initial referral were as follows (requests/BM involvement): diffuse large B-cell lymphoma, 51.59%/18.76%; mucosa-associated lymphoid tissue lymphoma, 23.54%/9.72%; follicular lymphoma, 8.00%/41.14%; chronic lymphocytic leukemia and small lymphocytic lymphoma, 5.12%/94.47%; mantle cell lymphoma, 3.14%/64.58%; nodal marginal zone lymphoma, 2.62%/21.67%; and Burkitt lymphoma, 2.62%/50.83%. Other B-lineage lymphomas with less frequent requests but high rates of BM involvement included (requests/BM involvement): splenic marginal zone lymphoma, 0.37%/94.12%; lymphoplasmacytic lymphoma including Waldenstrom's macroglobulinemia, 0.94%/88.37%; intravascular diffuse large B-cell lymphoma, 0.22%/80.00%; and systemic Epstein-Barr-associated B lymphoma, 0.09%/75.00%. Frequently requested T- or NK-lineage lymphoma subtypes at the initial referral and their rates of BM involvement were as follows (requests/BM involvement): NK/T-cell lymphoma, 29.55%/15.52%; peripheral T-cell lymphoma, 25.61%/34.33%; anaplastic large T-cell lymphoma, 17.71%/20.86%; angioimmunoblastic T-cell lymphoma, 10.45%/59.76%; and T-lymphoblastic lymphoma, 8.15%/40.63%. Moreover, two patients with adult T-cell lymphoma/leukemia and one each with intestinal T-cell lymphoma, T-large granular lymphocytic leukemia, and T-prolymphocytic leukemia were requested; all showed 100% BM involvement.

Conclusion: Our comprehensive analysis of lymphoma BM involvement according to disease subtype was the first of its kind among Koreans. Common subtypes showed similar frequencies of BM involvement as those reported in Western studies. High frequencies of rare-subtype BM involvement were notable, although a larger sample size is required for wider generalization.

Keyword: Lymphoma, Korean, Distribution, Bone marrow

PP05-13

MicroRNA-196a sensitizes B cell lymphoma cells to daunorubicin through FOXO1

Hyun Ju Hwang[1], Soyoung Kim[1], Young-Ho Ahn[2], Eun Seok choi[3], Sung Han Kang[3], Hyeri Kim[3], Sang-Hyun Hwang[4], Seongsoo Jang[4], Ho Joon Im[3], Kyung-Nam Koh[3*] and Nayoung Kim[1]

[1] Asan Institute for Life Sciences, Asan Medical Center, Korea
[2] Department of Molecular Medicine, Ewha Womans University, Korea
[3] Department of Pediatrics, University of Ulsan College of Medicine, Korea
[4] Department of Laboratory Medicine, University of Ulsan College of Medicine, Korea

Background: MicroRNAs (miRNAs) are small regulatory RNAs that repress the gene expression by directly binding to the 3' untranslated region of target mRNA. miRNAs are key regulators in cellular processes including stress responses. Thus we were interested in the potential roles of miRNAs in the pathogenesis of B cell leukemia and

lymphoma. miR-196a was known to be reversed drug resistance in non-small cell lng cancer and gastric cancer. Daunorubicin is one of the standard therapeutics for various leukemia and lymphoma.

Method: miR-196a was overexpressed in SU-DHL-6 cells, a human diffuse large B cell lymphoma cell line, by transfection of a lentiviral vector. Cell viability was measured by CCK8 assay (Dojindo), and apoptosis was assessed with Caspase3/7 assay (Promega). Cell cycle was investigated with flow cytometry using propidium iodine after fixation. The target gene of miR-196a was predicted by TargetScan, and the expression of FOXO1 was assessed by Q-PCR and Western blotting.

Results: We found that overexpression of miR-196a reduced the viability of SU-DHL-6 cells upon daunorubicin treatment. The reduced cell viability was results of increased apoptosis. The expression of FOXO1 was directly regulated by miR-196a, that was shown by Q-PCR and Western blotting.

Conclusion: We found that miR-196a could sensitize B cell lymphoma cells to daunorubicin though FOXO1. We further plan to investigate the underlying mechanism and clinical impact using clinical samples.

Keyword: B cell lymphoma, miRNA, Drung resistance

PP05-14

Clinicopathological correlation of mantle cell lymphoma

Harshita Dubey, Amar Ranjan* and Pranay Tanwar

Labortaory Oncology, Dr.B.R.A-IRCH, AIIMS, New Delhi, India

Background: Mantle cell lymphoma (MCL) is a malignant lymphoma that arises in the follicular mantle zone and has unique histologic and biologic characteristics. Blastic and diffuse-type MCL is associated with aggressive disease, while lymphocytic cytology and nodular patterns have a comparatively better prognosis. The clinical significance of these features is unclear. We wish to establish clinic-pathological correlation in MCL cases

Method: The database included a search from the digital records and case files of MCL.

Results: The median age at presentation was 58.0 years (IQR 39.0-80.0). The male to female ratio was 3:1. The elderly population (>60.0 years) was 40.0%. Nodal involvement is seen in almost all cases. The extranodal involvement was seen in 26/33 (78.7%) patients, bone marrow (BM) being the most common site 21/33 (63.6%). Other sites included gastrointestinal tract 12.1%, soft tissue 9.1%, and lung 9.1%. Presentation in advanced stage (III/IV) was seen in 30/33 (91%). Out of 33 patients, 14/33 (42.4%) presented with anaemia (<10gm/L), 13/33 (39.4%) with high serum LDH and 11/33 (33.33%) with leucocytosis (>11,000.0/mm3).

Treatment: The most common first-line therapy was BR, given to 19 (57.58%) patients. Other therapies were R-CHOP, NORDIC, etc. After the first line of therapy, 3/33 (9.09%) patients underwent autologous stem cell transplant. Rituximab-based maintenance was given in 10/33 (30.3%) patients. No second-line therapy was needed for 17 (51.52%) patients. However, 16% of the patients needed various second-line therapies. None of the patients received transplants after second-line therapy. Single relapse was seen in 26/33 (78.79%) patients. The second relapse was seen in 7/33 (21.21%) patients and managed.

Survival: The date for cut-off for patients' inclusion for this study was 31 March 2021. Our median follow-up for this cohort was 26 months. The median overall survival (OS) was 47.83 months, 95% CI (28.8 months -NR). The median event-free survival (EFS) was 33.87 months, 95% CI (18.13 to 52.17).(Figure 1)

Conclusion: Early diagnosis is the clue to increase OS. Unfortunately, we fail to get MCL cases in the early stage. A large cohort study is required to identify it in the early stage. Physicians working at primary health care levels need to be educated for this effort.

Keyword: MCL, Overall survival

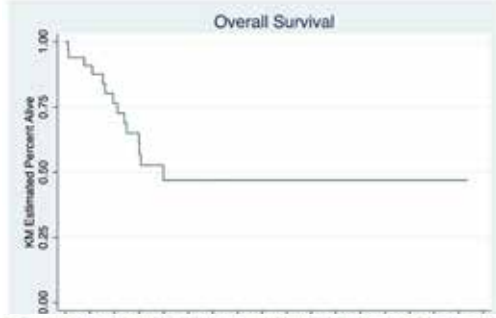


Figure- Kaplan-Meier analysis showing survival analysis. The median overall survival time was 47.83 months. The estimated the 1-, 2-, and 3-year overall survival rates were 90.8%, 72.62%, and 52.86%, respectively.

PP05-15

Epigenetic priming improves salvage chemotherapy in diffuse large B-cell lymphoma via endogenous retrovirus-induced cGAS-STING activation

Jun Liu[2], Ja Min Byun[1,2], Dong-Yeop Shin[1,2], Youngil Koh[1,2], Junshik Hong[1,2*] and Sung-Soo Yoon[1,2]

[1] Department of Internal Medicine, Seoul National University College of Medicine, Korea

[2] Cancer Research Institute, Seoul National University College of Medicine, Korea

Background: Although the majority of patients with diffuse large B-cell lymphoma (DLBCL) achieve complete remission after first-line rituximab-containing immunochemotherapy, up to 40% of patients experience disease relapse or refractoriness. For those patients, salvage chemotherapy is required, but it has limitations in terms of severe toxicity and insufficient response. A hypomethylating agent, 5-azacytidine, has shown a chemosensitizing effect when used for priming before chemotherapy in lymphoma cell lines, newly diagnosed DLBCL patients and several kinds of solid tumors. However, the potential of 5-azacytidine to improve the outcomes of salvage chemotherapy in DLBCL has not been investigated. We aimed to elucidate the potential and mechanism of 5-azacytidine as a chemosensitizer in a cisplatin-based salvage regimen.

Method: Six DLBCL cell lines were exposed to 0.3 μM 5-azacytidine for three consecutive days. The cell lines were then cultured for 24 hours and exposed to increasing doses of cisplatin for 48 hours and cell viability assay was conducted. Analysis phospho-H2AX and Dot blot assay were done to check whether 5-azacitidine-induced chemosensitization was dependent on DNA damage or demethylation. To check 5-azacitidine induced changes of transcriptome and methylome of the cell lines, RNA-seq and MBD-seq analysis were conducted respectively. Realtime quantitative PCR and Western blots were conducted to measure expressions of genes and proteins. In vivo study was conducted with 6~8 week old female athymic nude mice. Mice received an 0.5 mg/kg of 5-azacytidine or PBS intraperitoneally (I.P) for five consecutive days starting after the development of tumors S.C. injected into the back of the mice. Then mice received 5 mg/kg of cisplatin or PBS I.P. four times every two days. Tumor length and width were measured twice a week with calipers for the volume calculation.

Results: Epigenetic priming using low dose 5-azacytidine improved the response to cisplation treatment among cisplatin-resistant DLBCL cell lines to different degrees. Low-dose 5-azacytidine induced DNA demethylation without DNA damage. Low-dose 5-azacytidine treatment altered the expression of cisplatin sensitivity-related genes but did not have a dominant effect on the transcriptome. Rather, this chemosensitizing effect was attributed to endogenous retrovirus (ERV)-induced viral mimicry responses. In these responses, the cGAS-STING axis was a critical contributor to the chemosensitization benefits, which delineated a strategy to overcome the limitations of cisplatin-containing salvage chemotherapy in DLBCL.

Conclusion: Epigenetic priming using 5-azacytidine could potentially improve cisplatin chemosensitivity in cisplatin-resistant DLBCL cell lines. The cGAS-STING pathway was the critical contributor to resensitization. Our ongoing phase II trial (CISL EPIC trial; NCT03719989) with parallel biomarker analysis will reveal whether the results we obtained in this preclinical work are translatable to the clinic and can be applied in the future.

Keyword: Diffuse large B-cell lymphoma, Epigenetic priming, Salvage chemotherapy, Lymphoma, Azacitidine

PP05-16

Morphologic variant of hairy cell leukemia: a diagnostic challenge

Go Eun Bae[1], Hyun-Young Kim[1], Seok Jin Kim[2], Duck Cho[1], Hee-Jin Kim[1] and Sun-Hee Kim[1*]

[1] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[2] Department of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Hairy cell leukemia (HCL) is indolent mature B-cell lymphoid neoplasm characterized by typical morphology of oval nuclei and cytoplasmic hairy projection. However, it becomes a diagnostic challenge when the typical morphology of hairy cells (HCs) is not observed or is present in small numbers. Here, we report the case of a patient with HCL with an unusual morphologic feature of noticeable ring-shaped nuclei.

Method: A 43-year-old male with splenomegaly was referred for treatment of B-cell lymphoma. Complete blood count showed white blood cell, 4.69 x 109/L with a differential count of 29% neutrophils, 63% lymphocytes, and 6% monocytes; hemoglobin, 13.7g/dL; and platelet 70 x 109/L. Initial bone marrow (BM) biopsy specimen was reviewed and the diagnosis of low grade marginal zone lymphoma was made. A positron emission tomography (PET)/computed tomography (CT) scan showed mild hypermetabolic regions involving enlarged spleen and retroperitoneal lymph nodes, and bone marrow. He was treated with rituximab, cyclo-

phosphamide, vincristine, and prednisolone (R-CVP), and response evaluation was performed after 6 cycles. PET/CT scans showed no significant changes in retroperitoneal lymph nodes and bone marrow, although there was a slight decrease in metabolism and size of the spleen. Complete blood count showed white blood cell, 3.18 x 109/L; hemoglobin, 12.3g/dL; and platelet 134 x 109/L without any morphologic abnormal lymphoid cells, and BM examination was conducted.

Results: The BM aspiration smear showed 40% of abnormal lymphoid cells. The majority of abnormal cells were medium to large in size and had distinct ring-shaped nuclei (Fig. 1A). Flow cytometry revealed 33% of clonal B-cells positive for CD11c, CD19, CD20 (bright), CD22, CD25, CD123, FMC7, and surface Kappa light chain and negative for CD5 and CD10, which were typical immunophenotypes of HCL. The BM biopsy showed hypercellular marrow with 90% of cellularity and was packed with abnormal cells with ring-shaped nuclei (Fig. 1B). Immunohistochemical (IHC) stains showed positive for CD20 and partial positive for annexin A1 on abnormal cells. BRAF V600E mutation was detected by Mutant Enrichment with 3'-Modified Oligonucleotides (MEMO) PCR and sequencing on BM specimen. Although typical HCs were not apparent in this patient's BM specimen, HCL was finally diagnosed based on the result of flow cytometry, IHC stains, and BRAF mutation. We morphologically reviewed the initial BM aspiration before treatment and confirmed that atypical HCs with ring-shaped nuclei were identically present in the initial BM aspiration that was misdiagnosed as marginal zone lymphoma.

Conclusion: To our best knowledge, this is the first case of HCL with an atypical morphology of ring-shaped nuclei in Korea. Since the therapeutic approach for HCL patients is unique, differential diagnosis of HCL from other B cell lymphomas is essential for patient management. HCL with noticeable ring-shaped nuclei is extremely rare, however, this could be recognized as a unique morphologic variant of HCL. Therefore, the awareness of morphologic variant of HCL is greatly important for accurate diagnosis and appropriate treatment.

Keyword: Hairy cell leukemia, Ring-shaped nuclei, Atypical hairy cell, BRAF mutation

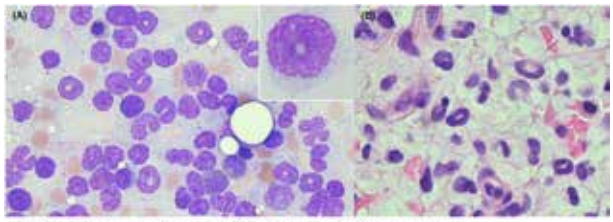


Fig. 1. (A) BM aspiration (W&G stain, x400) and (B) biopsy (H&E stain, x1,000)

PP05-17

Diagnostic challenge for composite mature B cell lymphoma and CD8+ T cell lymphoma

Sholhui Park[1], Min-Kyung So[1], Dong Jin Park[1], Min-Sun Cho[2], Seonggyu Byeon[3], Young Hoon Park[3], Yeung Chul Mun[3] and Jungwon Huh[1*]

[1] Department of Laboratory Medicine, College of Medicine, Ewha Womans University, Korea

[2] Department of Pathology, College of Medicine, Ewha Womans University, Korea

[3] Department of Internal Medicine, College of Medicine, Ewha Womans University, Korea

Background: Composite lymphoma (CL) refers to developing two or more morphologically and immunophenotypically distinct lymphomas in a single site. Since CL is very rare, it is difficult to diagnose at the initial diagnosis unless the possibility of composite lymphoma is suspected.

Method: Here, we report a patient diagnosed with this rare CL developed by CD8+ T-cell lymphoma within one month after chemotherapy for B-cell lymphoma.

Results: A 71-year-old male was admitted for enlarged cervical lymph nodes for six months. Initial laboratory test showed anemia: hemoglobin 9.0 g/dL, WBC count 9.72×10^9/L with 46% neutrophils, 42% lymphocytes, 10% monocytes, 1% eosinophils and 1% basophils, and platelet count 424×10^9/L. Serum protein electrophoresis showed a monoclonal peak of 2.7g/dL. Immunofixation revealed IgG, Kappa monoclonal gammopathy. The patient underwent lymph node biopsy and bone marrow (BM) examination, and both specimens showed the same finding of diffuse infiltration of small to medium-sized B cells and a few plasma cells. In BM differential counts, lymphocytes were 84.0%, and plasma cells were 4.6%. 46% of the lymphocytes expressed CD19, CD20, surface immunoglobulin kappa but were negative for CD10, CD22, CD23, surface immunoglobulin lambda. Plasma cells predominantly expressed light chain kappa. The patient received Bendamustine plus rituximab chemotherapy with a differential diagnosis of lymphoplasmacytic lymphoma or nodal marginal zone B cell lymphoma. When the patient was hospitalized for the second cycle of chemotherapy, pancytopenia with neutropenia progressed with fever, and at the same time, abnormal-looking lymphocytes began to increase in the peripheral blood. In the 2nd BM core biopsy specimen, the cellularity was 90-100% of packed marrow, so BM aspiration was dilute. In flow cytometry, unlike the 1st BM, B lineage cells were observed in 2.2% of total nucleated cells (TNC), whereas CD8+/CD4-/CD3+ T cells were observed in 74% of TNC. In

PB, the WBC count was 1.860×10^9/L with 94.7% lymphocytes, and most of the lymphocytes (83% of T cells) were CD8+/CD4-/CD3+ T cells. IgH gene rearrangement was positive in both the initial lymph node and the 2nd BM core biopsy samples, whereas TCRG gene rearrangement was negative in the initial lymph node but positive in the 2nd BM core biopsy samples. On chest CT, the sizes of multiple lymph nodes were reduced. Gene panel test revealed IKZF1 (NM_006060.6:c.405_406insC, (p.Lys136GInfsTer64) with 8.2%of variant allele frequency (VAF) and NM_006060.6:c.409A>G, (p.Arg137Gly), 8.3% of VAF, tier 2, respectively), DNMT3A (NM_022552.4:c.2711C>T, (p.Pro904Leu), 10.6% of VAF, tier 3) and PRPF8 (NM_006445.4:c.1985-3delC, (p.?), 50.0% of VAF, tier 3) mutations. After the final diagnosis of coexistence of T cell lymphoma and B cell lymphoma, the patient started CHOP chemotherapy. The IKZF1 mutation disappeared in the gene panel test with PB on the 14th day after starting the first cycle of CHOP treatment. The patient has received six cycles of CHOP treatment so far and is awaiting treatment response evaluation.

Conclusion: This case reminds us of a rare and difficult-to-diagnose composite lymphoma. In addition, we confirmed that IgH gene, TCRG gene, and gene panel tests could be essential for diagnosing lymphoma. Diagnosing difficult cases requires constant suspicion and rapid re-evaluation.

Keyword: B cell lymphoma, T cell lymphoma, Clonality, Flowcytometry, Next generation sequencing

PP05-18

Exosomal miR-155 and miR-21 in ibrutinib-resistant diffuse large B cell lymphoma cells

Bon Park[1], Myung Eun Choi[1], Kyung Ju Ryu[1], Jung Yong Hong[2], Won Seog Kim[2], Chaehwa Park[1] and Seok Jin Kim[1,2*]

[1] Department of Health Sciences and Technology, Samsung Advanced Institute of Health Science and Technology, Sungkyunkwan University, Korea

[2] Department of Medicine, Samsung Medical Center, Sungkyunkwan University, Korea

Background: Diffuse large B cell lymphoma (DLBCL) is the most common aggressive B-cell lymphoma, and ibrutinib, an orally administered BTK inhibitor targeting B-cell has been tried as a treatment for DLBCL. However, ibrutinib-resistance is a problem because patients become resistant to ibrutinib during continuous administration of ibrutinib.

Method: To explore the underlying mechanism for ibrutinib-resistance, we analyzed exosomes derived from ibrutinib-resistant DLBCL because exosomes might contribute to ibrutinib-resistance via cell-to-cell communication. We established ibrutinib-resistant DLBCL cell line OCI-LY1 continuously exposed to 2uM ibrutinib, and isolated exosomes from ibrutinib-resistant DLBCL through ultracentrifugation.

Results: The ibrutinib-resistant DLBCL-derived exosomal microRNA (miRNA) profiles showed 118 up-regulated and 36 down-regulated miRNAs compared to ibrutinib-sensitive DLBCL. Among them, negative regulator of the PI3K-AKT pathway, miR-155 and miR-21 were increased in exosomes of ibrutinib-resistant DLBCL, and their intracellular levels were also higher than that of ibrutinib-sensitive DLBCL. The analysis of cellular signaling also showed significant activation of AKT and MAPK pathway in ibrutinib-resistant DLBCL. In addition, miR-155 and miR-21 mimic were transfected to OCI-LY1 to establish miR-155 and miR-21 over-expressed cells. The NF-kB pathway increased in over-expressed cells, and the number of colonies in over-expressed cells increased compare to control cell in colony formation assay. Thus, the NF-kB pathway may be related to cell proliferation.

Conclusion: In conclusion, exosomal transfer of miR-155 and miR-21 might have role in the acquaintance of ibrutinib-resistance in patients with DLBCL.

Keyword: Diffuse large B-cell lymphoma, ibrutinib, Exosome, microRNA

PP05-20

Impact of the Epstein-Barr virus positivity on consolidation RT for hodgkin's lymphoma

Tong Yoon Kim[1], Seok-Goo Cho[1*], Daehun Kwag[1], Gi June Min[1], Sung-Soo Park[1], Silvia Park[1], Young-Woo Jeon[2], Seung-Hawn Shin[3], Seung-Ah Yahng[4], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Seok Lee[1], Chang-Ki Min[1], Jong-Wook Lee[1] and Hee-Je Kim[1]

[1] Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[2] Department of Hematology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[3] Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[4] Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

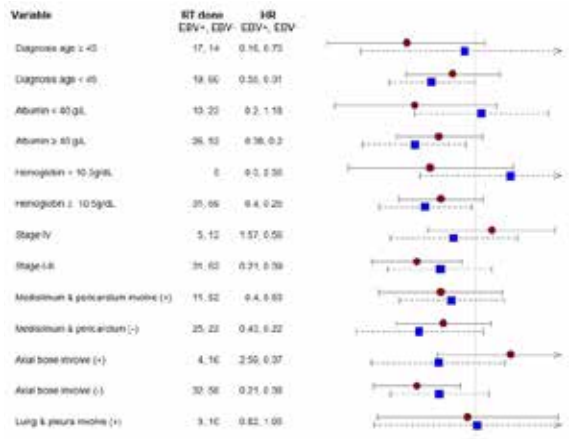
Background: There have been some reports that RT consolidation therapy showed benefit in progression-free survival in patients with HL. Despite the effectiveness of RT in Epstein-Barr Virus–Related Lymphoproliferative disease, data on the role of RT consolidation in EBV-positive-HL are lacking.

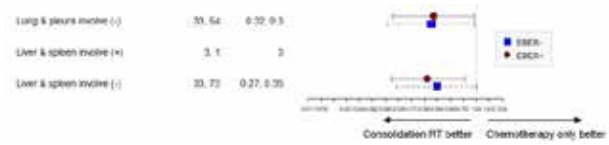
Method: We retrospectively analyzed a total of 182 patients with Hodgkin lymphomas diagnosed from June 2007 to June 2020 in Seoul Saint's Mary hospital. Patients who fulfilled the following criteria were enrolled in this study: Available records of PET-CT data to identify the involved site, absence of treatment-related death, and EBV status confirmation by biopsy specimens.

Results: Among 182 patients, 68 (37.4%) and 114 (62.6%) patients were classified as EBV-positive and EBV-negative by EBER in situ hybridization. After a median of 5.3 years among the survivors, Patients with RT-consolidation had superior 6 year-progression free survival(PFS) than those who were not (88.6% vs. 71.1%, p-value 0.003). In the subgroup analysis, EBV-positive group had more PFS gain by RT-consolidation (82.5% vs 60.2%, p-value = 0.03) than EBV-negative group (91.8% vs. 79.6%, p=0.06). Next, we evaluated the PET CT involved site. Mediastinum involvement was more frequent in EBV negative group than EBV positive group (p-value < 0.01). On contrary, extra nodal involvement other than mediastinum is more common in the EBV-positive group (Hepatosplenic, rib, vertebrae, lung involvement). RT consolidation is not frequently done in extranodal involve other than mediastinal involvement. In EBV positive group, PFS benefits were more prominent by RT in stage I-III (HR 0.21, 95% CI 0.06-0.70, p=0.01) than stage IV (HR 1.57, 0.29-8.57 p=0.6). In EBV negative group, RT-consolidation could not discriminate the PFS in either stage I-III (HR 0.39, 95% CI 0.10-1.55, p=0.2) or stage IV (HR 0.5, 0.10-3.08, p=0.5).

Conclusion: In conclusion, radiotherapy could be more effective in EBV-positive HL with stage I-III disease than EBV-negative group. But considering disperse distributions in the EBV-positive group, other treatment strategies are needed for advanced EBV-positive-HL

Keyword: Hodgkin lymphoma, Radiotherapy, Epstein-Barr virus





PP05-21

Cytokine profile in patients with DLBCL: prognostic value of IL6 and C- reactive protein in predicting poor survival- a prospective study

Gaurav Prakash*, Vaishali Agrawal, Nidhi Jain, Manupdesh Singh, Arihant Jain, Deepesh Lad, Aditya Jandial and Pankaj Malhotra

Clinical Hematology and Medical Oncology, Postgraduate Institute of Medical Education and Research, India

Background: Cytokines dysregulation plays a major role in tumor growth in diffuse large B-cell lymphoma (DLBCL). However, there is limited literature concerning use of cytokines as prognostic markers in DLBCL. A possible relationship between cytokines and lymphoma is supported by recent reports on higher risk of developing lymphoma related to genetic variations in genes encoding pro-inflammatory and anti-inflammatory cytokines. There is only a limited information documenting the correlation of pro-inflammatory cytokine level with IPI, and chemotherapy response in DLBCL patients.

Method: STUDY SETUP: This cohort study was carried out in treatment naive DLBCL patients from Northern India. In this study, levels of immunomodulatory biomarkers C-reactive protein (CRP), T-helper 1 (Th1) cytokines(TNF, IFN-γ and IL-2), T-helper 2 (Th2) cytokines (IL-4, IL-6, IL-10) and T-helper 17(Th17) cytokine (IL-17A) in pretreatment serum of 53 treatment naïve DLBCL patients were evaluated as prognostic markers.

TESTS PEFORMED: CRP quantification was done by using nephelometry while cytokine profiling was carried out using BDTM Cytometric Bead Array (CBA) assay.

TEST COHORT: 53 patients with newly diagnoses DLBCL

CONTROL COHORT: Ten healthy individuals were enrolled for the study as controls and similar cytokine assay was performed on control samples as well. A written informed consent was obtained from all DLBCL cases as well as control subjects.

All patients were treated with standard chemotherapy regimen of choice of the clinical team. The treatment response was assessed

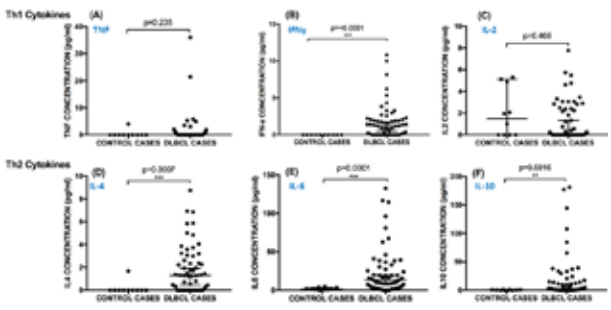
by an interim PET-CT scan after completion of four cycles of chemo-immunotherapy and the end-of-treatment scan performed one month after completion of all courses of chemo-immunotherapy ± radiotherapy.

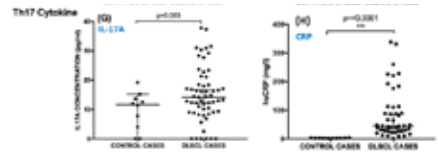
Serum was isolated from blood samples collected prior to any anti-neoplastic treatment through centrifugation at 3000 rpm and it was stored at -80˚C. Cytokine profiling was carried out using BDTM Cytometric Bead Array (CBA) Human Th1/Th2/Th17 Cytokine Kit (560484, Becton Dickinson Biosciences, USA) To study the protein-protein interaction between the C-reactive protein (CRP) and secreted Th1/ Th2 and Th17 cytokines, we performed the protein-protein interactome analysis using STRING software

Results: The serum levels of IL-6 (p=0.0001), IFN-γ (p=<0.0001), IL-4 (p=0.0007), IL-10 (p=0.0016) and CRP (p=<0.0001) were significantly elevated in DLBCL patients as compared to controls. The serum level of TNF, IL-2 and IL-17A were elevated in DLBCL patients but the difference was not statistically significant. Evaluation of the cytokines with event free survival (EFS) and overall survival (OS) showed high IL-6 levels were associated with poor EFS (p=0.001, 95% CI 3.98 (1.49-10.69)) and poor OS (p=0.0011, 95% CI 4.01 (1.43-11.26)). High IL6 levels were also associated with poor response to chemo-immunotherapy in the study patients. CR rate in patients with low vs. high IL6 level was 73% and 31.3%, respectively (P=0.01). High CRP levels at a cut-off value of 30 mg/L predicted poor 5-year-OS (p=0.025; 95%CI 7.21 (2.53-20.52)).High IL-10 levels showed a trend towards poorer 5-year-OS (p=0.08), however, it was not statistically significant.

Conclusion: The cytokine profile in DLBCL patients was polarized towards increased Th2 response. Elevation of both IL6 and CRP emerged as prognostic markers for predicting EFS and OS while high levels of IL6 was associated with inferior complete response rates. Considering easier access to cytokine assessment, both IL6 and CRP have potential to get incorporated in the existing prognostic scores. This may result in improved risk stratification of DLBCL patients Future Direction: To validate these results in a multi-center cohort study and to study the variations in cytokine profile before and after cytoreductive therapy

Keyword: DLBCL, biomarkers, CRP, Th1 cytokines, Th2 cytokines, Th17 cytokine, IPI





PP05-22

Bloodless treatment of Jehovah's Witnesses patients with lymphoma: single center experience

Kyoung Ha Kim, Sun Young Jeong, Seug Yun Yoon, Min-Young Lee, Namsu Lee and Jong-Ho Won*

Internal Medicine, Soonchunhyang University College of Medicine, Soonchunhyang University Hospital, Seoul, Korea

Background: Jehova's Witnesses (JW) usually refuse transfusions based on their religious beliefs, and they request bloodless medicine at medical centers. The most troublesome patients who request bloodless medicines are patients with hematologic malignancies. Bloodless chemotherapies in JW patients with hematologic malignancies can increase the risk of adverse events, such as bleeding and cardiovascular complications, so clinicians hesitate chemotherapies despite the disease's aggressiveness. In addition, there is little published data on the treatment of hematologic malignancies of JW patients as well as standard guidelines. In the case of lymphoma, such as aggressive lymphoma or high IPI lymphoma, the patient's state is critical at the time of diagnosis, and frontline chemotherapy is often troublesome. In such a case, if the patient is JW patient, treatment is even more difficult. Since 2000, our hospital has been a bloodless center. This study was retrospectively analyzed for lymphoma patients with bloodless treatment in Soonchunhyang university hospital.

Method: A retrospective review of medical records was performed of 25 patients with lymphoma who request bloodless medicine from January 2006 to January 2021 at Soonchunhyang university hospital. We analyzed 23 patients, excluding a marginal zone lymphoma patient who received only local radiotherapy and a marginal zone lymphoma patient who received only Helicobactor pylori eradication.

Results: The median age of the study population at the time of diagnosis was 66 years (range 21-84). Baseline patient and disease characteristics are presented in the table.
Of 23 patients, 21 patients were treated with chemotherapies or radiotherapy, and two patients were treated with supportive care only.

Of 21 patients, 18 patients were treated with optimal treatment, and 3 patients were treated with suboptimal treatments (eg. modification of doses or drugs) in consideration of bloodless treatments. Mean Hemoglobin and platelet at diagnosis were 10.9g /dL (3.6-17.3g/dL) and 204 X109/L (11-488 X109/L), respectively. Mean Hemoglobin and platelet nadir were 8.3g /dL (2.7-15.5g/dL) and 94 X109/L (3-309 X109/L), respectively.
Among 23 patients, 13 patients died. Median overall survival was 57.9 months, and 2 years' rate of OS was 60.6% (95% CI, 37.8-77.2). 11 of the deaths (84%) were affected by bloodless treatments. The mean hemoglobin nadir or patients who died within one year and survived more than one year were 10.75 g/dL and 4.5 g/dL, respectively (p<0.001).

Conclusion: Bloodless treatments are a limiting factor in lymphoma treatment and affect survival. For the treatment of JW patients with lymphoma., anemia is the main factor influencing treatment outcomes, and active transfusion replacement therapy and supportive care are needed. Therefore, further studies are needed to improve their survival.

Keyword: Jehovah's Witness, Bloodless, Lymphoma

	Number of patients (n=23) No. %
Age (years)	
Median (range)	66 [21-84]
Gender	
Male	12 (48)
Female	11 (52)
Histologic subtype	
B cell lymphoma	13 (56.5)
Diffuse large B cell lymphoma	10 (43.5)
Mantle cell lymphoma	1 (4.3)
Follicular lymphoma	1 (4.3)
Lymphoplasmacytic lymphoma	1 (4.3)
T cell lymphoma	9 (39.1)
Angioimmunoblastic T cell lymphoma	3 (13.0)
Anaplastic large cell lymphoma	1 (4.3)
Peripheral T cell lymphoma, unspecified	1 (4.3)
Enteropathy associated T cell lymphoma	1 (4.3)
Hepatosplenic T cell lymphoma	1 (4.3)
NK/T cell lymphoma	2 (8.7)
Hodgkin's lymphoma	1 (4.3)
Stage	
1	2 (8.7)
2	6 (26.1)
3	4 (17.4)
4	8 (34.8)
Relapsed	3 (13.0)
ECOG	
0-2	20 (87.0)
3-4	3 (13.0)
IPI	
0-1 (low)	5 (21.7)
2 (low-intermediate)	6 (26.1)
3 (high-intermediate)	3 (13.0)
4-5 (high)	9 (39.1)
BM involvement	
Yes	5 (21.7)
No	18 (78.2)
Combined Infection	
Yes	9 (39.1)
No	14 (60.9)

PP05-23

Long term effectiveness of autologous peripheral blood stem cell transplantation (auto-PBSCT) using busulfan, melphalan, and thiotepa (BMT) regimen in patients with recurrent or refractory CNS lymphoma: single center experience

Youngwoo Jeon[1,2], Gi June Min[3], Sung-Soo Park[3], Silvia Park[3], Jae-Ho Yoon[3], Sung-Eun Lee[3], Ki-Seong Eom[3] and Seok-Goo Cho[1,2,3*]

[1] Hematology, The Catholic University of Korea, Yeouido ST. Mary's Hospital, Korea

[2] Institute for Translational Research and Molecular Imaging, Catholic Institutes of Medical Science, College of Medicine, Seoul St. Mary's Hospital, Korea

[3] Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Background: The prognosis of primary central nervous system lymphoma (PCNSL) is poor compared to other extranodal lymphomas with a 5-year survival rate of 22 – 40%, Moreover, although data on recurrent or refractory PCNSL or secondary central nervous system lymphoma (SCNSL) are very limited and negligible, the prognosis of recurrent or refractory PCNSL or SCNSL are regarded as remarkably poor with a median survival of 2–5 months. High-dose chemotherapy (HDC) followed by autologous peripheral blood stem cell transplantation (Auto-PBSCT) is a promising alternative treatment option in front-line treatment as well as salvage therapy. We report our experience with HDC followed by auto-PBSC using Busulfan, Melphalan, and Thiotepa (BMT) in recurrent or refractory PCNSL or SCNSL.

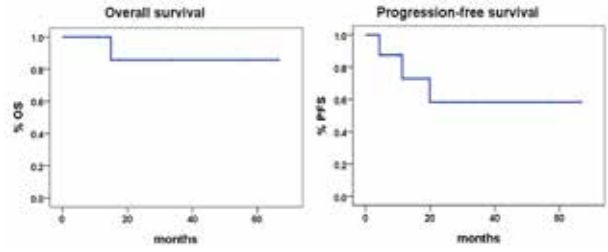
Method: Eight consecutive PCNSL or SCNSL patients were treated with HDC followed by auto-PBSCT using BMT regimen at catholic bone morrow transplant center from Jan 2013 to May 2020. After induction or salvage chemotherapy, auto-PBSCT was performed with conditioning using BMT (Busulfan 1.2mg/m2 qid, day -8 to day-6;

Melphalan 40mg/m2, day-5 to day-4; thiotepa 200mg/m2, day-3 to day-2) regimen.

Results: All of eight patients (5 recurrent patients,PCNSL; 3 SCNSL, 2 DLBCL of large intestinal, 1 testicular) had been achieved a complete remission (CR) after induction or salvage chemotherapy. and then, all patients underwent auto-PBSCT with adequate stem cell dose (a minimum of 2.0 x 106 CD34+ stem cells/kg) with no transplantation related mortality. Three patients had relapsed after auto-PBSCT. all three patients with post-auto-PBSCT were treated with another salvage chemotherapy with or without additional brain radiotherapy. 1 patient of those was died by disease progression (table 1). The estimated 2-year OS and PFS were 85% and 58%. median OS (31.3 months) and PFS (28.4 months) was not reached yet (fig. 1).

Conclusion: Our approach is safe and feasibility, and a remarkably favorable outcome compared with the median OS of 5~15 months typically achieved with other conventional chemotherapy, even if all of included patients was belong to high risk group as recurrent or secondary disease. Auto-PBSCT using BMT conditioning regimen results in good positive modality for patients with limited alternatives.

Keyword: Primary CNS lymphoma, Autologous stem cell transplantation



PP06-01

18F-FDG PET/CT for identifying the potential primary diseases and predicting prognosis of secondary hemophagocytic lymphohistiocytosis in children

Ang Wei, Honghao Ma, Sitong Chen, Zhigang Li, Tianyou Wang and Rui Zhang*

Hematology center, Beijing children's hospital, China

Background: Hemophagocytic lymphohistocytosis (HLH) also called hemophagocytic syndrome, is a rare potentially fatal illness characterized by impaired natural killer (NK) cell and cytotoxic T-cell function. HLH often occurs in adolescents and children. According to whether or not a definite genetic basis, HLH can be divided into primary HLH (pHLH) and secondary HLH (sHLH). HLH can be triggered by different stimuli, which include infection, malignant tumours, autoimmune disorders, and so on. Infection is the most common trigger in sHLH in children, especially the Epstein-Barr Virus (EBV). Identifying the primary underlying disease is even more crucial for sHLH to enable initiation of life-saving treatment. Up to now, only a few reports have described the value of fluorine-18 fluorodeoxyglucose (18F-FDG) positron-emission tomography/computed tomography (PET/CT) in diagnosing performance and prognosis prediction in adult with sHLH. However, rare studies reported the role of 18F-FDG PET/CT in children. Therefore, the aim of the study was to assess the value of 18F-FDG PET/CT in the etiology detection and prognosis prediction in children with sHLH.

Method: Sixty- six newly diagnosed sHLH children aged 9 months - 14 years, who underwent 18F-FDG PET/CT examination from July 2018 to December 2020 were retrospectively analysed. 4 cases were excluded due to unknown etiology, other patients were divided into malignancy associated HLH (M-HLH,n = 13) and non-malignancy associated HLH (NM-HLH, n = 49). The metabolic parameters of liver (Li), spleen (Sp), bone marrow (BM), lymph nodes (LN), and their ratios to liver background (LiBG) and mediastinum (M) were compared between two groups.These metabolic parameters were evaluated for correlation with laboratory parameters and prognostic parameters.

Results: The SUVmax-LN/ Sp/ Li and SUVmean-Sp in M-HLH were significantly higher than those in NM-HLH (P=0.031, 0.035, 0.016 and 0.032). Malignant disease should be considered when SUVmax-LN was higher than 4.41 (sensitivity 61.5%, specificity 81.6%). Hypermetabolic lesions in extranodal organs were more likely to occur in M-HLH than in NM-HLH (P=0.011). IFN- γ was positively correlated with SUVmax-BM/Li/Sp and SUVmean-BM/Li/Sp ($P < 0.05$). Ferritin, sCD25, IL-6 and IL-10 were positively correlated with SUVmax-Sp and SUVmean-Sp ($P < 0.05$). In Epstein-Barr Virus associated HLH (EBV-HLH), almost all SUV parameters of bone marrow, including SUVmax-BM, SUVmean-BM, SUV BM/LiBG ratio and SUV BM/M ratio, were significantly correlated with poor 2-week treatment response, overall survival and event-free survival ($P < 0.05$).

Conclusion: Some metabolic parameters of 18F-FDG PET/CT are helpful to identify the etiology of sHLH in children. Malignant disease should be considered when the SUVmax-LN is higher than 4.41 and hypermetabolic leisions in extranodal organs occurs. In EBV-HLH, higher SUV of bone marrow is associated with poorer prognosis.

Keyword: Children, Hemophagocytic lymphohistiocytosis, 18F-FDG PET/CT, Prognosis

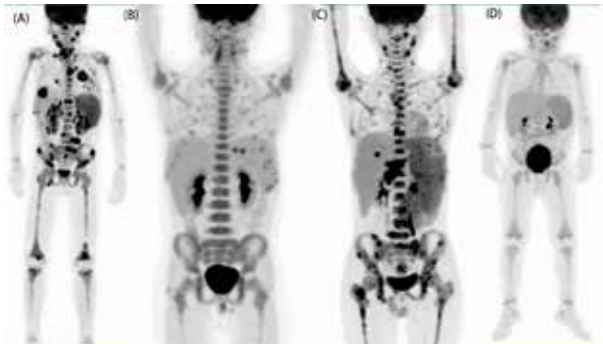


Figure 2 18F-FDG PET/CT maximum intensity projection of sHLH in 4 children. Hodgkin's lymphoma (A), CAEBV (B), EBV-HLH (C, D), presenting as hepatosplenomegaly and increased FDG uptake of spleen (A, B, C, D) and liver (A, C). (A) A 6-year-old boy with multiple enlarged lymph nodes (SUVmax:11.74, SUVmean:9.3); multiple focal increased FDG uptake in extranodal organs, including left external auditory canal skin, lungs, liver, kidney, right adrenal gland, small intestine, and bone marrow (SUVmax:11.16, SUVmean:7.15). The child died three months later after admission. (B) An 8-year-old boy with multiple lymph nodes in the neck, supraclavicular and mediastinum, the FDG uptake was lower than that of the liver, SUVmax:1.83, SUVmean:1.54. FDG uptake of Bone marrow increased diffusely (SUVmax:4,01, SUVmean:3.65). There were multiple focal increased FDG uptake in the spleen. The children survived until the end of follow-up after hematopoietic stem cell transplantation. (C) A 14-year-old boy with multiple lymph nodes enlargement, increased FDG uptake and multiple focal FDG uptake in bone marrow. He was died of multiple organ failure. (D) A 2-year-old boy with multiple lymph nodes in the neck, supraclavicular, axilla, abdomen and groin, whose FDG uptake was slightly lower than that of the liver. He was still alive until the end of follow-up.

PP06-02

Clinical analysis of chronic active EBV infection involving gastrointestinal tract: a retrospective analysis of a single-center

Ang Wei, Honghao Ma, Liping Zhang, Zhigang Li, Tianyou Wang and Rui Zhang*

Hematology center, Beijing children's hospital, China

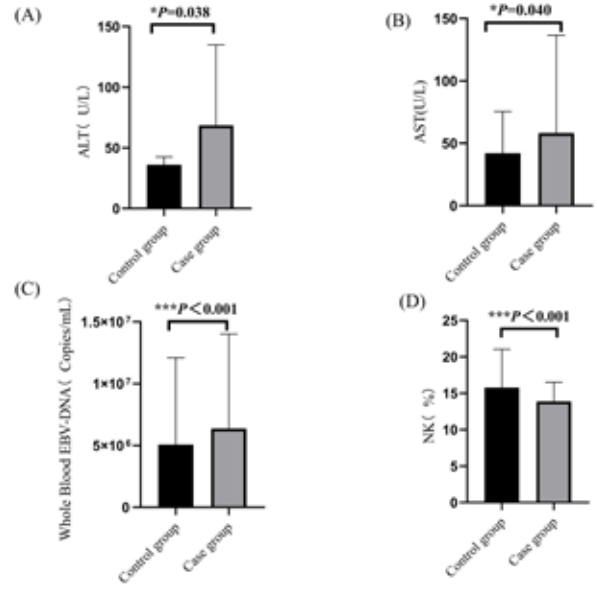
Background: CAEBV has two characteristics: systemic inflammation and neoplastic disease. The main clinical finding of CAEBV is inflammation, which is characterized by fever, lymphadenopathy, liver dysfunction, hepatosplenomegaly, and an abnormal hemogram. However, CAEBV combined with gastrointestinal tract involvement has been rarely reported, and sometimes it may be clinically mimicking gastroenteritis or inflammatory bowel disease (IBD). The treatments for those two diseases are completely different, and misdiagnosis may lead to bad outcomes. Herein, we report 15 cases of pediatric patients diagnosed CAEBV with gastrointestinal tract involvement.

Method: Children with CAEBV associated with gastrointestinal tract involvement hospitalized at Beijing Children's Hospital, Capital Medical University from June 2017 to Jun 2021 were analyzed. Children with CAEBV without gastrointestinal involvement were selected as the control group. The clinical manifestations, laboratory and ultrasound examinations, treatment and prognosis of the children were collected in both groups.

Results: There were 15 children with CAEBV combined with gastrointestinal involvement, including 11 males and 4 females, accounting for 20.8% (15/72) of CAEBV patients in the same period, with an onset age of 3.71 (0.64-14.47) years. The most common clinical manifestation at onset was diarrhea (13/15). Gastrointestinal ultrasound showed air accumulation accompanied by intestinal wall swelling and thickening, mild to moderate swelling of the surrounding mesentery and omentum, and enhanced echo. The endoscopic features were hyperemia, edema, and ulcers of variable morphological characteristics. Pathological examination showed lymphocyte infiltration with EBER (+), and the most common involvement location were colon (n=6) and gastric antrum (n=3). The median follow-up time was 13.26 (0.31-51.89) months. Ten patients were survived and 5 patients died (including one patient died of intestinal perforation due to necrotizing enterocolitis). Compared with control group, the case group had higher level of alanine aminotransferase, aspartate aminotransferase and whole blood EBV-DNA copies (P=0.038, 0.040 and < 0.001) and lower NK cell activity (P < 0.001). The 3-year overall survival rate of case group was significantly lower than that of control group (59.3%±12.9% vs. 79.4%±4.9%, P=0.021).

Conclusion: The incidence of CAEBV with gastrointestinal tract involvement was low. The most common involvement location was colon. CAEBV with gastrointestinal involvement had poor prognosis. Patients who had high whole blood EBV-DNA copies levels early in their illness were more likely to develop gastrointestinal involvement.

Keyword: Epstein-Barr virus, Gastrointestinal tract, Clinical characteristics, Prognosis



PP06-03

Clinical-biological characteristics and treatment outcome of children with multisystem Langerhans cell histiocytosis and secondary hemophagocytic lymphohistiocytosis

Lingling Fu, Dong Wang, Honghao Ma And Rui Zhang*

Hematologic Diseases Laboratory, Hematology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China

Background: Langerhans cell histiocytosis (LCH) is a rare myeloid neoplasm. A few patients with multisystem (MS)-LCH developed secondary hemophagocytic lymphohistiocytosis (HLH), a life-threatening, hyperinflammatory syndrome.

Method: A total of 28 pediatric patients with coexisting MS-LCH and HLH at diagnosis were enrolled in this study. Patients were firstly treated with initial induction first-line therapy (vindesine-steroid combination), then patients with poorly controlled HLH were shifted to the second-line chemotherapy (cytarabine and cladribine) or targeted therapy (dabrafenib).

Results: Patients with MS-LCH and secondary HLH were aged < 2 years, harbored high frequencies of RO, skin, or lymph nodes involvement, and most of them (about 90%) carried BRAF-V600E mutation in lesions or plasma. Among the 22 BRAF-V600E-mutant patients, only two patients got resolution of HLH after the first initial induction therapy. Furthermore, patients treated with dabrafenib had prompt resolution of clinical HLH signs and symptoms compared with the second-line chemotherapy. Moreover, the progression/relapse rate for patients given dabrafenib tended to less than those treated with chemotherapy (33.3% vs. 70%, P = 0.198).

Conclusion: The targeted therapy provides a promising treatment option for LCH and secondary HLH.

Keyword: Langerhans cell histiocytosis, Hemophagocytic lymphohistiocytosis; BRAF-V600E mutation, Dabrafenib, Outcome

PP06-04

Clinical significance of soluble CD25 in cerebrospinal fluid in hemophagocytic lymphohistiocytosis with central nervous system involvement

Wenxin Ou

Hemotology, Beijing Children's Hospital, China

Background: To analyze the clinical characteristics and significance of soluble CD25 (sCD25) levels in cerebrospinal fluid in children with hemophagocytic lymphohistiocytosis (HLH) central nervous system (CNS) involvement.

Method: All patients admitted to Beijing Children's Hospital during the period of January 2017 and October 2021 diagnosed with HLH and HLH-related indexes and cerebrospinal fluid (CSF) sCD25 tested at admission were included in this study.

Results: Among 374 children with HLH, 122 children with CNS involvement were diagnosed, accounting for 32.6%。According to whether CNS was involved or not, the difference of CSF sCD25 level between CNS group and No-CNS group was statistically significant (269.00(41.00 ~ 33643.00)pg/ml vs. 110.00(18.00 ~ 501.00) pg/ml, P < 0.001). While there was a positive correlation between CSF sCD25 and serum sCD25 (r = 0.426, P < 0.001). The best cut-off value of CSF sCD25 was 198.0pg/ml(AUC=0.894, 95%CI：0.857 ~ 0.931), with sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) being 79.5%, 90.1%, 79.5% and 90.1%. Kappa value was 0.696. The 3-year overall survival(OS) of the CNS group was lower than that of the No-CNS group (82.8%±3.8% vs. 93.1%±1.7%, P=0.004). According to the severity of CNS involvement, there was no significant difference in CSF sCD25 between severe CNS involvement group and non-severe CNS involvement group (P>0.05). The 3-year OS of children with severe CNS involvement was significantly lower than that of children with non-severe CNS involvement (67.8%±8.6% vs. 91.0%±3.2%, P=0.008). According to the optimal CSF sCD25 cut-off value, the incidence of abnormal CSF and magnetic resonance imaging(MRI) in the case group was higher than that in the control group (P<0.001). The 3-year OS of the case group was lower than that of the control group, and the difference was statistically significant (84.2%±3.7% vs. 92.4%±1.7%, P=0.041).

Conclusion: CSF sCD25 can assist in the diagnosis of children with HLH complicated with CNS, and the best cut-off value is 198.0pg/ml. Patients with CNS involvement with high level of CSF sCD25 are more likely to have abnormal CSF and MRI, which are related to the prognosis of the patients. The diagnosis of HLH should be considered in patients who have high levels of CSF sCD25 and the treatment should be followed as soon as possible.

Keyword: Hemophagocytic lymphohistiocytosis, Central nerve system, Cerebrospinal fluid, Solute CD25, Children

PP06-05

Effect analysis of ruxolitinib combinations liposomal doxorubicin, etoposide methylprednisolone +/- PEG-asparaginase in treatment of refractory and relapsed hemophagocytic lymphohistiocytosis in children

Ang Wei, Tianyou Wang* and Rui Zhang

Hematology center, Beijing children's hospital, China

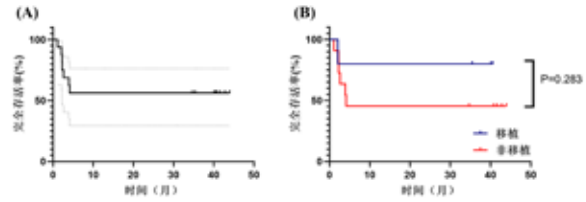
Background: Hemophagocytic lymphohistiocytosis (HLH), also called hemophagocytic syndrome (HPS), is a rare potentially fatal illness characterized by impaired natural killer and cytotoxic T-cell function. Patients present with hemophagocytosis, cytopenia, and multi-organ failure1. HLH can be categorized into two forms: primary or familial HLH (FHL) and secondary HLH. The HLH-94/04 protocol is currently still considered the therapeutic standard, which can bring most patients' diseases under control. However, there are still some patients who cannot achieve at least partial remission (PR) under the HLH-94/04 protocol. Thus, a new treatment strategy is urgently required.

Method: A retrospective analysis was performed on 16 patients with refractory/relapsed(R/R) hemophagocytic lymphohistiocytosis at Beijing Children's Hospital from January 2018 to January 2020. The efficacy and adverse events of the RU-DEP+/-L(ruxolitinib, liposomal doxorubicin, etoposide, methylprednisolone +/-PEG-asparaginase) regimen were evaluated.

Results: A total of 16 patients were enrolled in this study, including 13 males and 3 females, with a median age of 1.71 years (0.57~5.76 years) at diagnosis. Thirteen patients were diagnosed with EBV-HLH, 2 with EBV-induced primary HLH, and 1 with unclear etiology, among which 3 patients were co-infected with CMV. After the frst-line treatment, 11 patients had no remission and 5 patients relapsed after complete remission. Nine patients received RU-L-DEP regimen, and 7 patients received Ru-DEP regimen. The overall response rate and complete response of RU-DEP +/-L treatment were 62.50% (10/16) and 18.75% (3/16), respectively. The negative conversion rate of plasma EBV-DNA was 46.7% (7/15). The median follow-up time was 19.8 months (1.13~43.97) months. After Ru-DEP +/-L treatment, 5 patients accepted allogeneic hematopoietic stem cell transplantation(HSCT), and 4 patients survived. Eleven patients did not accepted HSCT, and 5 patients survived. The 3-year overall survival rate was 56.25%±12.40%. Among the 16 patients, 9 patients (56.25%) had varying degrees of myelosuppression, and 13 patients (81.25%) had infection.

Conclusion: RU-DEP +/-L can be used as a salvage treatment in R/R pediatric HLH, which can provide a bridge to HSCT and play an important role in control of HLH. The main side effects are myelosuppression and infection, which can be tolerated.

Keyword: Children, Hemophagocytic lymphohistiocytosis, Relapse, Refractory, Prognosis



PP06-06

The role of pre-therapeutic 18F-FDG PET/CT in pediatric hemophagocytic lymphohistiocytosis with epstein-barr virus infection

Liping Zhang, Ang Wei, Rui Zhang and Tianyou Wang

Hematology, Beijing Children's Hospital, China

Background : 18F-FDG PET/CT is a whole-body scan widely used in many diseases, such as infection, malignant disease, and rheumatic immunity disease. In various lymphoma, it is used in differential diagnosis, treatment planning, response evaluating and prognosis predicting. 18F-FDG PET/CT is better than conventional radiography, as it can display the extranodal lesions better and measure the metabolism in semi- quantitative analysis. 18F-FDG PET/CT could evaluate the involvement of organs of potential disease of HLH, and guide the biopsy of lesions. In HLH with EBV infection, 18F-FDG PET/CT is now recommended for the detection of neoplastic lesions, as the lymph nodes and extranodal organs are usually involved, especially in M-HLH. Moreover, studies reported that PET/CT parameters, such as SUVmax spleen/mediastinum ratio, could predict prognosis of HLH.

Method : This retrospective study included 29 HLH children (1-16 years) with EBV infection, who underwent pre-therapeutic 18F-FDG PET/CT from July 2018 to November 2020. Pathology results were considered as the reference standard. These patients were divided into two groups: EBV-induced malignancy-associated HLH (M-HLH, n = 9) and EBV-induced non-malignancy-associated HLH (NM-HLH, n = 20). The regions of interest (ROI) of the liver, spleen (Sp), bone marrow, lymph nodes (LN), hypermetabolic lesions, liver back-

ground (LiBG), and mediastinum (M) were drawn with 3D-Slicer. The volumetric and metabolic parameters, including maximum standard uptake value (SUVmax), metabolic tumor volume, and total lesion glycolysis of these ROIs, clinical parameters, and laboratory parameters were compared between the two groups. The efficacy of the above parameters in predicting the therapy response and overall survival (OS) were analyzed.

Results : Receiver operating characteristic curve analysis indicated that SUVmax-lesions and SUVmax-LN/M (AUC = 0.822,0.819, cut-off = 6.04, 5.74, respectively) performed better in differentiating M-HLH from NM-HLH. It had the best diagnostic performance when age was added with the SUVmax-LN/M (AUC = 0.933, sensitivity = 100%, specificity = 85.0%). The presence of extranodal hypermetabolic lesions in multiple organs indicated the M-HLH (P = 0.022). Older age, higher SUVmax-LN and SUVmax-lesions, and the presence of serous effusion were associated with poorer therapy response at the 2nd and 4th week (not reaching partial remission). Multivariate analysis showed that SUVmax-lesions > 7.66 and SUVmax-Sp/LiBG > 2.01 were independent prognostic factors for overall survival.

Conclusion : 18F- FDG PET/CT is a valuable technique for identifying the underlying tumor and predicting prognosis in pediatric HLH with EBV infection. M-HLH should be considered when SUVmax-lesions > 6.04, SUVmax-LN/M > 5.74, and the presence of extranodal hypermetabolic lesions in multiple organs in 18F- FDG PET/CT. SUVmax-lesions and SUVmax-Sp/LiBG are independent prognostic factors for OS.

Keyword : Hemophagocytic lymphohistiocytosis, Children, Epstein-Barr virus, 18F-FDG PET-CT

PP06-07

A case report of adult bone eosinophilic granuloma

Altanshagai Boldbaatar[1], Ulzii-Orshikh Namkhai[2], Erdenetsetseg Battulga[3], Elbegjargal Erdenebaatar[1] and Khishigjargal Batsukh[1*]

[1] Center of Hematology, Blood and Marrow Transplantation, The First Central Hospital of Mongolia, Mongolia

[2] General Laboratory of Clinical Pathology, The First Central Hospital of Mongolia, Mongolia

[3] Diagnostic Imaging Center, The First Central Hospital of Mongolia, Mongolia

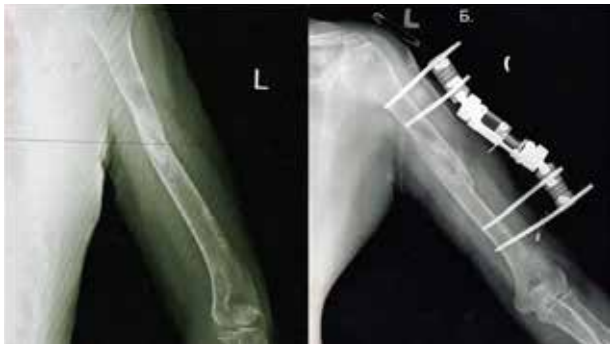
Background: The eosinophilic granuloma (EG) is characterized by abnormal proliferation of histiocytes, localized or multifocal; it mainly affects skull bones, ribs, pelvis, mandible, femur, and spine. It is more frequent in children and teenagers. The possible factors involved in EG are an inflammatory response to an unknown etiological agent, immune system dysfunction, and metabolic changes; however, so far, there is no definitive proof. The disease is just known not to be inherited or familial, it is not contagious and does not present racial predominance. ECD is caused by clonal proliferation of myeloid progenitor cells, as demonstrated by detection of the characteristic BRAF V600E mutation in subsets of dendritic cells, mature monocytes, committed myeloid progenitors, and CD34+ cells of affected patients. Somatic mutations of BRAF or other components of the MAPK signaling pathway are present in most patients with ECD. In some studies, BRAF V600E has been detected in approximately half of ECD cases.

Method: A 36-year-old man complains of a left humerus small ulcer with pain for three months. He was treated with analgesics, but he developed resistance to analgesic therapy. He denied previous diseases and traumas. An X-ray revealed a well-defined osteolytic lesion in the middle of the left humerus. The patient underwent surgical treatment anatomopathological evaluation was made, which was confirmed by radiological examination. After three months of follow-up, the patient revealed headache, weakness and radiographic examination showed the signs of relapse. At initial evaluation, the nodule was 2.5 cm in diameter without apparent skin and lymph node alteration. The study was complemented with CT, MRI, and SPECT-CT by identifying lytic lesions with soft tissue component and contrast enhancement, without diffusion restriction, guiding the diagnostic hypothesis of eosinophilic granuloma. We report a case of EG with a photographic recording of the diagnostic methods and the surgery, besides the anatomical pathological analysis and literature review.

Results: In cases of multiple or recurrent lesions, chemotherapy is indicated, as well as systemic or intralesional corticosteroids. in triplet combination with prednisolone, vinblastine, and bisphosphonate. He remained pain-free on headaches and both humerus after 6 months of treatment. Following up for 6 months has been monitoring and continuing treatment. We result of treatment has been controlling and processing the next treatment plan 6 months later. Picture: Upper extremity X-ray: Image A – Left humerus middle 1/3 part of oblique fracture and osteoporosis with external fixation nails. Image B –Fracture healing of the middle 1/3 part of the left humerus after removal of the external fixation nails.

Conclusion: This case illustrates a typical presentation of an uncommon disease in adults. It must, therefore, be included in the differential diagnosis of lytic lesions of the bone. Besides, we need to has detection of BRAF gene mutations because it significantly affects the methodology of diagnostic and therapeutic procedures.

Keyword: eosinophilic granuloma, osteolytic lesion, chemotherapy



& sPCL in above-mentioned variables except, LDH, which showed a differential trend between the two.

LDH was higher in sPCL in comparison to pPCL with a mean value for pPCL 213 ± 44.9 and sPCL 516 ± 290. On applying the Wilcoxon rank-sum (Mann-Whitney) test we found the p-value <0.08.

Conclusion: In this pilot study, we can affirm that LDH may play a role in the prediction of sPCL in cases of MM.

Keyword: Plasma cell leukemia, LDH, Multiple Myeloma

PP07-02

Significance of LDH level in development of secondary plasma cell leukemia

Harshita Dubey, Amar Ranjan* and Pranay Tanwar

Labortaory Oncology, Dr.B.R.A-IRCH, AIIMS, New Delhi, India

Background: Plasma cell leukemia (PCL) is defined as >2 × 109/liter plasma cells (PC) in peripheral blood or by >20% PC IN differential leukocytes count . Secondary PCL (sPCL) develops in 2%-4% of multiple myeloma (MM) cases . In comparison to pPCL, sPCL shows a higher incidence of lytic lesions and renal failure. Whereas the lesser incidence of extramedullary involvement.In this study, we are trying to predict the development of PCL in cases of MM

Method: Among 160-180 new cases of plasma cell dysplasia per year at our center, we retrieved all the cases of plasma cell leukemia. We found 17 cases (pPCL: sPCL:: 9: 8) PCL in duration of 2016-2021. The male and female ratio was 10:7. The range of age ranged from 39 – 71, with mean age of 55.2 yrs. Age ≤50 years was 4/17 cases (39, 39, 45, 50).
Hematological parameters were in the range of as below:
hemoglobin 3.5 – 13.1 gm%, total leukocyte count 2600- 34500/cmm and Platelet count was 15000-230000/cmm. Plasma cell in peripheral blood smear was 5-90% and in bone marrow aspirate (BMA) was 40-90%. B2 microglobulin (B2M) ranged from 1.1 to 12.6 mg/L.
Statistical analysis was done to establish a correlation between pPCL & sPCL in using the following variables:
Age, sex, hemoglobin, TLC, plasma cell % in PS, plasma cell % in BM, Platelet count, B2M, positive M- band in serum & urine, positive M-band in urine only, immunofixation, presence or absence of renal disease (evaluated by the higher value of urea &/ or creatinine), overall survival (months), values of M-band, serum levels of kappa(K), lambda (L), K/L ratio, IgG, IgM, IgA & LDH.

Results: We couldn't find any significant correlation between pPCL

PP07-03

Clinical benefit of measurable residual disease assessment by fragment analysis or next-generation sequencing in patients with multiple myeloma

Hyunsoo Cho[1], Saeam Shin[2], Haerim Chung[1], Ji Eun Jang[1], Yu Ri Kim[1], June-Won Cheong[1], Yoo Hong Min[1], Seung-Tae Lee[2], Jong Rak Choi[2] and Jin Seok Kim[1*]

[1] Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Korea

[2] Department of Laboratory Medicine, Yonsei University College of Medicine, Korea

Background: Measurable residual disease (MRD) negativity is a strong prognostic indicator in patients with multiple myeloma (MM). However, the optimal use of MRD in daily clinical practice has been hampered by technical and practical limitations including standardization and feasibility of MRD testing.

Method: We examined the clinical relevance of commercially available MRD modalities based on immunoglobulin gene-based clonality assays by fragment analysis with IdentiClone® (n = 73 patients) and next-generation sequencing (NGS) with LymphoTrack® (n = 116 patients) in newly diagnosed patients with MM who received autologous stem cell transplantation (ASCT). Following achievement of at least very good partial response after induction therapy, MRD was assessed at the end of induction treatment (pre-ASCT) and/or at 100 days after ASCT (post-ASCT).

Results: MRD remained positive in 41.1% and 28.8% patients pre- and post-ASCT, respectively, by fragment analysis and 56.9% and 51.7% were MRD positive pre- and post-ASCT, respectively, by NGS. Post-ASCT MRD positivity was significant higher in NGS cohort compared with fragment analysis cohort. NGS-based MRD negativ-

ity pre- or post-ASCT was beneficial in terms of PFS and OS. Moreover, NGS-based MRD negativity was independently associated with improved PFS and OS, and MRD positive patients both at pre- and post-ASCT had inferior survival compared with patients with sustained MRD negativity. Clinical benefit of MRD negativity by NGS was highlighted selectively in patients who achieved complete response after induction therapy, and initial adverse prognostic features by high-risk cytogenetics could be mitigated upon achieving MRD negativity by NGS, suggesting that risk may be dynamic. However, benefits of MRD negativity were not observed when MRD was assessed with fragment analysis.

Conclusion: We demonstrate the feasibility and clinical benefit of achieving MRD negativity by commercially available NGS-based MRD assay in MM and support incorporating the simple MRD modality by NGS, but not by fragment analysis, to tailor our therapeutic strategies in real-world practice.

Keyword: Multiple myeloma, Measurable residual disease, Fragment analysis, Next-generation sequencing

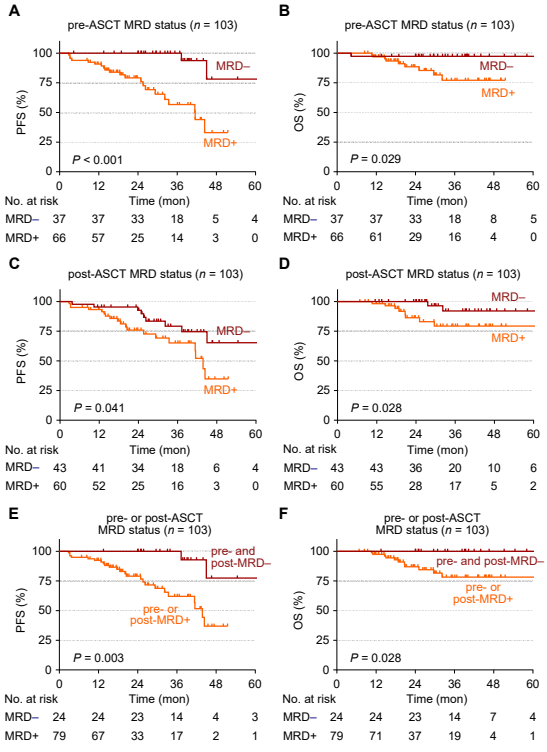


Figure. Clinical benefit of MRD detection by clonality assay with NGS in MM patients who underwent ASCT.

Survival outcome according to the measurable residual disease (MRD) status measured by clonality assay with NGS pre-, post-, or pre- or post- autologous stem cell transplant (ASCT). Kaplan-Meier curves for progression free-survival (PFS) (A, C, E) and overall survival (OS) (B, D, F) of the indicated number of patients and *P*-values were determined by log-rank test.

PP07-04

Updated risk assessment and staging systems in multiple myeloma - real world scenario

Ritu Gupta[1*], Akanksha Farswan[2], Anubha Gupta[2], Sriram K[3], Atul Sharma[4] and Lalit Kumar[4]

[1] Department of Laboratory Oncology, All India Institute of Medical Sciences (AIIMS), New Delhi, India

[2] SBILab, Department of Electronics and Communication, Indraprastha Institute of Information Technology-Delhi, New Delhi, India

[3] Department of Computational Biology, Indraprastha Institute of Information Technology-Delhi, New Delhi, India

[4] Department of Medical Oncology, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Background: Multiple Myeloma (MM) is a malignancy of plasma cells with overall survival ranging from 6 months to more than 10 years. The variability in the outcome is an implication of the biological heterogeneity underlying MM. The current risk predictors of MM have been established on western populations and do not integrate ethnicity-specific information, the impact of which on disease biology cannot be overlooked. Besides, an efficient readily employable risk prognostication method is desirable in settings where genomics tests cannot be performed owing to disparities in the health infrastructure.

Method: In a systematic evaluation, we established the impact of ethnicity in MM risk prediction and validated two efficient and robust AI-enabled risk-stratification systems, namely 1) Modified risk staging (MRS) in patients in whom genomic data on high-risk cytogenetic aberrations (HRCA) is not available and 2) Consensus-based risk-stratification system (CRSS) in patients with the availability of genomic data.

For MRS, K-adaptive partitioning (KAP) was used to find new thresholds for six easy-to-acquire parameters i.e. age, albumin, β2-microglobulin (β2M), calcium, estimated glomerular filtration rate (eGFR) and hemoglobin followed by deduction of risk staging rules via training a J48 classifier. The CRSS was designed using Gaussian mixture model and agglomerative clustering and validated via Cox hazard proportional methods, Kaplan-Meier analysis and Log-rank tests on progression-free survival and overall survival. A Shapley Additive explanation was utilized to establish the biological relevance of the risk predictions.

Results: The MRS and CRSS, established on Indian cohorts, were compared with the Revised International staging system (R-ISS), the current standard of care but established on western patients of MM. Both MRS and CRSS performed better than R-ISS in terms of C-index and p-values. Simple online tools have been designed to allow automated calculation of MRS and CRSS.

Conclusion: Our work discovers changes in cut-offs of prognostic features in Indian MM patients. Our findings establish the significance of integrating ethnicity-specific information in devising robust risk-staging models for MM. With adequate data, this model can be extended to other ethnicities from diverse geographical areas.

Keyword: AI in cancer research, Consensus clustering in cancer, Risk-stratification of multiple myeloma

PP07-05

Light chain multiple myeloma presenting as AL amyloidosis

Dawpadee Dharmasena*, Sanka Vijayabandara and Dhammika Palangasinghe

Teaching Hospital, Karapitiya, Galle, Sri Lanka

Background: Light chain multiple myeloma (LCMM) accounts for 15% of cases of multiple myeloma and it has more aggressive course. Amyloidosis is a rare disease characterized by the deposition of insoluble extracellular fibrillar proteins in various tissues of the body. It is primary systemic amyloidosis (AL Amyloidosis) when associated with some immunocyte dyscrasias. This is the most common form seen in 5–15% of multiple myeloma. We report a case of LCMM presenting as AL amyloidosis with multi system involvement.

Method: Case Report

Results: A 60 year old male was admitted with the complaints of loss of appetite, loss of weight and slurring of speech for three months duration. Furthermore, he complained of bilateral ankle swelling and numbness of both feet for 2 months duration. Examination revealed, a thin built male (BMI of 17kg/m2) with an enlarged, indented tongue. Both submandibular glands were enlarged, but no lymphadenopathy was found. He had bilateral pitting ankle oedema, elevated jugular venous pressure and a postural drop in blood pressure. There was hepatomegaly without splenomegaly. Neurological examination revealed symmetrical stocking type pain and touch sensation impairment in lower limbs up to mid calves with normal power, tone and reflexes. Joint position sensation and vibration sensation were normal. There were no thickened peripheral nerves. Apart from dysarthria, no other cerebellar signs were found. Cranial nerves and fundal examination were normal. His past history included surgery for bilateral carpal tunnel syndrome and he complained no significant improvement after surgery. Full blood count revealed low haemoglobin (Hb – 10.2g/dL, RBC – 3.26x 1012 /L, HCT – 31%) with normal white cell (WBC - 7900/mm3, N - 61%, L - 36%, E – 02%) and platelet counts (228,000/ mm3). Blood picture showed normochromic ,normocytic anemia with mild rouloux formation. ESR was elevated(62 mm in 1sthr). However, renal functions were normal(serum creatinine 102 umol/L) and urine was negative for proteinuria.
Electrocardiogram showed low-voltage complexes and there was hypoechoic myocardium on echocardiogram suggestive of cardiac amyloidosis. Abdominal fat biopsy confirmed the diagnosis of amyloidosis.
The underlying cause for amyloidosis was investigated. Skeletal survey showed lytic lesions on skull. Serum protein electrophoresis was negative for monoclonal band, but serum immune fixation showed a monoclonal increase of "Kappa" light chain. Bone marrow biopsy and immunohistochemistry was suggestive of multiple myeloma. Thus the final diagnosis of light chain myeloma-associated AL amyloidosis was made. Patient was referred to oncology unit for further management.

Conclusion: When multiple myeloma and AL amyloidosis are diagnosed in the same patient, the myeloma is typically diagnosed before the time of amyloid diagnosis, wise-versa in our case. This also aims to increase the awareness of LCMM and of AL type amyloidosis which is rare but often a fatal disease. Detection of AL amyloidosis may facilitate earlier diagnosis of multiple myeloma and thus allow initiation of prompt and specific therapies, which are indispensable in order to improve disease prognosis.

Keyword: Light chain multiple myeloma (LCMM), AL Amyloidosis

PP07-06

Overexpression of PFKFB4 promotes adaptation to hypoxic microenvironment in multiple myeloma

Jie Yang, Fei Wang and Baoan Chen*

Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, China

Background: Multiple myeloma (MM) is a hematological malignancy with monoclonal proliferation of plasma cells, which is closely

related to hypoxic bone marrow microenvironment. Previous studies have found that 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 4 (PFKFB4) is involved in glycolysis, cell cycle progression, autophagy, and metastasis in various tumor diseases and overexpression of PFKFB4 is associated with poor prognosis. However, the underlying mechanism of PFKFB4 in hypoxia adaptation in MM has not been reported.

Method: We analyzed expression profile GSE80140 and GSE80545 downloaded from National Center for Biotechnology Information-Gene Expression Omnibus (NCBI-GEO) database, and conducted cell transcriptome sequencing. 5MPN, a specific inhibitor of PFKFB4, was employed to evaluate the effect of PFKFB4 in hypoxia adaptation in MM by cell proliferation, apoptosis, and cell cycle assays, glucose uptake assay, and Western blot.

Results: MM cell lines (RPMI-8226 and U266) was found to express higher level of PFKFB4 under hypoxia (1% O2) compared to normoxia (20% O2). 5MPN inhibited MM cells proliferation, suppressed glucose uptake, and induced cell cycle arrest in G1 phase. Inhibition of PFKFB4 function had no significant effect on inducing cell apoptosis. Western blot detected the expression of proliferation, apoptosis and cell cycle related proteins, and the results were consistent.

Conclusion: Overexpression of PFKFB4 promotes MM proliferation and cell cycle progression. 5MPN effectively reserves the process, suggesting that PFKFB4 is a potential therapeutic target in MM.

Keyword: PFKFB4, Hypoxia, Glycolysis, Multiple myeloma

PP07-07

Case series: daratumumab monotherapy in relapsed and refractory multiple myeloma patients with severely compromised forced expiratory volume in one second

Jin-Hyo Kim[2], Sung-Soo Park[1*], Jae-Ho Yoon[1], Sung-Eun Lee[1], Hee-Je Kim[1] and Chang-Ki Min[1]

[1] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University, Korea

[2] College of Medicine, The Catholic University, Korea

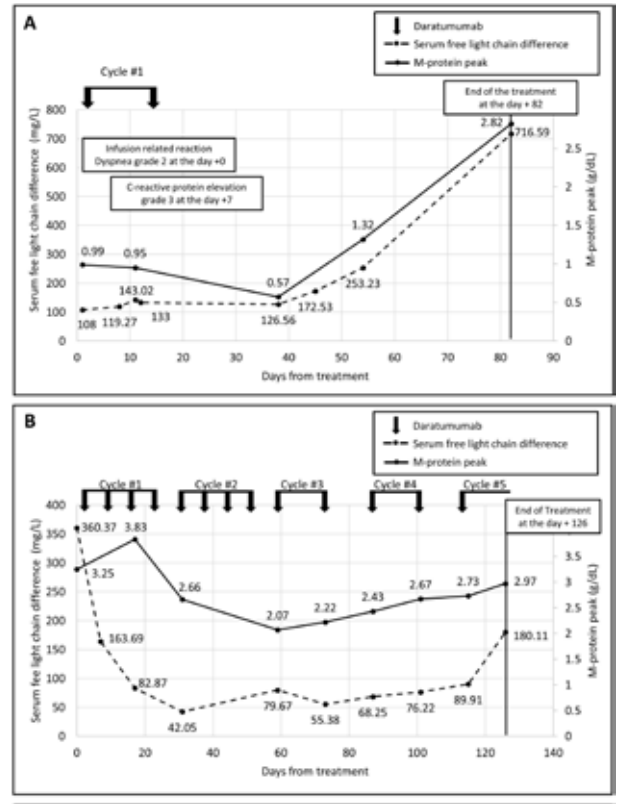
Background: Daratumumab was introduced based on the results of clinical trials that excluded a lung function of forced expiratory volume in one second (FEV1) of < 50% in patients with relapsed or refractory multiple myeloma (RRMM), real-world safety for patients with comprised lung function is not guaranteed. Therefore, the administration of daratumumab to patients with low FEV1s of < 50% could emerged as a difficult challenge.

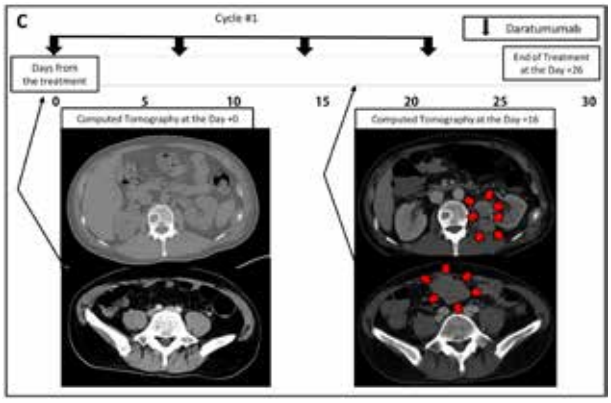
Method: The cases of three RRMM patients who received daratumumab monotherapy despite low lung function with an FEV1 of 43% (case 1), 40% (case 2), and 44% (case 3) were explored. All patients received daratumumab monotherapy at a dose of 16 mg/kg with the intention of weekly treatment for the first 8 weeks (cycles 1 and 2), then every 2 weeks from 9 to 24 weeks (cycles 3 – 6), then every four weeks thereafter (cycles 7 and higher).

Results: We observed grade 2 dyspnea in the patient in case 1 on the day of the first daratumumab infusion, but it was resolved with supportive care. The patient in case 1 also experienced one episode of a grade 3 elevation in C-reactive protein after the first infusion of daratumumab, and the daratumumab schedule was delayed for a week before the second infusion. There were no infusion-related reactions or treatment-emergent adverse events in case 2 and case 3. The best response of the RRMM patients was limited to less than a minimal response.

Conclusion: Conclusively, if the chemotherapeutic options for patients with RRMM are limited, daratumumab monotherapy should not be considered an absolute contraindication for patients with an FEV1 of 40 – 50%.

Keyword: Myeloma, Daratumumab, FEV1, Safety, Lung





PP07-08

Multiple myeloma in Borneo Sarawak Malaysia: a decade of experience in a single center

Tze Shin Leong[1*], Adelyn Fen Ein Tee[1], Ching Tiong Ko[2], Grace Wan Chieng Lee[1] and Lee Ping Chew[1]

[1] Haematology Unit, Medical Department, Sarawak General Hospital, Malaysia

[2] Chemotherapy Drug Reconstitution Unit, Pharmacy Department, Sarawak General Hospital, Malaysia

Background: Sarawak, is the largest state of Malaysia situated on the island of Borneo. Sarawak General Hospital is the tertiary referral center of Sarawak (serving a population of 1 million people). It is 980 km away from its national haematology/transplant referral center in Kuala Lumpur, Malaysia, which is accessible only by air route. Hence, treatment of patients with multiple myeloma in this part of the state is a big challenge due to its geographical constraint.

Method: This is a retrospective study examining basic characteristics and clinical outcomes of multiethnic patients, diagnosed with multiple myeloma between 2010 and 2021 in Sarawak General Hospital. Patients' case notes were traced and the relevant information was entered into a pre-designed data collection form. Data was analysed and interpreted via IBM SPSS Statistics version 27.0.

Results: There were a total of 149 patients with almost equal male to female ratio. The median age for patients was 62 years old (range 29 to 87 years old). Majority of them are local natives of Iban or Bidayuh descendants (n=67, 45.0%) followed by Malay (n=44, 29.8%) and Chinese (n=38, 25.2%). Most common type of multiple myeloma is of IgG variant (n=77, 52.0%). The most common myeloma related organ or tissue impairment (ROTI) is anaemia (n=120, 80.7%) followed by bone lesion (n=112, 75.3%), renal impairment (n=66, 44.5%) and hypercalcaemia (n= 45, 30.5%). More than half presented late with International Staging System - stage III disease (n=84, 56.7%). More than 80% (n= 123) has been treated with either Thalidomide/Dexamethasone or Cyclophosphamide/Thalidomide/Dexamethasone combination. Forty two patients (28.2%) received bortezomib based treatment such as VCD or VTD. Seven patients (n=7, 4.7%) have undergone high dose chemotherapy and autologous stem cell transplant.

Based on a 10 year analysis from 2010 to 2019, eighty two patients died (n=82, 64.7%). Median survival time was 22 months. Two year overall survival (OS) was 48% and progression free survival (PFS) was 40.8%. Multivariate analysis showed age as the only independent predictor of OS. Patients with age more than 60 year old has a lower OS (HR 1.733, CI 1.06-2.84, p value= 0.03). There was a statistical improvement in terms of median overall survival, 12 months vs 17 months (p=0.012) comparing the year 2010 -2014 vs 2016-2019.

Conclusion: Baseline characteristics of patients with multiple myeloma in Borneo Sarawak are similar to the rest of Asia. However, our median overall survival was comparatively lower to our counterparts. This could be due to reasons such as late presentation as a result of lack of awareness of disease; logistic and economic constraints that lead to poorer access to healthcare as well as expensive but effective myeloma medication.

Keyword: Multiple Myeloma, Sarawak, Malaysia, Survival Outcome

PP07-10

Talquetamab, a GPRC5D X CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma: updated phase 1 results from monumental-1

Amrita Krishnan[1*], Monique C. Minnema[2], Jesus G. Berdeja[3], Albert Oriol[4], Niels W.C.J. van de Donk[5], Paula Rodríguez-Otero[6], Elham Askari[7], María-Victoria Mateos[8], Luciano J. Costa[9], Raluca Verona[10], Joanne Ma[11], Suzette Girgis[11], Shiyi Yang[12], Brandi W. Hilder[13], Jeffery Russell[13], Jenna D. Goldberg[13] and Ajai Chari[14]

[1] Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, USA

[2] Department of Hematology, University Medical Center Utrecht, Netherlands

[3] Center for Blood Cancer, Sarah Cannon Research Institute and Tennessee Oncology, USA

[4] Clinical Hematology Service - Clinical Trials Unit, Institut Català d'On-

cologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Spain
[5] Department of Hematology, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Netherlands
[6] Central Clinical Trials Unit, Clínica Universidad de Navarra, Spain
[7] Hematology and Hemotherapy Service, Hospital Universitario Fundación Jiménez Díaz, Spain
[8] Hematology and Hemotherapy Service - Myeloma Unit, University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Spain
[9] Division of Hematology & Oncology, University of Alabama at Birmingham, USA
[10] Oncology Translational Research, Janssen R&D, USA
[11] Clinical Pharmacology, Janssen R&D, USA
[12] Clinical Biostatistics, Janssen R&D, USA
[13] Oncology, Janssen R&D, USA
[14] Medicine, Mount Sinai School of Medicine, USA

Background: G protein-coupled receptor family C group 5 member D (GPRC5D) has limited expression in healthy human tissue but is highly expressed in malignant plasma cells, making it a promising target for immunotherapy approaches for multiple myeloma (MM). Talquetamab (JNJ-64407564) is a first-in-class bispecific antibody that binds to both GPRC5D and CD3 receptors to redirect T cells to kill MM cells. Updated and new results of talquetamab at the recommended phase 2 doses (RP2Ds) are reported (NCT03399799).

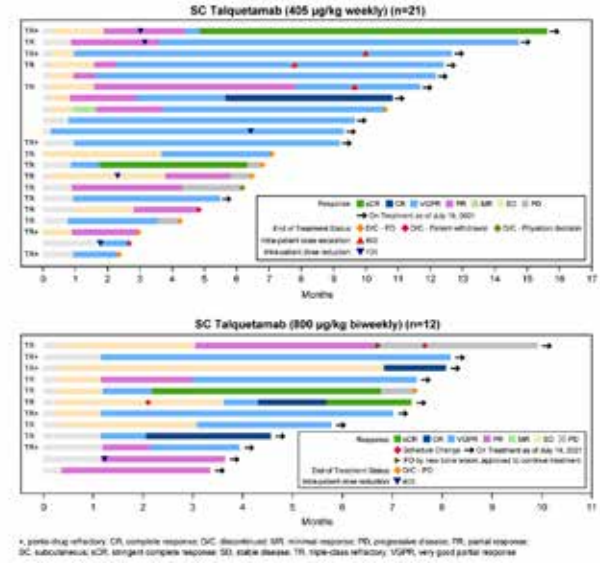
Method: Eligible patients had relapsed/refractory MM (RRMM) or were intolerant to standard therapies. Patients who were previously treated with B-cell maturation antigen (BCMA)-directed therapies were eligible. This analysis focuses on patients who received talquetamab subcutaneously (SC; range: 5.0–800 µg/kg) weekly (QW) or biweekly (Q2W) with step-up dosing. The primary objectives were to identify the RP2D (part 1) and assess talquetamab safety and tolerability at the RP2Ds (part 2). Adverse events (AEs) were graded by CTCAE v4.03; cytokine release syndrome (CRS) was graded per Lee et al 2014 criteria. Responses were investigator-assessed per IMWG criteria.

Results: As of July 19, 2021, 95 patients had received SC talquetamab. The original RP2D was 405 µg/kg SC talquetamab QW with step-up doses, and a second RP2D of 800 µg/kg SC talquetamab Q2W with step-up doses was also identified.
30 patients received 405 µg/kg QW (median 61.5 years [range 46–80]; 63% male; 100% triple-class exposed; 80% penta-drug exposed; 77% triple-class refractory, 20% penta-drug refractory; 30% prior BCMA-directed therapy; median follow-up [mF/U]: 7.5 mo [range 0.9–15.2]). 23 patients received 800 µg/kg Q2W (median 60.0 years [range 47–84]; 48% male; 96% triple-class exposed; 70% penta-drug exposed; 65% triple-class refractory, 22% penta-drug refractory; 17% prior BCMA-directed therapy; mF/U: 3.7 mo [range 0.0–12.0]). No treatment discontinuations due to AEs were reported at either RP2Ds. Most common AEs at the 405 µg/kg QW were CRS (73%; 1 grade 3 CRS), neutropenia (67%; grade 3/4: 60%), and dysgeusia (60%; grade 2: 29%). Skin-related AEs occurred in 77% of patients and were all grade 1/2 (nail disorders: 30%). Infections occurred in 37% of patients (1 grade 3 COVID-19 pneumonia). Most common AEs at 800 µg/kg Q2W were CRS (78%; all grade 1/2), dry mouth (44%; all grade 1/2), and neutropenia (44%; grade 3/4: 35%). Skin-related AEs occurred in 65% of patients with grade 3 events in 13% (nail disorders: 17%). Infections occurred in 13% of patients (1 grade 3 pneumococcal sepsis).
In 30 response-evaluable patients treated at 405 µg/kg QW, the overall response rate (ORR) was 70% (very good partial response or better [≥VGPR]: 57%). In 17 response-evaluable patients treated at 800 µg/kg Q2W, the ORR was 71% (≥VGPR: 53%). Responses were durable and deepened over time with both RP2Ds (Figure). Median duration of response (DOR) was not reached at either RP2D; 6-month DOR rate was 67% (95% CI: 41–84) at 405 µg/kg QW. Serum trough levels of talquetamab were comparable at both RP2Ds. Pharmacodynamic data at both RP2Ds showed peripheral T cell activation and induction of cytokines.

Conclusion: SC talquetamab is well tolerated and highly effective at both RP2Ds. Preliminary data suggest that less frequent, higher doses of SC talquetamab do not negatively impact the safety profile. Further evaluation of talquetamab as monotherapy (phase 2; NCT04634552) and in combination with other therapies in patients with RRMM is underway.

Keyword: Multiple myeloma, Bispecific antibody, T cell redirection, Relapsed/Refractory, GPRC5D, Talquetamab

Figure. Duration of Response



PP07-11

The recovery of absolute lymphocyte count predicts a good prognosis in daratumumab-treated patients with relapsed/refractory multiple myeloma

Hee Jeong Cho[1], Jae-Cheol Jo[2], Yoo Jin Lee[2], Myung Won Lee[3], Do-young Kim[4], Ho Jin Shin[4], Sung Nam Lim[5], Ji Hyun Lee[6], Sung Hwa Bae[7], Young Rok Do[8], Won Sik Lee[9], Min Kyung Kim[10], Jung Min Lee[1], Ju-Hyung Kim[1], Dong Won Baek[1], Sang-Kyun Sohn[1] and Joon Ho Moon[1*]

[1] Department of Hematology/Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Korea
[2] Ulsan University Hospital, University of Ulsan College of Medicine, Department of Hematology and Oncology, Korea
[3] Department of Hematology-Oncology, Chungnam National University Hospital, School of Medicine, Chungnam National University, Korea
[4] Department of Hematology-Oncology, Pusan National University Hospital, Pusan National University School of Medicine, Korea
[5] Department of Hematology-Oncology, Inje University Haeundae Paik Hospital, Korea
[6] Department of Hematology-Oncology, Dong-A University Hospital, Korea
[7] Department of Hematology-Oncology, Daegu Catholic University Hospital, Daegu Catholic University School of Medicine, Korea
[8] Department of Hematology-Oncology, Keimyung University School of Medicine, Korea
[9] Department of Hematology-Oncology, Inje University Busan Paik Hospital, Korea
[10] Department of Hematology-Oncology, Yeungnam University Hospital, Korea

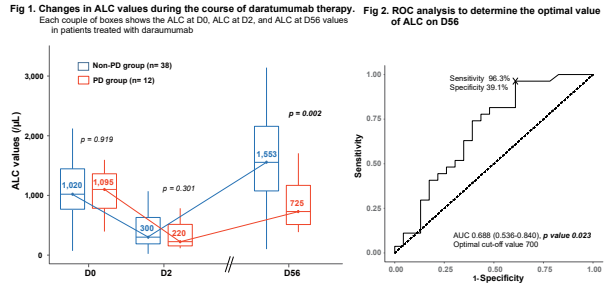
Background: Daratumumab selectively binds to CD38, which is highly and ubiquitously expressed in malignant plasma cells, and has shown an encouraging antitumor effect in patients with multiple myeloma (MM). Daratumumab was known to alter T cell repertoire by inhibiting CD38-expressing immunosuppressive cells. We aimed to evaluate the recovery of absolute lymphocyte count (ALC) as a surrogate marker that predicts the survival outcomes in daratumumab-treated patients with relapsed/refractory MM (RRMM).

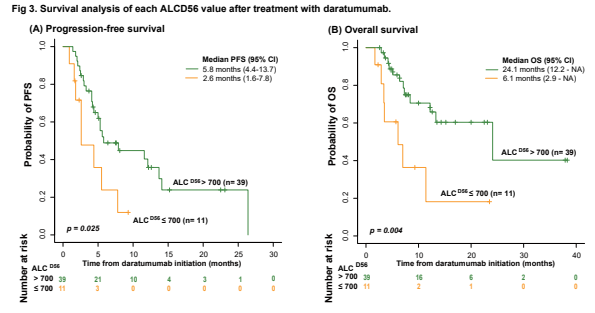
Method: The medical records of RRMM patients treated with daratumumab monotherapy from 10 centres in South Korea between 2018 and 2021 were reviewed. We collected the ALC data at pre-infusion (D0), day 2 after the first infusion (D2), and prior to the third cycle of daratumumab therapy (D56). A receiver-operating characteristic curve (ROC) analysis was conducted to determine the optimal cut-off value of ALC that predict the treatment outcomes.

Results: Fifty patients who were administrated at least two cycles of daratumumab were included. Patients received a median of four previous lines (range, 3–7) of therapy including proteasome inhibitors, or immunomodulatory agents, before daratumumab treatment. The median number of daratumumab cycles was 4.5 (range, 2–25). Twenty-seven patients (54.0%) achieved partial treatment response or better after two cycles of daratumumab treatment. On D2 after daratumumab, almost all patients experienced a marked reduction in ALC. However, an increase in ALC on D56 (ALCD56) was observed in patients with non-progressive disease: 1,020/μL, 300/μL, and 1,553/μL on D0, D2, and D56, respectively, whereas failure of ALC recovery was noted in those with progressive disease: 1,095/μL, 220/μL, and 725/μL on D0, D2, and D56, respectively (Fig 1). The cut-off value for ALCD56 by ROC analysis was 700/μL (area under the curve [AUC] =0.668, p=0.023) (Fig 2). Patients with ALCD56>700/μL (n=39, 78.0%) had a prolonged progression-free survival (PFS) and overall survival (OS) than those with ALCD56≤700 (median PFS: 5.8 vs. 2.6 months, p=0.025; median OS: 24.1 vs. 6.1 months, p=0.004) (Fig 3). In addition, ALCD56 > 700/μL was a significant favourable prognostic factor for PFS (hazard ratio [HR]: 0.22, p= 0.003) and OS (HR: 0.23, p=0.012).

Conclusion: ALC recovery during daratumumab treatment was significantly associated with prolonged survival outcomes in patients with RRMM. The ALC value could predict the clinical outcomes in patients treated with daratumumab.

Keyword: Multiple myeloma, Daratumumab, Absolute lymphocyte count, Prognosis





PP07-12

Galectin-1, Galectin-3, Galectin-9 and their role in monoclonal gammopathy of undetermined significance and multiple myeloma in residents of the Gomel region of Belarus

Zhanna Kozich[1], Viktor Martinkov[1], Janna Pugacheva[1] and Natalya Klimkovich[2]

[1] Hematology department, Republican Research Center for Radiation Medicine and Human Ecology, Belarus

[2] Hematology department, Belarusian Medical Academy for Postgraduate Education, Belarus

Background: MM is a malignancy of lymphoid tissue which passes through the stage of MGUS in its development.

Currently, there are no effective biomarkers associated with MGUS and MM progression.

There are not enough evidence on galectins levels in blood serum at plasmocell dyscrasia in literature.
We have studied galectins levels in blood serum in patients with firstly determined MM and MGUS.
Method : The study included 101 patients (46 patients with firstly determined MM and 56 with MGUS) observed in RRCRM&HE for 2018-2021 period.
The average age of patients with MM is 63.8 years
The average age of patients with MGUS is 59.6 years.
Females prevailed in both groups.
The galectin-1, galectin-3, galectin-9 concentration was determined quantatively using ELISA kit by Wuhan Fine Biotech Co accorng to the Producer's manual.

Results: The progression of MGUS to MM during the observation period was recorded in 10.9% (20) of cases.

Galectin-1 levels in serum ranged from 0.84 to 100 (mean 14.9).
Patients with MGUS who progressed into MM, were detected with increased galectin-1 level (p=0.059 for the Mann-Whitney test)
These were MGUS patients with plasmacytoma or single destructions.The increase in the galectin-1 level in patients was significantly more common in MM patients with multiple bone tissue destruction (p=0.039).
The galectin-3 level varied from 7.5 to 77.9 (mean value 23.4). A significant increase of galectin-3 was detected in MM patients with kidney damage (p<0.001 for the Mann-Whitney test). A significant increase of galectin-3 was also detected in MGUS patients with immunoglobulin light chain secretion or kidney damage (p<0.001 for the Mann-Whitney test).These patients showed a significant increase of β2-microglobulin level over 3 g/l (p<0.001). In patients with a high percentage of tumor plasma cells in the bone marrow, multiple destructions in the bones and kidney damage, an increase of both galectin-1 and galectin- 3 in serum was revealed (p<0.001 and p=0.037 for the Mann-Whitney test).
The galectin-9 level varied from 0.22 to 1.5 (average 0.72). The increase of this galectin-9 was revealed in all patients with MM and MGUS. No differences were found among both groups.

Conclusion: As result it was determined that the increase of galectin-3 was revealed significantly more often in MM and MGUS patients with kidney damage or immunoglobulin light chain secretion in relation to other patients.

The increase of galectin-1 was more common in patients with bone lesion syndrome.
Our results show that increase of galectin-1 and galectin-3 in MGUS and MM patients is a sign of progression and unfavourible prognosis. Detection of these markers at MGUS stage can be efficient for clinisist in determining the high risk groups.

Keyword: Multiple myeloma, Monoclonal gammopathy of Undetermined significance, Galectin-1, Galectin-3, Galectin-9

PP07-13

CC-92480 when combined with bortezomib/dexamethasone enhances cell-autonomous cytotoxicity through G_2/M transition blockade in multiple myeloma

Chad C. Bjorklund[1*], Michael Amatangelo[1], Jian Kang[2], Hsiling Chiu[2], Archana Mukhopadhyay[1], Krista Wollerman[3], Michael Pourdehnad[4], Patrick Hagner[1] and Anjan Thakurta[1]

[1] Translational Medicine-Hematology, Bristol Myers Squibb, USA

[2] Research & Development, Bristol Myers Squibb, USA

[3] Pharmaceutical Development, Bristol Myers Squibb, USA

[4] Early Clinical Development, Hematology/Oncology and Cell Therapy, Bristol Myers Squibb, USA

Background: CC-92480, a novel cereblon E3 ligase modulator (CELMoD®) agent, is being investigated in relapsed/refractory multiple myeloma (RRMM) patients (pts) in combination with bortezomib (BORT) and dexamethasone (DEX) (NCT03374085/NCT03989414). Pomalidomide (POM) is an established agent in RRMM; the mechanistic synergy of POM/BORT/DEX in MM cell lines

was shown previously (Katz M, et al. Blood 2018;132[suppl 1]. Abstract 1934). Here we compared and differentiated the mechanisms of action (MOAs) for cell autonomous cytotoxic activities of CC-92480 or POM ± BORT/DEX.

Method: Comparative analysis of antiproliferative activity was performed on H929 and MM1.S cell lines. Ikaros/Aiolos degradation was evaluated by flow cytometry. Transcriptomic and gene set enrichment analyses (GSEA) were performed to identify key pathways responsible for synergistic combination and pathway differences between single and combined agents. DNA fragmentation by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), with cell cycle flow cytometry, was used to examine how these pathways contributed to cell cycle specific apoptotic induction.

Results: In MM cells, CC-92480 demonstrated a more potent inhibition of proliferation at 100-fold lower doses compared with POM. Titration of POM or CC-92480 + 1 h BORT pulse showed an enhancement of antiproliferative capacity in doublet and triplet combinations compared to single agents. Combination indices for POM/BORT/DEX or CC-92480/BORT/DEX resulted in values < 1 for most combinations indicating a synergistic effect. POM or CC-92480 + BORT or DEX, or in triplet combinations, increased induction of apoptosis (>90% for each triplet compared to POM [20%] and CC-92480 [40%]). Compared to treatment with single agents, MM cells treated with POM/BORT/DEX or CC-92480/BORT/DEX at clinically relevant concentrations showed slight kinetic delay in Aiolos/Ikaros depletion at early time points, and were indistinguishable at 24 h.

Pathways dysregulated by POM or CC-92480 included previously identified interferon, protein homeostasis, and proliferation gene sets. GSEA showed substantial pathway differences when comparing the triplets, including general cell cycle progression, cell division, and chromatin segregation. One of the most significant differences identified was in genes involved in the negative regulation of G_2/M transition.

Temporal assessment demonstrated a rapid accumulation of bromodeoxyuridine (BrdU) incorporation in all cell cycle phases when treated with POM/BORT/DEX or CC-92480/BORT/DEX, indicating cell death was occurring within all phases. However, a marked enhancement of G_2/M BrdU incorporation (80% vs 40% of G_2/M population) was observed at 18-24 h when treated with CC-92480/BORT/DEX vs POM/BORT/DEX. G2/M transition-dependent cyclins A and B were shown to be dysregulated by CC-92480 but not by POM. These data indicate that CC-92480 + BORT potentiates a G_2/M arrest that is not observed with POM in MM cells.

Conclusion: These results show that CC-92480 ± BORT/DEX elicits a more potent cytotoxic effect on MM cells compared to POM. Importantly, POM or CC-92480 MOA was not appreciatively affected when the single agent was combined with a proteasome inhibitor (eg, BORT). A key differentiating mechanism of cell autonomous activity was also identified for CC-92480 + BORT/DEX where MM cells enhance apoptotic induction at the G_2/M stage compared to POM. This mechanistic difference suggests that pts treated with CC-92480/BORT/DEX have a greater cytotoxic response compared to POM/BORT/DEX.

Keyword: Multiple myeloma, Plasma cell disorders, Translational research

PP07-14

The GNRI (geriatric nutritional risk index) as a prognostic factor in patients with newly diagnosed multiple myeloma

Sewon Lee[1], Seounggye Byeon[2], Yeung-Chul Mun[1] and Young Hoon Park[1*]

[1] Hematology-Oncology, Ewha Womans University College of Medicine, Mokdong Hospital, Korea

[2] Hematology-Oncology, Ewha Womans University College of Medicine, Seoul Hospital, Korea

Background: Malnutrition has negative impacts on treatment outcomes and prognosis in various clinical settings including cancer. To date, the Geriatric Nutritional Risk Index (GNRI) is well-established nutritional assessment tool which was developed as an index to predict morbidity and mortality in geriatric patients. Recent studies have shown that GNRI is a simple and important prognostic factor in various cancers. However, whether GNRI can be a useful prognostic marker for newly diagnosed multiple myeloma (NDMM) has not been addressed.

Method: We retrospectively reviewed data of 127 NDMM patients in our institution between 2008 and 2020. The GNRI score calculated from albumin and body weight at the time of diagnosis (14.89 x albumin [g/dL] + 41.7 x [actual body weight/ideal body weight]). A receiver operating characteristic (ROC) curve was used to determine the best cutoff value of the GNRI for predicting survival and patients were classified into two groups based on ROC curve: Low-risk (GNRI ≥90) and high-risk (GNRI <90) group (sensitivity 80.5%, specificity 64.0%).

Results: There were 127 patients with NDMM, including 55.1% (n=70) males and 44.9% (n=57) females, with the median age of 66.6 years (range, 40-97). The median level of each parameter at the time of diagnosis of MM were 3.2 g/dL (range, 1.6-4.7) in serum albumin, 59.5 kg (range, 36.2-89.2) in body weight, and 90.3 (range, 50.6-125.0) in the GNRI. Based on cut-off value of GNRI score, 48.0% (n=61) of patients were classified as high-risk group and 52.0% (n=66) as low-risk group. The median OS were 30.0 months at high-risk group and 53.5 months at low-risk group. In univariate analysis,

high-risk group (GNRI <90), high International Staging System (ISS), and high revised ISS (R-ISS) were significantly associated with overall survival (OS; p=0.001, 0.19, and 0.002), respectively. Pearson's correlation analysis demonstrated that both ISS and R-ISS correlated with GNRI: ISS and GNRI (r=-0.33, P<0.001), and R-ISS and GNRI (r=-0.29, P=0.001). A multivariate analysis demonstrated that high ISS (hazard ratio [HR] 4.64, 95% confidential interval [CI] 0.262-1.370, p=0.002) and high-risk group (GNRI <90, HR 2.1, 95% CI 1.268-3.478, p=0.004) were independent poor prognostic factors for OS.

Conclusion: We suggest that the GNRI score is simple to calculate and maybe a useful prognostic factor in patients with NDMM.

Keyword: Geriatric Nutritional Risk Index, Multiple myeloma, Nutrition, Prognostic value

PP07-15

Treatment outcome and prognostic factors of newly diagnosed multiple myeloma receiving bortezomib-based induction in Hong Kong: an analysis of 448 patients

Hoi Ki Karen Tang[1], Chi Yeung Fung[1], Yu Yan Hwang[1], Harold Lee[2], Sze Fai Yip[3], Howard Wong[4], Chi Kuen Lau[5], Kwan Hung Leung[6], Elaine Au[7], Bonnie Kho[4], Eric Tse[1], Joycelyn Sim[1], Yok Lam Kwong[1] and Chor Sang Chim[1*]

[1] Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong
[2] Department of Medicine, Princess Margaret Hospital, Hong Kong
[3] Department of Medicine, Tuen Mun Hospital, Hong Kong
[4] Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong
[5] Department of Medicine, Tseung Kwan O Hospital, Hong Kong
[6] Department of Medicine, United Christian Hospital, Hong Kong
[7] Department of Pathology, Queen Mary Hospital, University of Hong Kong, Hong Kong

Background: In Hong Kong, newly diagnosed multiple myeloma (NDMM) receive bortezomib-based triplet induction. NDMM ≤65 years of age are considered transplant-eligible (TE), and upfront ASCT is offered to all TE patients ≤65 years, unless medically unfit (TE-unfit) or refused (TE-refused).

Method: Data was retrieved for our cohort of 448 patients to assess the outcomes of NDMM and post ASCT recipients.

Results: For the entire cohort, adverse factors for both event free survival (EFS) and overall survival (OS) were male gender, advance ISS, R-ISS stage 3 and high LDH. Multivariate analysis excluding high-risk cytogenetics (due to incomplete data) showed that male gender (p=0.023), advance ISS (p=0.001), high LDH (p=0.00012) were negative predictors for OS, while CR/nCR post-induction (p=0.000198) and post-ASCT (p=0.000258) were protective factors for OS. In the TE group, upfront ASCT were conducted in 252 (76.1%). Among TE patients who had undergone ASCT, adverse risk factors for OS and EFS included advanced ISS, R-ISS stage 3 and high LDH. Multivariate analysis excluding high-risk cytogenetics (due to incomplete data) showed age≥60 (p=0.002), ISS3 (p=0.004) and high LDH (p=0.001) were adverse factors for OS. High-risk FISH (p=0.022) negatively impacted OS despite ASCT. Among the TE patients, ASCT was not performed in 63, due to being medically unfit (TE-unfit) (N=41; 12.4%) or patient refusal (TE-refused) (N=22; 6.6%). Compared with transplanted MM, failure to undergo ASCT in TE patients rendered an inferior OS (TE-unfit p=1.06x10-8 and TE-refused p=0.002) and EFS (TE-unfit p=0.00013 and TE-refused p=0.002), with survivals comparable to that of TIE patients (p=0.614).

Conclusion: Our data reaffirmed the favorable impact of ASCT and importance of CR/nCR. Importantly, among TE patients, triplet induction, followed by ASCT has not abolished the adverse impact of advanced ISS or R-ISS. Age>60 remained an adverse factor. Finally, refusal of ASCT rendered an inferior EFS and OS comparable to TIE MM that requires due consideration when providing counselling on ASCT.

Keyword: Multiple myeloma, Prognostic factor, Autologous stem cell transplant, Transplant eligibility, Bortezomib-based induction

PP07-16

Favorable outcomes of 3-weekly daratumumab-based regimens in relapsed/refractory multiple myeloma: impact of MRD, rapid doubling time, LDH, triplets and quadruplets

Cheong Ngai[1], Hoi Ki Karen Tang[1], Chi Yeung Fung[1], Yu Yan Hwang[1], Kai Chung Vincent Wong[2] and Chor Sang Chim[1*]

[1] Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong
[2] Department of Pharmacy, Queen Mary Hospital, University of Hong Kong, Hong Kong

Background: In relapsed or refractory MM (RRMM), addition of daratumumab (dara) rendered superior response rates and survivals. Herein, using 3-weekly dara as the backbone, we evaluated the outcomes of dara-based regimens in RRMM.

Method: Forty patients with RRMM were treated at Queen Mary Hospital, Hong Kong, using either dara-IMid-dexamethasone (dara-IMiD-triplet), dara-IMiD-dexamethasone + proteasome inhibitor (dara-IMiD-quadruplet) or dara-(non-IMid) regimens (dara-cyclophosphamide/carfilzomib-dexamethasone or dara-carfilzomib-cyclophosphamide-dexamethasone). Daratumumab was used every 3 weekly until maximum response or at least 8 doses, followed by either IMiD maintenance till disease progression, or no maintenance, after maximal response. Responses were documented after one cycle and four cycles, and at best responses. Overall survival (OS), event free survival (EFS) and progression free survival (PFS) were computed. Minimal residual disease (MRD) was studied by next generation sequencing using LymphoTrack System. Risk factors for OS and PFS were also evaluated.

Results: Of the forty patients, the median age was 64.5 (range: 46 - 91 years), and number of prior lines of treatments was two. Ten patients (25%) were refractory to bortezomib, 21 (52.5%) to lenalidomide, and 24 (62.5%) to last treatment. Twenty-five patients (62.5%) have undergone ASCT. High-risk cytogenetics occurred in 7 (25.9%) patients. All patients achieved a response with 33 (80%) achieving ≥very good partial response (VGPR) at best responses. Median time to VGPR is 2.5 months. The median OS was not reached in both dara-IMiD-triplet and dara-IMiD-quadruplet but 17 months in dara-non-IMiD regimens (p=0.004), and median PFS was not reached in dara-IMiD-quadruplet, 23 months in dara-IMiD-triplet and 15 months in dara-non-IMiD regimen (p=0.014). Among the dara-IMiD group, dara-IMiD-quadruplet yielded superior PFS than the dara-IMiD-triplet (median not reached vs 23 months, P=0.02) while the median OS were both not reached (P=0.813). In the entire cohort, inferior OS was associated with high lactate dehydrogenase (LDH) at relapse (median: 27 months vs not reached, P=0.004). Shorter PFS was noted in patients with 1q gain (16 months vs 39 months, P=0.02) and a rapid doubling time of paraprotein (18 months vs not reached, p=0.016). Among the fifteen patients with MRD studied at ≥near CR, MRD-negativity was achieved in three (37.5%) of dara-IMiD-triplet and 3 (75%) of dara-IMiD-quadruplet (p=0.545). MRD negativity rendered superior median EFS (not reached vs 14 months, p=0.013).

Conclusion: A 3-weekly daratumumab-based regimen, especially in combination with IMiD, is highly effective in RRMM. Risk factors for survival included LDH, rapid doubling time, 1q gain and MRD. A prospective study is warranted.

Keyword: Daratumumab, relapsed or refractory multiple myeloma, 3-weekly daratumumab, Minimal residual disease, Triplets, Quadruplets

PP07-17

Effective substances for the treatment of multiple myeloma using a prohibitin-targeted chromanone compound derivatives

Young Eun Lee[1,2], Ju Heon Park[1], Ha Jin Lim[1], Hye Ran Kim[3], Jong Hee Shin[1] and Myung Geun Shin[1,2*]

[1] Department of Laboratory Medicine, Chonnam National University Hwasun Hospital, Hwasun, Korea

[2] BioMedical Sciences Graduate Program (BMSGP), Chonnam National University and Chonnam National University Hwasun Hospital, Hwasun, Korea

[3] College of Korean Medicine, DongShin University, Naju, Korea

Background: More than 70% of multiple myeloma (MM) occurs in elderly patients over the age of 65, and the incidence of MM has remarkably increased in Korea over the past 20 years, so it is possible to discover a new therapeutic agent that can be safely used in elderly patients. Lenalidomide-based therapeutics and proteasome inhibitors, which are currently used as the basis for the treatment of MM in clinical practice, are accompanied by systemic side effects such as pancytopenia, peripheral neuropathy, and severe skin lesions. Therefore, it is necessary to develop new therapeutic agents that can overcome the serious side effects, treatment tolerance or resistance of these therapeutic agents.

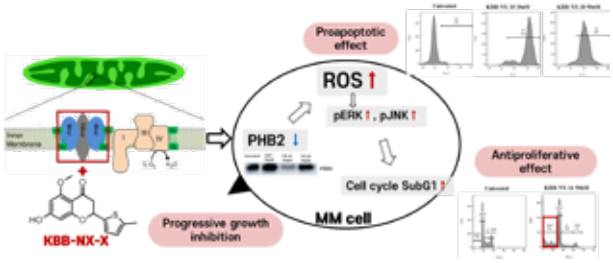
Method: A chromanone-based (KBB-NX derivatives) low-molecular compound was synthesized targeting prohibitin (PHB), which is our own companion diagnostic marker for hematologic cancer such as MM. For the synthesized low-molecular weight synthetic substances, effective substances are discovered through efficacy verification tests at the cell line level, blood stability tests, pharmacokinetic tests using laboratory animals, and single-dose toxicity tests. After that, after conducting an efficacy test using the MM mouse model that we built ourselves, we want to discover a lead compound that can be used for non-clinical testing at the GLP level.

Results: In this study, 30 kinds of KBB-NX-based active substances that have an apoptotic effect on MM cells by blocking PHB2 protein were obtained. When these active substances are treated on MM cells, PHB2 function is inactivated to increase intracellular reactive oxygen species (ROS) production, and then, proapoptotic and anti-proliferative effects are induced to kill MM cells. Among the discovered active substances, when KBB-NX16 was exposed to a MM cell line, the amount of target PHB2 protein decreased by more than 90%, confirming high molecular-target binding ability. Among the compounds synthesized by itself as a KBB-NX derivative, KBB-NX20 was found to have an IC50 of less than 1μM. In an initial pharmacokinetic test conducted using rats for KBB-NX16 and KBB-NX20

compounds, their half-lives were very short, less than 1 hour and 40 minutes, so the need for formulation studies emerged. The need for early pharmacokinetic testing has been raised.

Conclusion: We developed effective substances for the treatment of MM using a PHB-targeted chromanone compound with an apoptosis mechanism by the excessive production of intracellular ROS. These results might provide an important clue for the development of a new chemotherapeutics for MM using a PHB2 target chromanone compound.

Keyword: Multiple myeloma, Anticancer drugs, Chromanone



PP07-18

Determinant factors for early mortality in newly diagnosed multiple myeloma patients

Javad Alizargar

Nursing, Taipei University of Nursing and Health Sciences, Rep of China (Taiwan)

Background: In the recent years we have observed a great improvement in the survival of patients with multiple myeloma (MM), because of the novel treatments and drugs. But the challenge still remains for the survival of about 10% of MM patients who die very fast after the disease diagnosis. In this study we try to investigate the associated factors for early mortality in MM patients.

Method: We evaluated 315 newly diagnosed MM patients from the registry of Alzahra Hospital between 2006 and 2017. Early mortality (within 2 month of diagnosis) were detected among those patients and disease history and baseline characteristics and laboratory data were used in univariate and multivariate analysis to find the independent factors which are associated with the early mortality.

Results: Thirty six patients (11.4%) experienced early mortality. In the univariate analysis male gender, Hemoglobin less than 10 g/dL, platelet less than 150,000/μ, serum albumin less than 3.5 g/dL, corrected serum calcium more than 12 mg/dL, serum creatinine more than 2 mg/dL, lactate dehydrogenase (LDH) more than 250 U/L and serum beta 2 microglobulin more than 5500 md/L were associated with early mortality (all p values less than 0.05). Multivariate analysis showed that male gender (OR= 3.2, CI=2.8-4.9), having the serum albumin less than 3.5 g/dL (OR= 2.2 CI=1.5-6.1), corrected serum calcium more than 12 mg/dL (OR=1.3, CI=1.1-3.6), LDH more than 250 U/L (OR=1.7, CI=1.3-5.2) had independent effects on the early mortality when controlling for other risk factors.

Conclusion: We can conclude that male MM patients with serum albumin less than 3.5 g/dL, corrected serum calcium more than 12 mg/dL and LDH more than 250 U/L have a greater risk for the early mortality.

Keyword: Multiple Myeloma, Mortality, Serum albumin level, Lactate dehydrogenase

PP07-19

Clinical profiles and survival outcomes of adult patients with multiple myeloma at a tertiary hospital in the Philippines

Jeremiah Vallente*, Carlo Francisco Cortez and Ma. Angelina Mirasol

Department of Medicine, University of the Philippines – Philippine General Hospital, Philippines

Background: The Filipino population is largely underrepresented in the currently available literature on multiple myeloma (MM). Herein, we aimed to determine the clinical profile, treatment, and outcomes of adult Filipinos with MM.

Method: The records of 74 patients with MM seen at our institution from 2016 to 2019 were retrospectively reviewed.

Results: The median age at diagnosis was 54 years, with the majority lumped in the 40-65 years age group. At diagnosis, anemia (hemoglobin <100 g/L) was present in 64.3% of patients, but hypercalcemia (calcium ≥11.0 mg/dL) and azotemia (creatinine ≥2.0 mg/dL) were seen in only 20.0% and 34.0% of patients, respectively. Novel drugs (bortezomib, thalidomide, lenalidomide) were used in 84.4% of patients for frontline treatment. The overall response rate was 70.0% and the median overall survival was 60 months. On univariate analysis, only the hemoglobin and the serum albumin levels affected survival.

Conclusion: There is a trend towards a younger age at diagnosis in adult Filipinos with MM. Aside from this, there are no other unique clinical characteristics of MM seen in Filipinos. The longer overall survival may reflect the availability of newer drugs in the recent decade, but larger studies are needed to investigate the prognostic significance of several clinical and treatment parameters.

Keyword: Multiple myeloma, Clinical profiles, Survival, Retrospective study, Filipino

PP07-20

Treatment outcomes with reduced-dose bortezomib in adult patients with multiple myeloma: a single-center experience

Jeremiah Vallente*, Carlo Francisco Cortez and Ma. Angelina Mirasol

Department of Medicine, University of the Philippines – Philippine General Hospital, Philippines

Background: Bortezomib vial-sharing is commonly employed to maximize the treatment of patients with multiple myeloma (MM) in the resource-limited setting. This strategy minimizes delays in treatment but reduces the dose of bortezomib received by the patient. Herein, we aimed to determine the treatment patterns and outcomes in Filipino patients with MM who received reduced-dose bortezomib.

Method: The records of 47 adult patients with MM, seen at our institution from 2016 to 2019 and treated with reduced-dose bortezomib, were retrospectively reviewed.

Results: The median age of the patients at diagnosis was 55 years; 59.6% were male. VCD (bortezomib, cyclophosphamide, dexamethasone) regimen was the most commonly used (70.7%) bortezomib-based treatment. Among the newly diagnosed patients, bortezomib-based treatment afforded an overall response rate (ORR) of 79.3%. The median overall survival (OS) was not reached. Univariate analysis showed that the hemoglobin level affected response while age, hemoglobin and calcium levels, the choice of induction regimen, and the depth of response all had an impact on survival.

Conclusion: This study is the first to investigate the real-world outcomes of reduced-dose bortezomib in MM treatment and may provide initial evidence that bortezomib vial-sharing is an acceptable strategy in the treatment of MM in the resource-limited setting.

Keyword: Multiple myeloma, Bortezomib, Treatment outcomes, Retrospective study, Filipino

PP07-21

Inhibition of mitochondrial thioredoxin by auranofin increases bortezomib-induced cell death through autophagy and mitochondrial ROS in multiple myeloma cell line

Young Hoon Park, Jee Young Ahn and Yeung-Chul Mun*

Division of Hemato-Oncology, Department of Internal Medicine, Ewha Womans University Mokdong Hospital, Korea

Background: The thioredoxin (Trx) system is one of the major cellular antioxidant systems and is comprised of thioredoxin, thioredoxin reductase (TrxR), and NADPH. Auranofin (ARF), a TrxR system inhibitor, induces multiple myeloma (MM) cell death. Preclinical studies have reported synergistic cytotoxicity with dual blockade of the proteasome and autophagy in MM. Here, we aimed to correlate ARF-induced inhibition of TrxR system activity with bortezomib (BTZ)-treated MM cell death and to study the interactions of mitochondrial Trx with autophagy and mitochondrial reactive oxygen species (ROS).

Method: We performed western blot assay using non-reducing or reducing gel, MTT assay, and flow cytometry analysis to evaluate the change of cell death, autophagy, proliferation, mitochondrial ROS and cellular level of redox enzymes in a human MM cell line, MM.1S, treated with BTZ. We also administered chloroquine (CQ) or ARF with BTZ in MM.1S to inhibit late stage of autophagy or mitochondrial Trx system, respectively.

Results: Mitochondrial ROS of MM.1S was elevated significantly after 18 hours of BTZ (2-5 nM). Autophagy of MM.1S after BTZ treatment was increased in concordance with mitochondrial ROS increment and apoptosis of MM.1S. N-acetylcystein (NAC) reversed BTZ-induced mitochondrial ROS elevation and apoptosis of MM.1S as well. When ARF was administered to MM.1S, further increased expressions of cleaved PARP and Caspase-3 were observed during BTZ-induced MM cell apoptosis compared to BTZ treatment alone. LC3-II and SQSTM-1 expression were also elevated along with increment of mitochondrial ROS and decrement of proliferation after BTZ plus ARF treatment. Inhibition of autophagy with CQ was observed in a further increase in BTZ-induced apoptosis and mitochondrial ROS in MM.1S. When CQ was administered to BTZ-treated MM.1S,

PRX4 dimerization was decreased. NAC reversed decreased PRX4 dimerization and apoptosis of MM.1S after BTZ treatment as well.

Conclusion: Our experiment showed crosstalk between autophagy and mitochondrial ROS and its redox enzymes during BTZ-induced MM.1S apoptosis. ARF, a TrxR system inhibitor, potentiates BTZ-induced apoptosis of MM.1S through increasing mitochondrial ROS. Our results provide new perspective on the cellular mechanism of action of BTZ in mitochondrial specific Trx and ROS and support the synergism of BTZ together with autophagy by TrxR system inhibitor in MM.1S.

Keyword: Multiple myeloma, Thioredoxin, Bortezomib, Auranofin, Autophagy, Reactive oxygen species

PP07-23

Real-world toxicity and efficacy of ixazomib, lenalidomide, and dexamethasone in Asian patients with relapsed and refractory multiple myeloma

Ji Hyun Lee[1], Sung-hyun Kim[1], Hye Ryeon Kim[1], Joon Ho Moon[2], Chang-Ki Min[3], Je-Jung Lee [4], Ho-Jin Shin[5], Jae-Cheol Jo[6], Ji Yun Lee[7] and Ki-Hyun Kim[8]

[1] Department of Internal Medicine , Dong-A University College of Medicine, Korea
[2] Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, Korea
[3] Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea
[4] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea
[5] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[6] Department of Internal Medicine , Chonbuk National University Medical School, Korea
[7] Department of Internal Medicine, Pusan National University Hospital, Korea
[8] Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Korea

Background: Ixazomib, lenalidomide, and dexamethasone (IRd), have proven efficacy with excellent safety profile and convenience in relapsed and refractory multiple myeloma (RRMM). However, there are limited reports of IRd regimens in the real-world Asian population with RRMM in terms of the safety and efficacy.

Method: Sixty patients with RRMM, treated with ixazomib, supported by the patient assistance program, in combination with lenalidomide and dexamethasone, were retrospectively analyzed by the electronic medical record review.

Results: The median patient age was 68 years. Forty percent of the patients were trial-ineligible. The patients received a median of one prior line of therapy. The overall response rate was 80%, and the progression-free and overall survival were not reached after a median follow-up of 9.2 months. Thalidomide non-refractoriness and thalidomide response duration of ≥12 months significantly reduced the risk of progression. Non-hematologic adverse events (AEs) were more common than hematologic AEs, most commonly skin rash followed by gastrointestinal toxicities, and infections. Grade 3 or higher AEs were observed in less than 5% of the patients. The summary of this study compared with the other published data to date are listed in Table 1.

Conclusion: Ixazomib and Rd combination therapy showed comparable effectiveness with a favorable toxicity profile, especially in the early relapse of Asian patients with RRMM.

Keyword: Relapsed, Refractory multiple myeloma, Ixazomib, Lenalidomide, Real-world, Asia

Table 1. Summary of the published data on IRd for RRMM

	Korea – This study	Hungary [14]	Israel[15]	UK single center[16]	UK multicenter[17]	Greece, UK, Czech[18]	Czech [19]	Latin America [20]	INSIGHT-RMG [21]	US[22]	Japan[23]	China Continuation[13]	TOURMALINE-MM1[3, 12]
Study design	Retro	Retro	Cohort	Retro	Retro	Retro	Cohort	Retro	Cohort	Retro	Retro	Phase III	Phase III
N	60	77	64	85	116	155	127	10	263	154	122	57	360
Median age, (years)	68	66	68	65	69	68	66	67	68	70	72	61	66
Median prior lines	1(1–2)	2	≥1	2(1–4)	2(1–4)	1(1–7)	1(1–9)	2	1–2 (80%)	≥1	4	1–2	1–2
Clinical trial ineligibility	40%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	0
ISS III	50%	22%	27%	13%	34%	NA	27%	40%	35%	NA	39 %	9%	12%
High-risk cytogenetics	7%	27%	48% (HR/IR)	0	NA*	NA	28%	44%	7%	NA	NA	NA	21%
CrCl < 30 mL/min	8%	0	NA	NA	NA	NA	NA†	NA‡	NA	NA	NA	0	1%
EMD	16%	NA	7%	NA	NA∫∫	NA	14%	20%	NA	NA	NA	NA	NA
Prior ASCT	42%	58%	35%	65%	47%	52%	62%	80%	55%	17%	28 %	14%	59%
Prior refractory to PI	27%	NA	NA	13%	28%	NA	NA	50%	10%	10%	46 %	NA	1%
Prior refractory to IMiD	12%	NA	NA	NA	NA	NA	NA	10%	7%	25%	66 %	65%	21%
ORR (≥ VGPR)	80% (50%)	67% (23%)	88%	78 (26%)	67%	74% (35%)	73%	70% (40%)	73%	NA	NA	56% (24%)	78% (48%)
DOT (mo)	7.7	7.2	17	NA	16.6	9.6	NA	7.5	NA	8.5	NA	9.7	17
Median follow-up duration (mo)	9.2	13	22	21	16	16	21	NA	15	13	10	7.4	85
Median PFS (mo)	NR	11	24	TTNT 19 mo	18	28	18	19	21	TTNT 11 mo	12	6.7	20.6
Median OS (mo)	NR	NA	NR	NR	NR	NA	37	NA	NR	NA	NR	20.2	53.6

Abbreviations: IRd, ixazomib-lenalidomide-dexamethasone; Retro, retrospective; Cohort, prospective coh
N, number of patients; ISS, International Staging System; CrCl, creatinine clearance; EMD, extramedul
disease; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory dr
ORR, overall response rate; VGPR, very good partial response; DOT, duration of therapy; PFS, progressi
free survival; TTNT, time-to-next treatment; OS, overall survival; NA, not available; mo, months; NR,
reached.
Clinical trial ineligibility = Patients with any one or more of the listed features: ECOG performance status
CrCl < 30mL/min, PLT < 75000/μL, uncontrolled cardiovascular disease, or refractory to any proteaso
inhibitors
* Data from patients who had high-risk cytogenetics were not available, but 23% patients were included
clinical high-risk. Data from patients with CrCl < 30 mL/min were not available, but †6% of the patients
creatinine > 176 μmol/L and ‡20% of the patients with renal insufficiency were included in the analysis.
Data from patients with EMD were not available, but 4 patients had EMD or plasma cell leukemia.

PP07-24

Prognosis of chronic kidney disease stage 5 or under dialysis in Asian multiple myeloma patients - on behalf of Korean multiple myeloma working party (KMM177 study)

Ji Hyun Lee[1], Sung-HyunKim Kim[1], Ki-Hyun Kim[2], Chang-Ki Min[3], Je-Jung Lee [4], Sung-Hoon Jung[4], Sung-Soo Yoon[5], Dong-Yeop Shin[5], Ja Min Byun[5], Jae-Yong Kwak[6], Ho-Young Yhim[6], Byeong Seok Sohn[7], Jin Seok Kim[8], Hyo Jung Kim[9], Ho Sup Lee [10], Sung Hwa Bae[11], Gyeong-Won Lee[12], Sungwoo Park[12], Jae Hoon Lee[13], Min Kyoung Kim[14], Young Rok Do[15] and Jun Ho Yi[16]

[1] Department of Internal Medicine , Dong-A University College of Medicine, Korea

[2] Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[3] Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea

[4] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea

[5] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea

[6] Department of Internal Medicine , Chonbuk National University Medical School, Korea

[7] Department of Internal Medicine, Pusan National University Hospital, Korea

[8] Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Korea

[9] Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Korea

[10] Department of Internal Medicine, Kosin University College of Medicine, Korea

[11] Department of Internal Medicine, Catholic University of Daegu School of Medicine, Korea

[12] Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, Korea

[13] Department of Internal Medicine, Gachon University Gil Medical Center, Korea

[14] Department of Medicine, Yeungnam University College of Medicine, Korea

[15] Division of Hematology-Oncology, School of Medicine, Keimyung University, Korea

[16] Division of Hematology-Oncology, Department of Medicine, Chung-Ang University, Korea

Background: About one-third of the multiple myeloma (MM) patient are recognized to have renal impairment (RI) at initial diagnosis of MM and up to 10% of the patients present with RI severe enough to require dialysis. The prognosis of MM with RI has improved significantly over the past decade owing to the availability of new agents (including proteasome inhibitors and immunomodulatory drugs) and improvement of the supportive care measures. A recent data revealed an upward movement of survival curves after the introduction of bortezomib into the MM treatment. However, conventional staging systems are insufficient to prognosticate MM patient with RI. This study aimed to investigate the prognostic factors and treatment outcomes in multiple myeloma patients with chronic kidney disease (CKD) 5 or patients under dialysis.

Method: Patients who were confirmed multiple myeloma between January, 2001 to December, 2016 and had an estimated glomerular filtration rate (eGFR) of less than 15 ml/min/1.73m2 at the time of multiple myeloma diagnosis or receiving hemo- or peritoneal dialysis at the time of multiple myeloma diagnosis were included into the study. A total of 248 patients from 17 centers participating Korean multiple myeloma working party were analyzed. Renal reversibility was defined by international myeloma working group recommendation: renal complete response (CRrenal) as best eGFR of ≥ 60 ml/min/1.73m2, renal partial response (PRrenal) of 30-59 ml/min/1.73m2, and renal minor response of 15-29 ml/min/1.73m2. Overall survival (OS) was defined by the date of MM diagnosis to the date of death by any cause or follow-up loss.

Results: Median age was 63.5 years (range, 32-91 years) and median eGFR was 8.9 ml/min/1.73m2 (1.0- 40.0 ml/min/1.73m2). 126 (50.8%) of the analyzed patients were under dialysis or were dialysated just after the diagnosis of MM. 79.4% of the patients received bortezomib and/or thalidomide (new agents group) as an induction regimen and 35.1% of the analyzed cohort underwent autologous stem cell transplantation (auto-SCT group). Dialysis stop rates were higher in the new agents group compared with no new agent group (49.5% versus 27.8%, P=0.088) and in the auto-SCT group compared with no auto-SCT group (77.6% versus 40.4%, P=0.000). With a median follow-up duration of 24.42 months (range, 0.20-134.93 months), the median OS in the total cohort was 46.83 months (95% confidence interval, CI, 29.39-64.27 months). OS was not different between the groups with or without new agents incorporated into the induction chemotherapy, but auto-SCT group showed a significantly prolonged OS compared with no auto-SCT group: 67.63 (95% CI, 36.07-99.19) vs. 40.60 months (28.94 - 52.26 months) (P=0.001). By the conventional international staging system (ISS) or revised international staging system (R-ISS), OS was not different between the groups. However, age (65 years or more), Eastern cooperative group performance status (2 or more), high risk cytogenetics by fluorescent in situ hybridization (FISH), and C-reactive protein (CRP) 1.0 mg/dL or more significantly affected OS by both univariate and multivariate analysis (Table 1).

Conclusion: Autologous stem cell transplantation in MM patients with CKD5 or under dialysis is able to effectively reverse renal function and prolong overall survival. Conventional ISS or R-ISS was

insufficient to predict survival outcome in this cohort. Other prognostic markers incorporating age, performance status, cytogenetics by FISH, and CRP should be considered for patients with poor renal function.

Keyword: Multiple myeloma, Chronic kidney disease 5, Dialysis, Asia

Table 1. Univariate and multivariate analysis of factors affecting overall survival

	Univariate analysis		Multivariate analysis	
	HR	P-value	HR	P-value
Age				
< 65 years				
≥ 65 years	1.603 (1.093-2.350)	0.016	2.236 (1.250-4.002)	0.007
ECOG PS				
0 or 1				
≥ 2	2.117 (1.460-3.069)	0.000	2.201 (1.289-3.759)	0.004
Charson comorbidity index (renal disease excluded)				
0 or 1				
≥2	0.861 (0.584-1.269)	0.448		
BMI				
≥ 20 kg/m²				
< 20 kg/m²	1.735 (1.092-2.757)	0.020	0.997 (0.518-1.919)	0.993
serum albumin				
≥ 3.5 mg/dL				
< 3.5 mg/dL	1.835 (0.582-5.782)	0.300		
serum b2 microglobulin				
< 5.5 mg/L				
≥ 5.5 mg/L	1.835 (0.582-5.782)	0.300		
LDH				
≤ normal				
> normal	1.905 (1.289-2.828)	0.001	1.236 (0.736-2.077)	0.423
Cytogenetic risk by FISH				
Standard risk				
High risk	2.341 (1.423-3.850)	0.001	2.916 (1.620-5.250)	0.000
ISS				
I and II				
III	1.657 (0.529-5.222)	0.388		
R-ISS				
I and II				
III	1.601 (0.572-2.639)	0.065		
CRP				
< 1.0 mg/dL				
≥ 1.0 mg/dL	1.684 (1.099-2.580)	0.017	1.838 (1.020-1.313)	0.043

Abbreviation: ECOG PS, Eastern Cooperative Group performance status; BMI, body mass index; LDH, lactate dehydrogenase; FISH, fluorescent in situ hybridization; ISS, international staging system; RISS, revised international staging system; CRP, C-reactive protein

PP07-25

The benefit of pomalidomide in RRMM with plasmacytomas - on behalf of Korean multiple myeloma working party (KMM1907 study)

Ji Hyun Lee[1], Sung-Hyun Kim[1], Ki-Hyun Kim[2*], Chang-Ki Min[3], Sung-Soo Park[3], Je-Jung Lee[4], Sung-Hoon Jung[4], Sung-Soo Yoon[5], Ja Min Byun[5], Jae-Yong Kwak[6], Ho-Young Yhim[6] and Ho-Jin Shin[7]

[1] Department of Internal Medicine , Dong-A University College of Medicine, Korea

[2] Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[3] Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Korea

[4] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea

[5] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea

[6] Department of Internal Medicine , Chonbuk National University Medical School, Korea

[7] Department of Internal Medicine, Pusan National University Hospital, Korea

Background: Plasmacytoma at the time of relapse of multiple myeloma is associated with poor response and survival. However, data on the activity of the recently available new drug or drug combinations in RRMM with plasmacytoma in the real-world clinical practice is limited. Pomalidomide and dexamethasone (Pd) with or without cyclophosphamide is an active therapeutic combination in relapsed and refractory multiple myeloma (RRMM) after 2 lines of previous line of therapy.

Method: This study aimed to analyze the clinical outcome of the pomalidomide-based regimen in RRMM with plasmacytoma. Clinical data of 221 patients who were treated with Pd with or without cyclophosphamide from 7 hospitals participating in the Korean multiple myeloma working party were retrospectively analyzed by electronic medical chart review. All the of patients were previously treated with at least 2 lines of therapies including bortezomib and lenalidomide in most of the patients. Plasmacytoma was diagnosed by the computed tomography, magnetic resonance imaging or FDG-PET scan.

Results: Twenty-nine patients among the 221 patients analyzed (13.1%) had plasmacytoma at the time of pomalidomide-based chemotherapy. Patients were previously treated with a median 4 lines of therapy (range, 2-14), including bortezomib, lenalidomide, autologous stem cell transplantation in 97%,100%, and 52% of the patients, respectively. Patients who were double refractory to bortezomib and lenalidomide were included in 35% of the patients. Median length of time from the first diagnosis of MM to the time of pomalidomide was 51.4 months (range, 6.6-307.5 months). 14 patients were treated with Pd and 15 patients had been treated with Pd and cyclophosphamide (PCd). Median number of sites of plasmacytoma involvement was 2 (range, 1-9), including paraskeletal and soft tissue involvement in 83% and 52% of the patients. Sites of soft tissue involvement were: 5 pleura, 4 lymph nodes, 4 subcutaneous, 3 liver, 3 muscle, 2 pancreas, 1 kidney, 1 pericardium, 1 peritoneum, 1 adrenal gland, and 1 stomach. 50% patients (13 among the 26 response evaluable patients) had responded to Pd with or without Cy: 2 complete response, 2 very good partial response, 9 partial response, 1 stable disease, 2 minimal response, and 10 progressive disease. Patients who were treated with PCd showed a better response compared with Pd therapy (53% versus 29%, P=0.264). Best response rate of the plasmacytoma among the 15 response evaluable patients was 47% (7/15) with 6 CR, 1 PR, 1 SD and 7 PD. After a median follow-up of 9.33 months (range, 0.30-52months), patients with plasmacytoma versus no plasmacytoma showed a

progression-free survival of 3.57 (95% CI, 0.35-6.78 months) versus 8.40 months (95% CI, 7.00-9.80 months) (P=0.002) and an overall survival of 3.33 (95% CI, 0.00-7.82 months) versus 19.67 months (95% CI, 13.39-25.95 months) (P=0.001).

Conclusion: RRMM patients with plasmacytoma was responsive after pomalidomide-based chemotherapies. The addition of cyclophosphamide to Pd seemed to result in a better response compared with Pd only. However, RRMM patients with plasmacytoma had poorer survival compared with patients without plasmacytoma even after Pd with or without cyclophosphamide.

Keyword: Relapsed and refractory multiple myeloma, Extramedullary disease, Pomalidomide

PP07-26

A pilot study to identify role of minimal residual disease in multiple myeloma patients who received autologous stem cell transplantation

Sung-Soo Park[2], Jung Yeon Lee[2], Ari Ahn[3], Yonggoo Kim[3], Myungshin Kim[1] and Chang-Ki Min[2*]

[1] Department of Biochemistry, College of Medicine, Catholic University of Korea, Korea

[2] Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, Catholic University of Korea, Korea

[3] Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea

Background: Minimal residual disease (MRD) testing is increasingly important to predict long-term prognosis in patients with multiple myeloma (MM). We performed a pilot study to identify the natural course of MRD following autologous stem cell transplantation.

Method: Among total of 360 consecutive MM patient who evaluated MRD between December 2019 and January 2021 at our center, we included 111 patients as the cohort of current study based on following inclusion criteria: (i) Patient who received autologous stem cell transplantation (ASCT) as a part of the front-line treatment (ii) patients who have available MRD data at 120 ± 60 days post-ASCT (iii) patients who achieved complete response at the time performing evaluation of MRD. Multi-parametric flow cytometry (MFC) was performed according to manufacturer's instructions. Fresh EDTA anticoagulated bone marrow aspirate samples were collected from treated patients with MM. Red blood cells were lysed using Versafix solution (VersaLyse supplemented with 0.25% IOTest Fixative Solution, Beckman Coulter) and cell suspensions containing 5×106 nucleated cells were transferred to DuraClone RE PC tubes (Beckman Coulter, Marseille, France). DuraClone RE PC antibody panel was composed of CD81-FITC, CD27-PE, CD19-PC5.5, CD200-PC7, CD138-APC, CD56-APC-A750, CD38-Pacific Blue, CD45-Krome Orange. MRC was performed by 10-color, 3-laser NAVIOS flow cytometers and Kaluza analysis software, version 2.1 (Beckman Coulter) and analyzed by manual serial gating according to our protocol.

Results: Of all, there were 80 patients showed MRD-negative (MRD-) while 31 patients presented MRD-positive (MRD+). Interval between time of ASCT and measured MRD were not significantly different between two group (median 90.5 days vs. 97 days). MRD result was statistically independent from existing clinical characteristics, including International Staging System, cytogenetic abnormality, type of induction treatment, presence of extramedullary disease at diagnosis, or level of lactate dehydrogenase. With median follow-up of 14.3 months (95% CI, 10.5-15.2), patients with MRD- had a trend of favorable median progression-free survival rather than patients with MRD+ (Not reached vs. 19.7 months, p = 0.114). Among 80 MRD-, MRD of 21 patients were serially evaluated after one year from the first measurement of MRD: there were 14 patients showing sustained MRD- whereas seven patients (33.3%) were converted to MRD+. Regarding 31 patients of MRD+ for the first measurement, 13 patients who did not any subsequent therapy showed inferior median PFS compared to remaining 18 patients who received maintenance therapy and/or tandem ASCT (18.6 months vs. Not reached).

Conclusion: We suggest that post-120 days MRD measurement could be an independent biomarker from well-known prognostic variables. Current study also illustrated that it could be worthy to establish individualized subsequent treatment post-ASCT based on post-120 days MRD despite limitation of short follow-up duration. Based on the result of current pilot study, we believe that our strategy of measurement for MRD could be extended to future study.

Keyword: Minimal residual disease, Multiple myeloma, Autologous, Stem cell transplantation, Indivisualized, Personalized

PP08-01

Splenic infarction in patient with Philadelphia-negative myeloproliferative neoplasm

Myung-Won Lee[1], Sang-Hoon Yeon[1], Hyewon Ryu[1], Ik-Chan Song[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1], Seon Young Kim[2], Kyung Sook Shin[3] and Deog-Yeon Jo[1*]

[1] Division of Hematology/Oncology, Department of Internal Medicine, Chungnam National University College of Medicine, Korea
[2] Department of Laboratory Medicine, Chungnam National University-College of Medicine, Korea
[3] Department of Radiology, Chungnam National University College of Medicine, Korea

Background: Splenic infarction occurs in patient with Phliladelphia chromosome-negative myeloproliferative neoplasm (Ph- MPN). However, the prevalence of splenic infarction has rarely been reported and its clinical outcome is mainly based on case reports. In the present study, we retrospectively analyzed the prevalence and clinical features of splenic infarction and its outcomes in patients with Ph- MPN.

Method: Patients who were diagnosed with essential thrombocythemia (ET), polycythemia vera (PV), prefibrotic/early primary myelofibrosis (pre-PMF), or overt PMF from January 1996 to October 2020 at Chungnam National University Hospital were enrolled, and their medical records were reviewed. Splenic infarction was arbitrarily classified into to 4 types by the pattern and extent of infarction on abdominal CT as follows: (1) Single, small infarct - the length of the base is within the neighboring two ribs. (2) Single, large infarct – the length of the base is beyond the neighboring two ribs. (3) Multifocal infarct – two or more infarcts, regardless of their size. (5) Extensive infarct – infarct involving half or more of the splenic volume.

Results: A total of 347 patients (143 ET, 129 PV, 44 pre-PMF, and 31 PMF; 201 male and 146 female) with a median age of 64 years (range: 15-91 years) were enrolled and were followed up for a median of 4.7 years (range: 0.1-26.5 years). Of the 347 patients, 15 (4.3%) patients had splenic infarction at the time of MPN diagnosis. It was most frequent in PMF patients (12.9%), followed by pre-PMF (9.1%), and PV (5.4%). No ET patients had splenic infarction at diagnosis. During follow-up, 5 (1.4%) patients developed splenic infarction: 1 each in ET (0.7%), pre-PMF (2.3%), and PMF (3.2%) patients, respectively, and 2 (1.6%) in PV patients. Splenic artery or venous thromboses were not observed. Regarding the extent of infarction, multifocal infarction (60.0%) was most frequent, followed by single, small (20.0%), single, large (13.3%), and extensive (6.7%). Cumulative incidence of thrombosis in patients with splenic infarction tended to be higher than that in patients without splenic infarction in both PV (10-year cumulative incidence: 46.7% vs. 21.0%; p=0.215) and pre-PMF (10-year cumulative incidence: 33.3% vs. 17.9%; p=0.473), but statistical significance was lacking. Any complications, including abscess, fistula, splenic rupture, intraperitoneal bleeding, or peritonitis, were not observed during follow-up. In Fine and Gray regression analysis, palpable splenomegaly (HR, 14.89; 95% CI, 4.00-55.35; p <0.001) was only independent risk factor for developing splenic infarction at MPN diagnosis.

Conclusion: Splenic infarction occurs in a small population of Ph-MPN patients who has volumetric or palpable splenomegaly. The clinic course of the splenic infarction is generally mild and serious complication is rare.

Keyword: Splenic infarction, Myeloproliferative neoplasm, Essential thrombocythemia, Polycythemia vera, Primary myelofibrosis

PP08-02

Volumetric splenomegaly in patients with polycythemia vera

Myung-Won Lee[1], Sang-Hoon Yeon[1], Hyewon Ryu[1], Ik-Chan Song[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1], Seon Young Kim[2], Jeoung Eun Lee[3], Kyung Sook Shin[3] and Deog-Yeon Jo[1*]

[1] Division of Hematology/Oncology, Department of Internal Medicine, Chungnam National University College of Medicine, Korea
[2] Department of Laboratory Medicine, Chungnam National University College of Medicine, Korea
[3] Department of Radiology, Chungnam National University College of Medicine, Korea

Background: Non-palpable splenomegaly in patients with polycythemia vera (PV) has seldom been addressed. In this retrospective study, we evaluated non-palpable, volumetric splenomegaly defined based on age- and body surface area (BSA)–matched criteria in patients with PV diagnosed according to the 2016 World Health Organization diagnostic criteria.

Method: Patients with PV who underwent abdominal computed tomography (CT) and who had palpable splenomegaly at diagnosis from January 1991 to December 2020 at Chungnam National University Hospital were enrolled in the study. The spleen volume of each patient was determined by volumetric analysis of abdominal CT and adjusted for the patient's age and BSA. Then the degree of splenomegaly was classified as no splenomegaly, borderline volumetric splenomegaly, overt volumetric splenomegaly, or palpable splenomegaly.

Results: Of the 87 PV patients enrolled in the study, 15 (17.2%) had no splenomegaly, whereas 17 (19.5%), 45 (51.7%), and 10 (11.5%) had borderline volumetric, overt volumetric, and palpable splenomegaly, respectively. Spleen volume was significantly positively correlated with lactate dehydrogenase level (r = 0.227, P = 0.042) and tended to be positively related to white blood cell count (r = 0.209, P = 0.055) and monocyte count (r = 0.210, P = 0.059) at diagnosis. Spleen volume was not correlated with hemoglobin level, platelet count, or JAK2V617F burden at diagnosis. The degree of splenomegaly did not affect the cumulative incidence of thrombotic vascular events (10-year incidence: 7.7%, 0%, 22.3%, and 50.7%, respectively, P = 0.414). By contrast, splenomegaly tended to adversely

affect myelofibrotic transformation (10-year cumulative incidence: 0%, 0%, 7.1%, and 30.3%, respectively, P = 0.062). Moreover, the cumulative incidence of myelofibrotic transformation was significantly higher in patients with overt volumetric or palpable splenomegaly than those with no or borderline volumetric splenomegaly (10-year incidence: 0% vs. 10.3%, respectively; 15-year incidence: 0% vs. 26.3%, respectively, P = 0.020). Overall survival (OS) differed among patients with different degrees of splenomegaly (15-year OS: 100%, 78.6%, 71.7%, and 51.9%, respectively, P = 0.021). The degree of splenomegaly was independent risk factor for both myelofibrotic transformation (hazard ratio [HR]: 7.75; 95% confidence interval [CI]: 1.87–21.10; P = 0.005) and OS (HR: 6.70; 95% CI: 1.89–23.72; P = 0.003).

Conclusion: The degree of splenomegaly, including volumetric splenomegaly, based on age- and BSA-matched reference spleen volumes at diagnosis reflects disease progression in PV patients. Therefore, volumetric splenomegaly should be evaluated at the time of PV diagnosis and taken into consideration when predicting the prognosis of patients with this disorder.

Keyword: Polycythemia vera, Spleen, Computed tomography, Splenomegaly, Myelofibrosis, Survival

PP08-03

Tuberculosis of the bone marrow in a patient with JAK2-positive myelofibrosis presenting with jaundice: a case report

Joseph Emmanuelle Siatan* and Chrystal Anne Catli-Burog

Division of Internal Medicine, National Kidney and Transplant Institute, Philippines

Background: Myelofibrosis is a disease characterized by the progressive deposition of fibrous connective tissue in the marrow matrix. It is an uncommon condition that may result from primary hematologic disorders, as in primary myelofibrosis, or secondary to other disease processes – including malignant, autoimmune, and infectious causes. The pathophysiology, diagnosis, and treatment of either conditions have been well-researched and documented.

Method: We present a case report with co-existent evidence of both non-clonal (tuberculosis-induced) and clonal myelofibrosis (JAK2-induced).

Results: A 59-year old presented with an 8-month history of abdominal enlargement, fever, and cholestasis. He previously underwent endoscopic retrograde cholangiopancreatography with findings of cholecystolithiasis. He had serial phlebotomies in 2015 following an episode of transient ischemic attack. He had no known primary hematologic disorders.

On examination, he had pallor and jaundice, with hepatosplenomegaly, 6 and 12 centimeters below right and left subcostal margins, respectively. He had shifting dullness and a negative Murphy's sign. Previous diagnostics showed serial blood counts with persistent anemia, leukocytosis, and thrombocytopenia. JAK2 mutation assay was positive. Further investigations revealed alkaline phosphatase (ALP) to alanine transaminase ratio consistent with cholestasis. Triphasic abdominal computed tomography scan showed hepatosplenomegaly with portal hypertension and ascites. Peripheral blood smear noted hypochromic red cells with signs of extramedullary hematopoiesis. Bone marrow biopsy showed marked hypercellularity with reticulin fibrosis grade 2-3 and granulomatous aggregates of epithelioid histiocytes with Langhans type multinucleated giant cells – consistent with JAK-2 induced myelofibrosis concurrent with marrow tuberculosis.

He was started on anti-Koch's regimen and received supportive treatment for anemia. Ascites was addressed with diuresis and protein supplementation. Fever trends, leukocytosis, and ALP levels decreased on continuation of therapy. He was sent home improved after 2 weeks. On follow-up at second month of treatment, anemia improved from 8.7 mg/dL on discharge to 12.6 mg/dL, with resolution of jaundice and abdominal enlargement. He was offered Jak-2 inhibitor Ruxolitinib upon completion of anti-tuberculosis regimen but was declined due to cost restrictions.

Conclusion: Previous studies have noted increased likelihood of tuberculosis among patients with primary myelofibrosis, especially during Ruxolitinib therapy – documenting only nodal and pulmonary involvement. Reversible myelofibrosis in marrow tuberculosis, on the other hand, have been attributed to TGF-β and mycobacterial antigen induction of pro-fibrotic changes. Our patient presented with the unique picture of both clonal and non-clonal myelofibrosis with demonstration of partial hematologic and clinical resolution with anti-tuberculosis treatment. Further investigation is needed to assess extent of reversibility of the marrow fibrosis and durability of response post-treatment.

Keyword: Hematologic, Extrapulmonary, Tuberculosis, Myeloproliferative, Neoplasm

PP08-04

Myelofibrotic and leukemic transformation in 2016 who-defined Philadelphia-negative myeloproliferative neoplasm

Ik-Chan Song, Sang Hoon Yeon, Myung-Won Lee, Hyewon Ryu, Hyo-Jin Lee, Hwan-Jung Yun, Seon Young Kim and Deog-Yeon Jo*

Department of Internal Medicine, Chungnam National University Hospital, Korea

Background: The information on the myelofibrotic and leukemic transformations in Korean Philadelphia chromosome-negative myeloproliferative neoplasm (Ph–MPN) patients is limited.

Method: This study retrospectively analyzed the transformations in patients diagnosed with essential thrombocythemia (ET), polycythemia vera (PV) prefibrotic/early primary myelofibrosis (pre-PMF), or overt PMF (PMF) on the basis of 2016 WHO criteria between January 1996 and December 2020 at Chungam National University Hospital, Daejeon, Korea.

Results: A total of 351 patients (144 with ET, 131 with PV, 45 with pre-PMF, and 31 with PMF; 204 males and 147 females) with a median age of 64 years (range: 15–91 years) were followed up for a median of 4.6 years (range: 0.2–24.8 years). The 10-year incidence of overt myelofibrosis was higher in pre-PMF compared to ET (31.3% and 13.7%, respectively; P=0.031) and PV (12.2%; P=0.003). More secondary myelofibrosis (SMF) patients were classified into the intermediate-2 or high-risk IPSS group compared to overt PMF patients (90.0% and 58.1%, respectively; P=0.038). Independent risk factors for developing SMF were high monocyte counts (>1.0 × 109/L) (HR: 3.57; 95% CI: 1.17–10.91; P=0.026) and CALR mutation (HR: 4.42; 95% CI: 1.20–16.37; P=0.026) in ET; abnormal karyotypes (HR: 18.20; 95% CI: 2.0–165.95; P =0.010) in PV. The 10-year incidence of leukemic transformation in PMF was significantly higher compared to that in ET (40.0% and 7.9%, respectively; P = 0.046), pre-PMF (4.7%; P=0.048), and PV (3.2%; P=0.031). High monocyte counts (>1.0 × 109/L) (HR: 4.05; 95% CI: 1.23–13.39; P=0.022) and abnormal karyotypes (HR: 5.60; 95% CI: 1.10–28.59; P=0.038) were risk factors for developing leukemia in univariate analysis, but not in multivariate analysis. The 5-year incidence of leukemic transformation in SMF patients was higher compared to PMF (19.0% and 11.4%, respectively; P = 0.040). The 5-year overall survival of SMF patients was significantly worse compared to pre-PMF patients (74% and 93%, respectively; P=0.027), but did not differ from that of PMF patients (57%; P=0.744). Prognosis of patients with secondary leukemia (N=11) was dismal with a median survival of 1.5 months (range: 0.5–14.5 months).

Conclusion: The rates and clinical courses of myelofibrotic and leukemic transformations in Korean Ph– MPN patients did not differ from those in Western populations.

Keyword: Myeloproliferative neoplasm, Essential thrombocythemia, Polycythemia vera, Primary myelofibrosis, Secondary myelofibrosis, Leukemia

PP08-05

Real-world outcomes of ruxolitinib in patients with myelofibrosis focusing on RBC transfusion: a multicenter study from the MPN working party of the KSH

Eunhee Jung[1], Junshik Hong[1*], Sung-Yong Kim[2], Young Park[3], Young Jin Yuh[4], Yeung-Chul Mun[5], Won-Sik Lee[4], Sung-Kyu Park[6] and Soo-Mee Bang[1]

[1] Department of Internal Medicine, Seoul National Universityi College of Medicine, Korea

[2] Department of Internal Medicine, Konkuk University Medical Center, Korea

[3] Department of Internal Medicine, Korea University Anam Hospital, Korea

[4] Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Korea

[5] Department of Hematology-Oncology, Ewha Womans University College of Medicine, Korea

[6] Department of Internal Medicine, Soonchunhyang University College of Medicine, Korea

Background: Ruxolitinib is an established treatment for myelofibrosis (MF) that has demonstrated clinical benefit by reducing spleen size and debilitating MF-related symptoms. However, despite the efficacy of ruxolitinib, anemia remains a major adverse event that causes dose modification or discontinuation in real-world practice. Additionally, dependence on red blood cell (RBC) transfusion (TF) is common during treatment. Therefore, we explored the outcome of ruxolitinib therapy with a primary focus on RBC TF.

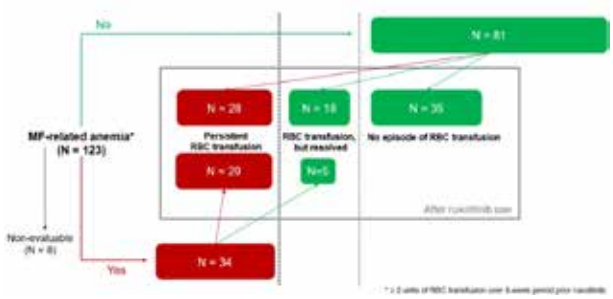
Method: We retrospectively reviewed the medical records of 123 patients with intermediate-2 or high risk MF treated with ruxolitinib between January 2012 and April 2020 at eight academic centers in Korea.

Results: At the time of ruxolitinib initiation, 38 patients (30.9%)

had MF-related anemia. The most common reason for permanent discontinuation was intolerant anemia (10/63, 15.9%). The most common reasons for temporary interruption were nonhematologic toxicity (26/55, 21.1%), anemia (23/55, 18.7%) and thrombocytopenia (13/55, 10.6%). Among the 123 patients in the study, 57 (46.3%), 42 (34.1%), and 40 patients (32.5%) who were receiving or stopped ruxolitinib therapy had a status of RBC TF dependence, long-term RBC TF dependence, or severe RBC TF dependence, respectively. The presence of MF-related anemia at ruxolitinib initiation was an independent risk factor for persistent RBC TF dependence.

Conclusion: In conclusion, the requirement for RBC TF due to progressive anemia is commonly encountered during the treatment of MF with ruxolitinib. Given these data, patients with MF-related anemia should be aware of the increased risk of TF dependency and the need for more supportive treatment for anemia in real practice. Newer treatment options with less development of anemia are eagerly awaited.

Keyword: Myelofibrosis, Anemia, Transfusion, Myeloproliferative neoplasms



PP08-07

Modified cell-based model of JAK2V617F mutation by using CRISPR/Cas9

Rujira Mekchaaum[1], Supaporn Kalasin[1], Krai Daotak[1,2] and Nungruthai Nilsri[1,2*]

[1] Department of Medical Technology, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand

[2] Cellular and Molecular Immunology Research Unit, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand

Background: JAK2 protein plays an important role in signal transduction via cytokine and growth factor receptors of hematopoietic stem cells. Mutation of JAK2V617F in Janus Kinase 2 gene (JAK2) is the most common genetic driver of Philadelphia chromosome negative myeloproliferative neoplasms (MPNs) which comprise polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis. Pathogenesis and treatment regimen of Philadelphia chromosome negative MPNs is still undefined.

Method: We attempt to establish the JAK2 gene mutations type V617F using the CRISPR/Cas9 technology in K562 cell lines. The JAK2V617F cell line were characterized JAK2 gene modification and cell proliferation. Furthermore, arsenic trioxide were tested on the modified cells to explore a potential for MPN therapy.

Results: JAK2V617F-K562 showed more yield cell proliferation when compared with K562 wild type (p value <0.01). Moreover, Arsenic trioxide preferentially inhibited cell proliferation of the K562 expressing mutant JAK2 compared with wild type (p value <0.001).

Conclusion: The modified cell-based model of JAK2V617F mutation may be used to investigate the mechanisms and explore new therapy of MPNs.

Keyword: JAK2 gene mutation, Philadelphia chromosome negative myeloproliferative neoplasms, CRISPR/Cas9

PP09-01

Pure red cell aplasia after ABO-mismatched allogeneic haematopoietic stem cell transplantation for very severe aplastic anaemia

Ching Soon Teoh

Haematology, Hospital Pulau Pinang, Malaysia

Background: Pure red cell aplasia (PRCA) is a syndrome characterized by severe normocytic anaemia, reticulocytopenia and absence of erythroblasts from bone marrow. Persistence of anti-donor isohemagglutinins following allogeneic haematopoietic stem cell transplantation (allo-HSCT) with major ABO incompatibility responsible for PRCA. This leads to frequent blood transfusion and iron overload.

Method: The data was retrieved from medical record, focusing on allo-HSCT procedure, laboratory and radiographic results, treatment for PRCA and its response.

Results: 30-year-old gentleman presented to a tertiary hospital for symptomatic anaemia and easy bruising. His white blood cell (WBC) was 1.99 x 10^9/L, absolute neutrophil count (ANC) 0.23, haemo-

globin (Hb) 6.4 g/dL and platelet (PLT) 19 x 10^9/L. Bone marrow aspirate (BMA) and trephine biopsy showed hypocellular marrow without dysplasia and excess blasts. Cytogenetic study showed normal male karyotype. Final workup confirmed very severe aplastic anaemia (VSAA). He underwent non-myeloablative, unmanipulated peripheral blood (PB) allo-HSCT within 2 months of diagnosis from his human leukocyte antigen (HLA) matched sister. A total of 4.15 x 10^6 CD34 infused. The blood group for recipient and donor was O Rhesus+ and A Rhesus+ respectively. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and methotrexate. He achieved both neutrophil and platelet engraftments on day +12. The haemoglobin upon discharge was 8.6 g/dL. He was given weekly erythropoietin (EPO) injection. On day +40, he was found to have severe anaemia and reticulocytopenia with Hb 6.8 g/dL. The WBC and PLT were normal. Anti-A titer was 8 while anti-B titer was 128. The lowest Hb was 5.3g/dL. He required weekly blood transfusion. EPO injection was discontinued in view of worsening anaemia and unable to exclude the presence of anti-EPO antibody. There was no clinical and laboratory evidence to suggest blood loss, acute GVHD and acute haemolysis. Both cytomegalovirus polymerase chain reaction (CMV PCR) and parvovirus B19 Ig M were not detected. Autoimmune screening, serum B12 and folate were normal. Chimerism study at D+60 reported 99.96% donor's DNA detected. BMA and trephine biopsy revealed normocellular marrow with absence of erythroid precursors, normal granulopoiesis and megakaryopoiesis. There were no dysplasia, blasts, abnormal lymphoid aggregates and fibrosis. The final working diagnosis was PRCA due to major ABO-mismatched allo-HSCT. He received immunoglobulin and steroid injection but no response. Weekly rituximab infusion was administered for a total of four doses. However, the Hb remained 6-7g/dL. Anti-A titer was 4 while anti-B titer was 64. He was offered bortezomib injection weekly for four weeks consecutively. There was significant hematological response after the 4th injection. His Hb and reticulocyte improved and normalized at 8th month after allo-HSCT. His blood group became A+, anti-A was not detected and anti-B titer was 64. A total of 15 units irradiated packed cells were transfused in this case. The patient developed grade 2 liver transaminitis at 6th month after allo-HSCT. Serum ferritin was 2828 ug/L. The ultrasound abdomen reported fatty liver while MRI T2* confirmed moderate liver iron overload requiring iron chelation.

Conclusion: This case illustrates PRCA as an early complication after major ABO-mismatched allo-HSCT. Frequent blood transfusion leading to iron overload is a common sequelae. Treatment for PRCA includes rapid tapering of calcineurin inhibitors, donor lymphocytes infusion, steroid, rituximab, bortezomib and plasma exchange. However, no standard of care has been established. Hence, a well-designed prospective study should be performed to investigate the role of interventions for PRCA.

Keyword: Pure red cell aplasia, allogeneic haematopoietic stem cell transplantation, very severe aplastic anaemia, rituximab, bortezomib.

PP09-03

Application of next-generation sequencing to distinguish inherited from acquired in bone marrow failure syndrome: a single-center study

WonKee Ahn, Seungmin Hahn, Jung Woo Han and Chuhl Joo Lyu*

Division of Pediatric Hemato-oncology, Department of Pediatrics, Yonsei University College of Medicine, Korea

Background: Bone marrow failure can be inherited or acquired, and inherited diseases comprise a series of syndromes caused by various genetic mutations. This disease results in cytopenia in one or more lineages of peripheral blood due to the ineffective hematopoiesis of the bone marrow. With advances in genetic techniques, it is possible to diagnose the disease and help to choose the proper treatment.

Method: From 2010 to 2020, patients with peripheral cytopenia and bone marrow failure without hematologic malignancy were classified by disease, and genetic mutation through Next-Generation Sequencing(NGS). Treatment methods and outcomes were reviewed retrospectively.

Results: A total of 69 patients with cytopenia were diagnosed with bone marrow failure. 35 patients underwent NGS, 27 patients were classified as aplastic anemia or myelodysplastic syndrome and 8(22.8%) patients were classified by inherited bone marrow failure syndrome. There were 4 patients with Fanconi anemia, 3 with Diamond-Blackfan anemia, 1 with Schwachman-Diamond anemia. Among patients with bone marrow failure syndrome, only 2 had congenital anomalies or deformities. 2 FANCA mutations and 2 FANCG mutations in 4 patients with Fanconi anemia, 2 RPS24 mutations, and RPL 11 mutation in 4 with pure red cell anemia. 5 patients underwent hematopoietic stem cell transplantation, and 2 patients are in preparation. There were 2 cases of progression of hematologic malignancies after engraftment failure after hematopoietic stem cell transplantation, and one died of disease progression.

Conclusion: Distinguishing inherited forms from acquired bone marrow failure is challenging. Inherited bone marrow failure syndromes could transform into hematologic malignancies like myelodysplastic syndrome, acute myeloid leukemia. NGS helps to differentiate inherited bone marrow failure patients who have cytopenia in peripheral blood with unclear clinical features. In case of recurrence after engraftment failure in bone marrow failure syndrome, it often progresses to hematologic malignancy, so it is necessary to find the optimal regimen and strategy for hematopoietic stem cell transplantation.

Keyword: Inherited bone marrow failure syndrome, Next-generation sequencing

PP09-04

Comprehensive genetic analysis for patients with inherited bone marrow failure syndrome

Jong Mi Lee[1,2], Hoon Seok Kim[1,2], Ari Ahn[1,2], Jisook Lim[1,2], Jae Won Yoo[3], Seongkoo Kim[3], Jae Wook Lee[3], Bin Cho[3], Nack-Gyun Chung[3], Myungshin Kim[1,2], Yonggoo Kim[1,2]

[1] Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

[2] Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

[3] Division Hematology/Oncology, Department of Pediatrics, The Catholic University of Korea, Seoul, Republic of Korea

Background: Inherited bone marrow failure syndromes (IBMFSs) are group of genetic disorders, characterized by progressive cytopenia due to ineffective hematopoiesis and elevated risk for developing myeloid neoplasms and solid cancers. They are consisted of more than 25 disease entities, including Fanconi anemia (FA), Diamond-Blackfan anemia (DBA), Schwachman-Diamond syndrome (SDS) and dyskeratosis congenital (DC). Some patients have typical morphologic features, such as café-au-lait spot, microcephaly, radial abnormalities, and ectodermal dysplasia etc, with or without familial history associated hematological disorders. However, the penetrance and expressivity of the disease is extremely diverse, and the clinical and laboratory findings overlap among different IBMFSs and other disease groups. Over 100 genes are considered causative genes; however, the precise genetic diagnosis of IBMFSs remains challenging.

Method: Total 124 consecutive patients suspected IBMFS and their family members were included. They consisted of 25 aplastic anemia, 18 FA, 14 pure red cell aplasia (PRCA), 12 idiopathic cytopenia, 9 immune thrombocytopenia (ITP), 9 myelodysplastic syndrome (MDS), 9 severe congenital neutropenia (SCN), 7 hereditary spherocytosis, 5 hemolytic anemia, 4 Wiskott-Aldrich syndrome (WAS), 3 hemophagocytic lymphohistiocytosis, 2 Diamond-blackfan anemia, 2 acute myeloid leukemia in Down syndrome, 1 congenital dyserythropoietic anemia, 1 hereditary elliptocytosis, 1 myeloproliferative neoplasm, unclassifiable, 1 Shwachma-Diamond syndrome SDS, and 1 thrombotic thrombocytopenic purpura diagnosed by medical evaluation. All patients had unexplained and persistent cytopenia at least 1 lineage (hemoglobin level lower than 2 SD for the age, neutrophil count < $1.5x10^9$/L, and /or platelet count < $150x10^9$/L). Physical examination, familial history, clinical course and laboratory test results were thoroughly reviewed. Targeted NGS panel covering 203 genes and WES covering 6,700 genes were performed. We also performed microarray and/or whole genome sequencing (WGS) to endeavor disease-causing copy number changes or novel mutations. Variant were classified in accordance with American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines.

Results: Using the combined pipelines, we were able to assign the causal or possibly causal variants in 93 patients (75%) involving 34 genes. The diagnostic yields of the targeted NGS panel, WES and microarray/WGS were 44% (60/128), 46% (29/63), and 50% (5/10), respectively.

Total of 66 patients were genetically diagnosed as classical IBMFS (53.2%). Among them, 52 and 9 cases were identified by targeted NGS panel and WES, respectively (78.8% and 13.6%). WGS and microarray aided to detect 5 variants (7.5%).

The most prevalent classic IBMFS was FA (34.8%, n=23). FANCA was the most frequently mutated gene (n=13) followed by FANCG (n=5). Mutations in BRIP1, UBE2T, BRCA2 and ERCC4 were assigned once. DBA (18.2%, n=12) was the second most common IBMFS. Mutational frequencies were as follow; RPS19 (n=4), RPS26 (n=3), RPS17 (n=2), RPL11 (n=1), RPL18 (n=1), RPL35A (n=1). There was a case of 1.5Mbp loss in RPS17 detected by microarray. Interestingly, among the 7 WAS patients, 3 patients with atopic dermatitis were clinically diagnosed as WAS, while 3 patients without the specific feature were diagnosed as ITP. Mutations in the category of myeloid neoplasm with germline predisposition were also identified, including RUNX1 (n=5), ETV6 (n=1) and DDX41 (n=1). Patients SDS, MYH9-related disease, DC, SCN and sideroblastic anemia were also found.

We provided 11 genetic diagnosis associated BMF for 13 patients (10.5%) using targeted NGS panel (38.5%, 5/13) and WES (61.5%, 8/13).

Finally, 14 patients with suspected IBMFS were revealed to have other genetic etiology. WES showed 6 times higher detection rate than targeted NGS panel (85.7% vs.14.3%) in this category. Interestingly, 9 of them were related with immune system defects (64.2%), but clinically presented as unexplained cytopenia. It is most likely due to an overlap of hematological and clinical features between IBMFSs and hereditary immune disease.

Conclusion: Using the combined and sequential strategy, we could provide genetic diagnosis up to 75% of IBMFS suspected patients. We also elucidated the genetic landscape of Korean IBMFS patients. Overall, well-known genetic causes of IBMFS were frequently detected by targeted NGS panel, whereas none-IBMFS related variants were predominantly found in WES, due to our study design. These unexpected genetic diagnosis may help to clinical management of patients. Therefore broad approach using extended gene panel in the clinical exome level will be useful as the first line method.

PP10-01

Performances of targeted RNA sequencing for the analysis of fusion, mutation, and expression in ph like B-ALL

Jing Li

R&D, SINO-US diagnostics, China

Background: The molecular characteristics of ph like B-ALL include alterations involving gene expression, gene fusion and gene mutation. Its molecular characteristics are of great significance for the diagnosis, prognosis and pathogenesis of the disease. However, the detection of its molecular characteristics often requires at least two methods and multiple test items. There is still a lack of a detection method that can detect all the molecular characteristics. RNA sequencing brings hope for comprehensive detection of molecular characteristics of ph like B-ALL.

Method: Using the targeted RNA sequencing panel of 56 B-ALL related genes, we analyzed the data of 12 clinical samples and 10 healthy population control samples.

Results: We detected a common known fusion gene, which is consistent with the results of quantitative real-time polymerase chain reaction (qPCR). Additionally, we also analyzed gene mutations. ALL the missense mutations (11/11) and frameshift mutations (3/3) identified at the DNA level could be detected at the RNA level, while splice site mutation (0/1) detected at the DNA level was not detected at the RNA level. The results of CRLF2 gene overexpression in 12 cases were 100% consistent with the results of qPCR. In gene mutation, NRAS / KRAS mutation accounted for 42% (5 / 12), followed by PTPN11, accounting for 25% (3 / 12). CRLF2 mutation, JAK1 mutation, lKZF1 mutation, ETV6 mutation and KMT2D mutation were also detected once, respectively.

Conclusion: Our results show that RAS mutation mostly occurs in ph like B-ALL with overexpression of CRLF2 gene. RNA sequencing, which has been further improved through experimental standardization, panel design and data analysis, is expected to replace the traditional molecular tool to detect gene expression, gene mutation and gene fusion.

Keyword: RNA sequencing, PH like B-ALL, Gene expression, Gene fusion, Gene mutation

PP10-02

Novel usefulness of krebs von den lungen 6 (KL-6) for assessing bone marrow fibrosis

Minjeong Nam[1], Mina Hur[2*], Mikyoung Park[3] and Hanah Kim[2]

[1] Laboratory Medicine, Korea University Anam Hospital, Korea
[2] Laboratory medicine, Konkuk University School of Medicine, Korea
[3] Laboratory medicine, Eunpyeong St. Mary's Hospital, Korea

Background: Bone marrow fibrosis (BMF) is manually assessed by reticulin and trichrome stain of bone marrow (BM) biopsy and graded on a semi-quantitative scale. Krebs von den Lungen 6 (KL-6) and Mac-2 binding protein glycosylation isomer (M2BPGi) are known to be associated with lung and liver fibrosis, respectively. We explored the usefulness of KL-6 and M2BPGi to assess BMF.

Method: A total of 250 patients who underwent BM biopsy with hematologic or non-hematologic diseases were included, and 42 patients with lung and liver diseases were excluded. The patients' data including age, sex, diagnosis, white blood cell, hemoglobin (Hb), platelet, and lactate dehydrogenase (LDH) were collected. Measured KL-6 and M2BPGi levels were compared with reticulin grade (RG) (grade 0-3).

Results: KL-6 levels significantly elevated with an increase of RG, but M2BPGi did not show a significant difference. Hb, LDH, or KL-6 were independent predictors for BMF (odds ratio: 1.96, 2.26, 2.91, respectively), but showed poor predictive ability (area under the curve [AUC] 0.62, 0.61, 0.60, respectively). The combination of Hb, LDH, and KL-6 showed significantly improved predictive ability for BMF (AUC 0.73; integrated discrimination improvement 0.057; category-free net reclassification improvement 0.625).

Conclusion: This is the first study to evaluate the usefulness of KL-6 for assessing BMF. The combination of Hb, LDH, and KL-6 would be an objective and relevant biomarker approach and be applied to risk stratification for BMF.

Keyword: Bone marrow fibrosis, KL-6, M2BPGi, Hb, LDH

PP10-03

Diagnostic validity %Micro-R of the Sysmex XN1000 for iron deficiency

screening in adolescent female without anemia

Ikky Nabila Nandinanti and Tri Ratnaningsih*

Departement of Clinical Pathology and Laboratory Medicine, Universitas Gadjah Mada, Indonesia

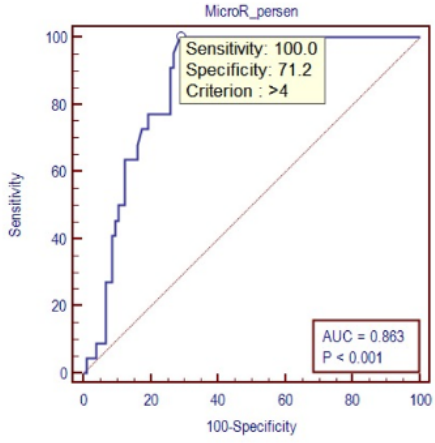
Background: Adolescent female is a group with high risk for suffering iron deficiency due to lack of iron intake and chronic bleeding due to menstruation. Iron deficiency conditions often cause health problems even though anemia has not yet occurred. Detection of this condition is also a diagnostic challenge. The %Mikro-R is a novel, cheap, easy and fast parameter and may be useful as a screening parameter to diagnose iron deficiency in individuals without anemia.

Method: Healthy female senior high school students with normal hemoglobin level were screened for iron deficiency. The %Micro-R parameters measured using Sysmex XN1000. Patients were divided into two groups: iron deficiency anemia and normal iron status as defined according to iron studies. The independent t test and Pearson correlation coefficient were used. The optimum %Micro-R cutoff values were performed by using receiving operation characteristic (ROC) analysis.

Results: One hundred twenty-six subjects were enrolled, consisted of 22 (17.5%) and 104 (82.5%) subjects had iron deficiency and normal iron status, respectively. There was a significant difference %Micro-R between the iron deficiency and non iron deficiency groups (p<0.0001). The area under curve (AUC) for %Micro-R (0.86, 95% CI 0.80-0.93) cutoff value >4% showed the optimum accuracy for screening iron deficiency with sensitivity 100% and specificity 71.2% (p<0.001).

Conclusion: The %Micro-R cutoff value >4% can be used as a screening parameter to diagnose iron deficiency before anemia occurs.

Keyword: %Micro-R, Iron Deficiency, Adolescent Female, XN1000



PP10-05

Evaluation of somatic hypermutation status and cytogenetic abnormalities in Korean patients with chronic lymphocytic leukemia

Heekang Choi[1], Haerim Chung[2], Hyunsoo Cho[2], Seung-Tae Lee[1], Jin Seok Kim[2] and Saeam Shin[1*]

[1] Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul 03722, Korea

[2] Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul 03722, Korea

Background: Compared to conventional Sanger sequencing, next-generation sequencing (NGS) enabled more precise detection of clonal immunoglobulin gene rearrangements. Presence of somatic hypermutation (SHM) in the immunoglobulin heavy variable (IGHV) gene is a favorable prognostic marker in patients with chronic lymphocytic leukemia (CLL). Several cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) and karyotyping are also markers for CLL prognostication. We evaluated the association between IGHV SHM status and cytogenetic abnormalities in CLL patients.

Method: In this study, 22 patients diagnosed with CLL were included. Bone marrow aspirates were evaluated for IGH rearrangements using the LymphoTrack® IGH FR1 assay kit (Invivoscribe, CA) on MiSeq (Illumina, CA) sequencer. Data analysis was done with the LymphoTrack-MiSeq version 2.4.3. software (Invivoscribe). The presence of SHM (IGHV mutated CLL) was defined as ≥2.0% of mutation rate to partial V-gene, according to the 2017 European Research Initiative on CLL recommendations. Cytogenetic abnormalities were assessed using G-banding karyotyping and FISH test using XL TP53/17cen dual spot, XL DLEU/LAMP dual spot, XL ATM/11cen dual spot (Metasystems GmbH, Germany), and Vysis LSI ETV6/RUNX1 ES probes (Abbott Molecular, IL). Statistical analyses were performed with R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). Differences with p values < 0.05 were considered statistically significant.

Results: Among 22 patients, 18 (81.8%) of patients showed clonal IGH rearrangement at diagnosis and 12 patients (54.5%) were classified as IGHV mutated CLL [mutation rate, median 7.81% (range 2.64-11.01%)]. The remaining 6 (27.2%) were classified as IGHV unmutated CLL, and one patient showed unproductive rearrangement with a stop codon. The most frequent IGHV usage was V3-23 (3/18 patients, 16.7%), and they are all belonged to IGHV mutated case. The number of patients with unfavorable cytogenetic abnormalities, such as 11q deletion, 17p deletion, or complex karyotype, were 3 (13.6%), 4 (18.2%), and 3 (13.6%), respectively. 13q deletion

was observed in 10 patients (45.5%), and five patients (22.7%) had 13q deletion as a sole abnormality. Normal karyotype and trisomy 12, intermediate prognostic variables, were present in five (22.7%) and six patients (27.3%), respectively. To validate the relation of IGHV mutation status and cytogenetic aberrations, we compared the frequency of patients with each cytogenetic abnormality in the group according to IGHV mutation using Fisher's exact test. Interestingly, high-risk cytogenetic abnormalities such as 17p deletion and 11q deletion were detected only in IGHV unmutated patients (p value=0.0007). Moreover, all 13q deletion cases as a sole cytogenetic abnormality, a favorable prognostic variable, were found exclusively in IGHV mutated CLL, although it wasn't statistically significant (p value=0.2451).

Conclusion: In this study, we evaluated the IGHV SHM status in diagnostic samples from Korean CLL patients using NGS and its relationship with cytogenetic abnormalities. In IGHV mutated cases, the proportion of favorable cytogenetic markers was relatively high, and that of unfavorable cytogenetic features was relatively low compared to the patients with IGHV unmutated cases. This finding suggests that the association between cytogenetic abnormalities and IGHV SHM status might affect the CLL patient's prognosis. Further large-scale studies will be needed to confirm this finding.

Keyword: Chronic lymphocytic leukemia, IGHV mutation, Cytogenetic abnormality

PP10-06

Aplastic anemia and risk of incident atrial fibrillation - the good, the bad and the ugly

Wei Syun Hu

Department, CMUH, Rep of China (Taiwan)

Background: This retrospective cohort study sought to follow up patients with aplastic anemia (AA) to evaluate their risk of developing atrial fibrillation (AF).

Method: From the National Health Insurance Research Database of Taiwan, this study identified an AA cohort (n=3,921), a general population cohort (n=17,617,843) and a propensity score-matched none AA cohort (PSM non-AA cohort in brief, n=15,684) in 2000-2010. By the end of 2011, the incident AF was higher in the AA cohort than in the general population and PSM non-AA cohorts (8.94 vs. 1.14 and 6.47 per 1,000 person-years, respectively).

Results: The adjusted hazards ratio of AF for the AA cohort was 2.12 (95% confidence interval 1.46-3.08) compared with the PSM non-AA cohort, after controlling for covariates. However, after further controlling for the competing risk of death, adjusted subhazard ratio was 1.21 (95% CI 0.97-1.50). Among those who developed AF, the AA cohort had a higher mortality rate (83.7 vs. 51.1 per 100), but a lower rate of incident stroke (26.0 vs. 41.5 per 100), compared with the PSM non-AA cohort.

Conclusion: Patients with AA could have an elevated risk for AF. The mortality risk increased further for those who develop AF.

PP10-07

Association of HTLV-1 bZIP factor with PICT-1 impairs the nucleolar stress inducible RPL11-MDM2 complex

Takayuki Ohshima

Faculty of Science and Engineering, Tokushima Bunri University, Japan

Background: Human T-cell leukemia virus type-1 (HTLV-1) is an oncogenic retrovirus and its infection causes adult T-cell leukemia (ATL) in 2-5 % of carriers after a long latent period. The HTLV-1 bZIP factor (HBZ) gene was identified and this protein expression is consistently observed in all ATL cells. Thus HBZ may play a critical role in the development of ATL, but these mechanisms remain unclear. In this study, we searched for cellular factors that interacted with HBZ by yeast two-hybrid screening system. This approach identified PICT1, also known as GLTSCR2, which has been reported as a regulator the tumor suppressor p53. PICT-1 bound to RPL11 in nucleolus and regulated the MDM2-mediated p53 degradation, especially in cells treated with nucleolar stress such as 5-FU, actinomycin D. Therefore, we focused the physiologincal significance of the interaction between HBZ and PICT-1 in RPL11-MDM2 pathway.

Method: We conducted a yeast two-hybrid screen using full-length HBZ as bait and newly identified PICT1. Interaction between HBZ and PICT1 was investigated in mammalian cells and binding domains both of HBZ and PICT1 were detected. Effect of HBZ in binding efficiency between PICT-1/RPL11/MDM was investigated. Subcellular distribution, when coproduction of HBZ together with PICT1 in cells were examined confocal microscopic.

Results: Association of HBZ with PICT1 was confirmed in mammalian cells by co-immunoprecipitation (Co-IP) assay. C-terminus domain of PICT1 bound to the N-terminus region of HBZ. The molecu-

lar interaction of HBZ with PICT1 might alter the mutual subcellular localization. Thus, we examined the cellular localization of HBZ and PICT1 in transiently transfected cells. As previously reported, GFP-HBZ localized to the nucleus as granular speckles. However, when GFP-HBZ and mCherry-PICT1 were co-expressed, GFP-HBZ no longer formed speckles but was accumulated in the nucleoli together with mCherry-PICT1, but not C-terminus deleted mutant of PICT1, suggesting that a physical interaction with PICT1 alters the distribution of HBZ. When in cells were treated with genotoxic reagents including 5-FU, the protein stability of PICT1 was enhanced by coproducing HBZ. Production of HBZ in cells resulted in an increase binding level of PICT-1 with RPL11, and then abrogated in the amount of RPL11/MDM2 complex. Our current study is focused on understanding the molecular significance by which the interaction between HBZ and PICT1 regulates the p53 pathway.

Conclusion: Our results suggested that HBZ may be affected the function of PICT1 and help us to understand the role of HBZ in ATL development.

Keyword: HTLV-1, ATL, HBZ, PICT1, MDM2, Ubiquitination

PP10-09

Myeloproliferative neoplasm (MPN)-associated gene mutations in non-MPN patients highlighting distinct features in plausible cases

Daehyun Chu[1], Young-Uk Cho[1*], Seongsoo Jang[1], Miyoung Kim[1], Chan-Jeoung Park[1], Eul-Ju Seo[1], Eun-Ji Choi[2], Je-Hwan Lee[2] and Kyoo-Hyung Lee[2]

[1] Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea

[2] Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea

Background: The myeloproliferative neoplasm (MPN)-associated gene mutations have been occasionally found in non-MPN myeloid neoplasms including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm (MDS/MPN). We sought to characterize non-MPN myeloid neoplasms that harbor these mutations and distinguish those that arise primarily from those that secondarily evolved from underlying MPN.

Method: Internal next-generation sequencing database of consecutive 878 patients with non-MPN myeloid neoplasms was queried to locate cases harboring MPN-associated gene mutations. We reviewed the corresponding clinical, pathologic and genetic findings of these cases.

Results: A total of 52 (5.9%) patients including 25 AML, 17 MDS and 10 MDS/MPN was detected. The JAK2 mutations (63.5%) was most common, followed by MPL (26.9%), CALR (5.8%) and concurrent JAK2 and MPL mutations (3.8%). Mutations were clonal in 35 cases (67.3%) and canonical in 31 cases (59.6%). In patients with AML, 14 (56.0%) were categorized in poor risk according to NCCN guideline. In patients with MDS, 13 (76.5%) were classified as higher-risk group according to IPSS-R scoring system. The cases were divided into two categories ("plausible" and "implausible") based on clinical (documented prior MPN) and pathologic (a significant myelofibrosis and proliferation of megakaryocytes with nuclear atypia) correlations. Plausible cases showed higher frequency of clonal mutations and canonical mutations ($P < 0.001$, respectively), compared with implausible cases. The frequencies of poor-risk AML and higher-risk MDS were higher in plausible cases (80% and 100% respectively) than in implausible ones (20% and 66.7%, respectively). The non-canonical JAK2 mutations included p.L184fs, p.E338fs, p.R426*, p.R683G/S, p.R867W, p.D873N and p.T979A. The non-canonical MPL mutations included p.S505N, p.K553Q, p.Y591D/N/H, p.R592Q,, p.R592*, p.I621T, p.H624D, p.L629Q, and p.W632C. The non-canonical CALR mutations were p.W347*. The recurrent non-canonical mutations include R683-affected mutations in JAK2, and Y591- and R592-affected mutations, S505N and H624D in MPL. The majority (78.6%) of MPL mutations were detected in implausible cases. The Y591-affected mutations in MPL was identified exclusively in MDS.

Conclusion: Non-MPN cases with MPN-associated gene mutations demonstrate somewhat different clinical and pathologic features and might have poor clinical outcome. In addition, our study suggest a potential role of non-canonical MPN-associated gene mutations, particularly of MPL mutations in MDS pathogenesis.

Keyword: Myeloproliferative neoplasm, Mutatons, Non-MPN neoplasm, MPL, Non-canonical

PP10-10

Deep sequencing for BCR-ABL1 kinase domain variants analysis in chronic myeloid leukemia patients with TKI treatment

Taekgyu Lee[1], Hyeon Ah Lee[1], Saeam Shin[2*], Seung-Tae Lee[2] and Jong Rak Choi[2]

[1] Department of Laboratory Medicine, Graduate School of Medical Science, Brain Korea 21 PLUS Project, Yonsei University College of Medicine, Seoul, Korea
[2] Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea

Background: Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder. It is characterized by the increased and upregulated growth of myeloid cells in the bone marrow and the accumulation of these cells in the blood. These are caused by BCR-ABL1 oncogenic tyrosine kinase formation from a translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11.2). Imatinib, the first tyrosine kinase inhibitor (TKI) for the treatment of CML, competitively binds to the ATP binding site of the BCR-ABL1 tyrosine kinase to prevent downstream signaling resulting in anticancer effects. Acquired mutations in the ABL1 kinase domain (KD) are the major cause of TKI resistance. Conventional Sanger sequencing (SS) has several limitations for detection of BCR-ABL1 KD mutation. To overcome the limitations of SS, we developed a targeted next-generation sequencing (NGS)-based testing for ABL1 KD mutation detection.

Method: RNA was extracted from bone marrow cells of CML patients and followed by cDNA synthesis. After polymerase chain reaction (PCR) for amplification of whole BCR-ABL1 fusion gene, sequencing was performed using Illumina NextSeq 550Dx sequencer (Illumina, CA, USA). GATK somatic variant calling pipeline was used to find ABL1 KD mutations. BCR-ABL1 transcript type was identified using Arriba. Transcript type and ABL1 KD mutation from NGS was compared with multiplex reverse-transcription PCR (RT-PCR) and SS, respectively. The limit of detection of our assay was evaluated using replicates of serially diluted RNA sets.

Results: In all tested samples, BCR-ABL1 transcript type from NGS was complete concordance with multiplex RT-PCR. Also, NGS-based assay identified a rare BCR-ABL1 transcript variant (c3a2). High-level mutations identified from SS was detected using NGS. NGS-based assay also showed low-level ABL1 KD mutations not identified from SS. The NGS-based assay identified mutations that reported actual resistance to TKI treatment, especially imatinib. This method enables identifying ABL1 KD mutations with high sensitivity and is more accurate than SS analysis.

Conclusion: Our NGS-based assay identified the early appearance of KD mutations that would not otherwise be detected by SS. Compound mutations, which can be related to ponatinib resistance, can also be detected from NGS. Using NGS, it is possible not only to detect ABL1 KD mutations but also to determine transcript types, including the rare variants at the same time. Our result showed that NGS-based assay could be a promising tool to guide selecting the most appropriate treatment in CML patients.

Keyword: Next-generation sequencing (NGS), Fusion gene, BCR-ABL1, Chronic myeloid leukemia (CML)

PP10-11

Routine use of targeted RNA sequencing in leukemia patients and comparative evaluation with commercially available panels

Young Eun Lee[1,2], Ha Jin Lim[1], Ji Hu Jeon[1], Ju Heon Park[1], Hye Ran Kim[3], Jong Hee Shin[1] and Myung Geun Shin[1*]

[1] Department of Laboratory Medicine, Chonnam National University and Chonnam National University Hwasun Hospital, Hwasun, Korea
[2] BioMedical Sciences Graduate Program (BMSGP), Chonnam National University and Chonnam National University Hwasun Hospital, Hwasun, Korea
[3] College of Korean Medicine, DongShin University, Naju, Korea

Background: Gene fusion not only plays an important role in the development of blood cancers such as leukemia, but is also important as an essential marker for diagnosis, risk assessment, optimal treatment selection, and residual lesion detection. Most clinical hematology laboratories use conventional cytogenetic testing, fluorescent in situ hydridization, and multiplex reverse transcriptase-PCR to detect gene fusions. However, the above methods currently used have great limitations in detecting various gene fusions occurring in blood cancer. In order to overcome these shortcomings, we developed a targeted RNA sequencing (RNA-seq) system that can be applied in clinical hematology laboratories and compared the results with the existing commercialized analysis system by applying clinical samples.

Method: A laboratory-oriented targeted RNA-seq system consisting of 84 genes was developed in consideration of test reporting time and operational efficiency in clinical laboratories (KBB-RNAseq NGS-Leukemia-PHB; KBlueBio, Hwasun, South Korea). For comparison with the existing analysis system, the Archer FusionPlex Heme v2 panel (ArcherDx, Boulder, CL) based on cDNA library for specific genes using anchored multiplex PCR was used. To evaluate the test performance of these systems, bone marrow specimens when diagnosing 93 patients with leukemia (15 acute myeloid leukemia, 35 adult B-acute lymphoid leukemia, 30 childhood B-acute leukemia and 13 T-acute lymphoid leukemia) were used.

Results: In all 93 leukemia patients, tier 1 or tier 2 gene fusions were observed in 72 (77%) patients. Gene fusions were detected in 83% (25/30) in pediatric B-acute lymphoid leukemia (B-ALL), and in adult B-ALL 94% (33/35). In patients with acute myeloid leukemia (AML) and T-ALL, fusion gene mutations were 53% (8/15) and 46% (6/13), respectively. For the comparative evaluation, 4 cases of B-ALL, 2 cases of AML, and 1 case of acute promyelocytic leukemia and T-ALL were used. The results of the two analysis systems were consistent in 7 of the 8 comparatively evaluated patients, but an IGH-CRLF2

fusion in a B-ALL case was detected only in the panel developed by the authors (Table 1). It is known that CRLF2 gene is a causative gene in a half of Philadelphia chromosome (Ph)-ALL cases, which account for 20-25% of B-ALL and are classified as a new type of ALL showing a very poor prognosis.

Conclusion: Laboratory-oriented targeted RNA-seq system (KBB-RNAseq NGS-Leukemia-PHB) showed a reliable and stable performance to detect various gene fusions occurring in blood cancers such as leukemia in clinical laboratories. Also, this targeted RNA-seq system was found to be very useful in diagnosing Ph-like B-ALL compared to Archer FusionPlex Heme system.

Keyword: Targeted RNA-seq, Clinical laboratory, Leukemia

Table 1. Comparison between results of two targeted RNA-seq systems (a commercially available system and a laboratory-oriented system developed in this study)

Sample no.	Diagnosis	Multiplex RT-PCR or FISH	Commercial targeted RNA-seq system2	Breakpoint		Our targeted RNA-seq system	Breakpoint	
1	APL	*PML-RARA*	*PML-RARA* (ex6-ex3)	chr15: 74325755	chr17: 38504568	*PML-RARA* (ex6-ex3)	chr15: 74325755	chr17: 38504568
2	B-ALL	*BCR-ABL1*	*BCR-ABL1* (ex1-ex2)	chr22: 23524426	chr9: 133729451	*BCR-ABL1* (ex1-ex2)	chr22: 23524426	chr9: 133729451
						BCR-ABL1 (ex2-ex1)	chr22: 23595986	chr9: 133589842
3	AML	*RUNX1-RUNX1T1*	*RUNX1-RUNX1T1* (ex6-ex2)	chr21: 36231771	chr8: 93029591	*RUNX1-RUNX1T1* (ex6-ex2)	chr21: 36231771	chr8: 93029591
			RUNX1-RUNX1T1 (ex6-ex1)	chr21: 36231771	chr8: 93074855	*RUNX1-RUNX1T1* (ex6-ex3)	chr21: 36231771	chr8: 93074937
			RUNX1-RUNX1T1 (ex6-ex1)	chr21: 36231771	chr8: 93074937	*RUNX1-RUNX1T1* (ex6-ex1)	chr21: 36231875	chr8: 93074774
4	B-ALL	*ETV6-RUNX1*	*ETV6-RUNX1* (ex5-in2)	chr12: 12022900	chr21: 36265263	*ETV6-RUNX1* (ex5-ex3)	chr21: 36265260	chr12: 12022903
			ETV6-RUNX1 (ex5-ex3)	chr12: 12022903	chr21: 36265260	*ETV6-RUNX1* (ex5-ex4)	chr21: 36259393	chr12: 1202290
			ETV6-RUNX1 (ex5-ex4)	chr12: 12022903	chr21: 36259393			
			ETV6-RUNX1 (ex5-in2)	chr12: 12022903	chr21: 36340571			
5	B-ALL		*P2RY8-CRLF2* (ex1-ex1)	chrX: 1655814	chrX: 1331530	*P2RY8-CRLF2* (ex1-ex1)	chrX: 1655814	chrX: 1331529
			EIF4E3-FOXP1 (ex7-ex3)	chr3: 71739161	chr3: 71542706			
6	B-ALL					*IGH-CRLF2*	chr14: 106329453	chrX: 1351126
						IGH-CRLF2	chr14: 106322373	chrX: 1351121
						IGH-CRLF2	chr14: 106330849	chrX: 1351119
7	AML	*CBFB-MYH11*	*CFB-MYH11* (ex5-ex33)	chr16: 67116211	chr16: 15814908	*CBFB-MYH11* (ex5-ex33)		
			CFB-MYH11 (ex5-ex33)	chr16: 67116242	chr16: 15814908			
8	T-ALL		*PICALM-MLLT10* (ex17-ex4)	chr11: 85692172	chr10: 21875223	*PICALM-MLLT10* (ex17-ex4)	chr11: 85692172	chr10: 21875223
			PICALM-MLLT10 (ex17-ex4)	chr11: 85689133	chr10: 21875228	*PICALM-MLLT10* (ex7-ex3)	chr11: 85687725	chr10: 21827841
			PICALM-MLLT10 (ex17-ex3)	chr11: 85692184	chr10: 21827830	*PICALM-MLLT10* (ex19-ex3)	chr11: 85670103	chr10: 21827841

RNA-seq, RNA sequencing; APL, acute promyelocytic leukemia; B-ALL, B-lymphoblastic leukemia; AML, acute myeloid leukemia; T-ALL, T-lymphoblastic leukemia; RT-PCR, reverse transcriptase-PCR; FISH, fluorescence in situ hybridization; ex, exon.

PP10-12

Hemoglobin concentration, leukocyte and platelet counts in patients with gestational diabetes

Nhu Cao Thi Bich, Thao Nguyen Van*, Tung Tran Thanh, Tuan Nguyen Huu, Thoa Nguyen Thi, Thao Nguyen Thi, Ha Vy The, An Pham Thi Thuy, Diem Pham Ngoc and Trung Thai Minh

Hematology, Cho Ray hospital, Viet Nam

Background: Gestational diabetes mellitus (GDM) is a disease caused by an increase in insulin requirement and secretion of certain hormones in pregnant women that leads to insulin resistance. The disease manifests itself between the 24-28th weeks of pregnancy. Hematological changes in normal pregnant women have been extensively studied and described in the literature. However, hematological changes in gestational diabetes patients have not been studied thoroughly. Therefore, we conducted this study to assess the hematological alterations in pregnant women with GDM. Aim: To assess the changes in Hemoglobin (Hb) concentration, leukocyte and platelet counts in women diagnosed gestation diabetes.

Method: This was a retrospective, descriptive study. Pregnant women at week 24 or beyond who were diagnosed with GDM according to the American Diabetes Association criteria at Cho Ray Hospital were included in the study. Automated complete blood counts were performed to assess Hb concentration, leukocyte and platelet counts.

Results: 120 patients were included in the study. The average age was 33.7 ± 3.9 years. PARA 0000: 57.5% PARA 1001:31.7%. Mean gestational age 38.1 ± 1.7 weeks.

Hb concentrations at weeks 24-28, 29-32, 33-36, 37-40 were 119.4 ± 13.9, 125.3 ± 10.9, 128.1 ± 15.7 and 130.3 ± 11.9 g / L, respectively. Frequency of anemia at weeks 24-28, 29-32, 33-36, 37-40 were 42.5%, 26.4%, 22.7% and 17.3%., respectively Frequency of leukocytosis at weeks 24-28, 29-32, 33-36, 37-40 were 31.7%, 29.1%, 15.5% and 12%, respectively. Thrombocytopenia occurred in 2-5% patients.

Conclusion: In patients with GDM, reduced Hb concentration, increasing leukocyte counts and decreased platelet counts are relatively common findings.

Keyword: Pregnancy, Diabetes, Gestational diabetes mellitus

PP10-13

Establishment of next-generation sequencing protocol for highly sensitive tracking of minimal residual disease in B-lymphoblastic leukemia

Hyeon Ah Lee[1], Jin Ju Kim[2], Saeam Shin[2*], Seung-Tae Lee[2] and Jong Rak Choi[2]

[1] Department of Laboratory Medicine, Graduate School of Medical Science, Brain Korea 21 PLUS Project, Yonsei University College of Medicine, Seoul, Korea

[2] Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea

Background: Detection of clonal rearrangement of immunoglobulin genes is a crucial component in diagnosing and monitoring of lymphoid malignancies. Next-generation sequencing (NGS)-based clonality assays for immunoglobulin heavy chain (IGH) and kappa light chain (IGK) genes can identify and sensitively track specific clonal DNA sequences using universal primers. In this study, we established protocols and validated the analytical performance of the LymphoTrack® IGH FR1 and IGK assays (Invivoscribe, Inc) with Novaseq600 sequencer for highly sensitive minimal residual disease (MRD) monitoring in B-lymphoblastic leukemia.

Method: Genomic DNA was extracted from 46 bone marrow aspirates of 20 patients diagnosed as B-lymphoblastic leukemia. All samples for targeting IGH FR1 and IGK loci were executed duplicated polymerase chain reaction (PCR) in a single NGS run, and 100 cell equivalents of DNA with a known clonal sequence (LymphoQuant, LQ) was added to 1000 ng of genomic DNA. Individual master mixes for IGH FR1 and IGK loci were used with 48 indices and 24 indices, respectively. Demultiplexed fastq data from NovaSeq 6000 sequencer were analyzed using LymphoTrack® Dx (v2.4.3) and MRD (v2.0.2) software. We analyzed frequency distributions, V-J usage, specific sequences for top sequencing reads, and the somatic hypermutation rate of IGH FR1 and IGK amplicons.

Results: We successfully analyzed the MRD status in all tested samples. We obtained on average 10 million reads per sample. Clonality assessment results from NGS confirmed 10-5 sensitivity in most cases with 95% confidence intervals. NGS identified more positive samples with low residual disease than conventional tests.

Conclusion: We established and validated the analytical performance of the highly sensitive MRD testing using NGS. The meaning of this study is that there has been no previous study that attempted LymphoTrack® Assays on NovaSeq 6000 sequencer. This method can be used in routine clinical practice and provides highly sensitive MRD results in B-lymphoblastic leukemia patients.

Keyword: Next-generation sequencing (NGS), Immunoglobulin heavy chain, Kappa light chain, Clonality assay, NovaSeq 6000, Lymphotrack® assay

PP10-14

Higher value of hemoglobin in optical methods of hematology analyzer Advia 2120 in diagnosing anemia

Adika Zhulhi Arjana and Tri Ratnaningsih*

Clinical Pathology and Laboratory Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia

Background: Anemia still becomes the burden of disease, especially in developing countries. Early detection and screening were needed to prevent further morbidity. The method used needs to be accurate in measuring Hemoglobin concentration in blood. Advia 2120 is a hematology analyzer that uses both spectrophotometer and optical methods. The use of the optical method does not involve the lysis process so that it measures value in intact erythrocytes such as cellular hemoglobin, CH, and CHCM levels. However, the diagnosis of anemia is still using the results of a spectrophotometric-based examination which requires lysis of erythrocytes. This study aims to determine the utilization of anemia parameters from optical methods of the Advia 2120 in diagnosing anemia.

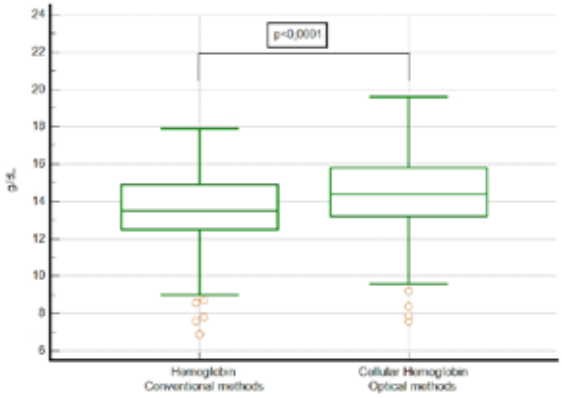
Method: This is a secondary study that uses previous research data entitled "Determination of the GAMA-CUTE Index and Validation of Smart Microscopes for Screening of Thalassemia Carriers". The research inclusion criteria were subjects who registered for the 2019 specialist doctor education program who had the results of the Advia 2120 hematology examination. Incomplete data were excluded from the study. Hemoglobin levels <13 g/dL in male subjects and <12 g/dL in female subjects were classified as anemia according to the World Health Organization guidelines. Data were presented descriptively, and Mann-Whitney analysis was performed to examine the differences between the corresponding conventional and optical methods. Kappa test was conducted to determine the agreement between hemoglobin and cellular hemoglobin in diagnosing anemia. The statistical test was declared significant if $p<0.05$. Statistical analysis using Medcalc version 20014. This research has received ethical approval with the number KE/FK/1025/EC/2020.

Results: A total of 806 subjects were included with a mean age of 25.35 years old. The comparison test showed significant differences between the median hemoglobin to cellular hemoglobin, MCH to CH, and MCHC to CHCM. Based on the current anemia reference value, it was found that 62 subjects were not diagnosed with

anemia when viewed from the value of cellular hemoglobin. This number represents 49% of all subjects classified as anemic. There were no non-anemic subjects classified as anemic based on cellular hemoglobin examination. However, the Kappa test showed good agreement in diagnosing anemia (K=0.64). Parameters of cellular hemoglobin, CH, and CHCM are the results of examination using optical methods that higher value from the results of the examination with conventional methods. The good agreement between the two methods demonstrates the usefulness of optical methods in diagnosing anemia although it requires adjustment of values regarding the reference value used.

Conclusion: Optical methods of hematology analyzer ADVIA 2120 result higher value of hemoglobin in diagnosing anemia. However, this still could be used for diagnosing anemia by adjusting the reference value. Further research is needed to compare the strength of the correlation between conventional and optical methods with reference methods study design.

Keyword: ADVIA 2120, Cellular hemoglobin, CH, CHCM, Optical methods



PP10-15

Diagnostic validity of percentage of hypochromic red cells (% HYPO) for iron deficiency screening without anemia

Andri Christianalusi and Tri Ratnaningsih *

Departement of Clinical Pathology and Laboratory Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada Yogyakarta, Indonesia

Background: Iron deficiency (ID) has no conspicuous signs, so people with ID are less likely to seek treatment. The use of parameters in modern hematological examinations, one of which is percentage of hypochromic red cells (% HYPO), is a new parameter that cheaper, fast, and can detect iron deficiency in individuals without anemia. Therefore, this study was aimed to evaluate the diagnostic performance of percentage of hypochromic red cells (% HYPO) for screening an iron deficiency in individuals without anemia

Method: This study is a diagnostic test with a cross-sectional design. Subjects were healthy residents candidate with normal hemoglobin levels. One hundred eleven residents (age range, 18 - 37 years) without anemia (hemoglobin ≥ 13 g/dL for male and ≥ 12 g/dL for female) and with serum ferritin < 15 µg/L were selected. We measured the % HYPO, red blood cell (RBC) count, hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), red blood cell distribution width (RDW) with the Advia 2120, and serum ferritin (SF), serum iron (SI), and total iron binding capacity (TIBC) using Cobas e601. Receiver operating characteristics (ROC) analysis was performed to assess % HYPO and other conventional hematological parameters in identifying ID. Receiver operator characteristic (ROC) curves demonstrated that the area under the curve (AUC) of % HYPO, RBC, MCV and MCH.

Results: One hundred eleven subjects consisted of 18 (16.22%) subjects with ID and 93 (83.78%) subjects with normal iron status. The % Hypo value was significantly higher in ID subjects than in normal iron status subjects, namely 1.85 (0.3 – 7.7) vs 0.8 (0.2 – 19.4) p = 0.003. Receiver operator characteristic (ROC) curves demonstrated that the area under the curve (AUC) for % HYPO (0.721) was significantly greater than that for RDW (0.695), RBC (0.652), MCV (0.573), dan MCH (0.542), (p = 0.001) with a cutoff of >1, with a sensitivity of 72.22% and a specificity of 63.44% in the screening of ID. Iron deficiency affects the production of hemoglobin which results in a decrease in the concentration of hemoglobin in erythrocytes. %Hypo as the percentage of red blood cells with a hemoglobin concentration of less than 280 g/L is a method of measuring the hemoglobinization of mature erythrocytes. %Hypo is related to iron status in the last 2-3 months and is recognized as an indicator of ID. The results showed that % HYPO was a better alternative parameters than conventional hematological parameters in the screening of ID in residents without anemia.

Conclusion: The %Hypo parameter can be used in screening for iron deficiency before anemia occurs.

Keyword: Iron deficiency, %Hypo, Diagnostic

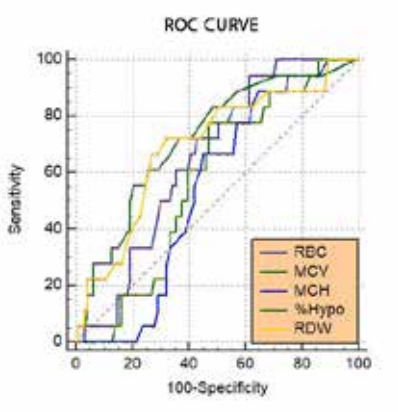


Figure 1. Receiver Operating Characteristic curves for % HYPO and conventional hematological indicators in the screening of ID.

PP10-17

Correlation of reticulocyte hemoglobin content (CHr) and iron status parameters

Pradita Sri Mitasari and Tri Ratnaningsih*

Clinical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Background: Iron deficiency is caused by imbalance between erythropoiesis and iron storage in our body. This can lead to anemia and further health problems. Detecting iron deficiency anemia needs more than complete blood test. Reticulocyte hemoglobin content (CHr) has short lifespan in circulation and can serve as early indicator of iron deficient erythropoiesis. This study aims to assess the correlation between CHr and iron status parameters.

Method: This was a analytical cross sectional study. Subjects were male and female at reproductive age, underwent testing in Faculty of Medicine, Public Health and Nursing, UGM, Yogyakarta. Subjects are excluded if hemoglobin level was below 9 g/dL. Hematology parameters were analyzed using ADVIA 2120 analyzer, including CHr. Serum iron, total iron binding capacity (TIBC) and ferritin were using Cobas c501. Subjects with ferritin < 12 ng/mL were grouped as iron deficient. Data analysis was performed using SPSS 23. Differences between group were analyzed using Chi Square, Mann Whitney U Test and independent t-test according to data distribution. Correlation between parameters were analyzed using Spearman test.

Results: Both groups had a higher proportion of female subjects (74,3% and 98,1%). Iron deficient group (n=52) had significantly lower CHr, serum iron and ferritin compared to non-deficient (n=148) with p<0,0001. Correlations between CHr and serum iron, ferritin, TIBC, saturation and ferritin were all significant (p<0,0001) yet show weak correlations (r=0,318, r=-0,283, r=0,330, r=0,232, respectively)

Conclusion: Patients with iron deficiency had lower CHr level. The CHr parameter was significantly correlated with iron levels parameter.

Keyword: Iron deficiency, CHr, Anemia, Iron status

PP10-18

Validation of a machine learning expert supporting system, immunogenius, using immunohistochemistry results of 3000 Korean patients with lymphoid neoplasms

Yosep Chong[1], Jamshid Abdul-Ghafar[1], Hye-Ra Jung[2], Seung-Sook Lee[3], and Gyeongsin Park[2]

[1] Department of Hospital Pathology, The Catholic University of Korea College of Medicine, Seoul, Korea

[2] Department of Pathology, Keimyung University, Daegu, Korea

[3] Department of Pathology, Korea Institute of Radiological and Medical Sciences, Seoul, Korea

Background: Immunohistochemistry (IHC) is an essential process of daily pathologic diagnosis and often very challenging due to exponentially increasing IHC data and complex cases such as synchronous multiple cancers. To support this qualitative analysis, a machine learning based expert supporting system, ImmunoGenius, was recently developed as mobile application and showed generally acceptable hit rate as 95% in the diagnosis of lymphoid neoplasm. Here, we evaluated the prediction accuracy of this software using nation-wide data to validate its clinical utility.

Method: We collected pathologically confirmed cases of lymphoid neoplasms and its corresponding IHC panel results from 25 major university hospitals in Korea from 2015 to 2016. We tested the ImmunoGenius software with these real IHC panel data and compared the precision hit rate between previously reported in-house data.

Results: A total of 3052 cases of lymphoid neoplasms were enrolled. Average 8.3 IHC were performed in each case. The precision hit rate was up to 84.5% for these cases while it was 95.0% for 984 in-house cases. It showed excellent results in most B-cell lymphomas and generally equivalent performance in T-cell lymphomas. The

primary reasons for inaccurate precision were atypical IHC profile of certain cases (e.g., CD15-negative Hodgkin lymphoma), a lack of disease-specific markers, and overlapping IHC profiles of similar diseases.

Conclusion: In this study, we verified that the machine-learning algorithm could be applied for diagnosis precision with generally acceptable hit rate in a nation-wide dataset. Because of the lack of origin-specific or disease-specific markers in the particular differential diagnosis, the contextual information such as clinical and histological features also should be taken into account for the proper use of this system in the pathologic decision-making process.

Keyword: Database, Expert supporting system, Machine learning, Immunohistochemistry, Probabilistic decision tree, Validation

PP11-01

Iron deficiency anaemia presenting as idiopathic intracranial hypertension

Sanka Vijayabandara*, Dawpadee Dharmasena and Malika Udugama

Teaching Hospital, Karapitiya,Galle, Sri Lanka

Background: Idiopathic intracranial hypertension (IIH) is a disorder of unknown aetiology that predominantly affects obese females of child bearing age. Common associations are use of oral contraceptives , antibiotic therapy and thyroid disorders. Iron deficiency anaemia (IDA) is a rare association of IIH. The primary problem is chronically elevated intracranial pressure which may lead to progressive optic atrophy and blindness. We present a case of severe Iron deficiency anaemia presentingas IIH.

Method: Case Report

Results: A 26 year old, averagely built, lady presented with progressively worsening global headache for 2 weeks duration. Ophthalmoscopic examination revealed severe papilloedema and bilateral Roth's spots. Rest of the neurological examination was unremarkable. A soft systolic murmur could be heard without peripheral stigmata of infective endocarditis. However, she was found to be severely pale. Magnetic Resonance Imaging(MRI) of head did not reveal any intracranial pathology and echocardiogram was negative for endocarditis. Cerebrospinal fluid(CSF) analysis was normal(protein-30mg/dl,polymorphs-nil,lymphocytes-nil, red blood cells-03). However, CSF pressure was elevated at 36cmH2O.The diagnosis of IIH was made. Detailed history failed to identify any other associations of IIH:OCP use, preceding antibiotic therapy.

FBC showed hypochromic microcytic anemia with haemoglobin of 2.2g/dL. Blood picture was suggestive of IDA. Serum Ferritin was 10 microgram/L (15-200)

The patient was managed with blood transfusion and started on haematenics and acetazolamide(500mg TDS). Following blood transfusion, haemoglobin raised to 11g/dl and headache improved markedly.

Further investigations were planned to identify underlying cause for IDA.During follow up, gradual improvement of papilloedema was noticed. Normal pressure of 19 cmH2O was detected on CSF manometry done 4 weeks after correction of anaemia.

Conclusion: Although, IIH is a rare complication of IDA, it can be the presenting manifestation. Identification and correction of anaemia is important to prevent IIH associated blindness in these circumstances.

Keyword: Idiopathic Intracranial Hypertension (IIH), Iron Deficiency Anaemia (IDA)

PP11-02

Risk factors associated with anemia among teens in Laguna, Philippines

Cherry Ann Durante[1*], Rufo Jr. Calixtro[2] and Estrella San Juan[1]

[1] Nursing, University of Perpetual Help - Dr. Jose G. Tamayo Medical University, Philippines

[2] Research, University of Perpetual Help - Dr. Jose G. Tamayo Medical University, Philippines

Background: Anemia is one of the most common blood disorders in underdeveloped countries. In the Philippines, iron deficiency anemia was the most prevalent micronutrient deficiency based on the national nutrition survey of 2019. This study aimed to discover the prevalence of anemia in teens and the risk factors associated with its occurrence.

Method: Utilizing a cross-sectional research design and convenience non-probability sampling, the study enumerated 402 participants aged 13-18 residing in Santa Rosa, Laguna at the time of data gathering. Online questionnaires were distributed from November 2020 to January 2021.

Results: The prevalence of IDA among the participants was 14.3%; while family history of IDA was 11.4%. Fifty-eight participants were diagnosed with anemia, among which, 74% were females. 6 out of 10 participants with anemia were residing in an urban location, with access to fast foods and reported to drink coffee every day. Based

on the results of the study, risk factors associated with anemia diagnosis were low socio-economic status, female gender, daily drinking of coffee, fast food meal consumption of more than 3 times a week, and low consumption of Vitamin C-rich fruits (p-value<0.001). 56% of participants with anemia agreed to the statement that "anemia is not a serious disease." Participants reported that reasons for not eating iron-rich foods daily were cost, inaccessibility and preparation time.

Conclusion: Due to the high prevalence of anemia among the participants, there is a need for health education on anemia, its risk factors, and possible health complication associated with the disease. Measures to increase access to iron-fortified foods and iron supplementation in females are also recommended.

Keyword: Risk factors of anemia

PP11-05

Impairment of invasion and maturation and decreased selectivity of plasmodium falciparum in G6PD Viangchan and Mahidol variants

Duangdao Palasuwan[1], Attakorn Palasuwan[1], Kanyarat Boonpeng[1], Mallika Imwong[2], Kasem Kulkeaw[3*] and Nutpakal Ketprasit[4]

[1] Oxidation in Red Cell Disorders Research Unit, Department of Clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, Thailand

[2] Department of Molecular Tropical Medicine and Genetics, Faculty of Tropical Medicine, Mahidol University, Thailand

[3] Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

[4] Department of Biochemistry and Pharmacology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Australia

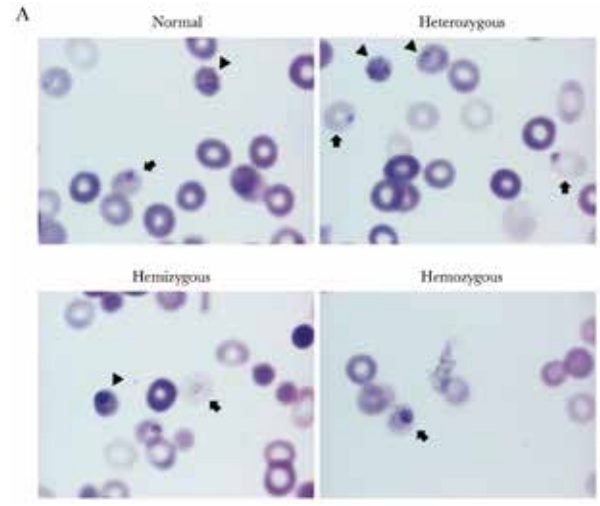
Background: Protection against Plasmodium falciparum is observed in a population deficient in glucose-6-phosphate dehydrogenase (G6PD), particularly in African and Mediterranean regions. However, such protection remains unknown among G6PD-deficient individuals in Southeast Asia.

Method: In this study, we assessed the invasion and maturation of P falciparum K1 in a culture of erythrocytes isolated from Thai subjects carrying Viangchan (871G > A) and Mahidol (487G > A).

Results: We found that the parasites lost their ability to invade hemizygous and homozygous G6PD-deficient erythrocytes of Viangchan and Mahidol variants in the second and third cycles of intraerythrocytic development. It is interesting to note that P. falciparum parasites selectively grew in erythrocytes from hemi- and homozygous genotypes with normal G6PD activity. Moreover, externalization of phosphatidylserine upon P. falciparum infection was significantly increased only in Viangchan hemizygous variant cells.

Conclusion: This study is the first to show that blockage of invasion in long-term culture and potentially enhanced removal of parasitized erythrocytes were observed for the first time in erythrocytes from Viangchan and Mahidol G6PD-deficient individuals.

Keyword: Plasmodium falciparum, Malaria, glucose-6-phosphate dehydrogenase (G6PD)



PP11-08

Association of hematologic parameters with TMPRSS6 gene variations in iron deficiency anemia patients

Azadeh Alizargar

Electrical Engineering and computer science, National Taipei University of Technology, Rep of China (Taiwan)

Background: TMPRSS6 gene is involved in the pathway of matriptase-2 which plays a part in the pathways signaling of hepcidin. Hepcidin is a factor in the keeping of the iron balance in the body. TMPRSS6 gene mutations cause a reduction in matriptase-2. This will increase hepcidin activity which blocks the iron absorption. Associations of three single nucleotide polymorphisms (SNPs) with

hematologic parameters have been evaluated in iron deficiency anemia (IDA) patients in this study.

Method: This study evaluated variations of rs855791, rs2413450 and rs4820268 SNPs of TMPRSS6 gene in 231 Iranian patients with confirmed IDA with Real-Time polymerase chain reaction (Real-Time PCR) technique. Blood cell counts and erythrocyte indexes, serum iron (µg/dl), hemoglobin (Hb, g/dl), hematocrit (Hct, %), red blood cell (RBC), mean corpuscular volumes (MCV, fL), mean corpuscular Hb (MCH, pg), mean corpuscular Hb concentrations (MCHC, g/dl), total iron binding capacity (TIBC, µg/dl), and ferritin (ng/ml) were analyzed by standard methods. Transferrin saturation (TS, %) was calculated by the division of serum iron level by total iron binding capacity was evaluated in this study.

Results: Wild type, heterozygous and homozygous form of rs855791 stands for 12.1%, 51.9% and 35.9% of the cases. These figures about rs2413450 was 13.4%, 61% and 25.5% and regarding rs4820268 was 12.5%, 57.5% and 29.8% respectively. All three SNPs variations were associated with increased RBC and TIBC but other measures were not significantly different between variations of these SNPs.

Conclusion: We can conclude that TMPRSS6 gene mutations as in rs855791, rs2413450 and rs4820268 SNPs can be associated with RBC and TIBC in IDA patients with IDA.

Keyword: TMPRSS6, Iron deficiency anemia, Single nucleotide polymorphism

PP11-09

Identification of genetic alterations in TMPRSS6 gene of anaemic patients from tribal region of Tamil Nadu, India

Balachandar vellingiri[1*], Dhivya Venkatesan [1], Nimmisha Eruppakotte[1], Soumya Kizhakkillach [1], Harsha Ganesan[1], Arul Narayanasamy [2] and Abilash Valsala Gopalakrishnan[3]

[1] Department of Human Genetics & Molecular Biology, Bharathiar University, India

[2] Department of Zoology, Bharathiar Univeristy, India

[3] Department of Biomedical Sciences, Vellore Institute of Technology (VIT), India

Background: India has the largest tribal population with 8.6 percent of the total population. Anaemia is a condition in which you lack enough healthy red blood cells to carry adequate oxygen to your body's tissues. Having anaemia, also referred to as low haemoglobin, can make you feel tired and weak. The study conducted genetic alterations in the TMPRSS6 gene from anaemic patients of the tribal population from the Tamil Nadu region.

Method: Totally 60 samples including 30 tribal adult anaemic patients and 30 normal healthy tribal adults were recruited as controls. Among the anaemic patients, 21 were females and 9 were males. The sample collection was done from patients of 14-70 years old. A questionnaire along with pedigree was taken and blood samples were collected with the informed consent of the study population. The study was approved by the Institutional ethical committee following the Declaration of Helsinki.

Results: Cytogenetic analysis was performed in anaemic subjects using Trypsin banding which showed a high degree of chromatin type of alteration in 9 subjects. Following chromosomal analysis, molecular studies were performed by sequencing technique which showed a mutation in 8 subjects in exon 15 of TMPRSS6 gene both in the patients and one control.

Conclusion: Hence, the study contributes to the knowledge of anaemia in Tamil Nadu tribal population, highlighting the gender and age of the anaemic subjects. Also, the study shows the importance of anaemia and emphasizing its prevalence in different aspects and the need of investigation on genetic alterations in anaemic patients of the population.

Keyword: Anaemia, Sequencing, TMPRSS6, Exon15

PP11-11

Identification of CYP2A6 alteration and its effect on sickle cell anaemia (SCA) in tribal population of Tamil Nadu, India

Dhivya V[1], Soumya K[1], Harsha G[1], Krishnaswamy R[1], Arul N[2] and Balachandar V[1*]

[1] Human Molecular Cytogenetics and Stem Cell Laboratory, Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore 641046, Tamil Nadu, India

[2] Disease Proteomics Laboratory, Department of Zoology, Bharathiar University, Coimbatore 641046, Tamil Nadu, India

Background: Tribes are indigenous population have various lifestyle practices that determines their health concerns. Smoking is one of the factors that causes various diseases and recognized as major public health concern. The present study conducted a survey in 20 tribal people of Tamil Nadu to examine their smoking pattern

(smoking and smokeless tobacco) and also determined the effects of smoking on CYP2A6 gene in order to identify the polymorphic effects on sickle cell anaemia (SCA) patients.

Method: The study was performed in two age groups: group I (>50) and group II (<50). The study conducted smoking assessment using pack-years; duration and number of cigarettes consumed per day in each individual and found out with significant association in males than in females. The total male individuals consuming tobacco products were n=11 and females were n=9. Serum cotinine level was measured by ELISA in each individual. Blood parameters were assessed by a hemocytometer. The genetic alterations were analyzed by PCR and sequencing method.

Results: Serum cotinine level found with significant results in both the age groups. Blood parameters were assessed and found out with increased level of haemoglobin, leucocytes and lymphocytes in smokers than in non-smokers. The smoking impact on CYP2A6 have been assessed in SCA patients in which they reported a profound association which needs further investigation

Conclusion: Hence, the study demonstrates an intense association of smoking with SCA which needs more examinations to confirm the findings with a defined mechanism. This survey would be limelight in tribal communities that would change their socio-cultural practices for a betterment of health.

Keyword: Tribes, Survey, Smoking pattern, Sickle Cell Anaemia, CYP2A6

PP11-12

Risk factors of anemia in pregnancy woman: primary healthcare centre

Fitri Rachmawati Putri

General Practitioner, Medika Mulya Hospital, Indonesia

Background: Anemia in pregnancy is still a major problem, especially in developing countries. According to WHO, as many as 40% of deaths of pregnant women with anemia in developing countries. According to Riskesdas data in 2013, the prevalence of anemia in Indonesia is 21.7% and for the prevalence of anemia in pregnant women in Indonesia is 37.1%. Data from the Indonesian Ministry of Health in 2013 said that most anemia in pregnant women is caused by iron deficiency and acute bleeding. To find out the factors that influence the incidence of anemia in pregnant women in the Puskeskas Sawangan II work area.

Method: This study used a cross sectional study design. Sampling in this study uses the total sampling method of the entire population. The population of this study were all third trimester pregnant women in the Puskesmas Sawangan II working area recorded at Puskesmas Sawangan II in the period January 2018 to November 2018. The research instrument used in this study was secondary data collection. The dependent variable in this study was the incidence of anemia in the 3rd trimester pregnant women recorded at Puskesmas Sawangan II and the independent variables were age, education level, number of gestations, number of Antenatal care visits that recorded in data collection at Puskesmas Sawangan II. Data processing and analysis use SPSS version 23 software. The analysis plan that will be used is Chi Square analysis to determine the relationship between the independent variable and the dependent variable followed by Multiple Linear Regression analysis to determine the most influential factor.

Results: there are 204 subject 3rd trimester pregnant woman in this study which have anemia 108 subjects (52,9%) and not anemia 96 subjects (47,1%). There was a significant relationship between age, level of education, gestation, and number of antenatal care with anemia in pregnant woman (p 0,028; 0,000; 0,016; 0,000). There was a significant relationship between age at high risk and the incidence of anemia ($p<0.05$) with OR 1.86; 95%CI (1.067-3.252), which means that the risk of anemia in third trimester pregnant women at risk age is 1.86 times greater than pregnant women aged 21-30 years. There is a significant relationship between education level and the incidence of anemia ($p<0.05$) with OR 2.82; 95%CI (1,598-4.981) which means that the risk of anemia in third trimester pregnant women in pregnant women with low levels of education (kindergarten, elementary, and junior high schools) has a risk of 2.82 times greater than pregnant women with high levels of education (Senior High School and college). There is a significant relationship between the number of gravidarum and the incidence of anemia ($p<0.05$) with an OR of 2.23; 95%CI (1.15-4.31) which means the risk of anemia in third trimester pregnant women in pregnant women, the higher the number ofgravidarum, the risk is 2.23 times greater than that of pregnant women with fewer gravidaurum.There is a significant relationship between the number of antenatal care and the incidence of anemia ($p<0.05$) with an OR of 5.21; 95%CI (2.75-9.86) which means that the risk of anemia in third trimester pregnant women if they do not perform ANC regularly is 5.21 times greater than pregnant women who routinely perform ANC. In multiple linear regression analysis, the most factor was significant is antenatal care and level of education.

Conclusion: The factors that influence the incidence of anemia in third trimester pregnant women in the Puskesmas Sawangan II working area for the January 2018 to November 2018 period are the number of ANC visits and the mother's low education level.

Keyword: Risk factor, Anemia, Pregnancy

PP11-13

Diagnostic performance of % Hypo as discriminator parameter of iron deficiency and hemoglobinopaties

Rhaina Khairani

Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, Indonesia

Background: Iron deficiency (ID) and hemoglobinopathies are common causes of microcytic hypochromic. Both conditions are important to correctly identify the differences in therapy. Parameter of %Hypo (erythrocytes with Hb concentration <28 g/dL) is a parameter that reflects the occurrence of long-term iron deficiency

Method: The study used a cross-sectional design with high school students who underwent anemia screening as a subject. Inclusion criteria were microcytic erythrocytes (MCV<80 fL) and/or hypochromic (MCH <26 pg) from hematological examination using the Advia 2120 device. Subjects were examined for iron status and hemoglobin analysis using capillary electrophoresis (CE) or High Performance Liquid Chromatography (HPLC) methods. The hemoglobinopathy group consisted of beta thalassemia trait (HbA2 ≥4%) and Hb E subjects (HbE ≥10% using the CE method or HbA2 10% using HPLC). The ID group were subjects with ferritin levels <12 g/L. Subjects were excluded when ferritin levels and Hb analysis were normal

Results: From 215 hypochromic microcytic subjects, 63 subjects were analyzed. The ID group was 48 (76,1%) people and hemoglobinopathy 15 (23,8%). The %Hypo value was higher in the ID group than in the hemoglobinopathy group [median 5,75 (1,90-66,9) vs 0,7 (0,20-2,20) p<0,001]. Distinguishing between ID and hemoglobinopathies, %Hypo had an Area Under Curve 0.92 (p<0.001) at a cutoff value of ≥8,45 with a sensitivity of 79% and a specificity of 93%.

Conclusion: %Hypo can be used as a discriminator for ID and hemoglobinopathies. Further research is needed on a heterogeneous population and a larger sample size

Keyword: Iron deficiency, Hemoglobinopathy, %Hypo, Erythrocyte

Tabel 2. %Hypo performance as a discriminator of iron deficiency and haemoglobinopathy

	Value	95% CI
AUC (Area under curve)	0,92	0,85-0,99
Youden Index	0,72	0,66-0,82
Sensitivity	79,2	67-6-90-6
Specificity	93,3	80,7-105,9
Positive Predictive Value	97,4	92,4-102,4
Negative Predictive Value	58,3	38,6-78,06

PP11-14

Favism a common but rare seen cause for hemolytic anemia for glucose-6-phosphate dehydrogenase (G6PD) deficiency. a case report

Jian An Boo[1*] And Shi Chyn Lim[2]

[1] Department of Paediatrics, Hospital Sultanah Bahiyah Alor Setar, Malaysia

[2] Neonatology Unit, Department of Paediatrics, Hospital Sultanah Bahiyah Alor Setar, Malaysia

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common X-linked recessive disorder known to predispose to acute hemolytic anemia. It is common in Malaysia and was shown to be more prevalent among Malays and Malaysian Chinese descents, and less common among the Indians. Therefore,G6PD deficiency screening was a routine screening in Malaysia. Since started the screening, favism was rarely seen.

Method: Descriptive study: case report.

Results: A Malay boy that born term was diagnosed of G6PD deficiency since delivered. He was presented to hospital with vomiting and reduce oral intake for one day associated with tea color urine. Further history noted patient had ingested fava bean that given by the aunty. On examination, patient was pale and mildly jaundice. His other systemic examinations were unremarkable. His hemoglobin level was noted to be low and packed cells transfusion was done. Peripheral blood film showed severe leucoerythroblastic anemia with features of oxidative hemolysis most likely secondary to G6PD deficiency induced by Fava bean ingestion.

Conclusion: This case illustrates an acute hemolytic anemia presentation in G6PD deficiency after ingestion of Fava bean. A high index of suspicious is necessary for accurate diagnosis even though it was a routine screening in Malaysia.

Keyword: Favism, G6PD deficiency, Acute hemolytic anemia

PP11-15

How do current health expenditure per capita, labor force participation rate, GDP per capita relate to the prevalence of

anemia among pregnant and non-pregnant women in the Philippines?

Putri Ayu

Economics, Andalas University, Indonesia

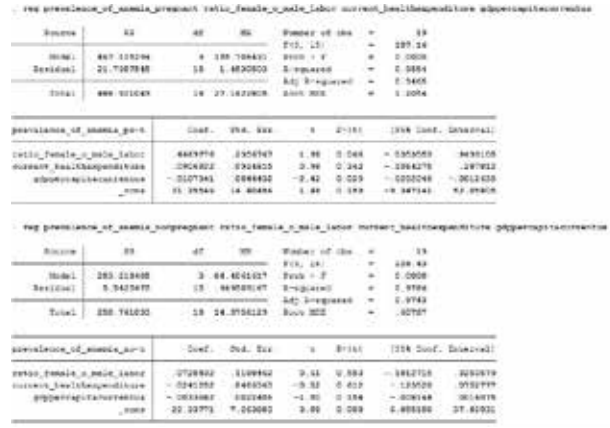
Background: Anemia is a disease related to hematology and is a threat, especially for women and children. The Philippines is one of the 5 founding countries of ASEAN which shows a decreasing prevalence of anemia patients every year from 2000-2019 (WHO, 2022). The interesting thing for the Philippines is that it is the only country that continues to experience a decline in anemia patients, both children and women. This study analyzes how the influence of current health expenditure per capita, labor force participation rate, GDP per capita on the prevalence of anemia among pregnant and non pregnant women (%) in the Philippines.

Method: The method used in this research is multiple regression analysis with quantitative data. The dependent variable used is the prevalence of anemia among pregnant and non pregnant women, while current health expenditure per capita, labor force participation rate, GDP per capita are independent variables. Data is taken from WHO, Global Health Observatory Data Repository.

Results: On average from 2000-2019 the prevalence of anemia among pregnant was 35.05% while those who were not pregnant was 17.65%. This means that more than 50% of women in the Philippines are anemic. The regression results show that the Labor force participation rate of women is significantly positive and GDP per capita negatively affects anemia in pregnant women, while Current health expenditure per capita is not significant. For women who are not pregnant, anemia is not significantly affected by Current health expenditure per capita, Labor force participation rate, GDP per capita. The R-square values for the prevalence of anemia among pregnant and non-pregnant women were 99.07 and 95.54, respectively. Of the three variables that have the greatest influence on anemia in pregnant and non-pregnant women, it is women's work participation as seen from the coefficient value.

Conclusion: The need for the State and individuals to continue to increase GDP per capita and find solutions so that working women also get good nutrition to reduce the occurrence of anemia for pregnant and non-pregnant women, such as consuming vitamin A and iron, as well as adequate hours of rest.

Keyword: Anemia, Current health expenditure per capita, Labor force participation rate, GDP per capita, Pregnant women, Non-pregnant



PP11-17

Analysis of the influence of the prevalence of anemia among pregnant women, current health expenditure and stunting on the prevalence of anemia among children in the Philippines

Derizal Derizal[1*] and Putri Ayu[2]

[1] Economics, State Islamic Institute of Bukittinggi, Indonesia

[2] Economics, Andalas University, Indonesia

Background: Anemia in children is a matter of great concern to the world of health because it will have an impact on the growth and development of children. The Philippines, one of the Southeast Asian countries, shows anemia in children on average 23%. However, if it is seen that there is a decrease in anemia in children in the Philippines. This study analyzes how the influence of anemia in pregnant women, health expenditures and stunting in children on anemia in children in the Philippines.

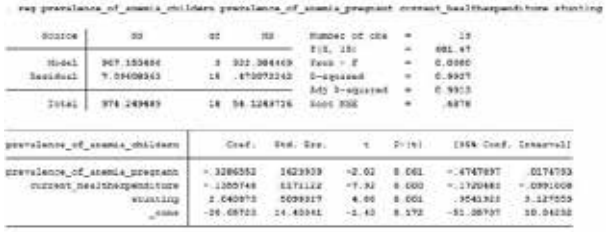
Method: The variable used is
The Prevalence of Anemia Among Pregnant Women, Current Health Expenditure and Stunting as independent variables, and The Prevalence of Anemia Among Children as dependent variables. The method used is multiple regression OLS for the period 2000-2019. Data samples were taken from WHO by using saturated samples.

Results: The results show that The Prevalence of Anemia Among Pregnant Women, Current Health Expenditure significantly negatively affects anemia in children, which is indicated by a p value that

is smaller than the 10% confidence level, while the stunting variable is significantly positive. the stunting variable is the biggest factor that affects anemia in children, it shows a large coefficient value of 2.04%, followed by the prevalence of pregnant women who can reduce anemia in children by 0.328% and health expenditures can reduce anemia in children by 1.35%.

Conclusion: The magnitude of the effect of stunting on anemia in children is more than 2% for every 1% increase in stunting, it is necessary for the government, families and health workers to suppress stunting in the Philippines in order to reduce anemia. the condition of pregnant women affected by anemia is able to reduce anemia in children, this does not mean that pregnant women must be anemic, but it is necessary to reduce the risk of anemia in pregnant women. Finally, the Philippine government should manage and improve the finances of the health department so that the condition of anemia in children can decrease.

Keyword: Women pregnant, Expenditure heath, Stunting, Anemia, Philippines, Women pregnant



PP11-18

The effect of analysis nutritional status and blood adding tablets on anemia in pregnancy

Andi Makkasau[1], Sumiyati Sumiyati[2] and Andi Nursanti[3*]

[1] Management, Bina Generasi Bangsa of College Foundation, Indonesia

[2] Nursing, Bina Generasi Bangsa of College Foundation, Indonesia

[3] Pharmacy, Andini Persada College of Health Sciences Indonesia, Indonesia

Background: Anemia is an indirect factor in maternal mortality because postpartum hemorrhage is a factor causing the high maternal mortality rate during childbirth. After all, it can cause a decrease in Hb levels in the blood which causes death. The purpose of this study was to determine the effect of nutritional status and distance of pregnancy on the occurrence of anemia in pregnancy

Method: This study uses a cross-sectional research design. Data collection was carried out by trained researchers and field workers including nutritional status, hemoglobin levels, consumption of Fe tablets for pregnant women. The subjects in this study were third-trimester pregnant women with a total sample of 80 people taken using cluster sampling techniques and inclusion criteria. Data were analyzed using the chi-square statistical test.

Results: The results showed that the frequency distribution based on the characteristics of Nutritional Status (LILA) showed that from 80 respondents (100%), the number of pregnant women with nutritional status (LILA) < 23.5 cm was 7 people (8.8%) while the number of pregnant women with the category of nutritional status (LILA) 23.5 cm as many as 73 people (91.3%). The frequency distribution based on the consumption characteristics of blood-added tablets (Fe) shows that out of 80 respondents (100%), the majority of respondents did not comply in consuming blood-added tablets, which was less than 90 tablets as many as 63 (78.8%). Meanwhile, the number of respondents in the obedient category in consuming blood-added tablets is more or equal to 90 tablets as many as 17 people (21.3%). The distribution of the frequency of events by category of anemia shows that of the 80 respondents (100%), the majority of respondents in the third trimester of pregnancy experienced anemia with a total of 75 people (93.8%), while 5 people in the third trimester of pregnancy who did not experience anemia (6,3%). The results of statistical tests using the Chi-Square test obtained nutritional status (p-value = 0.929) and consumption of Fe tablets (p-value = 0.036).

Conclusion: Based on the results and discussion, it can be concluded that there is one variable that has a significant effect on the occurrence of anemia in pregnancy on anemia in pregnancy, namely the consumption of Fe tablets and there is another variable that does not significantly affect the occurrence of anemia in pregnancy, namely nutritional status.

Keyword: Pregnant women, Anemia, Nutritional status, Fe tablets

PP12-01

Single nucleotide polymorphisms of the HIF1A gene are associated with sensitivity of glucocorticoid treatment in pediatric ITP patients

Hao Gu, Runhui Wu* and Zhenping Chen

Hematology center, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, China

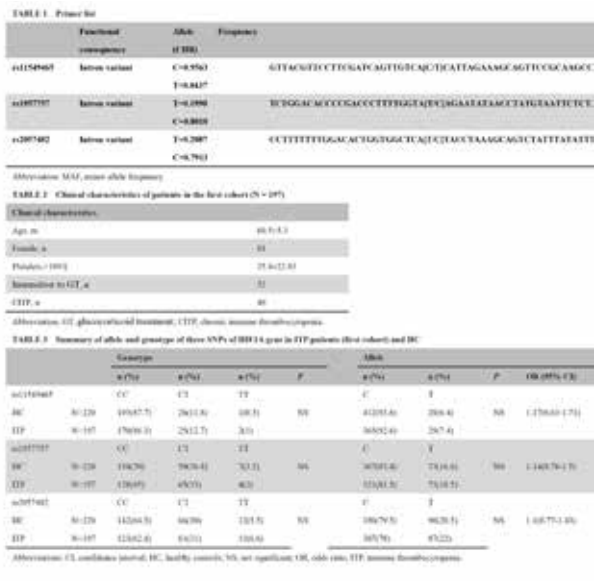
Background: Hypoxia-inducible factor-1α (HIF-1α) plays a crucial role in both innate and adaptive immunity. Emerging evidence indicates that HIF-1α is associated with the inflammation and pathologic activities of autoimmune diseases, suggesting that HIF1α may be involved in immune dysregulation in patients with immune thrombocytopenia (ITP). The purpose of this study was to evaluate whether single nucleotide polymorphisms (SNPs) of the HIF1A gene are associated with susceptibility to ITP and its clinical prognosis including incidence of chronic immune thrombocytopenia (CITP) and glucocorticoid sensitivity.

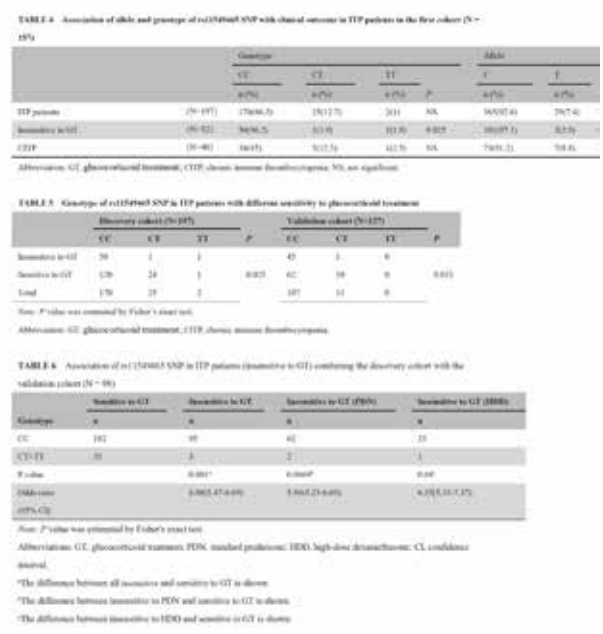
Method: This study involved 197 Chinese ITP pediatric patients (discovery cohort) and 220 healthy controls. Three SNPs (rs11549465, rs1957757, rs2057482) of the HIF1A gene were genotyped using specific TaqMan probes. We also employed another ITP cohort (N = 127) to validate the significant results of SNPs found in the discovery cohort.

Results: The frequencies of the four SNPs did not show any significant differences between the ITP and healthy control groups. The CT genotype at rs11549465 was significantly higher in ITP patients sensitive to glucocorticoid-treatment than in those insensitive to glucocorticoid-treatment (P = .025). These results were validated using another ITP cohort (N =127, P = .033). Moreover, the CC genotype was a risk factor for insensitive to GT the OR (95% confidence interval) was 5.96(5.23-6.69) in standard prednisone (PDN) (P=.0069) and 6.35(5.33-7.37) in high-dose dexamethasone (HDD) (P=.04).

Conclusion: Although HIF1A gene polymorphisms were not associated with susceptibility to ITP, the CT genotype at rs11549465 was associated with the sensitivity to glucocorticoid-treatment of ITP patients, suggesting that the rs11549465 SNP may contribute to the sensitivity of glucocorticoid treatment in pediatric ITP patients.

Keyword: ITP, SNP; HIF1A, Pediatrics, Glucocorticoid-treatment





PP12-02

Efficacy and safety of two different low-dose rituximab regimens for Chinese children patients with primary immune thrombocytopenia

Xiaojing Zhu, Xingjuan Xie, Jialu Zhang and Runhui Wu*

Hematology, Beijing Children's Hospital Affiliated to Capital Medical University, China

Background: ITP is one of the common hemorrhagic diseases in children. B lymphocytes play an important role in the occurrence and development of ITP. Rituximab is one of the second-line treatments for ITP. At present, there are few studies on low-dose rituximab, lacking of a large number of prospective and randomized trials to support the efficacy and safety of low-dose rituximab. We did this study to compare the efficacy and safety of two different regimens for low-dose rituximab of children patients with chronic / refractory ITP, so as to provide basis for clinical treatment.

Method: 83 children patients were enrolled in this study and non-randomly assigned to receive 100mg/200mg (body weight 30kg) rituximab weekly for 4 weeks (group A, 53 cases) or a single dose of 375mg / m2 rituximab (group B, 30cases). The study was follow-up for at least half a year.

Results: For group A,: Overall and complete response (OR and CR) rates were 35.8% and 15%, respectively; the side effects rate is 3.8%. In responders, the median time to response was 4 (1 -12) weeks, with a median follow-up time of 12 (6 ~ 36) months, 6 of 19 responders (31.6%) relapsed. For group B: OR and CR rates were 36.7% and 23%, respectively; the side effects rate is 10%. In responders, the median time to response was 1 (1 ~ 4) weeks, with a median follow-up time of 11.5 (6 ~ 17) months, 4 of 11 responders (36.4%) relapsed. No significant difference in the OR, NR, relapse free survival and incidence of side effects was observed in patients between the two groups.

Conclusion: The two different low-dose rituximab regimens (100mg/200mg weekly for 4 weeks or a single close of 375 mg/m2) both are the useful alternative therapy in children patients with ITP.

Keyword: Low-dose rituximab, Children, ITP

PP12-03

Comparison of AggreGuide A-100 with platelet function tests and thromboelastrography in patient with ischemic stroke

Hyunjung Kim, Hey Kyung Lee and Young Woo Kim*

Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: This study investigated the clinical utility and functional comparison of four platelet reactivity measured by four platelet function tests in patients with ischemic stroke and taking clopidogrel.

Method: From July 2018 to May 2019, thirty-five patients who developed acute ischemic stroke were enrolled. Patients received an initial loading dose of 300 mg clopidogrel followed by a 75 mg daily maintenance dose. Platelet aggregation was measured by newly introduced AggreGuide A-100, VerifyNow P2Y12 (VerifyNow), platelet function analyzer P2Y (PFA) and light transmission aggregometry (LTA). Five parameters were obtained using Thrombelastography (TEG) (Haemonetics, USA). Stroke type, region and other clinical data were obtained from chart review. Patients were monitored for one year for recurrence, bleeding complication and death.

Results: Artherosclerotic type was 25 patients, and small artery disease type was 10 patients. The stroke recurrence, bleeding complication and death did not occurred during the monitoring period. High on-treatment platelet reactivity (HTPR) rate was 18.2% in VerifyNow, Aggreguide 27.3%, PFA 7.2%, LTA 9.1%. Concordance rates were as follow; VerifyNow and PFA 92.6%, VerifyNow and Aggreguide 60.6%, VerifyNow and LTA 72.7%, PFA and Aggreguide 70.4%, PFA and LTA 88.9% and, Aggreguide and LTA 91.7%. The correlation between methods was not good (The correlation coefficient r was from 0.176 to 0.673). The clinical and other coagulation markers was described in Table 1. Blood viscosity and NIH stroke scale (NIHSS) were associated with HTPR on Aggreguide, and TEG K-time, blood viscosity and NIHSS were associated with HTPR on VerifyNow.

Conclusion: In this study, stroke recurrence was absent, therfore HTPRs were compared. The incidence of HTPR was lowest in PFA and highest in Aggreguide. Agreement between tests was good between VerifyNow and PFA, Aggreguide and LTA, and PFA and LTA. However correlation was not good, the data are not interchangeable.

Keyword: Stroke, Platelet function test, AggreGuide A-100, Thromboelastography

Table 1. Clinical and laboratory characteristics of the study population.

	Aggreguide-100 P2Y			VerifyNow P2Y12		
	Effective group (n=26)	HTPR group (n=9)	*P*-value	Effective group (n=27)	HTPR group (n=6)	*P*-value
Platelet counts	210 (192-144)	203 (166-274)	0.939	203 (173-229)	230 (190-314)	0.243
PT	11.4 (11.0-12.0)	12.0 (10.9-11.9)	0.416	11.3 (11.0-11.9)	12.7 (11.7-12.5)	0.102
aPTT	25.7 (24.0-27.6)	24.8 (24.3-25.7)	0.691	25.6 (24.5-27.3)	24.7 (23.3-26.2)	0.191
Fibrinogen	326.5 (252.0-369.2)	288.9 (221.6-330.8)	0.274	299.5 (246.8-352.5)	394.2 (333.1-451.8)	0.098
TEG R-time	4.6 (3.8-5.3)	4.6 (3.6-5.0)	0.650	4.6 (4.0-5.4)	4.2 (3.8-4.8)	0.326
TEG α-angle	73.1 (69.5-75.2)	73.2 (69.0-76.3)	0.806	71.5 (69.2-74.4)	75.6 (74.5-76.2)	0.072
TEG K-time	1.2 (1.0-1.3)	1.1 (0.9-1.5)	0.745	1.2 (1.0-1.4)	0.9 (0.9-1.0)	0.022
TEG MA	63.0 (58.1-67.0)	61.1 (56.1-67.9)	0.743	61.1 (57.0-66.2)	65.7 (57.6-72.7)	0.483
TEG LY30	2.7 (1.3-4.0)	5.4 (0.7-8.2)	0.373	2.7 (1.4-5.7)	1.9 (0.7-3.1)	0.515
Viscosisty (Systolic)	4.9 (4.0-5.4)	3.9 (3.5-4.4)	0.031	4.3 (3.9-5.1)	3.6 (3.2-4.4)	0.085
Viscosisty (Diastolic)	15.5 (12.8-18.8)	12.2 (10.6-14.7)	0.027	13.4 (12.3-17.7)	10.9 (7.6-13.8)	0.046
BMI	23.9 (22.2-25.2)	24.2 (23.3-26.1)	0.481	24.0 (22.5-25.7)	22.8 (22.0-23.4)	0.077
GCS	15(14-15)	15 (14-15)	0.568	15 (14-15)	14. (13-15)	0.301
NIHSS	3 (1-5)	0 (0-1)	0.013	2 (1-3)	5 (3-7)	0.022

PP12-04

Rare acquired bleeding disorders in adolescents and young adults

Young Shil Park

Department of Pediatrics, Kyung Hee University Hospital at Gangdong, Korea

Background: Acquired bleeding disorder is caused by autoantibodies to coagulation factors, causing its neutralization and/or accelerated clearance from the plasma. Acquired bleeding disorder is very rare in adolescents and young adults (AYAs) but potentially life-threatening clinical syndrome characterized by the sudden onset of bleeding in patients with a negative family and personal history.

Method: We reviewed cases of two AYA patients with unusual clinical manifestations. They were diagnosed with acquired bleeding disorders.

Results: The first case was 19-year-old female patient with right lower leg painful swelling. She had no past and family history of bleeding disorder. Initial laboratory findings showed prolonged activated partial thromboplastin time (aPTT) and uncorrected mixing test. Her factor VIII (FVIII) activity was below 1% and FVIII antibody was 22.4 Bethesda unit. Her diagnosis was acquired hemophilia A. Initial treatments started with recombinant activated factor VII as hemostatic management. Also, oral steroid as immunosuppression therapy started and her titer of FVIII antibody decreased. As a result, the symptoms improved and her FVIII recovered to 11.8% upon discharge. After 9 months, titer of FVIII antibody was negative and her FVIII activity was normalized. The second case was 17-year-old female patient with acquired von Willebrand syndrome (AVWS). She also had no past and family history of bleeding disorder. Initially, she was diagnosed with congenital von Willebrand disease. But when she visited the hospital again due to swelling and pain in both hands and wrists, the mixing aPTT test was prolonged and low von Willebrand factor antigen (VWF:Ag) and VWF ristocetin cofactor activity (VWF:RCo) were low even after administration of coagulation factors. Her additional laboratory findings were hypoalbuminemia, proteinuria, and low C3 results. Her VWF mutation was normal. She was diagnosed with lupus nephritis and AVWS. She is being monitored with immunosuppressions, but aPTT is still prolonged and low VWF:Ag and VWF:RCo are low.

Conclusion: Acquired bleeding disorders are very rare in AYAs, but require a high index of suspicion and close collaboration with laboratories for specialized coagulation testing. An early diagnosis of acquired bleeding disorders is mandatory for starting the appropriate treatment aimed at both controlling the acute bleeding episode and eradicating the anti-coagulation factor autoantibody, using immunosuppressive treatment.

Keyword: Acquired bleeding disorder, Adolescents and young adults, Acquired hemophilia

PP12-05

Incidence of complications in Korean patients with haemophilia a based on the Korean health insurance review and assessment service database: a study by the Korean pediatric hematology oncology group (KPHOG)

Ye Jee Shim[1*] and Young Bae Choi[2]

[1] Department of Pediatrics, Keimyung University School of Medicine, Keimyung University Dongsan Hospital, Daegu, Korea

[2] Department of Pediatrics, Ajou University School of Medicine, Ajou University Hospital, Suwon, Korea

Background: Haemophilia A (HA) is an X-linked recessive coagulation disorder caused by a mutation in the factor VIII (FVIII) gene with an incidence of one in 5,000 male live births. HA is classified as severe (FVIII activity <1%), moderate (FVIII activity 2–5%), and mild (FVIII activity 6–30%) based on the degree of FVIII deficiency. Although patients with mild HA generally bleed only after trauma or surgery, those with severe HA experience frequent spontaneous haemorrhagic episodes without any trauma. The damaging impact of hemarthrosis, the hallmark of haemophilia, on the life of patients is well established. Haemophilic arthropathy is a serious complication from repeated hemarthrosis, commonly called a 'target joint', and ultimately results in joint deformity and disability. Further, intracranial haemorrhage (ICH) is the main cause of mortality and morbidity in patients with haemophilia. ICH occurs spontaneously or following trauma and can result in various sequelae including developmental delay, epilepsy, or cerebral palsy. Modern treatment of haemophilia started in the 1970s and was based on human plasma-derived FVIII concentrates. The availability of FVIII replacement therapy has significantly improved the life span and quality of life (QoL) of patients with haemophilia. However, prior to the use of virus-inactivation procedures in plasma-derived products, patients with haemophilia had a high risk of infection with blood-borne viruses such as hepatitis B virus, hepatitis C virus (HCV), or human immunodeficiency virus (HIV). The aforementioned viral infections are associated with the morbidity and mortality of patients with haemophilia because they can cause chronic hepatitis or malignant neoplasm. These serious complications have been reduced following the use of recombinant FVIII (rFVIII) concentrates in patients with HA. Further, early prophylactic use of FVIII concentrates during childhood, before developing repeated hemarthrosis, resulted in the protection of the joint compared with delayed prophylaxis or on-demand therapy. In Korea, the production of plasma-derived products enriched with FVIII started in 1974. Since the 1980s, these low-purity products have

been replaced by plasma-derived FVIII concentrates with improved purity and viral inactivation. Further, rFVIII concentrates were first launched in 2002 for newborns with HA. The prophylactic use of rFVIII concentrates was gradually expanded for paediatric patients with HA and then for patients aged ≥18 years in 2018. In other words, before 2002, Korean patients with haemophilia were only able to use plasma-derived products, and they could not receive adequate prophylaxis with rFVIII concentrates. In recent years, non-factor products, including emicizumab, have become the standard for HA treatment worldwide. However, in Korea, FVIII concentrate is mainly used in managing patients with HA without inhibitors who are associated with the Korean national health insurance system. Considering the history of the management of HA in Korea, we can expect that older patients with HA who had received plasma-derived FVIII concentrate, mainly on-demand, are more likely to have several complications. In contrast, it can be expected that newborns with HA who will receive non-factor agents in the future will have a significantly improved QoL compared with older patients with haemophilia. However, there are no baseline data regarding the frequency of complications in Korean patients with HA. Thus, in this study, we investigated the prevalence of joint problems, viral infections, hepatic problems, and neurologic complications in Korean patients with HA. We also analysed the number of patients who underwent orthopaedic surgery, neurosurgery, and upper gastrointestinal (UGI) endoscopic bleeding control.

Method: Subject collection: This was a nationwide cross-sectional study by the Korean Pediatric Hematology Oncology Group. This study analysed data of Korean patients through the Healthcare Big Data Hub of the Health Insurance Review & Assessment (HIRA) Service (https://opendata.hira.or.kr/home.do). The study number is M20200409450 and the analysis period is from December 21, 2020 to January 11, 2022. This study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (approval no. 2019-09-042), and the requirement for informed consent was waived. The study was conducted according to the tenets of the Declaration of Helsinki. The inclusion criteria were as follows: Korean patients with congenital HA (hereditary FVIII deficiency, International Classification of Diseases (ICD)-10 code D66) who visited the hospital between January 2007 and February 2020. The exclusion criteria were as follows: 1) patients with HA without a high titre or high-responder inhibitors who were treated with an anti-inhibitor coagulant complex or recombinant activated factor VII and 2) patients with acquired haemophilia (acquired coagulation factor deficiency, ICD-10 code D68.4). Data collection of complications or invasive procedures: Patients with ICD-10 codes for joint problems (arthropathy, arthritis, arthrosis, joint derangements, joint disorders, or haemarthrosis) were collected. Patients with ICD-10 codes for viral infections and hepatic complications (chronic hepatitis B, chronic hepatitis C, HIV infection, chronic hepatic failure, fibrosis/cirrhosis of the liver, oesophageal varices, and malignant neoplasm of the liver) were collected. Patients with ICD-10 codes for neurologic sequelae (intracranial haemorrhages, epilepsy, cerebral palsy, hemiplegia, paraplegia, or tetraplegia) were collected. Patients with operation or procedure codes according to the Korean national health insurance system for orthopaedic surgeries (arthroplasty, synovectomy, arthrodesis, or meniscectomy) were collected. Patients with codes for neurosurgeries (burr hole, craniotomy, or clipping of cerebral aneurysms) were collected. Patients with codes for UGI endoscopic bleeding control were also included. The patients' age at receiving the interventions, FVIII concentrate used during procedures, admission duration, and the cost of admission were analysed. The development of respective complications of haemophilia—joint problems, viral infections or hepatic complications, and neurologic sequelae—was analysed according to the patients' age groups. Considering that rFVIII concentrates were first introduced and widely used in Korea from 2002, the prevalence of respective complications was compared between patients aged <20 years and those aged ≥20 years. To compare the variables according to age group, the $\chi 2$ test was performed. Statistical significance was set at $P<0.05$. Statistical analysis was performed using SPSS version 23 (IBM Corp., Armonk, NY).

Results: Baseline demographics of subjects: A total of 2,471 patients with congenital HA from January 2007 to February 2020 in Korea were recorded in the HIRA database. According to the classification of patients by age group, 278 patients were aged 0–9 years, 429 were aged 10–19 years, 526 were aged 20–29 years, 413 were aged 30–39 years, 349 were aged 40–49 years, 236 were aged 50–59 years, 129 were aged 60–69 years, and 111 were aged ≥ 70 years. Incidence of complications and invasive procedures: Among the 2,471 patients with HA, 1,084 (43.9%) had one or more complications; 855 patients (34.6%) with 1 complication, 214 patients (8.7%) with 2 complications, and 15 patients (0.6%) with 3 complications. A total of 829 patients (33.5%, 829/2,471) with HA had joint problems (Fig. 1). A total of 344 patients (13.9%, 344/2,471) had viral infections (chronic hepatitis C, chronic hepatitis B, unspecified chronic viral hepatitis, or HIV infection) (Fig. 2A). Furthermore, 324 patients (18.4%) had hepatic problems (chronic viral hepatitis, liver cirrhosis, oesophageal varix, or malignant neoplasm of the liver) (Fig. 2B). Finally, 170 patients (9.7%) with HA had non-traumatic ICH, traumatic brain damage, epilepsy, or cerebral palsy (Fig. 3). Among the 1,084 patients who suffered complications, 87 patients (8.0%) underwent 113 invasive procedures associated with complications of HA (Table 1). Each patient with HA underwent a median of one invasive procedure (range, 1–3) during the study period. The median patient age at undergoing invasive procedures was 38 years (range, 0.2–84 years). In the case of orthopaedic surgery, 57 patients underwent 71 surgeries. In terms of neurosurgery, eight patients underwent 12 surgeries. In the case of UGI endoscopic bleeding control, 25 patients underwent 30 procedures. The numbers of patients who underwent invasive procedures are shown in Fig. 4. Comparing the complications between groups: The incidences of joint problems, viral infections, hepatic complications, and neurologic complications according to the age groups are shown in Fig. 5. The incidence of joint problems in patients aged <20 years (25.2%,

178/707) was lower than that in patients aged ≥20 years (36.9%, 651/1764) (P<0.001) (Fig. 5A). The incidence of viral infections or hepatic complications in patients aged <20 years (0.7%, 5/707) was lower than that in patients aged ≥20 years (18.4%, 324/1764) (P<0.001) (Fig. 5B). In contrast, the incidence of neurologic sequelae in patients aged <20 years (10.2%, 72/707) was higher than that in patients aged ≥20 years (5.5%, 97/1764) (P<0.001) (Fig. 5C).

Conclusion: We investigated the frequency of complications in Korean patients with HA from January 2007 to February 2020. With active prophylaxis using rFVIII concentrates, orthopaedic complications, viral infections, and hepatic complications in Korean patients with HA appear to have decreased. However, neurologic sequelae did not decrease in Korean patients with HA; thus, additional efforts are needed to reduce ICH in patients with HA. A subject that requires future research is how the frequency of complications in Korean patients with HA changes when extended half-life products, novel non-factor products, and gene therapy become popular.

Keyword: Epidemiology, Haemarthrosis, Haemophilia A, Hepatitis, Intracranial Haemorrhage

Table 1

Fig1

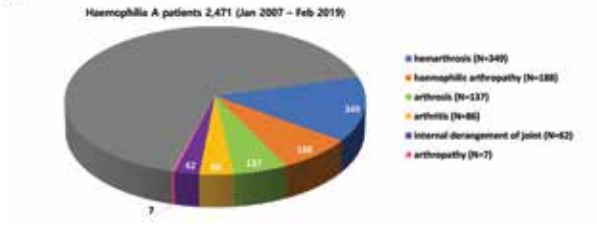


Fig2A

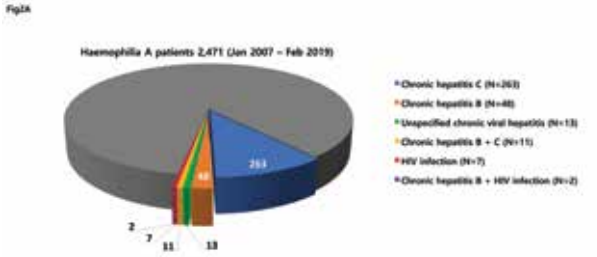


Fig2B

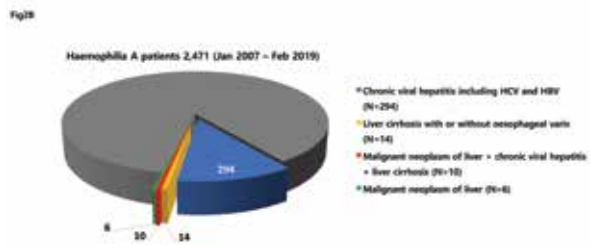


Fig3

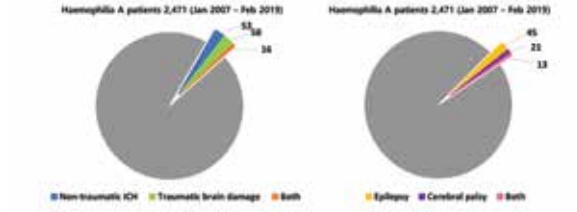


Fig4

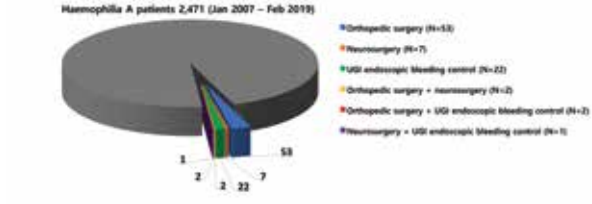


Fig5B

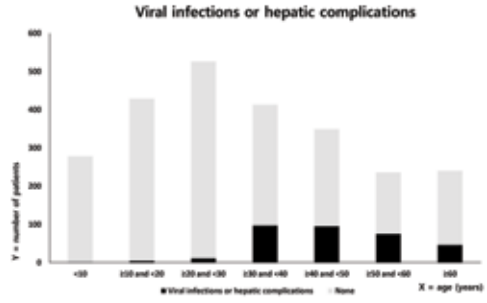
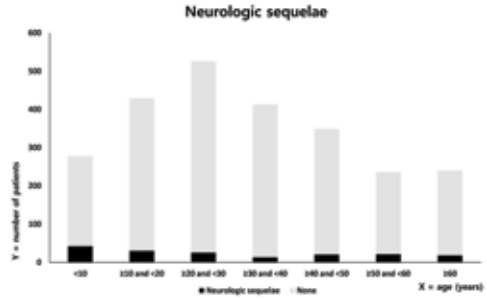
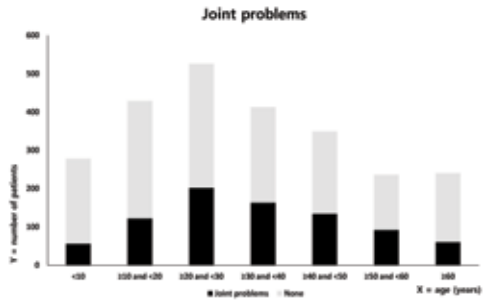


Fig5C



FigSA



PP12-06

CD4+CD25+FOXP3+, CD8+ predict development of chronic disease in newly diagnosed idiopathic thrombocytopenia

Zhi Wang[1,2,3], Zhenping Chen[1,2,3], Hao Gu[1,2,3], Jingyao Zhang[1,2,3], Shuyue Dong[1,2,3], Xinjuan Xie[1,2,3], LIngling Fu[1,2,3], Jlalu Zhang[1,2,3] and Runhui Wu[1,2,3*]

[1] Department of Hematology and Oncology, Beijing Children's Hospital, Capital Medical University, China

[2] Beijing Key Laboratory of Pediatric Hematology Oncology,, National Center for Children's Health, China

[3] Key Laboratory of Major Diseases in Children, Ministry of Education, National Key Discipline of Pediatrics, (Capital Medical University, China

Background: Background: Immune thrombocytopenia (ITP) is a disease characterized by isolated thrombocytopenia. Abnormal effector T cell is considered to an importent mechanism in immune thrombocytopenia (ITP). We aimed to investigate the predictive value of abnormal effector T cell for predicting the clinical course of ITP in children.

Method: We retrospectively analyzed children aged < 18 years with Chronic ITP (cITP, n = 12) and newly ITP (nITP, n = 23) from September 2018 to August 2020. The distribution of age, gender, and measured CBC parameters, including PLTs, white blood cells (WBCs), absolute lymphocyte count (ALC) and Hemoglobin (Hb) among the study were recomed and compared. Hematological indices including CD4+CD25+FOXP3+, CD4+, CD8+ and NK were measured and compared between the two groups.

Results: The median patient's age in nITP and cITP was 4.56 and 5.66 years (p >0.05), respectively. Even though the median patient's age was found to be higher in chronic ITP group than in newly ITP, but there was no significant difference between the two group(p >0.05). The median platelet, WBCs, Lymphocytes and Hb showed no statistical significance among the two groups. The CD8+ was significantly lower in the nITP group than in the chronic ITP group (p<0.05). However, CD4+CD25+FOXP3+ was significantly higher in the nITP group than in the chronic ITP group (p<0.05). Cutoff value of CD8+ at diagnosis that can differentiate between nITP and cITP was 37.38 % with sensitivity of 83.3% and specificity of 56.5%. Area under curve was 0.707, p-value was 0.048 (Figure2). The cutoff value of CD4+CD25+FOXP3+ that can differentiate between nITP and cITP was 5.205 % with sensitivity of 78.3% and specificity of 75%. Area under curve was 0.797, p-value was 0.004 which was statistically significant.

Conclusion: This study revealed that Chronic ITP had a higher CD8+ and lower CD4+CD25+FOXP3+ level than newly ITP at diagnosis. Therefore, an initial CD8+ value more than 37.38 % and CD4+CD25+FOXP3+ value less than 5.205 % may be used as a predictive factor for chronic course in children with ITP. The level of CD8+ and CD4+CD25+FOXP3+ at diagnosis may be regarded as a prognostic marker to predict the course of ITP in children.

Keyword: Immune thrombocytopenia, Response, No response, CD4+CD25+FOXP3+, CD8+, NK,

PP12-07

Case of acquired hemophilia A post COVID-19 vaccination

Guang Yong Chong* and Nor Rafeah Tumian

Department of Hematology, Hospital Canselor Tuanku Muhriz University Kebangsaan, Malaysia

Background: Acquired hemophilia A (AHA) is a rare bleeding disorder with an incidence around 1 per million. In AHA, patients develop auto antibodies directed against clotting factor VIII (FVIII). Elderly population and young females who are pregnant or postpartum often affected with AHA. Co-morbidities such as autoimmune disease and malignancy are also commonly associated with AHA. Bleeding AHA commonly involves the superficial tissue whereas congenital hemophilia A affects more in deep tissue. Infection or vaccination has been reported as possible trigger for AHA.

Method: We report on a case of asymptomatic AHA following Astra Zeneca SARS CoV-2 non-replicating viral vector vaccine.

Results: A 59-year-old Indian woman who had no history of significant bleeding disorder received her first dose of Astra Zeneca

covid-19 vaccine in May 2021. Vaccine injection was uneventful with no localized swelling or hematoma. She went for routine blood test 2 weeks later at private lab and incidental noted prolongation of activated partial thromboplastin time (APTT) at 60s (normal range=30–44.5s). She was then referred to hematology clinic Hospital Cancelor Tuanku Mukhriz for further investigation. Her comorbidities included hypothyroidism on thyroxine replacement 25mcg daily, beta-thalassemia trait with no history of blood transfusion and generalized anxiety disorder on sertraline 75mg daily. She is blessed with 3 children, no significant obstetrics complication during childbirth. She also claimed to be taking traditional herbs for 10years as health supplement. Her physical exam was unremarkable, with no palpable lymph nodes and no hepatosplenomegaly. We repeated her blood test showed normal complete blood count (hemoglobin 11.8g/dl [normal range = 12–15 g/dl] and platelets of 368× 109/L [normal range 150–410 × 109/L]). Her coagulation profile revealed a normal prothrombin time at 14.7s (normal range =11.8–14.5 s) and a severely prolonged APTT at 99.9s (normal range = 30–44.5 s). The mixing study showed no correction of APTT at 0 min, 83.3s, and still prolongation of APTT upon incubation 2 hours, 89.7 s, suggesting the presence of an inhibitor. Further testing revealed FVIII level at 16% (normal range 50-193%), and FVIII inhibitor titer at 2.2 Bethesda units, which were consistent with the diagnosis of AHA. She did not require FVIII inhibitor bypassing activity (FEIBA) or recombinant activated factor VII (FVIIa) in view she is asymptomatic without bleeding tendencies. She was started on prednisone dose of 1mg/kg orally. We had scheduled a CT imaging for her to look for malignancy and daycare appointment in 2 weeks post initiation of steroid.

Conclusion: This is the first reported case of AHA possibly triggered by COVID-19 vaccination in Malaysia. Our literature search found two cases of AHA associated with COVID-19 infection in the United States. We acknowledge that the emergence of FVIII inhibitors post vaccination is most likely be a coincidence especially when we don't have the baseline coagulation profile pre vaccination and CT imaging is pending. However, it is worth to consider the correlationship may exist as several case reports have suggested that COVID-19 infection and vaccines in general may trigger an autoimmune reaction. It is important to note that clinical trials involving COVID-19 vaccines will fail to detect rare reactions especially in asymptomatic patients. The purpose of this case report is to raise awareness among health-care workers about a possible rare side effect and relationship of covid-19 vaccine with autoimmune reactions.

Keyword: Acquired hemophilia, AHA, Factor VIII, Post COVID-19 Vaccination, COVID-19

PP12-08

Effect of anti-nuclear antibody positivity on adult newly diagnosed immune thrombocytopenia prognosis

Ngoc-Sang Nguyen*, Tuan Nguyen, Thanh-Thanh Suzanne and Tung Tran

Hemotology, Cho Ray Hospital, Viet Nam

Background: Adult idiopathic thrombocytopenia (ITP) is an acquired autoimmune disease that may be associated with other autoimmune disorders. Patients with primary ITP are occasionally found to have a positive Antinuclear Antibody (ANA). Our objective was to study the effect of positive ANA on ITP clinical course.

Method: This was a retrospective descriptive study of adult patients with newly diagnosed ITP, who were followed regularly at Hematology department, Cho Ray Hospital, Ho Chi Minh, Viet Nam from February 2020 till October 2021. Patients who were diagnosed with ITP and had ANA results during their initial work-up were included. The population baseline characteristics regarding age, sex, bleeding grade, hemoglobin level, platelets count at presentation, hospital length of stay, in-hospital amounts of blood products transfused, corticosteroid responsiveness, sustained response (SR).

Results: A total of 152 patients fulfilled the inclusion criteria and were eligible for analysis. ANAs were positive in 41 (27%) of the included patients, 3.3% had "uncertain" results with ELISA test. There was no difference in sex, age, history of disease, platelets count at presentation, hospital length of stay, amount of blood products between patients with positive and negative ANA ($p>0.05$). Patients with positive ANA had higher mean severe bleeding grade according to IWG criteria, and lower hemoglobin level at presentation than patients with negative ANA (10.63 g/dl vs 11.83 g/dl) ($p<0.01$).

The incidence of overall response (R) and complete response (CR) after 2 weeks of corticosteroids in ANA-positive patients was significantly lower than that in ANA negative patients (overall response: 52.6% vs 70.4%, $p<0.05$). This difference between positive and negative ANA patients remained significant after adjusting for sex, C3, C4, antiDsDNA ($p <0.05$). Patients with a positive ANA were 2.5 times (95% CI:1,01-6,2) more likely of not achieving a response defined as a platelet count of 30 x 10e9/ml or more after 2 weeks of corticosteroids. However, sustained response (SR) rates in ANA-positive patients at 12 and 18 months were the same as ANA-negative patients ($p> 0.05$). Persistent disease rates were 46.7% and 25.4%, respectively in patients with positive and negative ANA ($p<0.05$). The difference in persistent disease rates between positive and negative ANA patients remained significant after adjusting for sex, C3, C4, antiDsDNA ($p<0.05$). ANA were associated with persistent disease (OR: 3.68, 95% CI: 1.14-11.83).

Conclusion: We analyzed the relationship between positive ANA

and ITP clinical course. Compared to patients with negative ANA, those with positive ANA were had more severe bleeding, more likely to become steroid-resistant, had a higher risk of developing persistent ITP, and presented with lower Hemoglobin level. ANA test could be useful for predicting clinical and response in ITP.

Keyword: Antinuclear antibody, Idiopathic thrombocytopenic purpura, Autoantibody, Idiopathic thrombocytopenia

PP12-09

Eltrombopag affects interferon-induced antiviral response through iron metabolism pathway

Yuefen Hu, Sai Ma and Jun Peng*

Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China

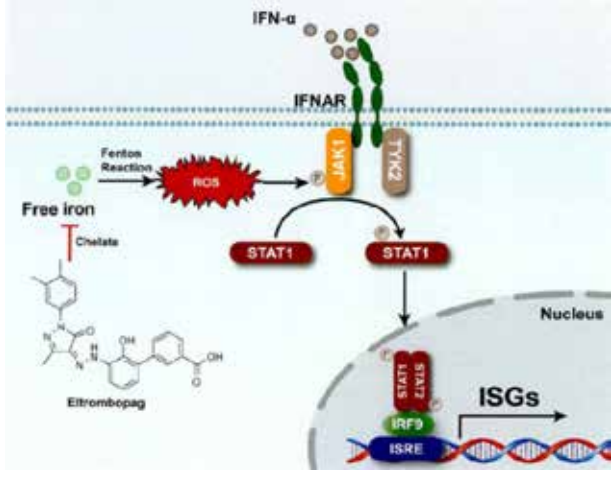
Background: Thrombocytopenia is a common complication in patients with viral hepatitis that restricts the use of antiviral treatment and results in an unfavorable prognosis. Pegylated interferon alfa (Peg-IFNα) is recommended as the first-line treatment option for chronic hepatitis B virus infection. It initiates antiviral immune defense by binding to IFN-α receptor, which then activates the Janus kinase signaling pathway and induces the expression of IFN-stimulated genes (ISGs). Eltrombopag (EP) is a small-molecule, non-peptide thrombopoietin receptor agonist (TPO-RA), which serves as a second-line therapy for primary immune thrombocytopenia (ITP) due to the competence to stimulate megakaryopoiesis and platelet production. The aims of our study is to explore the effects of EP on IFN-α induced anti-viral immune response in the treatment of hepatitis-associated thrombocytopenia (HBV-ITP).

Method: Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation. CD14+ cells were further sorted by immunomagnetic bead. Total RNA was extracted, and RNA-seq was taken. Differential expression analysis of two groups (before and after treatment) was performed using edgeR package. RNA and protein were determined by Quantitative RT-PCR (qRT-PCR) and Western blot, respectively. Reactive oxygen species (ROS) level was measured using 2,7-dichlorofluorescein diacetate. Intracellular labile iron pool (LIP) alterations were evaluated using an iron-binding compound Calcein AM.

Results: Firstly, we analyzed differential expression genes (DEGs) of PBMC from patients with HBV-ITP before and after treatment with eltrombopag. A total of 60 DEGs (padj≤0.05) were screened, and these genes were verified by qRT-PCR. We further explore the anti-viral effects of eltrombopag in patients with HBV-ITP. We found EP differently regulated the activation of ISGs in THP-1 cells and human monocytes. Specifically, EP promoted the expression of ISGs in THP-1 cells, while inhibited the expression of ISGs in human monocytes. And we further proved that EP inhibited the production of IFN-stimulated genes (ISGs) independent of TPO-R. Next, we found BOLA2 involved in iron metabolism exhibited changes in ex vivo EP-treated monocytes from HBV-ITP patients according to the RNA-seq results. The effects of BOLA2 interfering on ISGs was the same as that of EP, so we believed that EP might play a role through iron metabolism. We then examined the effects of EP on intracellular free iron ions and the ROS production in which iron ions participate. Finally, the results showed that EP reduced intracellular iron ions level and endogenous Reactive oxygen species (ROS) production, then affecting the antiviral response of IFN-α.

Conclusion: In conclusion, this research verified that eltrombopag's iron-chelating character leds to a decrease in ROS generation via reduced free iron. Thereby phosphorylation of JAK1 and STAT1 and ISGs expression induced by IFN-α were suppressed. Finally, antiviral signaling pathway induced by IFN-α was inhibited by eltrombopag.

Keyword: HBV-ITP, RNA-seq, Eltrombopag, IFN-α



PP12-10

Piper betel ethanolic extract prolongs prothrombin time (PT) in plasma of group O and group A blood donors

Evana Kamarudin

Medical Laboratory Department, University Technology MARA (UiTM), Malaysia

Background: Betel, scientifically known as Piper betle Linn, was common among the Malay community. Widely distributed throughout tropical and subtropical countries. Betel leaves had been used previously to treat nose bleeds and heal wounds. This study evaluates in vitro anticoagulant activities of ethanolic (EE) and aqueous (AE) P.betel Linn extracts on citrated blood from Group A and Group O healthy volunteer donors.

Method: Total phenolic and flavonoid contents in the extracts were determined using Folin-Ciocalteau and colourimetric assays with gallic acid and quercetin as standards respectively. Concentrations of each extract ranging from 20-100mg/ml were used to determine effects on activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) in plasma from donors. All assays were performed in triplicate and analysed for statistical significance using ANOVA.

Results: The total phenolic content of EE was slightly lower than AE measuring at 219.4 and 225.16ugGAE/100g dry wt. respectively. Conversely, total flavonoid content in EE (143.85ugQUE/100g dry wt.) was higher compared to AE (102.62ugQUE/100g dry wt.). Of significance, we show that EE caused a twofold increase in PT of blood Group O (37.4 secs, $p< 0.001$) and Group A (34.9 secs, $p< 0.001$) compared to control (14secs). The AE was less effective in prolonging PT, it nevertheless showed increased coagulation times for both O and A blood groups at 23.7 secs and 20.1 secs respectively compared to control. APTT and TT were also prolonged by EE and AE for both blood groups, although less significantly compared to control

Conclusion: In summary, ethanolic and aqueous extracts of P.betel leaves prolonged coagulation time with a significant effect observed with the ethanolic extract showing a greater effect on the extrinsic pathway (PT)

Keyword: Piper Betel, Anticoagulant, Blood O and A

PP12-12

Clinical characteristics of hemophilia in Korea – data from the Korean bleeding disorder registry (KBDR)

Jung Woo Han[1,2], Hee Jo Baek[3], Young Shil Park[4], Sang Kyu Park[5], Ki Young Yoo[6], Eun Jin Choi[7], Ji Yoon Kim[8], Soon Ki Kim[9*]

[1] Department of Pediatrics, Yonsei University College of Medicine, Korea

[2] Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Seoul, Korea

[3] Department of Pediatrics, Hwasun Hospital, Chonnam National University, Korea

[4] Department of Pediatrics, Kyung Hee University School of Medicine, Korea

[5] Department of Pediatrics, School of Medicine, University of Ulsan, Korea

[6] Seoul Clinic, Korea Hemophilia Foundation, Korea

[7] Department of Pediatrics, Daegu Catholic University School of Medicine, Korea

[8] Department of Pediatrics, Kyungpook National University School of Medicine, Korea

[9] Department of Pediatrics, College of Medicine, Inha University, Korea

Background: Hemophilia is the rare bleeding disorders. To investigate the epidemiology, natural history and medical environment of hemophilia, the patient registry is the pivotal research design. Many developed countries have their own registry data and published valuable clinical data on the bleeding disorders. For now, there was no nationwide bleeding disorder registry except for the data from the registration program of Korea Hemophilia Foundation (KHF). We developed the first registry for the bleeding disorders in Korea with the funding from the Korean Society of Pediatric Hemato-Oncology (KSPHO) and KHF. Here we report the first preliminary baseline characteristics of the registry.

Method: We developed the registry platform using iCReaT(Internet based Clinical Research and Trial management system) operated by National Institute of Health in Korea. The registry was designed as the combined retrospective and prospective study for bleeding disorders. At the first stage we first collected data in retrospective fashion to overview the clinical status and epidemiology of bleeding disorders in Korea. The data was collected under the approval of Institutional Review Board at each participating institution.

Results: Total 431 patients were registered. The current age of this cohort was mean 29.7 ± 19.9, median 26.5 [IQR, 12.7;44.1] years old. Geographic distribution was Gwangju (100, 23.2%), Chonnam (95, 22.0%), Seoul (65, 15.1%), Gyunggi (63, 14.6%), Inchon 42 (9.7%), Ulsan 20 (4.6%) and others. The types of hemophilia were hemophilia A (313, 72.6%), hemophilia B (84, 19.5%), hemophilia C (8, 1.9%), factor 7 deficiency (8, 1.9%) and others. For the severity of hemophilia, 54.3% and 28.6% of hemophilia A and B were severe hemophilia, respectively. In 431 patients, only 35 patients (8.1%) had genetic variant information. For proportion of prophylaxis, 74.8% of hemophilia A and 65.5% of hemophilia B received prophylaxis. Total 26 patients underwent joint operation for arthropathy. For viral infection, the patients had hepatitis A in 135 (31.3%), hepatitis B in16 patients (3.7%) and HIV in 2 patients.

Conclusion: In the first stage of registry development, 431 patients were registered. We described the baseline characteristics of hemophilia registry. Here we start the prospective registry further based upon the clinical findings in this retrospective data.

Keyword: Hemophilia, Registry, Bleeding disorders, Baseline characteristics

PP12-13

Increased TCRαβ++ double-negative T cells in pediatric primary immune thrombocytopenia

Xingjuan Xie[1], Runhui Wu[2*], Zhenping Chen[1], Hui Chen[1], Hao Gu[1] and Jingyao Ma[2]

[1] Hematology and Oncology Laboratory, Beijing Pediatric Research Institute, Beijing Children's Hospital, National Center for Children's Health, Beijing, China

[2] Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

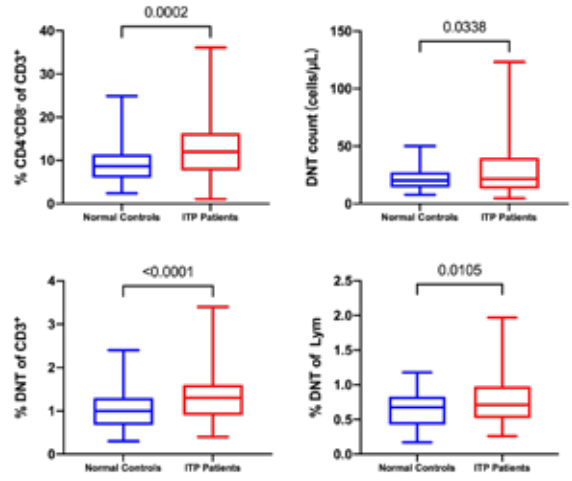
Background: Primary immune thrombocytopenia (ITP) is an autoimmune condition characterized by decreased platelet counts due to increased destruction and reduced platelet production. Multiple factors have been proved to mediate ITP pathogenesis, including T-lymphocyte dysfunctions. Some previous studies have demonstrated that TCRαβ+CD4-CD8- double-negative T (DNT) cells, as a small but vital portion of mature T lymphocytes, play a pro-inflammatory role in many autoimmune diseases. In this case-control study, we aimed to investigate the different levels of DNT cells between the ITP children and healthy controls.

Method: 110 pediatric patients diagnosed with initial primary ITP and 66 sex-and age-paired healthy controls (HCs) were involved in this study. The level of DNT cells was quantified by flow cytometry.

Results: The ITP patient group (1.38± 0.12) had a significantly higher percentage of DNT cells of CD3+ T cells compared with the healthy controls group (1.00 ± 0.10, P<0.0001). Also, the proportion of DNT cells of lymphocytes was analyzed, showing the same trend in ITP children (0.78 ± 0.07 vs 0.64± 0.06, P=0.0105). In addition, the specific count of DNT cells in peripheral blood increased in patients with ITP (28.30 ± 4.25vs 22.07 ± 2.54, P=0.0338).

Conclusion: Both the proportion of DNT cells of CD3+T cell and lymphocyte increases in patients with ITP is higher than healthy controls, suggesting that DNT cells may play a vital role in the development of ITP.

Keyword: Immune thrombocytopenia, TCRαβ+ double-negative T cell, Pathogenesis



PP12-14

FOXO1 SNPs are associated with the severity and clinical outcome of pediatric immune thrombocytopenia in the Chinese population

Xingjuan Xie[1], Zhenping Chen[1*], Runhui Wu[2], Hao Gu[2] and Jingyao Ma[2]

[1] Hematology and Oncology Laboratory, Beijing Pediatric Research Institute, Beijing Children's Hospital, National Center for Children's Health, Beijing, China

[2] Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

Background: Background: Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by a reduced platelet count and an increased risk of bleeding. With immense studies exploring the potential mechanism, it has been widely approved that many single-nucleotide polymorphisms (SNPs) have a significant effect on the mechanism of pathogenesis and development of ITP. FOXO1, as a predominant member of the forkhead transcription factor O family, plays a vital role in the immune system by the regulation of many immune-system-specific gene expressions. Emerging evidence indicates that FOXO1 is related to the development of some autoimmune diseases, suggesting that FOXO1 may be involved in immune dysregulation in patients with ITP. This study aims to evaluate the potential relationship between the four selected single nucleotide polymorphisms (SNPs) of the FOXO1 gene and the susceptibility, severity, clinical outcome of pediatric ITP.

Method: This study prospectively recruited 220 healthy controls and 327 children with ITP and followed up for one year. Four SNPs (rs17446593, rs17446614, rs2721068, and rs2721068) of the FOXO1 gene were detected using the Sequenom MassArray system (Sequenom, San Diego, CA).

Results: The frequencies of the four SNPs did not show any statistical significance between the ITP and healthy control groups. The polymorphisms of rs17446593 and rs17446614 in the FOXO1 gene are associated with decreased risk of severe ITP but increased risk of chronic ITP. (severity: rs17446593, AG vs AA, OR=0.500, CI=0.295~0.850, P=0.009; rs17446614, AG vs GG OR=0.464, CI=0.264~0.812, P=0.009. chronicity: rs17446593, AG vs AA, OR=3.069, CI=1.614~5.653, P = 0.0013; rs17446614, AG vs GG OR=2.509, CI=1.272~4.988, P= 0.0257). Although a positive result of FOXO1 rs17446593 and rs17446614 genotype has been found in subgroups, the FOXO1 mRNA expression level showed no significant difference among several genotypes of selected SNPs.

Conclusion: The result of our study shows FOXO1 gene polymorphisms of the rs17446593 and rs17446614 are associated with severity and chronicity of pediatric ITP, suggesting that these SNPs might be a useful predictor of the clinical presentation and disease course. However, how these SNPs affect the specific pathogenesis of severe or chronic ITP needs further analysis.

Keyword: Primary immune thrombocytopenia, FOXO1, Single-nucleotide polymorphism

PP12-15

The metformin effect in adult patients with ITP and pre-existing T2DM

Chaoyang Li, Ming Hou, Qi Feng* and Jun Peng

Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China

Background: Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease, characterized by reduced peripheral platelet counts and an elevated risk of bleeding. There are still a large number of patients failed or relapsed after the first line and second line treatments. So, more research are needed to clarify the complex pathogenesis of ITP. Type 2 diabetes mellitus (T2DM) is a chronic disease with high worldwide prevalence. A growing body of evidence have shown that pre-existing diabetes are associated with inflammatory/immune diseases. However, the impact of T2DM as a comorbidity in patients with ITP need to be clearly clarified. Meanwhile, recent research reported that metabolic pathways exert pivotal role in immune function and control the pathogenesis of autoimmune diseases. Metformin, a very safe medicine for type 2 diabetes mellitus (T2DM), could switch metabolic programming by favoring fatty acid oxidation and blocking oxidative phosphorylation. However, the impact of metformin in ITP patients with T2DM remains uncertain.

Method: The current study was a single center, retrospective cohort study and the study protocol was approved by the Medical Ethical Committee of Qilu Hospital, Shandong University. Participant enrollment began in January 2012 and ended in December 2021. All ITP patients, diagnosed according to the guidelines of the American Society of Hematology, were recruited at the Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China. A total of 458 ITP patients, aged between 18 and 80 years of age of both sexes, were enrolled for the study. Weekly platelet number, face-to-face interrogation and physical examination findings were recorded. The criteria for response were defined as follows: (1) complete response (CR): platelet count ≥ 100 × 109/L and absence of bleeding symptoms, (2) response (R): platelet count ≥ 30 × 109/L and at least two-fold growth from the baseline as well as absence of bleeding symptoms, and (3) no response (NR): platelet count < 30 × 109/L or less than two-fold increase from the baseline level or bleeding

Results: Here, we performed a retrospective cohort study of 458 participants with corticosteroid-resistant ITP, 35 of whom had pre-existing T2DM. Our results showed that the prevalence of T2DM in this cohort was 7.6%, which was slightly lower than the national wide prevalence-almost 10.9% in China. Meanwhile, the participants with pre-existing T2DM displayed a significantly higher response (69% vs. 53%) than those without T2DM. Furthermore, in the T2DM cohort, the response rate reached 82% when metformin was included in the treatment regimen.

Conclusion: In conclusion, these clinical evidences firstly prompt that metformin therapy improve the outcomes of ITP patients with T2DM. Further studies are needed to prove whether metformin could benefit all kinds of ITP patients.

Keyword: ITP T2DM metformin

Table: Therapy and outcome of ITP with pre-existing T2DM stratified by metformin therapy.

	Total (n=35)	With metformin therapy (n=17)	Without metformin therapy (n=18)	*P*
Age(year), median (IQR)	57 (55-66)	56 (53-66)	61 (56-66)	0.447[a]
Female gender, % (n)	54 (19)	47 (8)	61 (11)	0.061[b]
T2DM duration (year), median (IQR)	7 (2-10)	6 (2-10)	7 (1-10)	0.803[a]
Blood Glucose (mmol/L) at admission, median (IQR)	13 (10-17)	13 (11-20)	12 (9-15)	0.352[a]
Therapy, % (n)				
Corticosteroid	63 (22)	59 (10)	67 (12)	0.473[b]

Intravenous Immuno-globulin	31 (11)	24 (4)	39 (7)	0.328[b]
rhTPO	54 (19)	41 (7)	67 (12)	0.181[b]
Rituximab	14 (5)	12 (2)	17 (3)	0.679[b]
Decitabine	22 (8)	18 (3)	28 (5)	0.476[b]
Outcome				
Response, % (n)	69 (24)	82 (14)	56 (10)	0.037[b]
Complete Response, % (n)	29 (10)	29 (5)	28 (5)	0.604[b]

[a]Mann-Whitney U test. [b]Fisher exact or chi-square test. IQR: interquartile range.

PP12-16

Treatment and bleeding complications of cancer-associated venous thrombo-embolism: a Korean population-based study

Sang-A Kim[1], Ju Hyun Lee[1], Ji Yun Lee[1], Hun-Gyu Hwang[2], Yang-Ki Kim[3], Ho-Young Yhim[4], Junshik Hong[5], Jeong-Ok Lee[1] and Soo-Mee Bang[1*]

[1] Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Korea

[2] Division of Pulmonology, Department of Internal Medicine, Soonchunhyang University, School of Medicine, Gumi Hospital, Korea

[3] Division of Pulmonology, Department of Internal Medicine, Soonchunhyang University, School of Medicine, Seoul Hospital, Korea

[4] Division of Hematology and Medical Oncology, Department of Internal Medicine, Jeonbuk National University Medical School, Korea

[5] Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Hospital, Korea

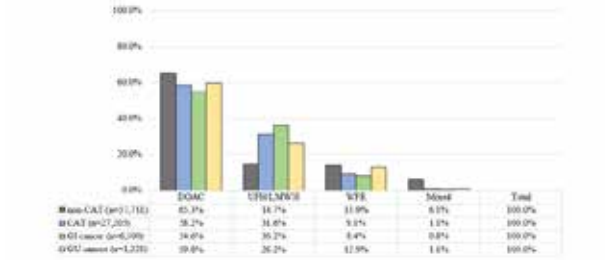
Background: Recent studies have shown that direct oral anticoagulants (DOACs) are an effective treatment option for cancer-associated venous thromboembolism (CAT). However, concerns on higher rate of bleeding complications still remain, especially in patients with gastrointestinal (GI) and/or genitourinary (GU) cancers. In this study, we investigated the treatment pattern and bleeding complications in real world pratice using national insurance data.

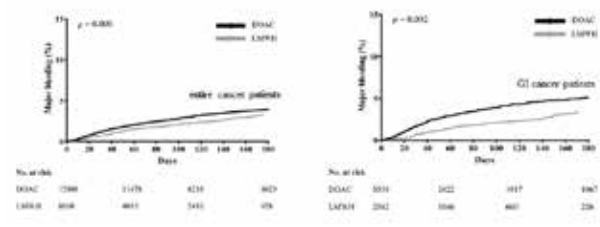
Method: Using Korean Health Insurance Review and Assessment service database from 2014 to 2018, we conduced nationwide study analyzing prescribing patterns and bleeding complications in CAT patients. CAT was defined to meet both of the following criteria: 1) to have diagnostic code of thromboembolism by the 8th Korean Standard Classification of Disease diagnostic codes and 2) to be registered as severe disease registration system with the malignant disease diagnostic code. To verify the bleeding events that were complicated with anticoagulant use, patients who had intracranial bleeding or GI bleeding within 90 days prior to VTE diagnoses were excluded.

Results: Fron 2014 to 2018, 27,205 CAT and 57,711 non-CAT patients were identified. The median age CAT patients were 68 years (interquartile range, 0.9-98 years). In CAT group, pulmonary embolism accounted for 63.5% of all cases, which was significantly higher than that in non-CAT group (48.0%; p<0.001). Cardiovascular disease including hypertention, acute coronary syndrome, and stroke were more prevalent in non-CAT group, resulting in more prevalent concurrent use of antiplatlet agents compared with CAT group (p<0.001). Lung cancer (n = 6,256, 23.0%) accounted for the largest proportion among CAT patients, followed by GI cancer. In both CAT and non-CAT groups, DOACs were the most frequently prescribed anticoagulant, accounting for 58.2% in CAT group and 65.3% in non-CAT group. In the remaining patients, the frequency of LMWH prescription was almost twice as high in CAT than non-CAT patients (31.6% vs. 14.7%). Compared with entire CAT patients, GI cancer patients showed a relatively high rate of LMWH prescription (54.6% treated with DOAC and 36.2% treated with LMWH in GI cancer patients; p<0.001). The cumulative incidence of any/major bleeding was significantly higher in CAT (9.6%/4.7%) than in non-CAT group (5.3%/2.2%; p<0.001). Major gastrointestinal bleeding was also higher in CAT than in non-CAT group (4.0% vs. 1.6%; hazard ratio [HR], 2.50; 95% confidence intereval [95% CI], 2.23 - 2.97; p<0.001). Especially, GI cancer showed higher risks of major bleeding compared with non-GI/GU cancer patients (4.6% vs. 3.5%; HR 1.33; 95% CI, 1.14–1.55; p<0.001]. When comparing bleeding with DOAC and LMWH, the cumulative incidence of major GI bleeding was relatively higher with DOAC than with UFH/LMWH in both entire CAT group (3.4% vs. 2.7%; HR 1.35; 95% CI, 1.12-1.63; p=0.004) and GI cancer subgroup (4.9% vs. 3.0%; HR 1.88, 95% CI, 1.31–2.70; p=0.001).

Conclusion: Over the 5 years since reimbursement of DOAC for CAT in Korea, DOACshave become the most prescribed anticoagulant in Korea. In actual clinical practice, with anticoagulant treatment, the frequency of bleeding complications was higher in CAT than non-CAT, and this feature was more pronounced in GI cancer. In addition, patients treated with DOAC showed higher risk of bleeding than with LMWH in CAT patients. DOAC should be cautiously considered in patients with cancer, and bleeding should be carefully monitored to ensure optimal treatment.

Keyword: Direct oral anticoagulant, Low-molecular weight heparin, Cancer-associated thromboembolism, Hemorrhage





At present, there is a lack of high-quality evidence-based guidelines for the diagnosis and treatment of childhood ITP in China. The evidence resources formed by the adaptation of the guidelines provide high-quality evidence support for the clinical practice of childhood ITP in China.

Keyword: Guideline, Primary immune thrombocytopenia

PP12-17

Evaluation of guidelines for childhood primary immune thrombocytopenia

Jialu Zhang

Hematology Center, Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

Background: To evaluate the quality of clinical practice guidelines related to the diagnosis and treatment of primary immune thrombocytopenia, and to select source guidelines for the adaptation of Chinese childhood ITP guidelines.

Method: Guided by the ADAPTE method of adapting the guideline, we searched PubMed, Embase, CNKI, Wanfang Database, VIP Database, China Biomedical Literature Database and Medlive (http://guide.medlive.cn), UpToDate(https://www.uptodate.com/contents/search), Practice Guideline Registry Platform(http://www.guidelines-registry.cn). The search time limit is from the establishment of the database to May 2020. Apply the Clinical Guideline Research and Evaluation System II (AGREE II) to evaluate the quality of the included ITP guidelines. Include guidelines with high overall quality and scores higher than 70% in the domain called Rigour of Development for content consistency evaluation, and finally selected high-quality evidence-based guidelines to provide evidence for the adaptation of the guidelines.

Results: 19 guides in the past 10 years were included and evaluated by 4 researchers using AGREE II tools. The overall quality of the 19 guides is not high. The domain called Clarity of Presentation has the highest average score of 79.68% in each domain, while the " Stakeholder Involvement" domain has the lowest average score of 23.68%. Three of the guidelines have high overall quality and scores higher than 70% in the domain called Rigour of Development. They have passed the content consistency evaluation and were included as the basis for the adaptation after discussion by the guideline adaptation group.

Conclusion: The average quality of the included guidelines is low.

PP12-18

Adapted guideline for the diagnosis and treatment of primary immune thrombocytopenia in children in China (2021 edition): recommendations external review

Jialu Zhang

Hematology Center, Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

Background: Adapted Guideline for the Diagnosis and Treatment of Primary Immune Thrombocytopenia in Children in China (2021 Edition) is the first pediatric primary immune thrombocytopenia (ITP) guideline in the framework of GRADE in China. The guideline panels met two recommendation consensus in July 18th, 2020 and February 28th, 2021, finalized 24 recommendations. The purpose of the current study was to assess the property of recommendations and further revise them.

Method: We commissioned the external review of recommendations by questionnaire onilne. Physicians were investigated for appreciations, clarity and feasibility of 24 recommendations as well as other suggestions about the guideline. The guideline panels discussed the result of external review and revised recommendations based on it.

Results: A total of 57 physicians from 14 hospitals and 3 guardians of patients participated in the external review. The overall appreciation degree of recommendations was 90.42%, the overall clarity degree of recommendations was 97.29%, and the overall feasibility degree of recommendations was 87.36%. Among them, appreciations, clarity and feasibility degree of all recommendations were over than 50%. 99 subjective suggestions were received. After review of the results, the guideline panels split the 24 recommendations into 25 recommendations and completed the full article.

Conclusion: The external review was participated by ITP-related clinical staff and guardians of patients, which improved the clarity and feasibility of the recommendations and provided a reference for the formulation of follow-up guidelines in China.

Keyword: Clinical practice guideline, External review, Recommendation

PP12-19

Immune thrombocytopenia and incidence of H. pylori infection - a prospective study from India

Rajeev Sandal[1], Gaurav Parkash[2*], Pankaj Malhotra[2], Shamoli Bhattacharya [2], Neelam Varma[2], Jasmina Ahluwalia[2] and Vishal Sharma[2]

[1] Department of radiotherapy and oncology, Indira Gandhi Medical College, India

[2] Department of clinical Hematology and Medical Oncology , PGIMER, Chandigarh, India

Background : Immune thrombocytopenia (ITP) is a heterogenous acquired autoimmune disease, which is characterized by the destruction of platelets by auto antiplatelet antibodies and decrease production due to defective megakaryopoiesis. It can be primary when no underlying cause is identified or secondary where an underlying cause of autoimmune destruction is found. In eight percent of cases, the cause could not be determined.

Method : This was a prospective interventional study. Three hundred sixteen consecutive patients with isolated thrombocytopenia (defined as per ASH guidelines for ITP 2011) were enrolled in the study after taking informed consent. Demographic data including age, place, gender, occupation, socioeconomic status of patients were recorded. A detailed history of patients about bleeding symptoms was documented. It included site and severity of bleeding (as per WHO bleeding scale), duration of bleeding, previous history of prolonged bleeding after surgery, hemostasis during pregnancy in women, systemic symptoms like loss of weight, loss of appetite, history of fever, jaundice, headache, and symptoms of autoimmune disorders such as arthralgia, photosensitivity, skin rash, Raynaud's phenomenon, alopecia, and venous thrombosis. Risk factors for HIV infection were noted. History of medications, which may lead to thrombocytopenia, was documented. Histories of indigenous medications/alternative medications were recorded. History of aspirin, which may exacerbate bleeding, was documented. Transfusion history and family history of thrombocytopenia were documented. After taking a detailed history, a clinical examination of the patient was done. Type of bleeding (including retinal hemorrhages) and severity of bleeding were recorded. Stigmata of chronic liver disease were documented. Detailed examination of the patient was done to rule out evidence of secondary ITP or other disorders associated with thrombocytopenia like leukemia. All eligible ITP patients underwent urea breath testing (UBT) during the study period. Patients who were found to be UBT positive underwent upper gastrointestinal endoscopy with histopathological examination for H. pylori infection.

Results : Among 316 patients, 184 were females (58.2%) and 132 were males (41.8 %). The median age of the study population was 36 years (range 13 -76 years). Out of 316 patients, 202 patients (63.9%) had a history of bleeding like cutaneous bleed, gum bleed, menorrhagia, hematochezia, CNS bleed, hematuria, and hematemesis. The urea breath test was performed in 299 patients. Pregnant ITP patients (n=17) of the study population were not subjected to UBT. Out of 299 patients, 34 patients (11.4%) were found to have positive UBT. Out of 34 patients, sixteen (47.1%) were males, and eighteen (52.9%) were females. There was no difference in the clinical presentation of UBT positive patients from UBT negative patients. Of these 34 patients, 19 gave consent for an upper gastrointestinal endoscopy. Out of these nineteen patients, eleven patients (57.8 %) were found to have chronic active H. Pylori gastritis on endoscopic antral biopsy. The median hemoglobin of UBT positive patients was 11.9 gm/dl (6.5-15.2 gm/dl), and the median platelet was 39500/µL) (5000-97000/µL). In the comparison of UBT positive (n=34) and UBT negative patients (n=265), UBT positive patients were found to have a higher mean platelet count as compared to UBT negative patients (P= 0.001). UBT positive patients have low reticulocyte count 1.2 (0.98-2.7) as compared to UBT negative patients 1.8 (0.97-5.98) (p=0.000). There was no gender-wise difference between UBT positive ITP patients. Further details of univariate analysis of various laboratory parameters among UBT positive and UBT negative patients have been provided in Table 1

Conclusion : We found H. Pylori as the most common infection in ITP patients in our region and chronic active gastritis is the most common presentation on histopathological examination. The clinical profile of H. Pylori infected ITP patients was similar to non-infected patients. In view of the high prevalence of H. pylori infection in India, its association with the ITP, and therapeutic benefit to the patient - routine testing may be considered in all ITP patients in our region

Keyword: Immune thrombocytopenia, H. pylori Infection, Urea breath test

	UBT positive (n=34) Median (range)	UBT negative (n=265) Median(range)	p-value
Age median (range)	39 years(16-60 years)	36 years (13-76 years)	0.965
Haemoglobin (gm/dl)	11.9 (6.5-15.2)	11.4 (6.0-15.6)	0.134
MCV(fl)	83.8 (63.0-98.0)	83.2 (60.8-105.0)	0.650
MPV(fl)	11.25 (7.90-14.6)	11.0 (7.60-14.80)	0.148

Reticulocyte count (%)	1.2 (0.98-2.70)	1.8 (0.97-5.98)	0.000
Automated Platelets(µL)	39500 (5000-97000)	15000 (1000-9700)	0.001
Manual platelets(µL)	47500 (5000-95000)	20000 (1000-95000)	0.001

PP12-22

To predict the pretest probability score in deep vein thrombosis (DVT) - a single center study

Madiha Abid[1*], Munira Borhany[2], Sidra Zafar[1] and Tahir Shamsi[2]

[1] Research and Development, National Institute of Blood disease and Bone Marrow Transplantation, Pakistan

[2] Clinical Hematology, National Institute of Blood disease and Bone Marrow Transplantation, Pakistan

Background: Thrombophilia is a disorder of haemostasis in which there is a tendency for the occurrence of thrombosis. This tendency can be inherited or acquired. It is not well studied whether gender influences the clinical presentation of deep-vein thrombosis (DVT) and the discriminative value of the Wells diagnostic pretest probability score. The aim of the study was to evaluate the impact of gender on clinical presentation and diagnosis of DVT and to assess the pretest probability score in DVT patients.

Method: In this observational study; 121 patients with thrombosis were enrolled from Jan-Dec 2021 at National Institute of Blood diseases (NIBD), after taking informed consent and patient medical history and diagnostic work-up for DVT was collected and analyzed using SPSS version 23.

Results: Total of 121 patients were recruited in the study; who had a diagnostic work-up for DVT, in which the males were 32(26.4) and females were 89(73.6). However, the prevalence of confirmed DVT was reported in 42(34.7) out of which, the ratio of females were more likely higher than males i.e. 28(66.6) vs. 14(33.3). Impact of confirmed cases of DVT showed insignificant association with gender i.e. (p-value i.e. $p>0.05$). Among patients with confirmed DVT, proximal DVT was more common in females (61.5% vs. 38.5% in male, $p>0.05$). Swelling of the leg, and Tenderness localized along deep venous system were more frequently reported in female ($p<0.01$). The percentage of patients with a high probability Wells clinical pretest score was higher in female than in male (55.6% vs. 44.4%, $p>0.05$). However, overall, the score equally differentiate risk groups for DVT in both sexes. The diagnosis of DVT was based on compression ultra-sonography in 28.6% of patients.

Conclusion: In conclusion, males were more frequently referred for a diagnostic work-up for DVT than females, but the prevalence of DVT was higher in female and their thrombotic events were more severe. However, the Wells clinical pretest probability score correctly identified low-and high-risk groups in both genders

Keyword: Deep-vein thrombosis, Gender, WELLs score, Thrombophilia

PP12-23

Management of chronic adult ITP patients: a single center study

Sidra Zafar[1*], Munira Borhany[2], Madiha Abid[1] and Tahir Shamsi[2]

[1] Research and Development, National Institute of Blood disease and Bone Marrow Transplantation, Pakistan

[2] Clinical Hematology, National Institute of Blood disease and Bone Marrow Transplantation, Pakistan

Background: The pathogenesis of chronic idiopathic thrombocytopenic purpura (ITP) involves antibody-mediated platelet destruction and reduced platelet production i.e. less than $100 \times 109/l$ with increased risk of bleeding. Therefore following study aimed to determine the frequency of chronic adult ITP patients and their management along with the outcome

Method: Recruitment for this observational study of chronic ITP patients was conducted from January to December 2021 at National Institute of Blood Diseases (NIBD) after taking the patients' informed consent. Patient's medical history, clinical data and outcome was collected and analyzed using SPSS version 23.

Results: Total of 96 chronic adult ITP patients were enrolled in the study. Among them 64 patients received eltrombopag, in which males were 23(35.9%) and females were 41(64.1%) with mean age 40.7 ± 16.12. Most common clinical manifestations observed were gums bleeding (34.4%), bruising (31.3%), epistaxis (30.3%), menorrhagia (20.3%) and joint bleeding (17.2%). However co morbidities such as hypertension 10(15.6%) and diabetes was observed in 12(18.8%) patients. laboratory parameters are presented in Table 1. Viral markers such as H.pylori was observed in 8(12.5%), HCV in 5(7.8), HBV in 3(4.7) while no case of HIV was reported in these patients. Ultrasound findings showed hepatomegaly in 2(3.1%), hepatosplenomegaly in 1(1.6) and splenomegaly in 9(14.1%) patients. All the patients were managed with eltrombopag in combination with steriod and azathioprine, with complete response observed in 27(42.2%), partial response was observed in 11(17.2%) and no response was observed in 26(40.6%) patients whereas splenectomy was done in 7(10.93%) patients with complete response observed

in 3(4.7%). Mean difference in LFT parameter during the study indicates the toxic effect of eltrombopag on liver.

Conclusion: The risk of liver dysfunction is high in patients with ITP on eltrombopag treatment. Therefore, patients should be closely monitored during treatment to enable timely intervention as needed.

Keyword: Eltrombopag, Chronic idiopathic thrombocytopenic Purpura, Liver dysfunction

Table 1: Laboratory parameters

Laboratory parameters	Mean and SD at base line	Mean and SD at 6m	Mean and SD at 12m
Complete Blood Count (CBC)			
Hemoglobin (g/dL)	11.9±2.4	12.3±1.8	12.2±2.0
Total leukocyte count (x109/L)	8.9±4.4	7.6±4.0	7.5±3.8
Platelets (x109/L)	49.59±74.4	139.5±193.3	136.5 ±143.1
Electrolytes			
Sodium (mEq/L)	137±3.4	135.0±0.0	139.8±2.8
Potassium (mEq/L)	3.9±0.54	4.6±0.0	3.9±0.8
Chloride (mEq/L)	102.6±3.7	103±0.0	103.5±3.1
Bicarbonate (mEq/L)	22.3±3.4	22.3±3.4	20.2±4.5
Liver function test (LFT)			
SGPT (u/l)	37.5±31.92	14.00±0.0	69.0±84.1
ALP (u/l)	143.54±143.09	47.00±0.0	337.0±140.9
Total bilirubin (mg/dl)	0.65±0.44	0.100±0.0	21.6±36.7
Direct bilirubin (mg/dl)	0.1±0.0	0.1±0.0	0.3±0.1
Other Biochemical test			
Urea (mg/dl)	38.6±45.6	23.2±1.0	24.0±6.1
Creatinine (mg/dl)	3.1±8.5	0.6±0.2	0.6±0.09

PP12-24

An escalating treatment strategy for children with chronic immune thrombocytopenia: prospective clinical study from a single center

Jialu Zhang

Hematology Center, Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

Background: Immune thrombocytopenia is the most common hemorrhagic disease in children, which is mainly caused by increased destruction and decreased production of autologous platelets due to abnormal autoimmune tolerance.

Method: The current international guidelines recommend that the second-line therapy drugs for children with chronic ITP are thrombopoietic agents (TPO-RAs) and rituximab. Efficacy of combination therapy has been reported. Our center used the escalating treatment strategy, including three steps: Step I (high-dose dexamethasone [HDD]), Step II (rituximab), and Step III (eltrombopag). The purpose of this study was to confirm the efficacy of escalating treatment strategy in the treatment of CITP.

Results: This was a single-center, retrospective cohort study. Patients were divided into 2 groups according to the treatment regimen: the combination group (escalating treatment strategy) and the monotherapy group (eltrombopag). We evaluated the therapeutic effect after 12 months of follow-up.A total of 58 cases (30 males and 28 females) were included. Overall response was achieved in 72.41% of patients in the combination group vs 68.97% in the monotherapy group, and the complete response (CR) rate was 34.48% in the combination group compared with 20.69% in the monotherapy group. There was no difference between these 2 groups ($p > 0.05$).

Conclusion: This study suggests that escalating treatment strategy can achieve the similar efficacy as TPO-RAs. It is an effective, safe and second-line treatment scheme suitable for Chinese patients. It is still necessary to further evaluate the feasibility of shortening the course of treatment and reducing the burden of treatment.

Keyword: CITP, Escalating treatment strategy, Children

PP12-25

HDAC3 single-nucleotide polymorphism rs2530223 is associated with increased susceptibility and severity of primary immune thrombocytopenia

Leng Shaoqiu, Liu Anli, Wang Shuwen, Peng J

Department of Hematology, Qilu hospital, Jinan, China

Background: Primary immune thrombocytopenia (ITP) is an autoimmune hemorrhagic disorder characterized by a low platelet count and increased risk of bleeding. We previously reported that low-dose chidamide, a histone deacetylase (HDAC) inhibitor, restores immune tolerance in patients with ITP. This study aimed to evaluate the association of a single nucleotide polymorphism (SNP) rs2530223 in the HDAC3 gene with susceptibility to ITP and its clinical features.

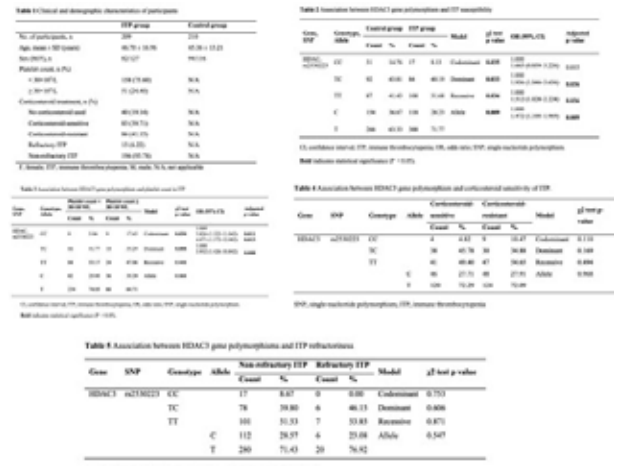
Method: 209 patients, diagnosed with primary ITP according to the ITP international guidelines, were recruited in the Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University. 210 age- and sex-matched healthy participants with normal platelet counts, without autoimmune diseases or infections were randomly recruited as the control group. Genomic DNA was extracted from the PBMCs using a DNA extraction kit. The genotyping of the SNP of HDAC3 (rs2530223) was conducted by the time-of-flight mass spectrometry system.

Results: Statistical analysis of the main clinical and demographic features of the recruited patients and healthy controls demonstrated that no significant difference was found in age or sex between patients with ITP and healthy controls (Table 1).

We used four models to analyze whether HDAC3 rs2530223 is relevant to ITP susceptibility. Under the recessive, dominant, co-dominant, and allelic models, the genotypic and allelic frequencies of HDAC3 rs2530223 were significantly associated with ITP susceptibility (Table 2). The T allele in place of C of rs2530223 in HDAC3 was significantly associated with ITP susceptibility after adjusting for sex and age using univariate binary logistic regression analysis. T allele showed a 1.472-fold increased risk of susceptibility. Moreover, under the codominant and recessive models, the TT genotype was significantly associated with ITP susceptibility, and for the dominant model, the TC/TT genotypes also showed significant association. Notably, the allelic and genotypic distributions of HDAC3 rs2530223 under the above three models all revealed an increased risk of ITP susceptibility.

We divided ITP patients into PLT <30×109/L (n = 158) and PLT ≥30×109/L (n = 51) groups to evaluate the relationship between HDAC3 rs2530223 and platelet count in patients with ITP. Co-dominant and dominant models suggesting a significant relation with platelet count in patients with ITP and the TC/TT genotypes of HDAC3 rs2530223 are relevant to the in increased risk of PLT <30×109/L (Table 3). However, there was no significant difference in the allelic or genotypic frequencies of HDAC3 rs2530223 between the corticosteroid-sensitive group and the corticosteroid-resistant group (Table 4). Moreover, neither allelic nor genotypic frequencies of HDAC3 rs2530223 were significantly different between the refractory group and non-refractory group (Table 5).

Conclusion: Our results revealed that HDAC3 rs2530223 polymorphism was obviously related to ITP susceptibility under the genetic and allelic models; the different distribution of HDAC3 rs2530223 under the four models all revealed an increased risk of ITP susceptibility. We also observed a strong association between HDAC3 rs2530223 and platelet count of patients with ITP under the codominant and dominant models, showing that the TT and TC genotypes increased the risk of PLT <30×109/L in ITP patients 4.071-fold and 3.862-fold, respectively.



PP13-01

Outcome of allogenic hematopoietic stem cell transplantation for pediatric acute lymphoblastic leukemia: a retrospective analysis of a single-center

Hongbo He, Huyong Zheng and Bin Wang

Hematology Center, Beijing Children's Hospital, China

Background: Acute lymphoblastic leukemia (ALL) is a heterogenous group of hematologic malignancies. Over the past several decades and with modern risk-adapted chemotherapy, the five-year survival rate in children with ALL has significantly improved (88.6%). Although the prognosis of most patients has improved, in the current intensive chemotherapy regimen, some patients still have a high risk of relapsed. Allogenic hematopoietic stem cell transplantation (allo-HSCT) is a feasible treatment for high-risk patients who are prone to relapsed with standard chemotherapy alone or relapsed after complete remission (CR).

Method: Children with ALL who underwent allo-HSCT in Beijing Children's Hospital, Capital Medical University, from January 2006 to December 2019 were retrospectively analyzed. Data relating to the clinical manifestations, engraftment, and prognosis of the children were extracted from medical records. All patients received allo-HSCT with a myeloablative conditioning regimen (vivo de-T regimen).

Results: Seventy-five patients, including 52 males and 23 females, with an medium age of 5.30 (0.52-14.30) years were enrolled in this study. The median time from diagnosis to transplantation was 1.64

(0.43-9.06) years. Fifteen patients accepted human leukocyte antigen (HLA) matched transplantation and 60 patients accepted haploidentical HSCT(haplo-HSCT). Before transplantation, 73 patients achieved CR and 2 patients didn't achieve remission. The median following time was 41.0 (1.0-144.0) months. By the end of follow-up, 51 patients survived and 24 patients died or given up due to relapse. The five- year overall survival rate, event free survival rate and relapse rate were 67.77%, 57.30% and 35.69% respectively. Acute graft versus host disease (GVHD) was observed in 40 patients and chronic GVHD was observed in 28 patients. The five- year OS of haplo-HSCT was higher than HLA matched-HSCT (p=0.048), but there was no significant difference in the engraftment time of neutrophils and platelets, the frequency of GVHD and the relapse rate after transplantation (p=0.374, 0.193, 0,184, 0.121 and 0.293, respectively). The five- year OS of patients with MLL gene rearrangement was higher than other types (p=0.042). The type of donor, conditioning regimen, immunophenotype and disease status before transplantation did not affect the outcome of transplantation.

Conclusion: Allo-HSCT was an effective treatment for children with ALL, with a high survival rate. Haplo-HSCT is superior to HLA matched-HSCT. The 5- year OS of patients with MLL rearrangement gene after HSCT is the highest and that of patients with BCR-ABL fusion gene is the lowest.

Keyword: Acute lymphoblastic leukemia, Hematopoietic stem cell transplantation, Pediatrics

PP13-03

Early infectious complications among adult autologous hematopoietic stem cell transplant recipients at the national kidney and transplant institute

Ernest Matthew Paggabao* and Lynn Bonifacio

Internal Medicine, National Kidney and Transplant Institute, Philippines

Background: Autologous hematopoietic stem cell transplant recipients (HSCT) are subjected to myeloablative chemotherapy causing marked immunosuppression. Infections are considered the most common cause of transplant-related morbidity and mortality. To date, no local study has been published regarding the incidence of early post-transplant infections in the Philippines.

Method: A single-center descriptive study involving all autologous transplants done at the National Kidney and Transplant Institute from February 2019 until June 2021 was conducted. The primary objective of the study was to determine the incidence of infections among autologous HSCT recipients in the first 100 days following transplantation. Secondary objectives include determination of the incidence of the infection per site, etiologic agents involved, and the average length of hospital stay during transplantation.

Results: A total of 19 patients were included in the study. The mean age was 38.68 ±12.59. Ten (52.6%) were female. Underlying malignancies consisted of multiple myeloma (52.9%), Hodgkin's lymphoma (42.1%) and non-Hodgkin's lymphoma (5.3%). In the first 30 days, 84% developed fever. Thirty-two percent had febrile neutropenia, 21% had catheter-related bloodstream infections and 21% had gastrointestinal tract infections. Of those with documented etiology, 4 were bacterial (2 Coagulase-negative Staphylococci and 2 Enterobacteriaceae) and 1 was parasitic (Entamoeba histolytica). Those with infection had a median duration of 16 days of hospitalization following transplant as opposed to 13 days among those who did not. From days 31-100, only 38.9% had subsequent infections.

Conclusion: Infection in the first 30 days following autologous hematopoietic stem cell transplantation is an important early in-hospital complication with an incidence of 84.2% in our institution. Febrile neutropenia is the most common cause of fever followed by catheter-related bloodstream infections and gastrointestinal tract infection.

Due to the small sample size and limited number of transplants being done in the country, a multi-center prospective cohort study to include a larger population is recommended.

Keyword: Hematopoietic stem cell transplantation, Autologous transplantation, Infections, Febrile neutropenia, Chemotherapy-induced febrile neutropenia

PP13-05

Haploidentical stem cell transplantation using post cyclophosphamide: a single –center initial experience in Viet Nam

Van Man Huynh

Stem Cell Transplantation, Blood Transfusion and Hematology Hospital, Viet Nam

Background: HLA-haploidentical peripheral blood stem cell transplantation (Haplo-SCT) is an alternative therapy for patients who do not have HLA-matched donors. We conducted this study to assess the preliminary results regarding the efficacy & complications of haplo-PBSCT using PTCy at the Ho Chi Minh City Blood Transfusion

and Hematology hospital (BTH).

Method: A retrospective case series study was conducted in 29 haploidentical transplant patients at BTH between January 2014 and December 2021. Conditioning regimen were Flu/Bu/low dose Cy: Fludarabine 30mg/m2/day, D-6 to D-2, Busulfan 130mg/m2/day, D-3 and D-2, Cyclophosphamide 14,5mg/kg/day D-6 and D-5 for 20 patients and Flu/Bu/Thiotepa: Fludarabine 30mg/m2/day, D-5 to D-1, Busulfan 130mg/m2/day, D-4 and D-3, Thiotepa 5-10mg/kg/D-6 for 9 ALL patients. TBI is not availble in Vietnam. Those 29 patients were used PT-Cy and MMF plus Tacrolimus or Cyclosporine A for GVHD prophylaxis.

Results: The majority of the patients in the present study were diagnosed with acute myeloid leukemia. All patients received reduced-intensity conditioning regimens. The engraftment rate was 86.2%. The median times to neutrophil and platelet engraftment were 17 and 31 days, respectively. Five patients (17,4%) reported severe acute GVHD (grade III-IV), two patients (6.9%) had grade I-II acute GVHD. Three patients experienced limited chronic GVHD of the skin, requiring topical steroids. The most common complication was bloodstream infection (60.9%). Cytomegalovirus reactivation occurred in 24 patients (82.8%) and 13.8% developed hemorrhagic cystitis. The 1-year relapse rate was 30.77%. The cumulative incidence of non-relapse mortality at 1 year was 17.23%. The 1-year OS and DFS rates were 59.7% and 52%, respectively. The 1-year GRFS rate was 46.9%. A high/very high DRI score was associated with worse OS after haplo-PBSCT (P=0.038).

Conclusion: Haploidentical transplant using PTCy is a feasible therapy for patients without suitably matched donors in Vietnam. Infection after transplantation remains a challenge and requires effective management.

Keyword: Haploidentical, Peripheral blood stem cell transplantation, PT-Cy

PP13-07

Efficacy of imatinib mesylate in patients with steroid-refractory chronic graft-versus-host disease

Dong Won Baek[1], Hee Jeong Cho[1], Ju-Hyung Kim[1], Jae Sook Ahn[2], Hyung Joon Kim[2], Sung Nam Lim[3], Jun Won Cheong[4], Sung-Yong Kim[5], Ho Sup Lee[6], Jong Ho Won[7], Ho-Young Yhim[8], Joon Ho Moon[1] and Sang Kyun Sohn[1*]

[1] Department of Hematology/Oncology, Kyungpook National University Hospital, Korea

[2] Department of Hematology/Oncology, Chonnam National University Hwasun Hospital , Korea

[3] Department of Hematology/Oncology, Inje University Haeundae Paik Hospital, Korea

[4] Department of Hematology/Oncology, Severance Hospital, Korea

[5] Division of Hematology, Department of Internal Medicine, Konkuk University Medical Center, Korea

[6] Department of Hematology/Oncology, Kosin University Gosper Hospital, Korea

[7] Department of Hematology/Oncology, SoonChunHyang University Hospital, Korea

[8] Department of Internal Medicine, Jeonbuk National University Medical School, Korea

Background: Graft-versus-host disease (GVHD) remains a vital hurdle in achieving successful allogeneic stem cell transplantation, and chronic GVHD (cGVHD), which develops in 30%–70% of the patients, is the most important cause of non-relapse morbidity after allogeneic stem cell transplantation. In this multicenter phase II study, we evaluated the safety and efficacy of imatinib in patients with steroid-resistant cGVHD and evaluated the quality of life of the enrolled patients using the Short Form 36 (SF-36) health survey questionnaire.

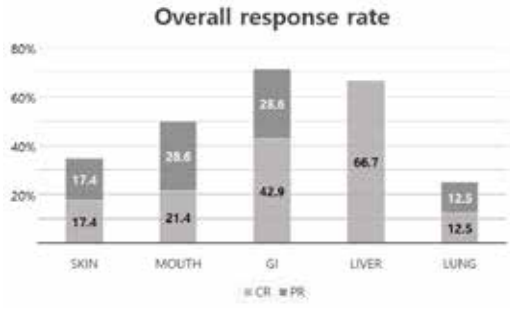
Method: Thirty-six patients who were diagnosed with steroid-refractory cGVHD and treated with imatinib between March 2013 and February 2019 received 100 mg/day imatinib for two weeks. Depending on the patient's condition and investigator's decision, the imatinib dose was allowed to be increased by 100 mg every two weeks up to 400 mg/day. Patients who achieved stable disease (SD), partial remission (PR), and complete remission (CR) at 3-month response evaluations continued imatinib for up to six months. Patients were evaluated for cGVHD every two weeks for six months based on the scoring of all involved organs using the National Institutes of Health (NIH) response criteria.

Results: The median age was 47.5 years, and majority of the patients had multi-organ cGVHD, with skin (63.9%), lungs (44.4%), mouth (38.9%), and eyes (38.9%) as the most common sites. Moderate and severe cGVDH were present in 20 (55.6%) and 16 (44.4%) patients, respectively, according to the NIH global severity score. The overall response rate was 58.3%, including 3 and 18 patients with CR and PR, respectively, and an overall decline in NIH severity scores were observed at study completion in the absence of significant adverse effects. The efficacy of imatinib was better on liver and gastrointestinal GVHD than on skin and lung GVHD. CR was achieved in 66.7% (2/3), 42.9% (3/7), 17.4% (4/23), and 12.5% (2/16) of the patients with liver, gastrointestinal, skin, and lung GVHD, respectively. The overall response rates were 70.5%, 66.7%, 34.8%, and 25% in patients with gastrointestinal, liver, skin, and lung GVHD, respectively. Factors representing emotional well-being were significantly improved based on the patient-reported quality of life (QOL) evaluation using SF-36. The effect of imatinib on steroid tapering, which was notable in responders, was also present in 50% of those who achieved SD

without worsening cGVHD.

Conclusion: Imatinib exhibited therapeutic efficacy in steroid-refractory and steroid-dependent cGVHD with tolerable toxicity. Patients treated with imatinib could reduce steroid dose and reported improvement in emotional well-being.

Keyword: Allogeneic stem cell transplantation, Chronic graft-versus-host disease, Steroid refractory, Imatinib, Quality of life



PP13-09

Immune reconstitution following autologous hematopoietic stem cell transplantation: a study from AIIMS

Mohini Mendiratta[1], Vineet Govinda Gupta[1], Sandeep Rai[2], Saroj Singh[2], Lalit Kumar[1], Ritu Gupta[2], Gajendra Smeeta[2] and Ranjit Kumar Sahoo[1*]

[1] Medical Oncology, All India Institute of Medical Sciences, India
[2] Laboratory Oncology, All India Institute of Medical Sciences, India

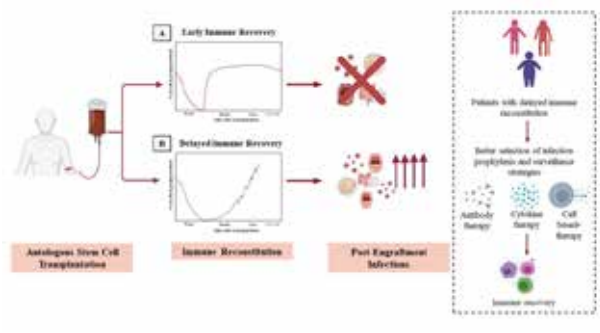
Background: Autologous hematopoietic stem cell transplantation (ASCT) is an important therapeutic modality in the treatment of hematological malignancies e.g. myeloma, lymphoma. Immune reconstitution (IR) consists of both numerical and functional recovery of cellular elements after ASCT. Since protection from infections depends on an intact immune system, patients remain at high risk for several infections in the time after transplantation.

Method: Fifty patients (Multiple myeloma, n=45; Lymphoma, n=5) who underwent ASCT were recruited into this prospective study from November 2019 to December 2021. The cellular immune profile was assessed at various time-points: Pre-ASCT, D+30, and D+180 post-ASCT using multiparametric flow cytometry to determine the kinetics of cellular recovery, the predictive factors for IR after ASCT, and correlation between the immune profile and post-engraftment infections. The cellular profile of the stem cell graft was also assessed to study the impact of graft components on IR. Serum immunoglobulin (IgG, IgA, and IgM) levels were quantified at the same time points using a nephelometry-based Optilite (Optimised Protein System) automated system to assess the functional recovery of B-lymphocytes. Post-engraftment infections were also documented prospectively between engraftment and D+180 post-ASCT.

Results: The pattern of lymphocyte-recovery subsets post-ASCT was NK cells, Dendritic cells > cytotoxic T-cells > helper T-cells > B-cells. We observed mature NK cells (CD56dim CD16+) constituted a major proportion (68%) than immature NK-cells (CD56+ CD16-) by D+30 post-ASCT. These subsets of NK cells also exhibited Killer Immunoglobulin-like Receptor (KIR) expression, which reflects their functional recovery. Similarly, dendritic cells (CD11c+ HLA-DR+) recovered in the majority of the patients by D+30 post-ASCT. Conventional dendritic cells (CD11c+CD123-) constitute the vast majority of circulating dendritic cells than plasmacytoid dendritic cells (CD11c+CD123+). The recovery of cytotoxic T-cells (CD3+CD8+) was rapid in contrast to helper T-cells (CD3+CD4+) which occurred by D+180 post-ASCT. The effector memory helper-T cells (CD45RA-CD45RO+CD25-CD127+) and central memory helper-T cells (CD45RA-CD45RO+CD25+CD127+) recovered by D+180 post-ASCT. Recovery of mature B-cells (CD19+CD20+) were incomplete by D+30, while circulating CD27+ IgD- switched memory B cells were more prominent in the patients by D+180 after transplant. The recovery pattern of B-cells correlated well with immunoglobulin levels in the patients. A significant association was noticed between the cellular content of the graft and the levels of NK-cells and T-lymphocytes by D+30/D+180, while no significant correlation was observed with the recovery pattern of B-lymphocytes. A median of one infection per patient was documented between engraftment and D+180 post-ASCT. Most infection episodes were mild and treated as per clinical syndrome with recovery in all cases. Four episodes (7%) required hospitalization for management and only 1 episode (2%) was life-threatening.

Conclusion: The lymphocyte recovery post-ASCT in the present study matches the previous study. The stem cell graft-content is important for recovery of NK- cells and T-Cells. Delayed immune recovery was associated with a high risk of infections in autologous recipients which was more prominent in older patients (analysis will be presented later). Conclusively, the current prospective study is the first from India to the best of our knowledge and would guide the clinicians to prevent post-engraftment infections at an early stage by employing strategies to enhance immune reconstitution.

Keyword: Autologous hematopoietic stem cell transplantation, Immune reconstitution, Post-engraftment infections, Stem cell graft



PP13-10

Post-transplant cyclophosphamide for GVHD prophylaxis in haploidentical peripheral blood stem cell transplantation

Jinhang Kim, Nanyoung Yun and Jeong-A Kim*

Hematology, St. Vincent Hospital, College of Medicine, The Catholic University of Korea, Korea

Background: Allogeneic peripheral stem cell transplantation (PSCT) is a potentially curative treatment for patients with hematological malignancies. However, HLA-matched related or unrelated donors are not always available. Haploidentical related donors are alternative donors for patients in the absence of a HLA-matched donor and in an urgent need of transplantation. However, haploidentical PBSCT(haploPBSCT) pose significant challenges due to HLA mismatch, which often leads to increased risk of graft versus-host disease (GVHD) and non-relapse mortality (NRM). A recent study led by the Johns Hopkins group pioneered the use of post-transplant cyclophosphamide (PTCY) in the haploPBSCT setting. In the haploPBSCT settings, the use of PTCY in combination with tacrolimus and mycophenolate mofetil (MMF) provides low rates of both acute and chronic GVHD and, as a consequence, low rates of NRM. Therefore, we conducted prospective study to evaluate the safety and efficacy of PTCy-haploPBSCT, and herein report the outcome.

Method: Eleven patients were enrolled in. 11 patients diagnosed with hematologic disease (AML, ALL, MDS and aplastic anemia; 4, 1, 4 and 2, respectively) and a median age was 35 (range, 24 to 55). Conditioning regimen was a combination of Fludarabine (150 mg/m2), busulfan (6.4 mg/kg), and total body irradiation (TBI, 3Gy). High dose cyclophosphamide (50 mg/kg/day on days 3 and 5), cyclosporine and MMF were used for GVHD prophylaxis. The median numbers of CD34+ cells of PBSCs were 10.64 × 106 /kg (range, 6.14–11.08 × 106 /kg).

Results: Event-free survival at 1-year was 80%. Neutrophil engraftment was achieved in 89% of patients with a median time of 14 days (range, 13–15 days). The cumulative incidence of grades I–IV and III–IV acute GVHD at 100 days were 50% and 10%, respectively. The cumulative incidence of chronic GVHD at 1-year was 35%. Overall survival OS, the cumulative incidence of NRM, and the cumulative incidence of relapse at 1-year were 87%, 10%, and 36%. Notably, 63% of patients with relapse-free survival stopped immunosuppressants at one year post PTCy-haploPBSCT.

Conclusion: Our results indicate that PTCy-haploPBSCT is a valid and safe strategy for preventing severe aGVHD, and may also provide better clinical outcomes in long-term disease control.

Keyword: Post-transplant cyclophosphamide, Haploidentical peripheral blood stem cell transplantation

PP13-11

Outcome of infant younger than 1 year with acute lymphoblastic or myeloid leukemia following intensive chemotherapy and hematopoietic stem cell transplantation

Bo Kyung Kim, Kyung Taek Hong, Jung Yoon Choi, Hong Yul An, Hyun Jin Park and Hyoung Jin Kang*

Pediatrics, Seoul National University College of Medicine, Korea

Background: Infant leukemia is rare aggressive disease and has poor prognosis. Older children who are diagnosed with leukemia have an 80 percent survival rate, but the survival rate for infants is less than 50 percent. And, neurocognitive dysfunction is an important long-term problem after transplantation of children. However, not much is known about neurocognitive dysfunction of children, especially infants. We reported the characteristics and outcomes including neurocognitive problem of infant acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) with intensive chemotherapy and hematopoietic stem cell transplantation (HSCT).

Method: We present the results of 20 patients underwent allogeneic HSCT with infant ALL and AML at Seoul National University Children's Hospital from 1995 to 2020. All patients used busulfan-based myeloablative contioning regimen. Anti-thymocyte globulin (2.5mg/kg/day, once daily from days -4 to -2) was administered in the patients except haploidentical HSCT. Patients who visited a psychiatric outpatient clinic after transplantation were considered

patients with predisposition of neurocognitive problems.

Results: In all 20 patients, the median age at diagnosis and HSCT was 7.2 months (range, 2.8-11.1 months) and 14.5 months (range, 7.5-22.4 months). Seven patients (35.0%) were ≤6 months of age at diagnosis. The patients included 16 ALL (80%) and 4 AML (20%). The median follow-period was 5.5 (range, 0.1-14.2 years) years after transplantation. Median white blood cell (WBC) count at diagnosis was 118.4x10^3/㎕ (range, 2.2-905.0x10^3/㎕). Central nervous system disease was present in 2 patients (10%). At transplantation, 18 patients (90.0%) were complete remission and 2 patients (10%) were persistent. Eight patients received HSCT from unrelated peripheral blood stem cell (PBSC), 7 from unrelated cord blood, 2 from haploidentical PBSC, and others from related bone marrow, unrelated bone marrow, and related PBSC. There was no engraftment failure. The cumulative incidence of acute graft-versus-host disease (GVHD) with grade II-IV was 31% and those with grade III-IV was 15.6%. Chronic GVHD appeared in only one case with moderate severity. Acute GVHD with grade II-IV was higher in male than female (62.5% vs 19.2%, p=0.013), but donor-recipient sex mismatch was not related to incidence of acute and chronic GVHD. The 5-year overall survival (OS) and event-free survival rates (EFS) and treatment-related mortality (TRM) were 84.4%, 83.3%, and 17.1%, respectively. And there were no significant differences in OS (ALL 80.4% vs AML 100%, p=0.359), EFS (ALL 85.7% vs AML 75.0%, p=0.691), and TRM (ALL 12.9% vs AML 0%, p=0.464) between ALL and AML. The OS and TRM over the age of 7.2 months at diagnosis was higher than that under the age of 7.2 months, but there was no significant difference statistically (OS 100% vs 72.7%, p=0.113, TRM 0% vs 18.2%, p=0.203). The patients with high WBC count (≥118.4x10^3/㎕) at diagnosis showed a low OS and EFS, but this was also not significant difference statistically (OS 70% vs 100% p=0.077, EFS 66.7% vs 100% p=0.065). Patients who visited a psychiatric outpatient clinic after transplantation were 37.3% (median 2.7 years after transplantation, range 2.0-9.1 years).

Conclusion: This study showed favorable outcomes of infant ALL and AML after intensive chemotherapy and HSCT during long period. And it is considered necessary to follow-up the neurocognitive function in patients who underwent intensive chemotherapy and HSCT at an early age. However, the number of patients was not large enough, further studies are needed for these high-risk patients.

Keyword: Infant, Acute lymphoblastic leukemia, Acute myeloid leukemia, Hematopoietic stem cell transplantation, Neurocognitive dysfunction

PP13-12

Symptomatic diarrhoeal and non-symptomatic clostridioides difficile infection (CDI) in hematopoietic stem cell transplantation recipients

Alka Khadwal

Clinical Hematology & Medical Oncology, Post Graduate Institute of Medical Education & Research, Chandigarh, India

Background: C. difficile colonises 2-3 % of healthy people and its colonisation may be as high as upto 20% in hospitalised HSCT recipients. It is considered as most common cause of nosocomial diarrhoea and HSCT recipients are at increased risk for same. We conducted the present study to identify incidence of Clostridioides difficile infection (CDI) in symptomatic diarrhoeal and non-symptomatic silent carriage patients undergoing hematopoietic stem cell transplantation (HSCT).

Method: A prospective C. difficile stool surveillance was done on 34 consecutive patients admitted to BMT unit till the patients got discharged. CDI positivity was confirmed with enzyme immunoassay for glutamate dehydrogenase (GDH), C. difficile toxin A and B (CDAB) and cultures.

Results: In the present study we analysed data of 34 HSCT recipients. The overall incidence of CDI was 26.47% (9/34) of which 14.70% (5/34) had silent carriage only. Fifteen patients (44.1%) and 19 (55.88%) cases were recipient of allogeneic and autologous HSCT respectively. Mean age was 33 years with male sex predominance (2:1). Indication of HSCT were- Multiple myeloma (26.4%), Lymphomas(17.64%), Acute Myeloid leukaemia (14.7%), Aplastic anaemia (11.7%) and Acute lymphoblastic leukaemia (8.8%). Myeloablative conditioning was used in 67.6%. Mean duration of diarrhoea in CDI positive was 2.56 days whereas it was 4.84 days in non-CDI group (p≤0.091) but CDI positive patients had a longer hospitalisation(Graft versus host disease (GVHD) developed in 11.76% (4/34) cases HSCT. One patient each in CDI confirmed diarrhoea and silent carriage group developed GVHD. The mortality was 14.70% (5/34) and there was no significant difference in mortality in the CDI versus non-CDI population in this study (Table-1).

Conclusion: This study highlights the importance of CDI in silent carriage population which could be one of the significant risk factors in HSCT patients and an important factor in CDI transmission.

Keyword: Clostridioides difficile, Diarrhoea, Infection, HSCT

Table -1. C. difficile identification in HSCT diarrhoea cases and silent carriage population and association with GVHD and mortality

Total Patients (n=34)	GDH Positive n (%)	CDAB toxin Positive n (%)	Culture Positive n (%)	Confirmed C. difficile (any 2 tests positive) n (%)	GVHD n (%)	Mortality n (%)	Average Hospital Stay (days)

With Diarrhoea (cases=18) (52.94%)	7 (38.88%)	3 (16.66%)	3 (16.66%)	4 (22.22%)	1 (25%)	0 (0%)	23
Without Diarrhoea (carriage= 16) (47.05%)	15 (93.75%)	5 (31.25%)	8 (50%)	5 (31.25%)	2 (40%)	2 (12.5%)	22

PP13-13

The management and protocol of bone marrow transplantation (BMT) in the era of the COVID-19 pandemic: strategy to minimize risk of exposure to hazards

Lintong Hottua Simbolon[1], Aprilia Grace A. Maay[2]

[1] Alumnus of University of Lampung, Indonesia

[2] Public Health, Institute of Health, Papua, Indonesia

Background: HSCT is amongst the predisposing factors that can potentially make HSCT recipients acquire SARS-CoV2 infection. Reactivation of latent viruses, such as herpesviruses, is frequent during the immunosuppression that occurs with HSCT. However, this situation has upended significant disruption in all aspects of healthcare worldwide and led to an inevitable decrease in HSCT activity. Clinician difficult decision to suspend or continue a life-saving procedure based on the scarce available evidence regarding the risk of transmission and mortality in immunosuppressed patients. Therefore, ethical frameworks balance the need for BMT.

Method: Using an electronic database under PRISMA guidelines, this review will provide an updated view of the impact of the pandemic on BMT programs worldwide. Ten articles were selected for inclusion regarding donor and recipient screening, strategies for waitlist prioritization, and post-transplant risk of infection and mortality.

Results: The mortality rate increased by 32,7% in HSCT candidates with COVID-19 because of respiratory viral infections, increased age, the presence of comorbidities, graft-versus-host disease, corticosteroids, and hypoalbuminemia. Previous symptomatic SARS-CoV-2 infection did not affect early post-transplant survival. The viral infection suggests that management of immunosuppression without mycophenolate mofetil and serology inhibitors may be beneficial. However, the dismal prognosis of patients with HSCT supports the adoption of strict precautions and urgent testing of the efficacy of vaccination in this population. Strategies to minimize risk exposure to the transplant population and health-workers include systematic virus screening, protection devices, social distancing, and reduction of patients visits to the transplant center.

Conclusion: Patients undergoing HSCT require to be inpatients for a prolonged period. This makes them more prone to acquiring nosocomial infections. Factors that should be preferentially considered are related a new strategy on medical care for patients with HSCT during the COVID-19 pandemic. Those centers where the activity continued or was heavily restricted were obliged to screen donors and recipients, design COVID-safe clinical pathways, and promote telehealth to prevent nosocomial transmission.

Keyword: HSCT, Covid-19, Clinical pathaway, Immunosuppression

PP14-01

Expansion of human megakaryocyte-axis progeny via aryl hydrocarbon receptor antagonism of CH223191

Dongchan Kim[1,2], Dong-Yeop Shin[1,2,3*], Jun Liu[1,2], Na-rae Jeong[1,2], Youngil Koh[1,2,3], Junshik Hong[1,2,3], Xinxin Huang[4], Hal E. Broxmeyer[5] and Sung-Soo Yoon[1,2,3]

[1] Cancer Research Institute, College of Medicine, Seoul National University, Seoul, Republic of Korea

[2] Center for Medical Innovation of Biomedical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea

[3] Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea

[4] Institutes of Biomedical Sciences, Fudan University, Shanghai, China

[5] Department of Microbiology and Immunology, Indiana University School of Medicine (IUSM), Indianapolis, Indiana, USA

Background: Aryl hydrocarbon receptor (AhR) is known to regulate the fate of human hematopoietic stem cells (HSCs), and its antagonism has been used for the expansion of functional HSCs. However, the study of AhR antagonism in regulating lineage-skewed differentiation of HSC has not been sufficiently studied. In this study, we investigate the effect of less-studied and AhR-selective antagonist CH223191 on the regulation of HSCs' differentiation. Methods

Method: Cord blood-derived CD34+cells and immune thrombocytopenia (ITP) patients' bone marrow (BM) cells were cultured ex vivo with CH223191 treatment for 14 days. For the analysis of phenotypical changes in cultured hematopoietic stem progenitor cells (HSPCs), multicolor immunophenotyping was performed with a fluorescent-activated cell sorter (FACS). Colony-forming units (CFU) assay in

vitro and engraftment assay in vivo were performed for functional validation of cultured HSPCs. By performing RNA-sequencing, the changes in transcript expression profiles under treatment of SR1 and CH223191 were analyzed.

Results: As similar with representative AhR antagonist StemRegenin1(SR1), CH223191 treatment tends to increase absolute numbers of various HSPCs, and this effect is predominant in phenotypic HSCs (Lin-CD34+CD38-CD90+CD45RA-). In addition, ex vivo culture with CH223191 sustains the short-term repopulating capacity of cultured HSC during the ex vivo culture period. Interestingly, CH223191 leads to a slight increase in the MEP population and eventually results in overall expansion of megakaryocyte (MK) lineage populations expressing integrin alpha 2b (CD41). And the treatment with CH223191 more effectively expands absolute counts of MK progenitors (CD34+CD41+), immature MKs (CD41+CD42b-), and mature MKs (CD41+CD42b+) for 14 days of culture than SR1. Moreover, this effect of CH223191 is restricted to the numbers of MK axis progeny and shows no significance to MK's functionality. AhR antagonism of CH223191 has a weak inhibitory effect on the AhR-associated genes except for CYP1B1 but showed an excellent activation of the megakaryocyte/platelet-associated genes, showing a different propensity from SR1. Furthermore, this effect of CH223191 is also shown in immune thrombocytopenia (ITP) patients' bone marrow (BM) cells. Treated cultures induce expansion of CD41+cells, including MK progenitors, mature MKs, and the p-selectin (CD62p) positive platelet-like particles in ITP patients' BM.

Conclusion: This result reports that CH223191 induces numerical expansion of MK axis progeny, including tetraploid MK via a distinct pathway from SR1. This approach using CH223191, which induces overall expansion of MK lineage progeny expansion accompanied by HSCs' lineage-skewed differentiation, may be applicable to the development of auxiliary treatment regimens for patients with abnormal thrombopoiesis.

Keyword: Aryl hydrocarbon receptor, CH223191, Umbilical cord blood, Hematopoietic stem and progenitor cell, Megakaryocyte, Immune thrombocytopenia

PP14-02

Genetic variation of method of producing human liver stem cells or projenitor cells by direct reprogramming

Haerani Haerani

Midwifery, Sekolah Tinggi Ilmu Kesehatan Bina Bangsa Majene, Indonesia

Background: Genetic variation refers to differences in the genetic makeup of individuals in a population. Genetic disease is mostly caused by familiarity in the genetic code. Genetic variation is necessary in natural selection. In natural selection, organisms with environmentally selected traits are better able to adapt to the environment and pass on their genes. This study aims to evaluate the variation of method of producing human liver stem cells or projenitor cells by direct reprogramming.

Method: Data obtained from 6 nucleotide sequences of method of producing human liver stem cells or projenitor cells by direct reprogramming sequence on secondary data form on https://www.ncbi.nlm.nih.gov/. The phylogeny analysis of variations and relationships of DNA sequences Constructed with Neighbor Joining using MEGA 7.0 software.

Results: Based on the analysis of variations, it is known that on the dendogram, 6 sequences were divided into 2 main groups, namely groups A consisting of 4 specimens and groups B consisting of 4 specimens. The optimal tree with the sum of branch length = 23.10190808 is shown. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Maximum Composite Likelihood method and are in the units of the number of base substitutions per site. The proportion of sites where at least 1 unambiguous base is present in at least 1 sequence for each descendent clade is shown next to each internal node in the tree. The analysis involved 6 nucleotide sequences. Codon positions included were 1st+2nd+3rd+Noncoding. All positions containing gaps and missing data were eliminated. There were a total of 2046 positions in the final dataset.

Conclusion: It can be concluded that the variation method of producing human liver stem cells or projenitor cells by direct reprogramming was quite varied. Information genetic variation can be used as an informative source to assembly of superior genes in living of human cells.

Keyword: Genetic Variation, Human Liver, Stem Cells, Projenitor Cells, Direct Reprogramming

PP14-03

BAFF blockade attenuates acute graft-versus-host disease directly via the dual regulation of T- and B-cell homeostasis

Youngwoo Jeon[1,2], Jung-Yeon Lim[3], Keon-Il Lim[2], Nayoun Kim[2] and Seok-Goo Cho[1,2,4*]

[1] Hematology, The Catholic University of Korea, Yeouido ST. Mary's Hospital, Korea
[2] Institute for Translational Research and Molecular Imaging, Catholic Institutes of Medical Science, College of Medicine, Seoul St. Mary's Hospital, , Korea
[3] Department of biomedical laboratory science, Inje University, Kimhae, South Korea, Korea
[4] Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Background: B-cell activating factor (BAFF belonging to the TNF family) is an important B cell survival factor, being primarily expressed by monocytes, macrophages, dendritic cells, neutrophils and mast cells, and functioning to stimulate B cell proliferation, differentiation, and survival. In addition, maintenance of B-cell homeostasis depends on in vivo soluble BAFF concentration. High level of BAFF is known to promote autoreactive B cells in autoimmune diseases as systemic lupus erythematosus and Sjogren's syndrome. BAFF levels respond to alterations in B-cell homeostasis. After allogeneic hematopoietic stem cell transplantation (HSCT) conditioning results in recovery of naive B cells before B-cell homeostasis is reached. A direct correlation between serum concentration of BAFF and severity of chronic graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (Allo-HSCT) has been identified. Relative B lymphopenia and high BAFF after HSCT could support potentially pathologic activated alloreactive and autoreactive B-cell populations in chronic GVHD patients. The BAFF/BAFF-receptor (BAFF-R) pathway is important to T cell activation, proliferation and differentiation. Specifically, host responses to transplantation can significantly reduce therapeutic effects by targeting BAFF binding to BAFF-R expressed by T cells. In autoimmune diseases, the proinflammatory cytokines IFN-a and TNF-b can induce expression of BAFF which may inhibit apoptosis of B cells in inflammatory microenvironments and increase autoantibody production in vivo. Constitutive overexpression of BAFF promotes the generation Th17 cell in vitro and in vivo, and aggravates the manifestation of Th17 cell-driven autoimmune disease. Although acute GVHD after Allo-BMT has been classically assumed to be a Th1-mediated response based on findings from animal models, a previous study demonstrated that in vitro-differentiated Th17 cells mediate lethal acute GVHD. In the present study, we suggest that acute GVHD could be prevented by targeting Th1 and Th17 cells through the blocking of BAFF signaling which is using belimumab during the early posttransplant period.

Method: Bone marrow transplantation and acute GVHD inductio. Treatment of Belimumab : Mice were injected intraperitonealy (IP) with 200ug Belimumab (Benlysta, GSK) twice weekly after BMT (BMT+day 0, 4). Control mice received IP injections of 200ug hamster IgG1 antibodies at the same time points. Isolation of Splenocytes and CD4+ T Cells and ELISA assay.

Results: BAFF modulates Th1, Th17, and Treg differentiation of donor CD4+ T cells in vitro:

BAFF is related to the induction and maintenance of T and B cell homeostasis. BAFF promotes T cell activation with cytokine production via BAFF-receptor (BAFF-R) in vitro and in vivo. Our results showed that BAFF-R expression on CD4+ T cell was higher in the allogeneic responses than in the Th17 inflammatory environment, but there was no difference with the BAFF-R expression by the presence or absence of recombinant BAFF (rBAFF). I

Blockade of BAFF level attenuates acute graft-versus-host diseases after allo-BMT with both T and B cells:

To assess the blockade of BAFF in vivo, we established acute GVHD mouse model that were exposed to a 800 cGy dose of radiation, and injected intravenously with 5 × 106 bone marrow (BM) and 5 × 106 spleen cells from donor mice (C57BL/6, H-2Kb). At days 0 and 4 after GVHD induction, mice were administered with 200ug belimumab for blocking BAFF production. Mice were monitored at different time points after GVHD induction for survival, body weight and clinical GVHD scores. To determine changes in T- and B-cells recipient mice were transplanted with whole donor BM and spleen cells. In this model, all recipients of belimumab therapy survived longer, had reduced clinical GVHD score compared with acute GVHD control group but there was no difference between belimumab therapy group and control group (Figure 2A). Interestingly, we found that BAFF levels were significantly increased in the acute GVHD mouse model of the early period of BMT (Figure 2B). These results showed that BAFF level related to chronic GVHD also plays an important role in acute GVHD model.

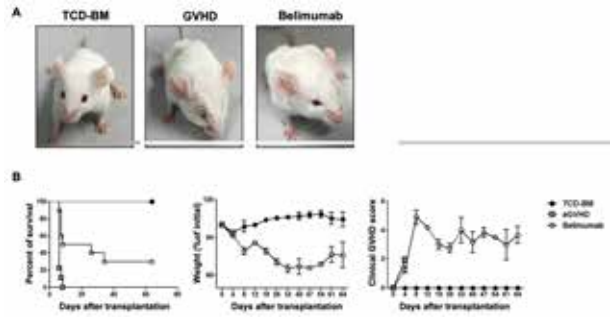
Blockade of BAFF inhibits acute GVHD through reciprocal regulation of Th1/Th2 and Th17/Treg cells:

BAFF promotes the expression of BAFF-R in T lymphocytes and contributes to T cell activation. To confirm the immunoregulatory functions of BAFF blockade related to Th1, Th2, Th17, and regulatory T (Treg) cells, we measured the cytokine expression and transcription factors of recipient mice. Recipients of belimumab therapy displayed decreased CD4+IFN-r+ and CD4+IL-17+ expression and increased CD4+CD25+Foxp3+ expression compared with recipients of GVHD control in the spleen cells by flow cytometry analysis. Similar to the in vitro results, there was no difference in CD4+IL-4+ expression between the two groups. These data showed that belimumab after disease onset could modulate immunoregulatory effects from effector T cells.

Conclusion: BAFF has a complex role in the regulation of immune responses depending on the diseases. The ability of BAFF to promote Treg cell expansion by their acceptance of islet allografts and delayed skin graft rejection. The ability of BAFF to promote Treg cell expansion was not T cell intrinsic, as Treg cells did not express high levels of BAFF-R, nor did excessive BAFF trigger NF-kB processing in Treg cells. Our group has reported that blockade of BAFF via belimumab therapy or blocking IL-21 signaling play a critical role in the

generation of CD4+CD25+Foxp3+ Treg cells in acute GVHD after Allo-BMT. These data imply that there may be other unknown mechanisms involved in the Treg cell expansion by BAFF. Together, BAFF plays a dichotomous effect on T cell immune responses. We confirmed that patients who received chemotherapy also significantly increased BAFF levels compared with healthy donor. In our study, we demonstrated that blockade of BAFF could modulate CD4+ T cell-induced acute GVHD early after Allo-BMT, and also suggested the possibility of simultaneously controlling chronic GVHD that may appear later after Allo-BMT.

Keyword: B cell activating factor (BAFF), Graft-versus-host disease, T cell homeostasis



PP15-01

Mesenchymal stem cells application improves face hyperpigmentation

Mahmood Saba

Human Genetics & Molecular Biology, University of Health Sciences, Pakistan

Background: Facial contour deformities associated with pigmentary changes are of major concern for plastic surgeons both being important and difficult in treating such issues. No definite ideal treatment option is available to address simultaneously both the contour defect as well as related pigmentation. The aim of the current study is to compare long term effects of conventional adipose tissue grafting and ex-vivo expanded MSCs enriched adipose tissue grafting for the treatment of contour deformities with pigmentary changes on face.

Method: In this study, eighty (80) patients of contour deformities of face with hyperpigmentation were recruited after informed consent. Two techniques i.e. conventional fat grafting (C-FG) and fat grafts enriched with expanded adipose stem cells (FG-ASCs) were used to address the pigmentation. Both techniques were explained to patients and enrolled patients were divided into two groups i.e. C-FG and FG-ASCs as per patients' choice and satisfaction. Patients of FG-ASCs group were treated with fat grafts enriched with expanded ASCs while patients of C-FGs group were treated with conventional fat grafting (without expanded ASCs).

Results: Patients were followed for 12 months and improvement in face pigmentation was assessed clinically as well as measured objectively. Patients' satisfaction was also documented as highly satisfied, satisfied and unsatisfied. This clinical trial was registered at www.clinicaltrials.gov with ID: NTC03564808. Mean age of patients was 24.42(±4.49), 66 patients were females. Forehead was involved in 61.20% cases, cheek in 21.20% cases, chin in 11.20% cases and nose in 6.20% cases. In GF-ASCs group, the integrated color density (ICD) was decreased (1.08×106 ±4.64×105) as compared to C-FG group (2.80×105±1.69×105). Patients treated with fat grafts enriched with expanded ASCs were significantly more satisfied as compared to patients treated with conventional fat grafting only.

Conclusion: MSCs enriched autologous fat grafting is reliable option for correcting contour defects and treating hyperpigmentation of face simultaneously because of its promising effects in improving the increased cutaneous pigmentation over the contour defects of face.

Keyword: Hyperpigmentation, Adipose stem cells, Color density, Enriched adipose tissue graft, Fat grafting, Contour deformities

Figure 4: A and C show pigmentation immediately after conventional fat grafting while B and D show pigmentation after 1 year follow up. Similarly E and G show

PP15-02

A combination of immunoadjuvant nanocomplex and dendritic cell vaccine in the presence of immune checkpoint blockade for effective

cancer immunotherapy

Manh Cuong VO[1], Sung-Hoon Jung[1], In-Kyu Park[2] and Je-Jung Lee[1*]

[1] Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Jeollanamdo, Korea

[2] Biomedical Science, Chonnam National University Medical School, Korea

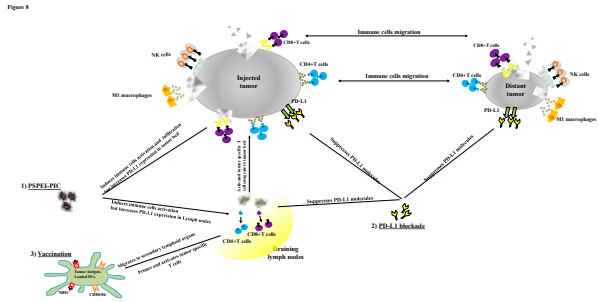
Background: Nanovaccines have emerged as a promising drug delivery platform and immunoadjuvants for cancer immunotherapy, particularly in combination with other anticancer therapies, which can modulate immune cells and tumor microenvironments.

Method: In this study, we investigated the therapeutic efficacy of a combination treatment consisting of an immunoadjuvant nanocomplex, a dendritic cell (DC) vaccine, and PD-L1 blockade in a murine colon cancer model. The immunoadjuvant nanocomplex was formulated by complexing poly I:C with positively charged polysorbitol-co-polyethylenimine (PSPEI-PIC).

Results: We found that peritumoral administration of PSPEI-PIC combined with DC vaccination and PD-L1 blockade (PSPEI-PIC + DCs + PD-L1 blockade) triggered long-lasting systemic anti-tumor immune response, which inhibited of both treated and non-treated distant tumors in the murine colon cancer model. Additionally, PSPEI-PIC + DCs + PD-L1 blockade significantly inhibited various immunosuppressive factors and enhanced the activation of immune effector cells in the serum, spleen, and tumor microenvironment.

Conclusion: These findings suggest that the combination of the immunoadjuvant nanocomplex and DC vaccination with PD-L1 blockade exerts potent anti-tumor effects by synergistically inhibiting immunosuppressive cells and activating effector cells with superior polarization of Th1/Th2 balance in favor of tumor immune response. Hence, this new combinatorial therapeutic approach paves the foundation for the future development of immunotherapeutic modalities that inhibit tumor growth and restore systemic immune. function.

Keyword: Nanovaccine, Dendritic cells, Immune checkpoint blockade, immunotherapy, PSPEI-PIC, Cancer vaccine



PP15-03

Antitumor activity of activated marrow-infiltrating lymphocytes in patients with multiple myeloma

Manh-Cuong Vo, Sung-Hoon Jung and Je-Jung Lee*

Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Jeollanamdo, Republic of Korea, Korea

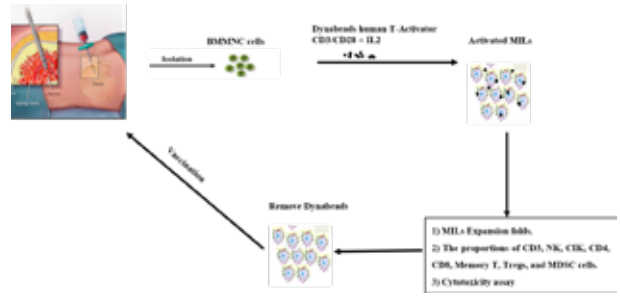
Background: Adoptive immunotherapy is a promising treatment approach for multiple myeloma (MM), but a major limitation of adoptive immunotherapy is the availability of tumor specific and nonspecific T cells. Here, we report an approach to generate ex vivo expanded marrow-infiltrating lymphocytes (MILs) from MM patients based on anti-CD3/CD28 beads.

Method: anti-CD3/CD28 beads were used to expand MILs in the presence of IL-2. Expansion rate, proportions of effector cells such as CD8, CD4 T cells, NK cells, memory T cells and functions of expanded MILs were determined over two weeks of culture.

Results: Co-culture of MIL with anti-CD3/CD28 beads resulted in remarkable expansion of MIL over 14 days culture period. In addition, expanded MILs showed increased proportions of CD8 T cells, effector memory T cells, and enhanced cytotoxicity towards target CD138+ primary MM cells from autologous patients, but not MM cell lines.

Conclusion: our findings suggest that MILs can easily be obtained from the BM and can be expanded to demonstrate enhanced antigen specificity toward CD138+ MM cells. Therefore, MILs are a distinctive set of T cells that have been shaped by the unique BM microenvironment and may play a future role as a novel immunotherapy for hematologic malignancies.

Keyword: Marrow infiltrating lymphocytes, Multiple myeloma, Memory T cells, Antitumor , MIL, BM microenvironment



PP15-04

Potent anti-myeloma efficacy of dendritic cell therapy in combination with pomalidomide and programmed death-ligand 1 blockade in a preclinical model of multiple myeloma

Van-Tan Nguyen, Tan-Huy Chu, Manh-Cuong Vo, Sung-Hoon Jung and Je-Jung Lee*

Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea

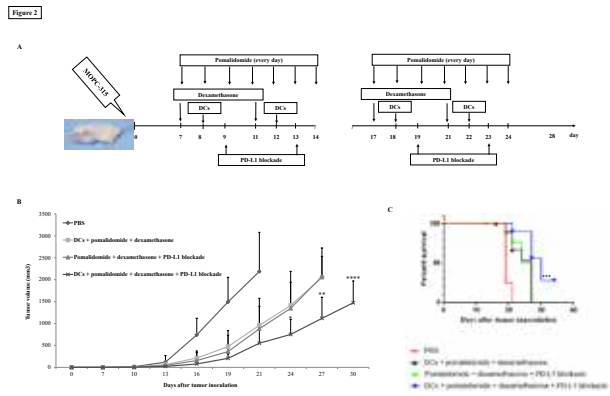
Background: Dendritic cells (DCs) are the most potent antigen presenting cells (APCs) that are recognized as a promising immunotherapeutic strategy against cancer; however, the efficacy of immunotherapy with DCs is hindered via immune checkpoints, such as programmed death-ligand 1 (PD-L1). PD-L1 expressed on APCs and cancer cells, can binds to programmed death-1 (PD-1) receptors on the activated T cells, which leads to the inhibition of cytotoxic T cells. Blocking of PD-L1 may lead to improve the efficacy of DC-based cancer immunotherapy.

Method: We created a plasmacytoma mouse model by injecting high toxicity MOPC-315 multiple myeloma (MM) cell lines into the right flank of immunogenic mice. Plasmacytoma is subtype of MM with a extremely poor prognosis. We investigated whether a DC based vaccine combined with pomalidomide and dexamethasone plus PD-L1 blockade has a synergistic effect in this murine MM model. The study was designed to closely mimic the clinical MM treatment protocol.

Results: Here we demonstrated that DC vaccination in combination with pomalidomide and dexamethasone plus PD-L1 blockade inhibited tumor growth of a MM mouse model, and significantly inhibited immune immunosuppressive factors and promoted proportions of immune effector cells in the spleen and tumor microenvironment. Additionally, functional activities of cytotoxic T lymphocytes and NK cells in spleen were enhanced by DCs + pomalidomide with dexamethasone + PD-L1 blockade.

Conclusion: Taken together, this study identifies a potential new therapeutic approach for the treatment of MM. These results also provide a foundation for the future development of immunotherapeutic modalities to inhibit tumor growth and restore immune function in MM.

Keyword: Anti-PD-L1, Cancer immunotherapy, Combination therapy, Dendritic cells, Myeloma, Pomalidomide



PP15-05

Novel IL-15 dendritic cells have a potent immunomodulatory effect in cancer immunotherapy

Hoyoon Shin, Tan-Huy Chu, Manh-Cuong Vo, Sung-Hoon Jung and Je-Jung Lee*

Hematology-Oncology, Chonnam National University Medical School and Chonnam National University Hwasun Hospital, Korea

Background: Dendritic cells (DCs) are the most potent antigen-presenting cells, and have thus been used in clinical cancer vaccines. However, the effects of DC vaccines are still limited, leading researchers to explore novel ways to make them effective. In this study, we investigated whether human monocyte-derived DCs generated via the addition of interleukin 15 (IL-15) had a higher capacity to induce antigen-specific T cells compared to conventional DCs

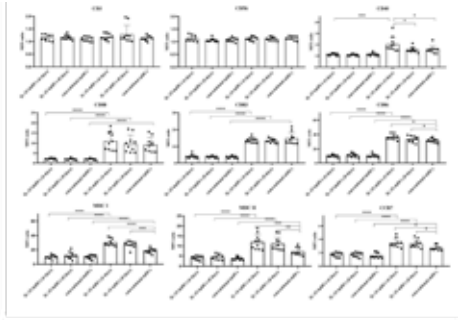
Method : We isolated CD14+ monocytes from peripheral blood from multiple myeloma (MM) patients, and induced immature DCs with granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-4 in the presence or absence of IL-15 for 4–6 days. Then we generated mature DCs (mDCs) with lipopolysaccharide for another 2 days [IL-15 mDCs (6 days), IL-15 mDCs (8 days), and conventional mDCs (8 days)].

Results: IL-15 mDCs (6 days) showed higher expression of MHC I and II, CD40, CD86, and CCR7, and the secretion of IFN-γ was significantly higher compared to conventional mDCs. IL-15 mDCs (6 days) showed superior polarization of naïve T cells toward Th1 cells and a higher proportion of activated T cells, cytokine-induced killer (CIK) cells, and natural killer (NK) cells for inducing strong cytotoxicity

against myeloma cells, and lower proportion of regulatory T cells compared to conventional mDCs.

Conclusion: These data imply that novel multipotent mDCs generated by the addition of IL-15, which can be cultivated in 6 days, resulted in outstanding activation of T cells, CIK cells, and NK cells, and may facilitate cellular immunotherapy for cancer patients.

Keyword: Dendritic cells, IL15, CIK, Immunotherapy, Cancer vaccine, Multiple myeloma



Characterization of dendritic cells (DCs). We analyzed the DC phenotype for expression levels of CD3, CD56, CD40, CD80, CD83, CD86, CCR7, MHC I, and MHC II using flow cytometry. The MFI ratios (MFI of samples/MFI of isotype controls) of each sample are shown as bar graphs. All of the mature DCs (mDCs) groups showed increased expression of maturation markers (CD80, CD83, CD86) compared to the immature DCs (imDCs) groups. The IL-15 mDCs (6 days) group showed significant increased expression of MHC I, MHC II, CD40, CD86, and CCR7 compared to the conventional mDCs group. Data are representative from ten independent experiments (n = 10). *P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001 (One-way ANOVA, multiple comparisons test: Tukey).

PP15-07

Filterless-filter: microfluidic approach for cell separation and concentration

Myeongwoo Kang[1], Taehwan Shin[1], Yujin Lee[1], Sunggyu Shin[1], Seungjung Song[1], Sungyoung Choi[2], Seong Soo A. An[3], Jaewoo Song[4], In Bum Suh[5] and Hoyoung Yun[1*]

[1] R&D, Curiosis Inc., Korea
[2] Department of Biomedical Engineering, Hanyang University, Korea
[3] Department of BionanoTechnology, Gachon University, Korea
[4] Department of Laboratory Medicine, Yonsei University College of Medicine, Korea
[5] Department of Laboratory Medicine, Kangwon National University College of Medicine, Korea

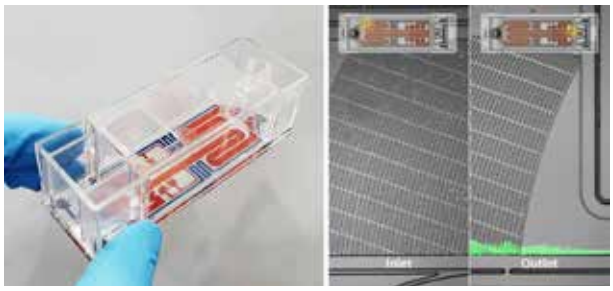
Background: Separating and collecting cells is an essential procedure for most cell culture-based experiments, including media exchange, cell washing and removal of debris during subculture, seeding and thawing. To date, cell collection has been achieved by pelleting cells using centrifuge. Centrifugation is a method of separating and settling down particles from a solution based on their shape, size, density, and rotor speed. Rotation of rotor generates a centrifugal force upon the cells in the liquid medium and biological centrifugation is a process of using this centrifugal force to separate and purify the cell mixture. Because the cell will sediment at the rate proportional to the centrifugal force applied, sometimes the strong centrifugal force provided by the centrifuge can be applied to each cell in the sample, especially at a high rotor speed. An increase of the applied centrifugal field at the high rotation speeds can induce centrifugation-mediated mechanical stress in cells and produce subsequent cytokine involved in inflammatory process. It has been also reported that the gravitational field by centrifugation causes changes in cellular traction forces and cytoskeletal rearrangement as part of the cellular mechano-response.

Method: Seven types of adherent or suspension cell lines were used to test the performance of the filterless filter technology. Jurkat, HL60, Raji and K562 cells were included in suspension cell test and NIH3T3, HeLa and MCF7 cells were used as adhesion cell line. Suspension cells were obtained from the culture vessel directly and adherent cells were gained from the culture vessel after trypsinization and addition of culture media. All type of cells were diluted at the concentration of 2x10^5 cells/ml or 2x10^6 cells/ml for evaluating the performance experiments. For measuring concentration of live and dead cells, the automated fluorescence cell counter was used. HL60 cells were centrifuged at 200g for 10 min and the supernatant was carefully aspirated using a suction pipette to compare with the yield of centrifug

Results: Cell pelleting by centrifugation makes it possible to concentrate the cells by removing the medium mixed with the cells. It was attempted to demonstrate that filterless filter efficiently concentrated the cells without spin-down of the cells. The microfluidic cell separation device separated and concentrated cells more than 20 times with 98% recovery rate. Moreover, filterless filter removed tiny debris about 88%.

Conclusion: We have recently developed microfluidic cell separation technology. A centrifugal force-free cell concentrating device that cuts down generated fluid shear stress into only a few seconds thus minimally affects the cells in terms of mechanical stress. Moreover, unlike centrifugation, a cell concentrate can be obtained without the need to carefully remove the supernatant after separation. The purpose of this study is to validate the performance of newly developed cell-enrichment chip in comparison to the conventional centrifugation method.

Keyword: Cell separation, Microfluidics, Cell therapy product manufacturing, Centrifuge-free



rhodamine phalloidin.

Results: After coculturing of cells, mitochondrial transfer from BM-MSCs to LHON mutant cells through TNT was observed using fluorescent dyes. The results obtained were captured by fluorescent microscope.

Conclusion: Mitochondrial transfer effectively protected the LHON mutant cell lines from mitochondrial damage effects and degeneration of cells. This stem cell based cellular therapy will helps the future therapeutics for ocular neurodegenerative diseases.

Keyword: Leber's hereditary Optic Neuropathy, Mitochondria, Tunneling nanotubes, Bone marrow mesenchymal stem cells

PP15-08

Analysis of bone marrow mesenchymal stem cells for its protective effect on Leber's hereditary optic neuropathy (LHON)

Mohana Devi Subramaniam* and Aswathy P Nair

SN ONGC Department of Genetics and Molecular Biology, Vision Research Foundation, India

Background: Leber's Hereditary Optic Neuropathy (LHON) is an inherited mitochondrial disease which cause degeneration of optic nerve and leads to vision loss. Primary cause of the disease is three mitochondrial primary mutations in the mitochondrial gene such as MT-ND1, MT-ND4 and MT-ND6. LHON is characterized by degeneration of retinal ganglion cells (RGC) through the mitochondrial damage especially associated with complex1 function and energy depletion. There is no effective treatment for this disease other than some supportive drugs. Mitochondrial transfer is an emerging and promising technique for rescue damaged cells from cell death by replacing damaged mitochondria with healthy mitochondria. Evidences suggests that stem cells can directly transfer healthy mitochondria to damaged cells through inter cellular connections and rescue mitochondrial damaged cells. In this study we are trying to explore the protective effect of mitochondrial transfer in LHON disease.

Method: Optimized the cell culture condition for LHON mutant (mt-ND1, mt-ND4 & mt-ND6) fibroblast cell lines and bone marrow mesenchymal stem cells (BM-MSCs). BM-MSCs and LHON mutant cell line were cocultured (1:1 ratio) together for the efficient mitochondrial transfer from BM-MSCs to LHON mutant cell lines. TNT (Tunneling Nanotubes) formation and mitochondrial transfer visualized through fluorescence microscopy using appropriate fluorescent tagged antibodies. Mitochondria of BM-MSCs are stained with mitotracker green FM and F-actin of TNTs are stained with

PP15-09

Material-based system for stem cell implant: aim to increase stem cell survival by drug

Saher Khan

Uttar Pradesh Rajarshi Tandon Open University, Uttar Pradesh Rajarshi Tandon Open University, Uttar Pradesh, India

Background: Stem cell based therapy has promising potential but rate of survival of cells is a big challenge. The main cause of cell death or low survival rate is due to ROS-mediated cell injury and ultimately death. In this study, we have developed a hydrogel-based porous scaffold to grow cells into the scaffold and protects the cells from hypoxic insult.

Method: Monostearin was used to develop hydrogel-based porous scaffold. Monostearin is a FDA approved material and it is biocompatible and safe for human use. We have confirmed the development of hydrogel-based porous scaffold using scanning electron microscope and infra-red spectroscopy. Release of drug was confirmed using spectrophotometric detection. Cellular morphology was assessed using microscope imaging. MTT assay was further employed for determination of stem cell viability.

Results: As shown by SEM images, our developed hydrogel-based porous scaffold contains porous structures along with fibers. Fourier transform-infra-red spectroscopic analysis clearly reveals that characteristics peaks of monostearin are present in hydrogel. The stability of hydrogel was assessed using rheometer and found that our develop hydrogel is stable and has injectability.

Conclusion: Our result showed that scaffold exerted cell protective

effects on MSCs by suppressing the hypoxia-induced cell death. However, more studies are needed to understand the effects of scaffold in protecting the cells.

Keyword: Stem Cells, Scaffold, Hypoxia, Hydrogel

PP16-01

Anaphylactic shock to a hematological disorder patient during transfusion of a platelet apheresis unit stored in platelet additive solution: a rare case report

Bala Bhasker

Transfusion medicine, Sparsh Hospital, India

Background: Adverse transfusion reactions from transfusion of apheresis platelets (AP) stored in platelet additive solution (PAS) are uncommon, as PAS is a balanced electrolyte solution developed to replace plasma from platelet concentrates as the storage medium. No anaphylactic reactions have ever been reported due to transfusion of AP stored in PAS.

Method: An AP product was donated by a blood group A male, processed using PAS. The patient developed severe hypotension with tachycardia immediately after 10 minutes of transfusion. Pre-transfusion and post transfusion recipient vitals showed a marked decrease in blood pressure from 110/70 mmHg to 70/50 mm Hg with pulse increased from 88 bpm to 118 bpm. Oxygen saturations were maintained normal without any changes in respiratory parameters. Serological testing included an antibody screen using gel technology, a direct antiglobulin test (DAT) using immunoglobulin G and C3d, and a Sterility testing of the transfused platelet product.

Results: A 61-year-old blood group O patient with aplastic anemia developed severe hypotension within the first 10 minutes of the start of AP in PAS transfusion despite premedication with inj. Avil and inj. Hydrocort. The post-transfusion reaction evaluation was non-significant showing negative antibody screen and also negative DAT, both for immunoglobulin G and C3d; No bacterial growth was seen in the transfused product and patient blood culture was sterile. Ruling out hemolytic and septic transfusion reactions. The patient was resuscitated with inj. Adrenaline and got shifted to ICU for further follow-up. The patient vitals got stabilized after 4 hours and got discharged in hemodynamically stable condition. Notably, a group O patient at a different hospital received a split of the same apheresis unit, with no reaction.

Conclusion: To our knowledge, this is the first case with anaphylactic shock reported from apheresis platelet transfusion stored in PAS. The fact that one transfusion recipient had anaphylactic shock whereas another did not have any reported reaction highlights the potential importance of recipient variables in adverse transfusion reactions.

Keyword: Platelet additive solution, Transfusion reactions, Apheresis platelets, Anaphylactic Shock

PP16-04

Detection of anti-B antibodies in a patient with A1B blood group: a case report and literature review

Hee-Jeong Youk[1], Jin Seok Kim[1], Hyungsuk Kim[2], Sang-Hyun Hwang[1], Heung-Bum Oh[1], Yousun Chung[3] and Dae-Hyun Ko[1*]

[1] Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

[2] Department of Laboratory Medicine, Seoul National University Hospital, Seoul, Korea

[3] Department of Laboratory Medicine, Kangdong Sacred Heart Hospital, Seoul, Korea

Background: ABO antibodies are naturally occurring antibodies and the most clinically important antibodies in transfusion. They usually exist as a form of alloantibodies, but there have been a few reports about auto-anti-A or B antibodies.

Method: A 58-year old male visited hospital for evaluation of inguinal mass. ABO blood group typing was performed during preparation of excisional biopsy.

Results: His red blood cells exhibited reactivity with anti-A and anti-B reagents, to reveal his blood group to be group AB which in general do not have anti-A nor anti-B antibodies. But when serum typing was performed, there was reactivity with B red cells. Results of direct antiglobulin tests and unexpected antibody screening tests were negative. The serum did not react with AB3 cells. The biopsy revealed that he had a diffuse large B-cell lymphoma. After completion of four cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) chemotherapy, his disease state was to be in a complete remission status and anti-B was disappeared upon retest for ABO typing.

Conclusion: In this report, we want to share our experiences about unexpected anti-B antibodies in a AB patient. To our knowledge,

this is the first report of anti-B occurred in a AB patient in Korea.

Keyword: Anti-B, ABO discrepancy, ABO blood group, Blood group typing

Table 1. Results of ABO typing and related tests

	Forward				Reverse	
	Anti-A	Anti-B	Anti-H	Anti-A1	A cell	B cell
IH-1000	3+	3+	NT	NT	-	-
Manual tube	4+	4+	1+	4+	-	3+

NT, not tested.

PP16-05

The effect of plasma transfusion platelet to red blood cell ratio on mortality and morbidity: update meta-analysis

Steven Irving[1*], Bastomy Eka Rezkita[1], Rabbinu Rangga Pribadi[2] and Marcellus Simadibrata[2]

[1] Department of General Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

[2] Division of Gastroenterology, Pancreatobiliary, and Digestive Endoscopy, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia

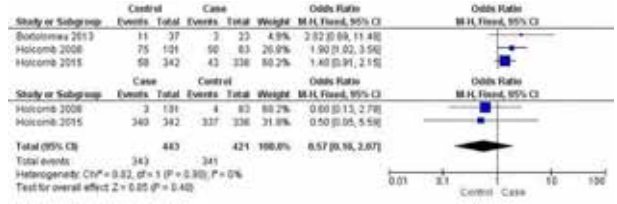
Background: Massive hemorrhage from traumatic injury remains one of the major cause of death, which potentially preventable with transfusion. To date, there are multiple conflicting recommendation for transfusion protocol in massive hemorrhage patient. The best ratio of platelet to red blood cell for transfusion is still unkown. Use of high platelet dose transfusion may improve Trauma-Induced Coagulopathy (TIC) and leading to 24-h mortality. On the other hand, high platelet dose might contribute to improve hemostasis by limiting hyperfibrinolysis. The aim of this study is to investigate the effect of plasma transfusion platelet to red blood cell ratio on mortality and morbidity.

Method: This study is a meta-analysis with Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) 2020 guideline. The research data for eligible publications were from PubMed and Embase databases. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using random- or fixed-effect model. Eligible studies enrolled adult patients in traumatic bleeding transfused with high platelet : RBC (2:1) as case group and compared to platelet : RBC (1:1) as a control group.

Results: Three studies (466 cases/458 controls) were included. Case group significantly improve 24 hour mortality (OR 95%CI= 1.61[1.14-2.26] p= 0.006). Subgroup analysis (443 cases/421 controls) showed that case group does not significantly improve transfer patients to ICU (OR 95%CI= 0.57[0.16-2.07] p= 0.40).

Conclusion: Among patients with severe trauma and major bleeding, high platelet : RBC (2:1) improves mortality as compared to platelet : RBC ratio (1:1), but not in morbidity.

Keyword: Platelet, Red blood cell, Transfusion



PP16-07

Clinical significance of hemagglutination grades determined using the IH-1000 automated blood typing system: real world data

Bosung Park[1], Jin Seok Kim[1], Hee-Jeong Youk[1], Yousun Chung[2], Hyungsuk Kim[3], Sang-Hyun Hwang[1], Heung-Bum Oh[1] and Dae-Hyun Ko[1*]

[1] Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea

[2] Laboratory Medicine, Kangdong Sacred Heart Hospital, Korea

[3] Laboratory Medicine, Seoul National University Hospital, Korea

Background: Automated analyzers enable more efficient blood group typing and their use is increasing but their ability to identify ABO subgroups in accordance with the reaction grade remains uncertain. We here compared the reaction grade results from an automated IH-1000 device and a manual method.

Method: A total of 211,280 samples that were tested for their ABO and RhD blood groupings were retrospectively investigated. IH-1000 data and final manual reading results were compared. The reaction grade of automated and manual test results were also compared in 24,629 cases in which a manual retest had been performed.

Results: In comparisons of the IH-1000 results with manual testing data from the forward typing of antigen A and antigen B, the vast majority of the ≥3+ reaction grades obtained with the automated system (99.92%) were determined as 4+ by the manual test. The proportion of 3+ grade cases categorized using the IH-1000 device was much higher for the B antigen than A antigen (59.22% vs. 24.03%). When the IH-1000 ≥3+ grade results for both the A and B antigens were analyzed, most were classified as AB group in the manual retest, with subgroup results appearing in 0.57% of the cases.

Conclusion: Gradings of 4+ using a manual tube method will be assigned a grade of 3+ in many cases, particularly for antigen B, using the IH-1000 automated analyzer. It will be a safe choice to determine the blood type and transfusion blood through manual retesting in conjunction with reverse typing when the antigen is 3+ reaction grade in IH-1000.

Keyword: Automated analyzer, Blood group typing, ABO typing, IH-1000 system, Manual method, Pretransfusion testing

PP16-09

Effects of Vitamin-C and L-Carnitine as additives in stored erythrocytes

Masannagari Pallavi

Biotechnology, JAIN (Deemed-to-be University), India

Background: Erythrocytes are exposed to oxidative stress during storage. Vitamin-C and L-Carnitine have proved beneficial in ameliorating the oxidative damage during blood/erythrocyte storage. The combination of these antioxidants, Vitamin-C and L-Carnitine as additives in storage solutions has not been explored. Therefore, this study investigates the effects of Vitamin-C and L-Carnitine on erythrocytes during storage.

Materials and Methods: Blood was collected from male Wistar rats and erythrocytes were isolated and stored in AS-7 (Additive Solution) at 4˚C for 35 days. Erythrocytes were grouped into Controls and Experimentals-Vitamin-C (10mM) & L-Carnitine (10mM). Hemoglobin, antioxidant enzymes (superoxide dismutase (SOD), catalase & Glutathione Peroxidase (GPX)), lipid peroxidation products (conjugate dienes & thiobarbituric acid reactive substances (TBARS), protein oxidation products (advanced oxidation protein products, protein carbonyls & Protein sulfhydryls), metabolic markers (glucose, lactate dehydrogenase (LDH)), superoxide and hemolysis were assessed. Statistical analyses were performed with Graphpad prism.

Results: SOD increased on day 7 in Controls and on day 7 & 14 in Experimental groups. Catalase increased on day 35 in both the groups. GPX increased on day 7 in Controls. Hemoglobin decreased on day 35 in both the groups. Hemolysis increased from day 7 in both the groups. Protein oxidation products were maintained throughout the storage. LDH decreased in Controls on days 21, 28 & 35, whereas were maintained in the on day 7 & 14 in Experimental groups. Superoxide and Conjugate dienes decreased from day 14. TBARS decreased on day 14, 21 & 35 in Controls and day 21 & 35 in Experimental groups.

Conclusion: Vitamin-C in combination with L-Carnitine has proved beneficial to erythrocytes in terms of hemoglobin, antioxidant enzymes and lipid peroxidation.

Keyword: Vitamin-C, L-Carnitine, Erythrocytes, Oxidative stress, Storage

PP16-12

Effect of patient characteristics on outcome of platelet transfusion in haemato-oncological patients

Rahul Katharia*, Vasundhara Singh, Rajendra Chaudhary and Priti Elhence

Department of Transfusion Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Background: Platelet transfusion support is the mainstay of management in haemato-oncological patients having thrombocytopenia. The outcome of prophylactic platelet transfusion depends on various patient related factors such as fever, sepsis, splenomegaly and drug intake. Refractoriness to platelet transfusion remains a common clinical problem. The aim of the study association of patient characteristics with transfusion outcomes in haemato-oncology patients receiving prophylactic platelet transfusions.

Method: A prospective analysis of 35 thrombocytopenic patients with haematological malignancy was done. Out of 35 patients, 24 had Acute Myeloid Leukaemia while 11 had Acute Lymphoblastic Leukaemia. Clinical details and pre-transfusion platelet counts were taken from patient's files. Patient's EDTA blood samples were withdrawn at 1-hour and 24-hours post-transfusion. The effectiveness of outcome of platelet transfusion was assessed by Corrected Count Increment (CCI) at 1 hour and 24 hours. Ethical clearance was duly taken from the Institutional Bioethical Committee

Results: A total of 273 prophylactic platelet transfusion episodes

were recorded for 35 patients. Mean 24-hour-CCI and PPR were 4299.31 and 9.36% for refractory patients; 7278 and 16.43% for non-refractory patients, respectively (p values 0.029 and 0.001 respectively). The mean 24-hour-CCI was significantly lower with intake of Amphotericin B (p value 0.023). The mean number of platelet transfusion episodes were 8.2 per refractory and 5.2 per non-refractory patients. Presence of splenomegaly and use of Amphotericin-B were statistically significant in episodes with adequate response vs inadequate response. The mean TI was 1 day for refractory patients and 2 days for non-refractory patients.

Conclusion: It was observed that some patients failed to attain the expected post-transfusion platelet increment. Apart from HLA and/or HPA alloimmunization non immunological causes are also an important factor to cause refractoriness to platelet transfusions in multiply transfused patients This may be caused by clinical factors such as splenomegaly and use of antifungal drugs like Amphotericin B.

Keyword: Thrombocytopenia, Platelet refractoriness, Correct Count Increment, Refractory and Non Refractory

Table: Factors influencing the response to platelet transfusion

Variable	Coefficient	p value	Odds ratio	95% C.I.	
Fever	0.521	0.416	1.683	0.479	5.91
Splenomegaly	2.315	**0.027**	10.128	1.294	79.295
Sepsis	-0.599	0.378	0.549	0.145	2.081
Antifungal	1.021	**0.045**	3.795	0.469	1.348
Chemotherapy	-0.451	0.528	0.637	0.157	2.585
Antibiotics	-0.208	0.318	0.812	0.54	1.221

PP17-01

Summary and analysis of 13 ras-associated autoimmune leukoproliferative disease clinical features

Lingling Fu, Jie Ma, Jiafeng Yao, Rui Zhang, Yunyun Wei, Bixi Yang, Ruixin Wang, Hongmin Li and Runhui Wu *

Hematologic Diseases Laboratory, Hematology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China

Background: Ras-associated autoimmune leukoproliferative disease (RALD) is a clinical syndrome, also known as autoimmune lymphoproliferative syndrome (ALPS) type IV, which belongs to primary immunodeficiency disease. However, there is still controversy about whether RALD is a chronic benign lymphoproliferative disease or a precancerous lesion.

Method: A retrospective analysis of the basic information, clinical characteristics, laboratory examination, treatment and prognosis of children with RALD admitted to Beijing Children's Hospital.

Results: We reported 13 patients with RALD in our single center, the ratio of male to female was 1.6:1, and the median age of onset was 6 months (ranging from 2 months to 29 months). Eight patients (61.5%) had KRAS somatic mutation, and five patients (38.5%) had NRAS somatic mutation. The most common features are splenomegaly (12/13 cases), autoimmune cytopenia (9/13 cases), mononucleosis (10/13 cases), repeated infection (7/13 cases), skin involvement (4/13 cases) and intestinal lesions (4/13 cases). Thirteen children were treated with immunotherapy, including glucocorticoids, intravenous immunoglobulin, cyclosporine, and sirolimus. The median follow-up time was 50 months (ranging from 3 months to 62 months). Four children died (2 cases of respiratory failure, 1 case of intestinal perforation and bleeding, and 1 case of sepsis with sudden respiratory and cardiac arrest). Nine children survived, seven children were treated with sirolimus, and no children developed into malignant tumors of hematopoietic system.

Conclusion: In conclusion, RALD needs long-term follow-up to monitor malignant tumor, and sirolimus is effective in treatment.

Keyword: Ras-related autoimmune leukoproliferative diseases, Autoimmunity, KRAS, NRAS

PP17-02

Effectiveness of sirolimus in partial DiGeorge syndrome with refractory immune cytopenia: spot of elevated TCRαβ + CD4- CD8-double-negative T cells

Hao Gu, Runhui Wu* and Zhenping Chen

Hematology center, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, China

Background: DiGeorge syndrome (DGS) is a common recurrent copy-number variant disorders caused by a microdeletion in chromosome 22q11.2 first reported by Angelo DiGeorge in 1965. Based on results of T cell receptor (TCR) excision circle and TCR-Vβ oligoclonal, DGS is divided into "partial type" and "complete type".1-2. Several retrospective studies and prospective studies have shown an increase in the incidence of autoimmune phenomena in patients with DGS, indicating that patients have potential immunomodulation deficiencies3. The increase of TCRαβ + CD4- CD8- double-negative

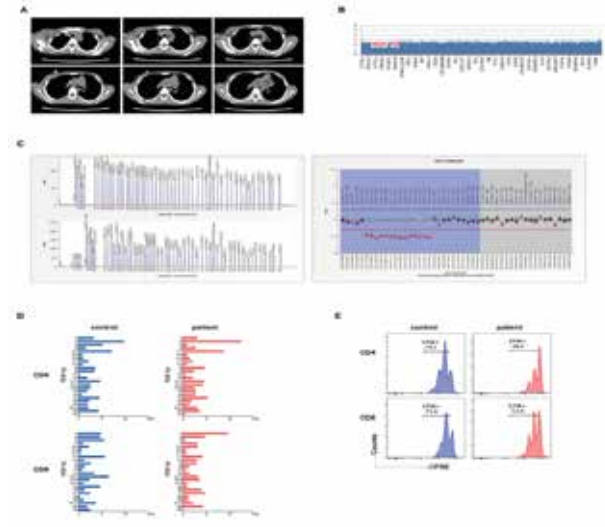
T cells (DNT) could be observed in some immunomodulation deficiencies include DGS4-5. The treatment of DGS is regular intravenous immunoglobulin (IVIG) infusion and active prevention of infection to improve the quality of life of children. Sirolimus is considered to be an effective and safe therapeutic option for multilineage immune cytopenia with elevated DNT.6 We speculate that sirolimus can also be used to treat DGS with increased DNT. Here we reported the efficacy and safety of sirolimus for treating a partial DGS patient with refractory immune cytopenia featured with elevated DNT subpopulation.

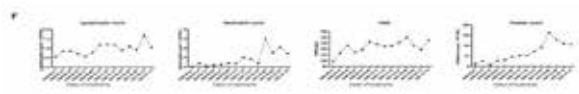
Method: A 10 year-old boy, born with caesarean section at full term to the parents without a consanguineous relation. Ventricular septal defect was identified at birth before being subjected to proper treatment at 7-month old. At 30-month old, thrombocytopenia was found (Plt 8×109 /L).The anti-glycoprotein (GP) IIb/IIIa was positive and bone marrow examination were normal. A diagnosis of immune thrombocytopenia (ITP) was made and he responded to glucocorticoid therapy. H relapsed at 33-month old eventually progressed with a notable splenomegaly (5 cm below the left costal margin) at 6years old. At 7 years of age, despite CRITP the patient developed multilineage immune-related cytopenia with low hemoglobin levels (99g/L) and neutropenia (0.15×109 /L) . It became obvious that he was developmentally delayed especially in speech. Retrospective CT examination in an infection revealed a decrease in the volume of the thymus (Figure 1A). He also showed growth retardation with 123 cm height (<P3) and 21.4kg weight at 8 years old (<P3). Serum IL-10 (8.28 pg/ml, reference range 1.2-4.55 pg/ml) was above the normal range while parathyroid hormone (8.9 pg/ml, reference range 10.2-50.5 pg/ml) was low. The proportions of lymphocyte subsets were abnormal (TABLE 1), especially decreased proportion of naïve T cells and elevated DNT (4.4% of CD3+ T cells). The patient initially received first-line treatment of immune thrombocytopenia (prednisone and IVIG). However, these treatments had no apparent effect on the symptoms. Considering his autoimmune and lymphoproliferative symptoms, imbalance of DNT/Treg proportion and elevated IL-10, we started sirolimus as mono-therapy (1.5mg/m2, actual blood concentration range: 4.0-5.2ng/ml) without any other immunosuppressive agent. After sirolimus treatment for 1 month, whole blood cells count was gradually restored (Figure1, F), with a decrease in the severity and frequency of infections, bleedings and size of the spleen. The anti-GP IIb/IIIa and Coomb's test turned negative after 3 months of sirolimus treatment, as did the cytopenia symptoms showed a complete response. Consistent with the clinical improvements, his Treg had increased (from 3.7% to 5.2%) and DNT had decreased (From 4.4% to 3.2%). Whole-exome sequencing revealed the presence of a heterozygous 2.520Mb copy number deletion on the 22q11.21(18893867-21414817) in the patient as indicated by the red circle while the parents' sequencing results is normal (Figure1B). To confirm the size of missing area, Multiplex ligation-dependent probe amplification (MLPA) analysis in 22q11DS was done with the standard MLPA kit (P250, MRC-Holland) MLPA also showed a 50% relatively decreased bar height, indicating a heterozygous deletion. (Figure1, C). Backtracking imaging data of thymic hypoplasia and decreased proportion of naïve CD4+ T cell, exclusion of the diagnosis of complete DiGeorge Syndrome has been made by the results of TCR-Vβ oligoclonal (Figure1, D). The patient has been followed up for 1years after sirolimus treatment and now lives without any obvious hematologic symptoms, indicating that sirolimus therapy is highly effective and may become an effective treatment option for partial DGS with immune related cytopenia. Sirolimus had previously been widely used in the treatment of ALPS patients and in support of our conclusion a partial rescue of DNT and Treg cell phenotypes was observed.7,8

Results: The clinical manifestations of DGS include hypoparathyroidism, conotruncal cardiac malformation, velopalatal insufficiency, facial dysmorphism and intellectual disability. We analyzed the patient's immune phenotype and cell proliferation (CFSE) (Figure1, E) for the current of refractory immune cytopenia. Suspicion of the autoimmune lymphoproliferative syndrome (ALPS) diagnosis is facilitated by elevated DNT proportion, decreased Treg ratio and higher levels of IL-10 with obvious splenomegaly. Since sirolimus is gaining increased recognition as an extremely effective agent in ALPS patients whose DNTs and serum levels of vitamin B12, IL-10, and sFASL would be normalized after response.9 Other potential benefit of sirolimus is promotion and expansion of Treg10 that often implicated in autoimmune disease pathogenesis. The response and sustainable recovery of the immune cytopenia and splenomegaly after application of sirolimus and the rebalance of abnormal immune phenotype, to some extent, meet the known of sirolimus in ALPS.

Conclusion : It is uncertain whether DNT involves the refractory immune cytopenia pathogenesis of DGS. Furthermore, as previously mentioned, various studies have suggested that sirolimus could be effective in a group of multilineage cytopenia characterized by DNT elevation. However, the role of sirolimus in its contribution to modulating DNT and Treg in different immune deregulation disease like this DGS case and their role in self-tolerance remain unclear.

Keyword: DiGeorge syndrome, ALPS, DNT, Treg, Sirolimus





PP17-03

Effectiveness of sirolimus in a novel CTLA-4 haploinsufficiency with ALPS phenotype

Hao Gu, Wenjun Mou, Zhenping Chen and Runhui Wu*

Hematology center, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, China

Background: CTLA-4 haploinsufficiency patients have heterozygous germline loss-of-function mutations in CTLA-4 and develop life-threatening autoimmune and lymphoproliferative complications [1-3]. It is difficult to recognize CTLA-4 haploinsufficiency accompanied by an elevated DNTs (TCRαβ+CD4-CD8-) from Autoimmune Lymphoproliferative Syndrome (ALPS) [1]. In case of cytopenia and lymphocytic infiltration in nonlymphoid organs like lung, brain, gut, spleen, liver, kidney and skin, a standard treatment has not been established in pediatric CTLA4 haploinsufficiency that may response to abatacept, rituximab, sirolimus, and corticosteroids by different extent [3, 4]. Sirolimus is considered to be an effective mammalian target of rapamycin (mTOR)-targeted monotherapy for children with ALPS and ALPS-like patients with elevated DNTs at baseline [4, 5]. Here we report an effective sirolimus therapy in CTLA4 haploinsufficiency patient with obvious autoimmune phenotype and the follow-up data.

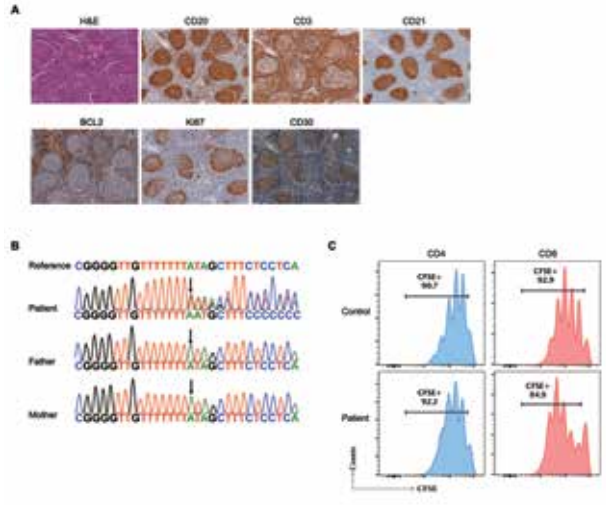
Method: The patient was born to nonconsanguineous Chinese parents, presenting with lymphadenopathy and splenomegaly at the age of 9 years. The patient was suspected as lymphoma at first. He underwent an excisional biopsy of a presumed submandibular lymph node, and the lymph node histopathology revealed reactive follicular hyperplasia (Fig. 1A).

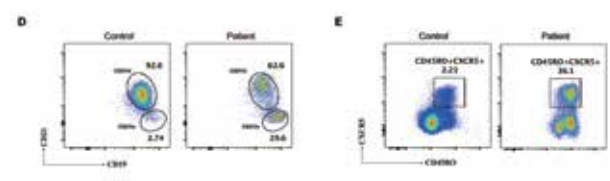
Results: At 11 years old, the patient developed multilineage autoimmune cytopenia (thrombocytopenia, 7×109/L; neutropenia, 0.27×109/L) with active hyperplasia of marrow. The patient initially received prednisone (2mg/kg, Qd for 2 weeks), intravenous immunoglobulin (800mg/kg, or 2 days), and recombinant human thrombopoietin (rh-TPO) for thrombocytopenia. However, these treatments didn't achieve a durable complete response on the platelet count (7-23×109/L) and absolute neutrophil count (0.27-0.3×109/L). The patient was found to have elevated DNTs (2.8% of CD3+ T cells, criteria for ALPS < 2.5%). The proportion of Tregs (CD3+CD4+CD25+Foxp3+) were decreased (2.53% of CD4+ T cells). Elevated serum levels of IL-10 (13.71 pg/ml, reference range 1.2-4.55 pg/ml) and vitamin B12 (1020 pg/ml, reference range 140-960 pg/ml), as secondary accessory criteria of ALPS, were observed. Next-generation sequencing for the patient revealed the presence of a novel de novo heterozygous CTLA4 NM_005214, c. 523dupT, p. Y177Lfs*2 mutation, with significantly truncated CTLA4 protein. Sanger sequencing confirmed that the patient was the only member of his family with this de novo mutation (Fig. 1B). Immunological investigations demonstrated that the proportion and absolute number of CD19+ B-cell was reduced, whereas the proportion of T-cell was elevated and the absolute number of T-cell was in the range of normal level (Supplementary Table 1). The percentage of naive CD4+ and naive CD8+ T cells was reduced while CD4+ central memory (CM) and CD8+ effector memory (EM) T-cell were increased (Supplementary Table 1). Functional studies revealed that the patient T cells possess normal proliferative phenotype stimulated with anti-CD3 and anti-CD28 (Fig. 1C). The absolute number of naive and memory B-cell was decreased (Supplementary Table 1). We found that the frequency of CD19hiCD21low B cells was greatly elevated in patient's peripheral blood (29.6% of B cells in the patient versus 2.74% in the control, Fig. 1D). We also found increased CD45RO+CXCR5+ Follicular helper T (TFH) cells, Fig. 1E. At 11 years old, the patient received the treatment based on traditional dose of prednisone and sirolimus (1.5mg/m2, aimed trough level range 5-15 ng/ml) to control lymphoproliferation. The blood trough level of sirolimus was monitored once a week at first month, and the dosage was then maintained with 1.5 mg/m2/d for one year (trough level of sirolimus range 6.78-10.13 ng/ml) (Fig. 2A, B). Seven days after application of sirolimus, platelet count returned to 106×109/L while neutrophil count returned to 4.38×109/L (Fig. 2C, D) with a continuous remission. Prednisone was weaned off after 3 months of sirolimus treatment (Fig. 2E). After prednisone treatment was stopped, the patient had been treated with sirolimus as monotherapy. Three months after application of sirolimus, massive lymphadenopathy and splenomegaly resolved. Ultrasound showed that the size of spleen and the number of enlarged bilateral axillary, mesenteric and inguinal lymph nodes had clearly decreased. Consistent with the clinical improvements, a reduction of DNTs (2.18% of CD3+T cells, Fig. 2F) and increase of Tregs proportion (3.45% of CD4+T cells, Fig. 2F) was observed. In the long-term following, sirolimus dosage were gradually adjust from 1 mg/m2 to 0.5 mg/m2. However, the re-emergence of elevated DNTs, lymphadenopathy and splenomegaly were observed during reduction of sirolimus while his blood platelet count and neutrophil count still remained normal. (Fig. 2B, C, D). We demonstrated that the immune function of cells was not compromised in the patient after 3.5 years' sirolimus treatment, because there were continued robust and appropriate responses to mitogen stimulation, and stable, if not improved, immune cell numbers (lymphocytes, CD3, CD4, CD8 and CD19 counts; supplementary Fig. 1). The patient has been followed up for 3.5 years after sirolimus treatment and now lives without any obvious symptoms, indicating that sirolimus therapy is a safe and effective, steroid-sparing monotherapy for children with CTLA-4 haploinsuffi-

ciency.

Conclusion: Given that CTLA-4 inhibits the CD28 pathway, which plays a role in T cell help for B cell responses, CTLA-4 loss might be expected to augment CD28-dependent TFH differentiation [2]. Accordingly, we observed increased percentages of TFH cells, which might be linked to impaired Tregs suppression in this patient. The autoantibody-mediated cytopenia in this patient appear to be explained, at least in part, by an accumulation of CD21low B cells, which have previously been described as exhausted, characterized by a state of functional unresponsiveness following persistent activation. Sirolimus, a widely used mTOR inhibitor, suppresses conventional T-cell responses but allows Tregs to preferentially expand and maintain their suppressive function because they resist its inhibitory effects. Similar to typical ALPS patients, abnormal DNTs/Tregs axis which can be rebalanced by sirolimus was obvious in this patient. It is worth noting that the application of sirolimus in this pediatric patient established a favorable improvement in clinical symptoms with few side effects. This improvement was associated with a decrease in DNTs, which also showed a dose-dependence with the sirolimus dosage drop as well. In the current patient, sirolimus leads to improvements in cytopenia and lymphoproliferation, suggesting that sirolimus should be considered as an operational, steroid-sparing treatment in managing of pediatric patients with CTLA-4 haploinsufficiency. However, treatment in CTLA-4 haploinsufficiency is challenging and its optimization is an ongoing process. Application of sirolimus in pediatric patients should be age- and dose-adjusted and always in consultation with experienced pediatricians for close monitoring. Further studies are still needed to determine whether or in what condition the discontinuation of sirolimus is possible, although we believe that the side-effect profile of sirolimus is more than safe and acceptable long term.

Keyword: CTLA-4 haploinsufficiency, ALPS, Sirolimus, DNTs, Tregs





PP17-04

Analysis of the relationship between the expression levels of neutrophil gelatinase-associated lipocalin and cytokine genes in bone marrow

Sungchul Mun[1], Min-Chul Park[2] and Chi-Hyun Cho[3*]

[1] Industrial Engineering, Jeonju University, Korea
[2] Center for Opto-Electronic materials and devices, Korea Institute of Science and Technology, Korea
[3] Laboratory Medicine, Korea University Ansan Hospital, Korea

Background: Recently, various associations of NGAL with several hematological cancers have been reported. However, given that the regulation of NGAL gene expression by cytokines is tissue-specific, NGAL expression in relation to those of cytokine genes has not been analyzed in bone marrow (BM) tissue. The purpose of this study was to analyze the association between NGAL and 48 cytokine gene expression levels in mononuclear cells (MNCs) of BM at the time of diagnosis of hematological malignancy and to explore the expression pattern of NGAL and related cytokine genes in patients with hematological malignancies and controls.

Method: BM MNCs were isolated from 48 patients, who were classified as patients presenting myeloproliferative neoplasm, acute myeloid leukemia, myelodysplastic syndrome, and as controls. NGAL and cytokine genes were analyzed using NanoString. Data on hematological parameters were collected from medical records. Single and multiple regression analyses were performed to analyze relationships.

Results: Normalized counts of 26 cytokine genes were related to NGAL normalized counts, while STAT3 and TLR4 normalized counts had the highest explanatory power. The following multiple regression model was developed: NGAL normalized counts=4316.825 + 9.056 × STAT3 normalized counts + 844.226 × IL5 normalized counts + 17.540 × TLR1 normalized counts - 28.206 × TLR2 normalized counts - 42.524 × IRAK4 normalized counts. In the multiple regression analysis, STAT3 and TLR4 normalized counts showed mul-

ticollinearity. NGAL, STAT3, IL5, and TLR4 normalized counts showed similar intergroup patterns.

Conclusion: NGAL normalized counts was predicted by a multiple regression model, while they showed similar intergroup patterns to STAT3, IL5, and TLR4 normalized counts.

Keyword: Neutrophil gelatinase associated lipocalin, Cytokine, Myeloproliferative neoplasm, Acute myeloid leukemia, Myelodysplastic syndrome, Bone marrow

PP17-06

Prolonged duration of the SARS-CoV-2 viral shedding in patients with oncohematological diseases

Igor Stoma[1*] and Maria Shapetska[2]

[1] Infectious Diseases, Gomel state medical university, Belarus

[2] Hematology №3, Minsk scientific and practical center of surgery, transplantology and hematology, Belarus

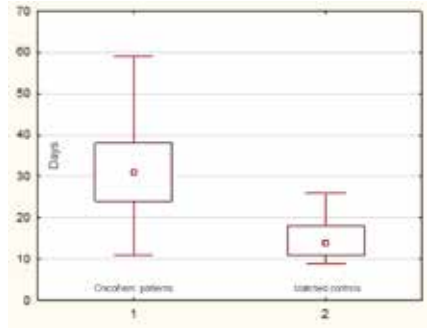
Background: Patients with oncological and oncohematological diseases, after hematopoietic stem cell transplantation, may suffer a severe form of COVID-19 infection, which is often fatal. The gold standard in the diagnosis of COVID-19 infection is the detection of SARS-CoV-2 virus RNA by real-time PCR from the naso/oropharyngeal swabs. Also, the shedding of virus may used as a possible marker of infectivity.

Method: Aim: to determine the duration of the SARS-CoV-2 shedding in patients with oncohematological diseases by PCR and compare it with a matched cohort of COVID-19 patients without oncohematological diseases. The study involved 36 patients with various oncohematological diseases (multiple myeloma, chronic lymphocytic leukemia, acute leukemia, etc.) and confirmed COVID-19 infection at the age of 21 to 88 years. Verification of the infectious process was carried out by the method of polymerase chain reaction (PCR) in real time with the detection of the RNA of the virus from the oropharynx and nasopharynx within the first two days after the onset of symptoms of COVID-19 infection. Further, the duration of the SARS-CoV-2 shedding was carried out on day 7, 14, 21 (+/- 1-2 days) and, if necessary, further every 7-10 days until a negative result of PCR was obtained. The control group consisted of 24 patients with confirmed COVID-19 infection by PCR without oncohematological pathology, matched by age and sex. The median and interquartile range (IQR) were determined using the Statistica 8.0 program.

Results: The duration of the SARS-CoV-2 shedding in patients with hematological malignancies with COVID-19 infection ranged from 11 days (minimum value) to 59 days (maximum value), median 31 days, IQR 24-38 days. In the control group, the duration of SARS-CoV-2 shedding ranged from 9 days (minimum value) to 26 days (maximum value), median 14 days, IQR 11-18 days (Fig 1, Duration of SARS-CoV-2 viral shedding in oncohematological patients and in a matched cohort of patients with COVID-19).

Conclusion: In most patients with oncohematological diseases, there is a long-term duration of the SARS-CoV-2 shedding (more than 21 days) confirmed by real-time PCR (naso/oropharyngeal swabs) during COVID-19 infection, regardless of clinical symptoms.

Keyword: Oncohematology, COVID-19, PCR, Viral shedding



PP17-07

Incidence of pregnancy-associated venous thromboembolism: second nationwide study

Hun-Gyu Hwang[1], Ju Hyun Lee[2] and Soo-Mee Bang[2*]

[1] Department of Internal Medicine, Soonchunhyang University, School of Medicine, Gumi Hospital, Korea

[2] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Korea

Background: Pregnancy is a well-known transient risk factor for venous thromboembolism (VTE). This was the second nationwide study to examine the relationship between the increased proportion of patients of advanced maternal age and the incidence rate of pregnancy-associated VTE (PA-VTE) during the study period (2014–2018) compared with those in a previous study (2006-2010).

Method: Using the Korean Health Insurance Review and Assessment Service database, we retrospectively identified all PA-VTE

events using both diagnostic and medication codes.

Results: Out of 124,228 VTE events, 510 (0.4%) cases of PA-VTE were identified in 499 women (median 34, range 20–49). The incidence rate of PA-VTE per 10,000 (PA-VTE/104d) in this second study (2.62) was 3.2 times higher than the rate in the first study (0.82). In the second study, the PA-VTE/104d of women in their 40s (5.46) was three times higher than that of women in their 20s (1.80) (relative risk [RR], 3.03; 95% CI, 2.04–4.51; p<0.01). The incidence rate in their 40s in second study was 2.3 times higher than that in their 40s in first study. Cases of PA-VTE/104d occurred more frequently in cases of multiparity than in those with nulliparity, in cesarean section compared with vaginal delivery, and in multiple compared with single pregnancies.

Conclusion: Most cases of PA-VTE present with postpartum pulmonary embolism. Obstetricians need to be cautious about the risk of VTE, particularly during postpartum in women in their 40s.

Keyword: Anticoagulation, Pregnancy, Delivery, Low-molecular-weight heparin, Venous thromboembolism

Table 1. Incidence rate ratio of VTE, DVT, and PE according to age and year between 2014 and 2018

	VTE		DVT		PE	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Age group(year)						
≤19	-		-		-	-
20 ~ 29	ref		ref		ref	
30 ~ 39	1.56 (1.24-1.96)	0.01	1.23 (0.91-1.66)	0.19	2.07 (1.45-2.95)	0.01
40 ~ 49	3.03 (2.04-4.51)	<0.01	1.66 (0.87-3.17)	0.18	5.16 (3.04-8.77)	<0.01
year						
2014	ref		ref		ref	
2015	0.95 (0.74-1.23)	0.77	0.98 (0.68-1.41)	0.98	0.93 (0.65-1.33)	0.76
2016	0.90 (0.69-1.17)	0.47	0.83 (0.56-1.23)	0.40	0.96 (0.67-1.39)	0.91
2017	0.91 (0.7-1.2)	0.57	1.02 (0.7-1.49)	0.99	0.82 (0.55-1.21)	0.36
2018	0.94 (0.71-1.24)	0.69	1.00 (0.68-1.49)	0.93	0.87 (0.59-1.3)	0.57

Abbreviation: VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism with or without DVT; Ref, reference; RR, relative risk; CI, confidence interval.

PP17-08

Pregnancy and the barriers in preventing anemia during COVID-19: result from a qualitative study of nurse-midwives perception in rural area

Mahyuddin Mahyuddin

Sociology, State Islamic Institute of Parepare, Indonesia

Background: Anemia in pregnancy is one of problem health in Indonesia. It remains a major problem over the past decade where based on Riskesdas (Basic Health Research) at 2018, pregnant women cases were 48.9 %. However, during the pandemic early detection of anemia was unsuccessfully implemented by nurse-midwives. Drawing on qualitative research, this study explores nurse-midwives in managing pregnant women with anemia in Primary Public Care

Method: Method Data were collected in three sites utilizing several qualitative methods; observation in health care facilities, case studies of pregnant women and in-depth interviews by digital communication with nurse-midwives and community health workers in three district in Polewali Mandar, West Sulawesi, Indonesia.

Results: This study found three main barriers during the COVID-19 pandemic, namely (1) process of care, (2) the governance and strategy, (3) cultural beliefs and low participation of family. The nurse-midwives realized that they difficult to check regularly and manage pregnant women with anemia during the pandemic. The husband and family involvement in antenatal care was constrained by the strength of cultural beliefs and lack of health information. Moreover, government prohibition to visit the Primary Health Care made it difficult to apply antenatal care the pregnant womens' need.

Conclusion: The availability of facilities and strategies from governance in Primary Health Care as well as pregnant women's family members contribute to the success of managing anaemia in pregnancy in the pandemic era. Nurse-midwives and pregnant women need to be empowered to achieve the optimum result of anemia management. We recommend a more comprehensive approach managing pregnant women with anemia from local governance in rural area, which synergizes between nurse-midwives and pregnant women

Keyword: Anemia, Pregnant women, Prymary Health Care, Rural Community

PP17-09

Machine learning in gene expression microarrays for leukemia cancer classification

Rifaldy Fajar*, Nana Indri Kurniastuti, Dewi Mustika Sari and Maria Rosalia

Computational Bioloy and Medicine Laboratory, Yogyakarta State University, Indonesia

Background: Cancer is a disease caused by the excessive and uncontrolled division of cells in the body. DNA microarray technology has made it possible to observe thousands of gene expressions at the same time. The level of gene expression can be used to determine the type of cancer cells of a patient. This study aims to evaluate the ability of machine learning to classify leukemia cancer using gene expression microarray data.

Method: In this study, the dataset used was 46 leukemia samples, consisting of 32 samples of Acute Lymphoblastic Leukemia (ALL) and 14 samples of Acute Myeloid Leukemia (AML). Each sample had 7129 gene expression profiles. These data are trained using several algorithms including artificial neural network (ANN), support vector machine (SVM), naive Bayes, logistic regression, k-nearest neighbor (KNN), and classification tree. To measure the performance of these methods, an evaluation is carried out using ten-fold validation and the leave-one-out method.

Results: The experimental results show that the artificial neural network has an accuracy of 98% higher than other algorithms. Based on the evaluation used, namely ten-fold and leave-one-out, it can be seen that the reliability of the artificial neural network algorithm is better than other algorithms in classifying gene expression data.

Conclusion: The conclusion from the results of this study is that the Artificial Neural Network has a better performance than the KNN, SVM, Logistics Regression, Classification Tree, and Naive Bayes algorithms. In addition, the ANN algorithm obtains very good classification level results approaching the perfect percentage result.

Keyword: Gene Expression, Leukimia, Cancer, Classification, Machine Learning

PP17-10

Clinical characteristics and real world burden of Kimura's disease in Korea

Hyun Jung Lee[1], Myung Hee Chang[2*], Do Yeon Kim[1], Dal Yong Kim[1] and Yueun Lee[1]

[1] Internal Medicine, Dongguk University Ilsan Hospital, Korea

[2] Internal Medicine, National Health Insurance Sevice Ilsan Hospital, Korea

Background: Kimura disease (KD) is rare chronic inflammatory disease that is characterized by peripheral eosinophilia and soft tissue mass in head and neck area. Although the clinical course of KD is reported as indolent, however the quality of life of patients with KD is very poor because of its typical mass lesions in head and neck area those result in cosmetic problem. Due to the lack of awareness by physicians on KD, treatment for KD was not systematic. Here, we report the real world data of small KD cohort to reveal the clinical characteristics and disease course of KD.

Method: We have made the cohorts of KD since 2018 and reviewed medical records of cohort till 2020 at Dongguk University Ilsan Hospital.

Results: Of all 36 in KD cohort, 34 (94%) were male, and mean age of diagnosis was 27.7 ± 12.52 years. Allergic disease (28%), thrombosis (8%) and renal disease (6%) were the frequently reported comorbidities in this cohort. Peripheral eosinophilia was reported all the patients and the mead number of absolute eosinophil count (AEC) was 3103 ± 3255/microL. High eosinophil count shown the trend toward the presence of itching sense (3028 ± 3051 in symptomatic patients vs. 1582 ± 1080 in asymptomatic patients), but there was no statistical significance (p=0.1592) For the cosmetic purpose, 72% (n=26) of patients underwent surgical resection and 36% (n=13) of patient got repeated surgical resection due to relapse after surgical resection. Radiotherapy (RT) was given to 39% (n=14) of patients and 5 patient achieved stable disease after RT. Systemic steroid was used in 72% (n=23) of the patients and only 10% (n=2) of the patient who were treated with systemic steroid reported durable response. For the patients were experienced disease progression and intolerance with systemic steroid treatment, other immune suppressive agents (ISAs) were used as a subsequent therapy. Among the patients (n=21) who were treated with cyclosporin A (CsA), 67% (n=12) of the patients were experienced long-term durable response. The quality of life (QoL) the patients with KD was highly associated with mass size that causing cosmetic problem and severity of itching sense. CsA was effective for QoL improvement. Higher age at diagnosis and lower C reactive protein (CRP) level before the CsA treatment were significantly associated with CsA responsiveness. TNF-alpha concentration was higher in KD patients with itching sense than in KD patients without itching sense (3.1 ± 1.1 vs. 2.1 ± 0.5 pg/mL, p=0.0212). Pre-treatment IL-4 concentration was showed possibility as a predictive biomarker of CsA treatment in this cohort study.

Conclusion: Although KD is an indolent disease that is not affect the normal life span of patients, the QoL is severely compromised due to its clinical features. Variable treatment methods were used for controlling KD, however no standard treatment method was established. CsA could be the effective therapeutic option for controlling KD and improving the QoL of KD patients. Further prospective study with well-designed cohort could be needed to investigate pathophysiology of KD.

Keyword: Kimura disese, Eosinophilia, Soft tissue mass, Thrombosis, Renal involvement, Cytokines

	Wax & Wane	Improvement	p
Male	3	8	0.14
Female	1	0	
Age at Dx	**22 ± 5.89**	**32.4 ± 13.41**	**0.0887**
Eosinophil (/microL)	1060 ± 861.86	1445 ± 1451.84	0.3199
IgE (KU/L)	2857 ± 2474.56	2491.9 ± 1065.70	0.3806
ESR (mm/hr)	9 ± 8.49	6.75 ± 5.50	0.3727
CRP (mg/dL)	**0.105 ± 0.035**	**0.04375 ± 0.02263**	**0.0068**
IL-4 (pg/mL)	**0.0256 ± 0.0093**	**0.0468 ± 0.0165**	**0.0203**
IL-10	0.2419 ± 0.0689	0.3074 ± 0.2781	0.3297
IL-17	0.7813 ± 0.3624	1.2230 ± 0.6399	0.1345
IFN-r	6.9436 ± 5.4715	5.2109 ± 2.8395	0.2382
TNF-a	2.0647 ± 0.2576	2.2044 ± 0.6380	0.3441

PP17-11

Epstein-barr virus-related lymphoproliferative disease mimicking acute leukemia after mRNA COVID-19 vaccination

Jae Hyun Cha[1], Myung-Hyun Nam[1*], Ka-Won Kang[2], Yunjung Cho[1] and Byung Soo Kim[2]

[1] Department of Laboratory Medicine, Anam Hospital, Korea University School of Medicine, Seoul, Korea

[2] Division of Hematology-Oncology, Department of Internal Medicine, Anam Hospital, Korea University School of Medicine, Seoul, Korea

Background: An mRNA vaccines elicit an immune response as follows: (1) mRNA vaccine is taken up by antigen-presenting cells (APCs); (2) APCs prime CD4 and CD8 T lymphocytes in lymph nodes; and (3) these T lymphocytes initiate a germinal center reaction and result in the formation of matured B cells. A variety of symptom and sign can occur associated with these sequences, often in severe forms. Here, we present a case of Epstein-Barr virus-related lymphoproliferative disease (EBV-LPD) mimicking acute leukemia after a 2019 coronavirus infection-19 (COVID-19) mRNA vaccination.

Method: The case was reviewed for medical history, laboratory and radiologic findings using an electronic medical record system.

Results: A 25-years-old female patient was admitted because of a high fever lasting one week and lymphadenopathy, three weeks after the first vaccination of the Pfizer-BioNTech BNT162b2 mRNA for COVID-19. In a test of complete blood count (CBC), hemoglobin, white blood cells count, platelet were 12.2 g/dL, 23.1 x 103/μL, and 157 x 103/μL, respectively. Furthermore, 8% of blastoid immature cells, 33% of abnormal lymphocytes, and frequent smudge cells were shown in peripheral blood smear. A computed tomography scan revealed lymphadenopathies in the cervical, axillary, and intra-abdominal areas. Lymphoid leukemia was suspected, then a bone marrow (BM) study and excisional biopsy for lymphadenopathy were performed. In BM aspiration section, majority of gated lymphoid cells showed CD2+, sCD3+, CD5+, CD7+, CD8+, and cCD3+, indicating proliferation of CD8+ T cells with no abnormal immunophenotype. TRB/TRG next generation sequencing (NGS) clonality tests revealed 3 TRB clones (estimated 20.10% of Total T-cells) and 2 TRG clones (estimated 22.89% of Total T-cells). In BM biopsy section, Epstein Barr Virus-encoded RNA (EBER) histochemical stain was positive. Biopsy of axillary lymph node revealed reactive T-cell hyperplasia. Serologic testing for Epstein Barr Virus (EBV) showed a compatible pattern with the acute phase of EBV infection. Taken together with these findings, the patient was finally diagnosed with EPV-LPD. After one month, the above abnormal findings on follow-up CBCs and CT scans all resolved spontaneously without any treatment.

Conclusion: In the case reported here, the patient showed a severe form of EBV-related disease mimicking acute leukemia after mRNA vaccination for COVID-19. These aspects may be occurred due to the mechanism of the mRNA vaccine, and sufficient tests such as pathology confirmation and/or genetic test may be needed to differentiate between benign hematologic disease from malignancy.

Keyword: COVID-19, mRNA vaccine, Epstein-Barr Virus, Reactivation, leukemoid reaction

PP17-16

Consideration of differences in SARS-CoV-2 vaccination strategies in patients with hematologic malignancies

Young Sok Ji[1], Sung Hee Lim[1], Jina Yun[1], Se Hyung Kim[1], Chan Kyu Kim[1], Jong Ho Won[2] and Seong Kyu Park[1*]

[1] Hematology/Oncology, Soonchunhyang University Bucheon Hospital, Korea

[2] Hematology/Oncology, Soonchunhyang University Seoul Hospital, Korea

Background: There is currently a critical need to determine the efficacy of SARS-CoV-2 vaccination for immunocompromised patients. A better understanding of the factors governing response to vaccination in cancer patients is critical to inform clinical decisions about the need for booster doses, the timing of vaccine administration, the need to interrupt treatment courses for vaccination, and general guidance about the level of protection achieved by vaccination in cancer patients. Neutralization assays are the gold standard for determining if a patient has effective antibodies and protective

immunity against SARS-CoV-2. Several studies reported that the neutralization level is highly predictive of immune protection.

Method: In this study, we determined the neutralizing antibody response in 102 cancer patients (53 with solid tumor, 49 with hematologic malignancies after they received two doses of SARS-CoV-2 vaccines. We used the surrogate virus neutralization test for both SARS-CoV-2 vaccines. Circulating neutralizing antibodies were detected using the GenScript SARS-CoV-2 sVNT kit (Genscript Biotech Corporation). The sVNT kit results were interpreted by the inhibition rate, which was calculated as follows: Inhibition = (1 - OD value of sample/OD value of negative control) X 100%. It was classified into positive and negative samples with a 30% cutoff. And we classified and analyzed the high titer when the antibody titer was 68% or higher, which is expected to be effective in preventing infection through previous studies.

Results: The antibody titers were significantly lower in patients with hematological malignancies compared to solid cancer patients (50.8 ± 37.3 vs 64.4 ± 33.7, p=0.038). And antibody-positive rates (>30%) were similar (65.3% vs 75.5%, p=0.260) between two groups, and fewer in patients with hematological malignancies had high antibody titer (38.8% vs 56.6%, p=0.072). In particular, patients with lymphoma and multiple myeloma tended to have lower antibody titers, but there was no statistical significance. In the analysis according to age, the antibody titers and the proportion with high antibody titer were significantly lower in patients aged 60 years or older (48.5 ± 33.5 vs 70.2 ± 35.7, p=0.002),(38.8% vs 73.6%, p<0.001), respectively. And there was a tendency for the antibody positive rate to be low (52.8% vs 66.7%, p=0.197). Other clinical factors such as gender, peripheral blood lymphocytes, comorbidity of underlying diseases, body mass index (BMI), etc. had no effect on antibody formation. During 6 months of follow-up, three of the hematologic malignancy patients developed a SARS-CoV-2 infection, but no infection occurred in patients with solid cancer. Although patients with hematologic malignancies have a high risk of death from SARS-CoV-2 disease, all patients recovered and returned to their daily lives.

Conclusion: Our results demonstrate an urgent need for novel immunization strategies for patients with hematologic malignancies against SARS-CoV-2, probably for those with lymphoid malignancies.

Keyword: Vaccination, SARS-CoV-2 , Hematologic malignancies, Neutralization assays, Protection,

PP17-17

Xanthohumol suppresses interleukin-1β secretion and prevents inflammation through inhibition of NLRP3 inflammasome

Cheng Zhang

Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, China

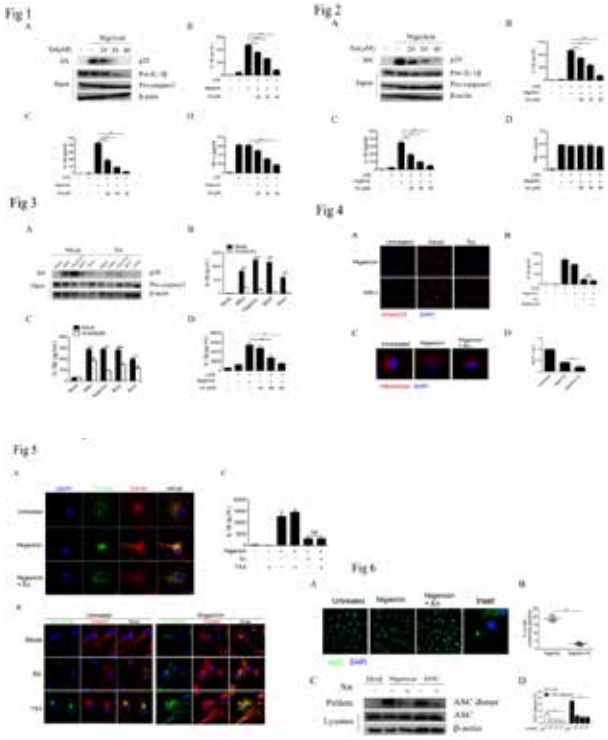
Background: Xanthohumol (Xn), the principal flavonoid present in hop cones, has demonstrated anticancer activity and anti-inflammatory activity. Xn also inhibits the oxidation of lipid peroxidation and can neutralize radical activity in humans. Therefore, by using mouse bone marrow-derived macrophages (BMDMs), we hope to investigate the mechanisms by which Xn inhibits the activation of NLRP3 inflammasome.

Method: 1.Cell culture and stimulation: LPS-primed BMDMs were stimulated with nigericin , MSU, Alum, and R837 to activate NLRP3 inflammsome.
2.ELISA assays were used to detect IL-1β, IL-18, TNF-α in cultural supernatant.
3.Western blot(WB) was used to analyze pro-IL-1β, pro-caspase-1, ASC dimer, β-actin expression in macrophage lysates.
4.Assay the activity of enzyme in culture supernatant using lactate dehydrogenase (LDH) release method in an attempt to analyze the effect of Xn on cytotoxicity and pyroptosis induced by NLRP3-caspase-1 pathway activation.
5.Confocal laser scanning microscopy was used to analyze cell fluorescent protein expression.
6.To analyze relative concentrations of NAD+ levels in different groups of cells, intracellular NAD+ levels were detected by using NAD/NADH quantification kit.

Results: 1.In mouse BMDMs experiments, Xn was given before LPS primed BMDMs, and WB results showed that Xn inhibited pro-IL-1β expression, caspase-1 activation and IL-1β secretion at 30-50 μM in a dose-dependent manner; ELISA results showed the reduced secretion of IL-1β, IL-18, TNF-α ($P < 0.01$).
2.After LPS primed BMDMs, Xn was administered and NLRP3 inflammasome was activated with nigericin. WB results showed that XN inhibited caspase-1 activation and IL-1β secretion at 30-50 μM in a dose-dependent manner. The results were further confirmed by ELISA experiment ($P<0.001$) with no effect on TNF-α secretion ($p>0.05$).
3.Different types of stimulis were used to activate NLRP3 inflammasome. WB found that Xn down-regulated the activation of caspase-1.
4.WB results showed that Xn can also inhibit the activation of caspase-1 and secretion of IL-1β by using experimental model of NLRP3 inflammasome activation in human THP1 cells.
5.Increased mitochondrial damage was found in the process of Xn inhibition of NLRP3 inflammasomes activation induced by nigericin or MSU, including the detection of indicators such as ROS, ΔΨm, NAD+.
6.Imaging showed that Xn prevented nigericin-induced transloca-

tion of impaired mitochondria to perinuclear area, and this microtubule-driven mitochondrial spatial localization process does not depend on microtubule acetylation level.
7.WB showed that Xn reduced the formation of ASC dimers during the assembly process of NLRP3 inflammasome and imaging indicated marked reduction of ASC speckles.
Conclusion: 1.Xn specifically inhibits the priming, assembly and activation of NLRP3 inflammasome;
2.Xn inhibits the activation of NLRP3 inflammasome by blocking spatial localization of downstream mitochondria, and the formation of ASC dimers and ASC speckles.

Keyword: Xanthohumol, NLRP3, IL-1β, Inflammation



PP17-18

Anticoagulation in patients with antiphospholipid syndrome-related venous thromboembolism: a nationwide study

Hun-Gyu Hwang[1], Ju Hyun Lee[2], San-A Kim[2], Yang-Ki Kim[3], Myung-Shin Kim[1], Junshik Hong[4], Ho-Young Yhim[5] and Soo-Mee Bang[2*]

[1] Department of Internal Medicine , Soonchunhyang University, School of Medicine, Gumi Hospital, Korea
[2] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Korea
[3] Department of Internal Medicine, Soonchunhyang University, School of Medicine, Seoul Hospital, Korea
[4] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[5] Department of Internal Medicine, Chunbuk National University Medical School, Korea

Background: Direct oral anticoagulants (DOACs) are widely used for prevention of arterial thrombosis and the treatment and secondary prevention of venous thromboembolism (VTE), but the efficacy and safety of DOACs for the treatment in patients with antiphospholipid syndrome-related VTE (APS-VTE) are uncertain.

Method: APS-VTE is defined as both VTE code and APS code (D686) being detected twice at least 12 weeks apart within 180 days of index initial VTE event. The efficacy outcomes were arterial thrombosis and recurrent VTE. The safety outcome was major bleeding

Results: APS-VTE patients (n=462) accounted for 0.54% of all VTE cases (n=84,916). Among VTE cases, 72.6% of APS-VTE patients were younger than 60 years-old. Among 410 individuals with APS-VTE (210 female, 51.2%), 209 patients received DOACs, and 201 patients received warfarin (n=201) for anticoagulation. The recurrent VTE occurred in 8 of 209 patients (3.8%) who received DOACs and in 7 of 201 (3.5%) who received warfarin (relative risk [RR], 1.099; 95% CI, 0.41–2.98; p=1). The arterial thrombosis occurred in 12 of 209 patients (5.7%) who received DOACs and in 23 of 201 (11.4%) who received warfarin (RR, 0.502; 95% CI, 0.26–1; p=0.059). The safety outcome (all bleeding) occurred in 7 of 209 (3.4%) in DOACs group and 7 of 201 (3.5%) in warfarin group (RR, 0.96; 95% CI, 0.34–2.69; p=0.84).

Conclusion: The VTE recurrence and bleeding outcomes in DOACs group are comparable to warfarin group in APS-VTE patients. The arterial thrombosis in APS-VTE patients on DOACs group showed low tendency compared with that on warfarin group.

Keyword: Anticoagulation, Antiphospholipid syndrome, Direct oral Anticoagulants, Venous thromboembolism, Warfarin

Table 1. Recurrent VTE and Newly-developed arterial thrombosis in subgroups of patients with APS-VTE treated with DOACs versus warfarin

	Total (n=410)	DOACs (n=209)	Warfarin (n=201)	RR	95% CI	*P*-value
VTE recurrence	16	8 (3.8)	7 (3.5)	1.099	0.41–2.98	1
Time to VTE recurrence, median (range)	564 (49–1147)	607 (116–1147)	403 (49–1145)			0.464
VTE recurrence in Subgroup						
Sex						
Male	4	3	1			
Female	12	5	6			
Age at VTE						

0-29	3	1	2			
30-59	4	4	0			
60-79	7	3	3			
≥80	2	0	2			
Site at VTE						
PE and/or DVT	13	7	5			
DVT	3	1	2			
Arterial thrombosis	35	12 (5.74)	23 (11.4)	0.5018	0.26–1	0.059
Time to ATE, median (range)	241 (7–1852)	144.5 (7–666)	325 (11–1852)			0.105
Stroke	8	3 (1.4)	5 (2.5)			0.496
Myocardial infarction	29	9 (4.3)	20 (10)			0.042

Abbreviation: APS, antiphospholipid syndrome; ATE, arterial thrombosis; CI, confidence interval; RR, relative risk; VTE, venous thromboembolism

PP17-19

Molecular abnormalities and their correlation with the prognosis of younger Indian patients with de novo myelodysplastic syndromes: AIIMS Study

Rekha Chaubey[1], Sudha Sazawal[1], Manoranjan Mahapatra[1], Sunita Chhikara[1], RM Pandey [2], Ashish Datt Upadhyay[2], Renu Saxena[1]

[1] Department of Hematology,All India Institute of Medical Sciences, India

[2] Department of Biostatistics, All India Institute of Medical Sciences, India

Background: Myelodysplastic Syndromes (MDS) in the Western and Eastern countries are mainly found in the elderly population but this disease is being increasingly reported in young adults in Asian countries. Presently very few studies on the molecular biology of young MDS patients have been reported from the Asian countries and the results are contradictory. Very limited data from India is available on MDS and molecular studies are almost absent. Probably this is the first largest study on the molecular biology of MDS from India.

Method: Conventional Cytogentics was done to study the karyotype. Molecular mutations screening of JAK2, IDH2, RAS and FLT3 genes, hTERT gene expression were done by PCR and RT-PCR. PCR-ELISA TRAP assay was performed to assess the telomerase activity. Methylation specific PCR was used to study the promoter methylation status of p15INK4b, SOCS-1, calcitonin and FHIT genes in a series of 100 MDS patients and the results were correlated with disease severity, progression and survival.

Results: Of all the 100 patients 67 were males and 33 were females with median age at presentation was 48 years (Range: 17-84 years). Frequency of patients with age <60 years was high as compared to the patients with age ≥ 60 years (75% vs. 25%). Transformation was observed in twenty one patients. The median time of progression was 15 months (Range 1-16 months). The median follow-up time of all the patients was 32 months (range, 5-121 months). Patients with age <60 years had significantly low IPSS scores (p< 0.001), more transfusion dependent (p< 0.02), and had a shorter median overall survival (p= 0.007). Karyotyping was successfully carried out in 51 patients. Abnormal karyotye was found in 25 (49%) patients with -7, 5q- and trisomy 8 as the most frequent abnormalities. Two rare chromosomal abnormalities (6q-, 3q-) with unknown prognostic significance were also found. The median overall survival was significantly shorter for the patients with poor and intermediate cytogenetics as compared to the patients with good cytogenetics (p=0.02). RAS mutations were present in 12% of cases. Six patients (50%) all aged< 60 years and had RAS mutations progressed to acute leukemia. FLT3-LM and FLT3-TKD-mutations were absent in all the patients. JAK2 mutation and IDH2 mutations were present in 26% and 6% of patients respectively. Telomerase activity (TA) was increased in 17% cases and of these, disease progression was observed in seven patients. hTERT expression was present in 17% cases and disease progression was observed in five patients. p15 INK4b gene rmethylation was present in 40% patients. Disease progression was observed significantly more frequent in patients with methylated p15INK4b gene (p<0.02). There was a significant difference observed between the progression free survival of patients with methylated and unmethylated p15 INK4b gene (p=0.006). SOCS-1 gene was methylated in 53% of patients. Patients with methylated SOCS-1 gene had significantly more frequent disease progression (p=0.006). The median overall survival was significantly shorter in patients with methylated SOCS-1 gene (p=0.001).Calcitonin gene methylation was present in 58% of patients and frequency was significantly higher in the group of patients with age ≥60 years. The median overall survival was significantly shorter in patients with methylated calcitonin gene (p=0.005).FHIT gene was methylated in 43% of patients. Significant difference observed between the progression free survival of patients with methylated and unmethylated FHIT gene (p=0.002). The median overall survival was significantly shorter in patients with methylated FHIT gene (p=0.008). After multivariate analysis, of all the molecular factors, only p15INK4b gene methylation was found as an important predictor for progression of disease in MDS patients (HR 5.15, 95% CI, 1.64-16.1 P=0.005).

Conclusion: Although there are many similarities between Indian patients with the Western data in terms of molecular biology, there are some differences also exits. These differences may be due the aetiology, ethnicity or environmental factors. To better explore the molecular biology of Indian patients who are much younger than rest of the world, studies which includes samples from India as well as rest of the world with large sample size is needed.

PP18-01

Acute critical illness and cancer risk: implications from a nationwide population based study in Asia

Wei Syun Hu

CMUH, Rep of China (Taiwan)

Background: The objective of this study was to identify the risk of incident cancer among patients with acute critical illness.

Method: The study applied the big database from the National Health Research Institutes in Taiwan. The risk of incident cancer over a 12-year period in patients with 4 types of newly diagnosed acute critical illness (septicemia/septic shock, acute myocardial infarction, hemorrhagic stroke and ischemic stroke) was investigated using Cox proportional hazards regression model with further controlling for the competing risk of death.

Results: This study included 42,675 patients in the acute critical illness cohort and 42,675 patients in the age- and sex-matched comparison cohort. Correlation between the incidence of cancer and critical illness was found after adjusting for age, sex, comorbidities and further controlling for death [adjusted subhazard ratio (aSHR) = 1.73, 95% confidence interval (CI) = 1.63-1.84]. Five common incident cancers associated with acute critical illness were hematologic malignancy (aSHR = 4.00, 95% CI = 3.11-5.14), cancers of liver (aSHR = 2.25, 95% CI = 1.93-2.63), uterus (aSHR = 1.86, 95% CI = 1.32-2.61), head and neck (aSHR = 1.79, 95% CI = 1.39-2.30) and esophagus (aSHR = 1.62, 95% CI = 1.09-2.42). Among these cancers, septicemia/septic shock was found to confer a higher risk of incident cancer compared to other subtypes of acute critical illness.

Conclusion: This research is the first to tackle this clinically relevant issue regarding the types of acute critical illness most associated with cancer development with a very large sample size and robust methods. After adjustment for the potential confounding factors and consideration of the competing risk of death, the association between having an acute critical illness and incident cancer was noted.

PP18-02

Comparison of CHA2DS2-VASc, CHADS2 and HATCH scores for the prediction of new-onset atrial fibrillation in cancer patients: novel messages for hematologist

Wei Syun Hu

CMUH, Rep of China (Taiwan)

Background: The current study was conducted to assess the ability of CHA2DS2-VASc, CHADS2 and HATCH scores in predicting new-onset atrial fibrillation (AF) among patients with cancer.

Method: Patients with newly diagnosed cancer between 1 January, 2000 and 31 December, 2011, from the Registry for Catastrophic Illness Patient Database, were defined as the study cohort. CHA2DS2-VASc, CHADS2 and HATCH scores were used for new-onset AF prediction in these study patients, and the predictive accuracy of the scores was assessed by the receiver operating characteristics (ROC) curve.

Results: A total of 760,339 cancer patients were identified as the study participants. The ROC curves were 0.68 (95% confidence interval [CI] = 0.68-0.69) for the CHA2DS2-VASc score, 0.67 (95% CI = 0.67-0.68) for the CHADS2 score and 0.69 (95% CI = 0.69-0.70) for the HATCH score. There were significant differences of c-statistics among CHA2DS2-VASc score, CHADS2 score and HATCH score (CHA2DS2-VASc score vs. CHADS2 score, $p = 0.01$; CHA2DS2-VASc score vs. HATCH score, $p = 0.002$; CHADS2 score vs. HATCH score, $p < 0.001$).

Conclusions: The current study is the first to assess the prognostic value of 3 AF risk scores (CHA2DS2-VASc, CHADS2 and HATCH scores) in patients with newly-diagnosed cancer. HATCH score was found to have a slightly but significantly better predictive performance than the other 2 scores.

PP18-04

Factors associated with quality of life in patients with leukemia

Elaheh Alizargar

Public Health, National Yangming Jiaotong University, Rep of China (Taiwan)

Background: Improvement of quality of life in leukemia patients can be of a great importance. Most studies have been focusing on

life expectancy rather than factors that influence quality of life in these patients. Treatment of cancer also induce fatigue in leukemia patients which also influence their quality of life. We primarily design this study to evaluate associated factors with quality of life and fatigue in leukemia patients receiving chemotherapy referring to shahid beheshti hospital of Kashan.

Method: One hundred and seventy six leukemia patients referring to Shahid beheshti hospital for chemotherapy have been included in this study between 2012~2018. Demographic information, leukemia related and fatigue related data were collected. 36-Item Short Form Health Survey (SF-36) was used in two domains, physical and mental health. Data were analysed using SAS 9.4.

Results: Mean age of patients was 34.5 ±6.1 years and 89 patients were men (50.5%) and 87 were women (49.5%). Majority of the patients were single 99 (56.2%), unemployed 102 (57.9%), and high school graduates 110 (62.5%). Average social support group and average economic support group were the majority groups with 115 (65.3%) and 102 (57.9%) patients in each group respectively. 163 (92.6) of the participants had leukemia related pain. Majority of those 163 subjects (125 patients (76.6%)) had moderate pain. Duration of leukemia in the subjects was 39±8.3 months. 111 subjects (63%) had Acute Myeloblastic Leukemia, 32 (18.1%) had Acute Lymphoblastic Leukemia, 17 (9.6%) had Chronic Lymphoblastic Leukemia and 16 (9%) had Chronic Myeloblastic Leukemia. Physical component aspect of quality of life had significant association and correlation with marital status and educational level and mental component aspect of quality of life had significant association and correlation with marital status, economic status and educational level (all p values<0.05). 166 (94.3%) of the individuals had experienced levels of fatigue. Age, economic, educational and employment status of the individuals was not correlated to fatigue but singles showed more fatigue than married people and correlation between levels of fatigue and pain was high (r=0.62, p<0.001).

Conclusion: marital status, economic status and educational level of leukemia patients should be considered as important factors in their quality of life when medical staff are dealing with those patients. As high rate of fatigue and pain and correlation between them, it seems to be necessary to correctly address these factors for the improvement of leukemia patient's quality of life. Knowing the patient's marital status can be of the great important in managing fatigue for quality of life improvements in leukemic patients.

Keyword: Leukemia, Chemotherapy, Quality of life,

PP18-06

Self-efficacy approach for the prevention of acute lymphoblastic leukemia (ALL) in Indonesia

Mega Dwi Septivani

Department of Science Management, Alumnae of Universitas Gadjah Mada, Indonesia

Background: Acute lymphoblastic leukemia (ALL) is a blood cancer that occurs in children. In Indonesia, the incidence of childhood cancer is estimated to be about 2-4% and the mortality rate is estimated to be 10% (Indonesian Child Oncology Foundation, 2014). Infant mortality from cancer is very high, and acute lymphoblastic leukemia (ALL) is the leading cause of death in children (Pereira, et al, 2017). One of the causes of death in children with leukemia is the period of infection during which the child is undergoing treatment and medication. This disease, which attacks white blood cells, is a concern for parents, especially those with children with ALL. Both parents and children face social, physical, psychological and emotional problems. Therefore, monitoring a child's response to side effects must be considered and understood by parents and children. So far, parents only know simple information such as hand washing and temperature measurement procedures for children. On the other hand, no other information, especially information on infection prevention in all children, has been obtained so far (Anggrasari, 2021). Meanwhile, other information, especially the prevention of infection in ALL children, has never been obtained (Anggrasari, 2021). Appropriate treatment of acute lymphoblastic leukemia is necessary to minimize both physical and psychological effects. One way to do this is with a self-efficacy approach.

Method: Secondary data was collected from The World Health Organization, The United Nations Development Program, The Human Developing Index, The Ministry of Health, Indonesia Child Oncology Foundation, The department of health and Indonesia internet service provider association website. Articles starting from 2001-2021 are collected from an electronic database. Then as many as 10 (ten) selected articles were reviewed to answer the objectives of this study.

Results: Self-efficacy is one of the individual's self-regulatory abilities to form behaviors that are relevant to certain tasks or situations (Bandura, 2006). Health education can be given to improve the ability of families to raise children. Koohkan (2019), states that the educational needs of parents when their child is diagnosed with cancer are the need for information on their child's illness, several alternative treatments and treatments that can be done, as well as the side effects of treatment that will arise later. The provision of health education about the risk of infection that arises during treatment is realized as an effort to overcome cancer deaths in children with ALL (Indonesian Ministry of Health, 2014). Education is a means to increase the knowledge and confidence (self-efficacy) of parents in raising ALL children (Karper et al., 2013. Parents who receive education will be able to increase their confidence in their abilities

(Anggrasari, 2021). This finding provides a better understanding of a more nuanced look at how parental cognition contributes to their ability to cope with their children's medication so as to improve the quality of life of pediatric patients with ALL.

Conclusion: The results stated that Self-efficacy is one of the many effective way to make better quality of life of school age children for the Acute Lymphoblastic Leukemia.

Keyword: Self efficacy, Quality of life, Acute lymphoblastic leukemia (ALL), Indonesia

MEMO

MEMO

MEMO

MEMO

MEMO

THE KOREAN SOCIETY OF HEMATOLOGY

[SCIENTIFIC COMMITTEE]

CHAIRMAN

Jin Seok Kim (Yonsei University)

EXECUTIVE SECRETARY

Dongyeop Shin (Seoul National University)

MEMBERS

Jihyun Kwon (Chungbuk National University)

Hyun-Young Kim (Sungkyunkwan University)

Meerim Park (National Cancer Center)

Yong Park (Korea University)

Sung-Eun Lee (The Catholic University of Korea)

Jae Wook Lee (The Catholic University of Korea)

Ho-Young Yhim (Chonbuk National University)

Young-Uk Cho (University of Ulsan)

Yoon Seok Choi (Ajou University)

Jung Woo Han (Yonsei University)

Kyung Taek Hong (Seoul National University)

Sang Mee Hwang (Seoul National University)

sysmex | Lighting the way with diagnostics

HbA1c Connected with Hematology

Hands-free Management

Just single sample loading allows most testing of EDTA tubes.

Workflow Enhancement

- CBC & HbA1c can be analyzed with one EDTA tube.
- Improve efficiency by minimizing workflow.

The future of laboratory testing
Fully automated clinical confidence in HbA1c

Decrease Turn Around Time

- G11 (HbA1c analyzer) connection enables quick reporting of the results.
- Streamline routine tasks to reduce testing time.

Intelligent Automation

Integrated sample classification, automated analysis, and data management.

시스멕스코리아㈜ Tel. 1833-5366 Fax. 02-3498-5312 www.sysmex.co.kr

디지털 피씨알 기법을 기반으로한 최초의 의료용 검사키트,

QXDx BCR-ABL %IS Kit, 식약처 허가 등록 완료

CE IVD

Bio-Rad's first CE-IVD test kit for ddPCR

식약처 허가 완료

Introducing the QXDx AutoDG ddPCR System and QXDx BCR-ABL %IS Kit

The **QXDx AutoDG ddPCR System** and **QXDx BCR-ABL %IS Kit** represent the first-ever digital PCR solution that can monitor and directly quantitate the molecular response of patients with chronic myeloid leukemia under tyrosine kinase inhibitor therapy.

To learn more, visit **bit.ly/brQXDx1**

For product availability, please contact **Bio-Rad Korea Ltd.**

Tel : **02-3473-4460** | Email: **sales.korea@bio-rad.com**

BIO-RAD

cobas t 711 and cobas t 511 coagulation analyzer

A New Era in coagulation

VENCLEXTA™
venetoclax tablets

POWERED BY

VIALE-A

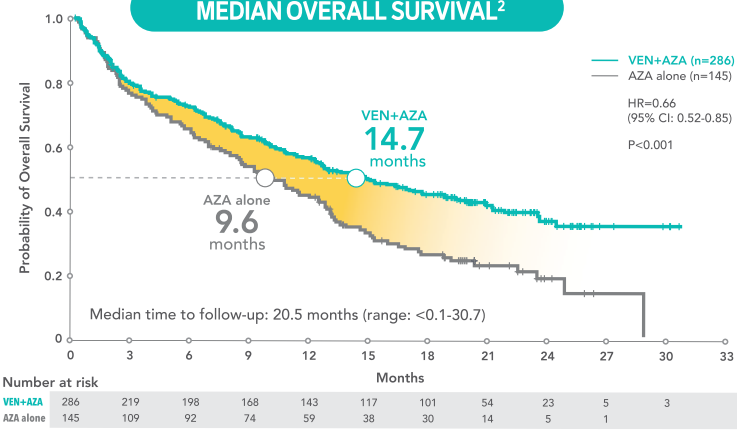
Indication[1]

In **combination with azacitidine or decitabine** for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Viale-A trial[2]:

A phase III, multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of azacitidine plus venetoclax, as compared with azacitidine plus placebo (the control regimen) in older patients with AML.

MEDIAN OVERALL SURVIVAL[2]



Overall survival (OS)

VEN+AZA **14.7 mo** Vs. AZA+pla **9.6 mo**

VEN+AZA significantly increased mOS by 5.1mo vs AZA; OS benefit across subgroups

34.0%

Risk Reduction of mortality

HR=0.66 (95% CI: 0.52–0.85)
P<0.001

Doubled remission (CR+CRi)[2]

VEN+AZA **66%** (95% CI, 60.6 – 71.9) vs. AZA alone **28%** (95% CI, 21.1 – 36.3)

Median time to first remission (CR or CRi)[2]

VEN+AZA **1.3 mo** (range: 0.6 – 9.9) vs. AZA alone **2.8 mo** (range: 0.8 – 13.2)

Longer remission, Median duration (CR+CRi)[2]

VEN+AZA **17.5 mo** (95% CI, 13.6 – not reached) vs. AZA alone **13.4 mo** (95% CI, 5.8 – 15.5)

- The appropriate dose-modification is required for the management of adverse events.[1]

AML, acute myeloid leukemia; CI, confidence interval; CR, complete response; CRi, complete response with incomplete hematologic recovery; HR, hazard ratio; mo, month; pla, placebo; VEN+AZA, venetoclax with azacitidine. [Reference] 1. 벤클렉스타®정 제품설명서. 개정1월일 2021년 1월 8일 2. DiNardo CD, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383:617-629.

벤클렉스타®정 제품요약정보 [효능효과] 만성 림프구성 백혈병: 이전에 치료받은 적이 없는 만성 림프구성 백혈병 성인환자에서 오비누투주맙과의 병용 요법, 이전에 적어도 하나의 치료를 받은 만성 림프구성 백혈병 성인 환자에서 리툭시맙과의 병용 요법, 화학면역억제법 및 8 세포 수준에 경로 저해제에 재발 또는 불응인 만성 림프구성 백혈병 성인 환자에서 단독 요법, 급성 골수성 백혈병: 만 75세 이상, 또는 동존 유도화학요법에 적합하지 않은 동반질환이 있는 새로 진단된 급성 골수성 백혈병 성인 환자에서 아자시티딘 또는 데시타빈과의 병용요법. **[용법용량]** 이전 1일 치료받은 적이 없는 만성 림프구성 백혈병: 이 약은 최대 1일 1회 동일한 시간에 식사 및 물과 함께 복용하도록 한다. 이 약은 통째로 삼켜야 하며, 쪼개거나 씹거나 으깨거나 분말로 만들어 투여하면 안 된다. 종양용해증후군(tumor lysis syndrome, TLS)의 위험을 낮추기 위해 이 약 첫 용량 투여 시작 전 TLS 위험 정도에 대한 환자별 요인을 평가하고 예방적으로 수분 섭취 및 항고요산혈증제제를 투여한다. 만성 림프구성 백혈병: 용량 증량 일정 (Dose Ramp-Up Schedule): 이 약은 1일 1회 20mg씩 7일간 투여로 시작하여 표1에 제시된 이 약의 용량에 따라 1일 최대 400mg이 될 때까지 주 단위 용량 증량 일정에 따라 투여해야 한다. 이 용량의 용량 증량 일정은 종양 부담(tumor burden)을 사서히 줄이고(debulk) TLS의 위험을 낮추기 위해 설계되었다. 표1. 만성 림프구성 백혈병 환자에서의 용량 증량 기간 동안의 용량 일정(Dosing schedule for ramp-up phase) (지면 관계상 표의 내용을 기술함) 1/2/3/4/5주: 이 약의 1일 용량 20/50/100/200/400mg. 오비누투주맙과의 병용: 이 약은 총 12주기 동안 투여한다. 6주기는 오비누투주맙과 함께 투여한 후, 1,001 6주기는 이 약을 단독 투여한다. 오비누투주맙은 1주기 1일째에 100mg을 투여한 후 1일째에는 1000 mg, 2일째에 900mg을 투여한다. 추가 3일에는 오비누투주맙 허가사항을 참조한다. 1주기 8일째와 15일째 및 이후로는 다섯 주기의 각 1일째에 1000mg씩 투여한다 (각 28일로 구성된 총 6주기). 이 약은 1주기 22일째부터 2주기 28일째까지 종양 일정에 따라 투여한다 (표1 참조). 종양 일정 종료 후, 오비누투주맙 투여 3주기 1일째부터 12주기까지 이 약 400mg을 1일 1회 투여한다. 리툭시맙과의 병용: 이 약의 용량 증량 일정(표1)에 따라 기describe 이 약 400mg 투여를 완료한 후, 리툭시맙의 투여를 시작한다. 리툭시맙은 총 6주기 (주기 28일) 동안 각 주기 1일째 투여하며 첫 번째 주기 1일째 375mg/m² 투여하고 두 번째~여섯 번째 주기 동안 각 주기 1일째 500mg/m² 투여한다. 리툭시맙의 첫 번째 치료주기 1일째부터 24개월간 이 약 400mg을 1일 1회 지속적으로 투여하아야 한다. 단독 요법: 이 약의 권장 투기 용량은 5주간의 용량 증량 일정(표1)을 완료한 후 1일 1회 400mg이다. 이 약은 질병이 진행되거나 수용할 수 없는 독성이 관찰될 때까지 1일 1회 경구 투여해야 한다. 급성 골수성 백혈병. 용량 일정(증량 일정 포함)은 표2에 나와 있다. 표2. 급성 골수성 백혈병 환자에서의 용량 증량 기간에 대한 용량 일정 (지면 관계상 표의 내용을 기술함.) 1/2/3/4일 및 그 이후: 이 약의 1일 용량 100/200/400/400mg 아자시티딘 또는 데시타빈과 병용하여 투여하는 경우 이 약은 아자시티딘 또는 데시타빈과 함께 1주기 1일째에 개시한다. 아자시티딘은 각 28일 주기의 1-7일째에 75mg/m² 체 정맥 또는 피하로 투여해야 한다. 데시타빈은 각 28일 주기의 1-5일째에 20mg/m²을 정맥 투여해야 한다. 이 약의 투여는 혈액학적 독성 및 혈구수 회복 관리를 위해 필요 시 일시 중단될 수 있다. 투여 중단 후 이 약 재시작 시에도 발생할 수 있다. 투여 중단 후 이 약에 대한 용량 조절은 표4의 표3을 참조한다. TLS의 위험은 종양 질환을, 특히 신기능 감소(크레아티닌 청소율 [CrCl]<80 mL/min)와 종양 부담(tumor burden)을 포함하는 다양한 요인을 기반으로 연계하여 조사한다. 비장 비대는 전체 TLS 위험의 한 요인이다. 모든 환자에서 방사선 평가 (CT 촬영 등)를 포함한 종양 부담 평가를 실시하며, 혈액학적검사(킬레이트, 요산, 인, 칼슘 및 크레아티닌)를 실시하고, 이 약의 치료를 시작하기 전에 기존의 비정상사항을 정상화한다. 이러한 위험도는 이 약의 치료로 종양의 부피가 줄어들면서 감소할 수 있다. 종양부담에 따른 TLS 예방 및 모니터링은 표3을 따른다. 예방 및 모니터링 일정을 최종 결정하기 전에 모든 환자의 동반질환을 고려한다.

표3. 만성 림프구성 백혈병 환자의 종양 부담에 따른 TLS 예방 및 모니터링

종양 부담		예방		혈액화학 모니터링[a,f]
		수분[b]	항-고요산혈증 제제[c]	평가 빈도
낮음	모든 림프절 5cm 미만 및 ALC 25 x10⁹/L 미만	경구 섭취 (1.5-2L)	알로푸리놀[e]	임해환자: 20mg 및 50mg 첫 투여, 투여 전, 6-8시간, 24시간 용량 단계: 투여 전
중간	어느 림프절이든 5cm 이상 10cm 미만 또는 ALC 25x10⁹/L 이상	경구 섭취 (1.5-2L) 및 추가적인 정맥 주입 고려	알로푸리놀[e]	임해환자: 20mg 및 50mg 첫 투여, 투여 전, 6-8시간, 24시간. 용량 증량 단계: 투여 전 20mg 및 50mg 첫 투여: CLcr <80ml/min인 환자는 입원을 고려한다; 입원 시, 8개의 모니터링을 참조한다.
높음	어느 림프절이든 10cm 이상 또는 ALC 25 x10⁹/L 이상 및 림프절 5cm 이상	경구 섭취 (1.5-2L) 및 정맥 주입 (가능한 한 150-200ml/시간)	알로푸리놀[e] 또는 요산가제리가 선호한 경우 라스부리카제 고려	입원환자: 20mg 및 50mg 첫 투여: 투여 전, 4, 8, 12, 24시간. 외래환자: 용량 증량 단계: 투여 전, 6-8시간, 24시간.

ALC=절대 림프구수(absolute lymphocyte count); CLcr=크레아티닌 제거율(creatinine clearance). [a]경구 수분 섭취가 불가한 모든 환자에 대해서는 정맥으로 수분을 투입한다. [b]이 약을 시작하기 2-3일 전에 알로푸리놀 또는 진단 신화효소 저해제를 시작한다. [c]혈액화학수치(칼륨, 요산, 인, 칼슘, 크레아티닌)을 평가한다; 실시간으로 검토한다. [d]TLS 위험이 있는 환자는, 각 용량 증량 시 6-8시간 및 24시간째에 혈액화학수치를 모니터한다.

급성 골수성 백혈병: 이 약의 일일 용량 증량 기간은 아자시티딘 또는 데시타빈 병용 시 3일이다 (표2 참조). 아래 방법으로 종양을 예방한다: •모든 환자는 이 약 개시 전에 백혈구수가 25X10⁹/L 미만이어야 하며 치료를 시작하기 전에 세포수 감소가 필요할 수 있다. •모든 환자는 이 약의 첫 용량 개시 이전 및 용량 증량 기간 중, 종양분해 수반을 줄금분고 항-고요산제와 수화를 포함한 적절한 예방요법을 받아야 한다. •모든 환자에 대해 혈액화학검사(칼륨, 요산, 인, 칼슘 및 크레아티닌)를 실시하고, 이 약 개시전에 기존의 비정상 수치를 교정한다. •투여 전과, 용량 기간 중 각 새로운 용량을 투여한 6-8시간 후 및 최종 용량에 도달한 24시간 후에, TLS에 대한 혈액화학수치를 모니터링한다. •TLS 위험요인 (예, 순환 모세포, 높은 골수 내 백혈병 침범, 치료 이전 높은 젖산 탈수소 효소(lactate dehydrogenase, LDH) 수치 또는 신기능 저하이 있는 환자는 실험실 수치 모니터링 증가 및 이 약 시작 용량 감량을 포함한 추가적인 조치가 고려되어야 한다. 특성에 따른 용량 조절: 만성 림프구성백혈병. 독성으로 인한 복용 중단 및/또는 용량 감소가 필요할 수 있다. 이 약과 관련된 독성에 따라 권고되는 용량 조절에 대하여, 표4와 표5를 참조한다. 첫 5주 동안의 용량 증량 기간 중 1주 이상 복용 중단했거나 용량 증량 기간 완료 후 2주 이상 복용 중단한 환자의 경우, TLS 위험을 재평가하여 감소된 용량으로 투여를 다시 시작해야 할 필요가 있는지 평가해야 한다(용량 증량 일정의 모든 또는 일부 단계). [e]4. 만성 림프구성 백혈병에서 독성으로 인한 이 약의 용량 조절(지면 관계상 표의 내용을 기술함) 종양 용해 증후군-혈액학적 수치 변화 또는 TLS를 감소하는 중심. 예번: 다음날의 이 약 투여를 중단한다. 마지막 투여 이후 24-48시간 이내에 재검사 및 권장에는. 동일한 용량으로 이 약의 치료를 다시 시작한다. 해결에 48시간 이상이 필요한 혈액화학 수치 변화가 발생한 경우, 감소된 용량으로 치료를 시작한다 (표5 참조). 임상적 TLS*가 발생한 경우, 해결 후 감소된 용량으로 치료를 시작한다(표5 참조). 비혈액학적 독성.3 또는 4등급의 비혈액학적 독성. 1번째 발생: 이 약을 일시 중단한다. 독성이 1등급 또는 베이스라인 수치로 해결되면, 동일한 용량으로 이 약의 치료를 재개할 수 있다. 용량 조절은 필요하지 않다.2번째 또는 추가 발생: 이 약을 일시 중단한다. 독성이 1등급 또는 베이스라인 수치로 해결되면, 동일한 용량으로 이 약의 치료를 재개할 수 있다. 3번째 발생: 이 약을 영구 중단한다. 독성에 따라 용량이 더 많이 감소될 수 있다. 혈액학적 독성.감염이.나 발열이 있는 3등급의 중성구 감소증, 또는 4등급의 혈액학적 독성에 따라 용량이 더 많이 감소될 수 있다. 혈액학적 독성.감염이.나 발열이 있는 3등급의 중성구 감소증, 또는 4등급의 혈액학적 독성(림프구 감소증 제외). 1번째 발생: 이 약을 일시 중단한다. 중성구 감소증과 연관된 감염 위험을 낮추기 위해 임상적으로 필요한 경우 과립구콜라이자극인자(G-CSF)를 이 약과 병용 투여할 수 있다. 독성이 1등급 또는 베이스라인 수치로 해결되면, 동일한 용량으로 이 약의 치료를 재개할 수 있다.2번째 또는 추가 발생: 이 약을 일시 중단한다. 임상적으로 지시된대로 G-CSF 사용을 고려한다. 독성을 해결한 후 이 약의 치료를 재개할 때, 표 5에 제시된 용량 감소 가이드라인을 따른다. 이사이 지정에 따라 용량이 더 많이 감소될 수 있다. 2주 이상 100ms 미만으로 혈소판 환자의 경우 이 약의 중단을 고려한다. a 이상반응은 NCI CTCAE version 4.0을 사용하여 분류됨. b 임상적 TLS는 급성 신부전, 심부전맥, 또는 급사 및/또는 발작과 같은 임상적 예후가 있는 실험실 검사 수치상 TLS로 정의됨 (이상반응 참 참조.). [c]5. 이 약으로 만성 림프구성 백혈병 치료 도중 독성으로 인한 용량 감소. (지연 관계상 표의 내용을 기술함.) 중단 시 용량, mg: 400/300/200/100/50/20. 재시작 용량, mg: 300/200/100/50/20/10. (a 용량을 증가시키기 전에 감소된 용량으로 1주일간 지속한다.) 감염 또는 지속되는 급성 골수성백혈병. 다른 독성으로 인한 용량 조정: 1주기 중로 시 관해를 평가한다. 그 후 및 치료하는 동안 필요에 따라 골수 평가를 권고하고, 혈구 감소증의 해결을 위해 혈구 수를 자주 모니터링한다. 일요한 경우 이상반응 관리 또는 혈구수 회복을 위해 이 약을 일시 중단하거나(경고및 및 이상반응 참 참조.), 이 약을 영구 중단한다. 열 또는 감염을 동반하거나 동반하지 않은 4등급 중성구 감소증(절대 중성구 수[ANC]<500/microliter); 또는 4등급 혈소판 감소증(혈소판 수 <25,000/microliter)에 대한 용량 조정은 표6을 참조하고(경고 및 참조), 표6. 이 약으로 급성 골수성 백혈병 치료 도중 독성으로 인한 용량 조정 (지연 관계상 표의 내용을 기술함) 열 또는 감염을 동반하거나 동반하지 않은 4등급 중성구 감소증, 또는 4등급 혈소판 감소증에 발생해야도 독성 관해 도달 전 발생심상적 지시대로, 혈액 제제 수혈, 예방적항 투여 및 항-감염약 치료, 대부분의 경우, 관해 도달 전에는 이 약과 아자시티딘, 데시타빈 주기를 혈구 감소증으로 인해 일시 중단해서는 안 된다. 관해* 도달 후 (가장 이상 지속시) 약과 아자시티딘, 데시타빈의 다음 투여 주기를 연기하고 혈구 수를 모니터링 한다. 중성구 감소증에 대하여 임상적으로 지시된 경우, 과립구-집락자극인자(G-CSF)를 투여할 수 있다. 지정 발생 독성이 1 또는 2등급 수준으로 해결되면, 이 약은 동일한 용량으로 아자시티딘, 데시타빈과의 병용 투여를 재개한다.[a]후 발생 독성이 1 또는 2등급 수준으로 해결되면, 이 약은 동일한 용량으로 아자시티딘, 데시타빈과의 병용 투여를 재개하고, 각 추속 주기 동안 이 약의 투여기간을 7일씩 단축한다(즉, 28일 대신 21일). (a 이상반응의 등급은 NCI CTCAE version 4.0을 사용하여 분류되었다. b 골수에서 모세포 5% 미만의 혈구 감소증 확인.) 3등급 또는 4등급 혈액학적 독성은 보조치료로 배정되지 않을 경우 이약 일시 중단하고 독성이 1등급 또는 베이스라인 수치로 해결되면 동일한 용량으로 이 약투여를 재개한다. CYP3A 저해제 또는 P-gp 저해제의 병용 시 용량 조정: 이 약을 강력한 CYP3A 저해제, 또는 P-gp 저해제와 병용 시 이 약의 노출(즉, Cmax 및 AUC0-t) 증가하므로 치료 시작 시와 용량 증량 기간 동안 TLS 위험이 증가할 수 있다. 만성 림프구성 백혈병 환자들은, 치료 시작 시와 용량 증량 기간 동안에는 이 약과 강력한 CYP3A 저해제를 병용투여해서는 안 된다. 모든 환자들은, CYP3A 저해제 또는 P-gp 저해제를 반드시 사용해야 할 경우, 약물 상호작용을 관리하기 위하여 표7을 따른다. 특성의 정후가 있는지 환자를 면밀하게 모니터링 한다. CYP3A 저해제 또는 P-gp 저해제 중단 후 2-3일 후부터 CYP3A 저해제 또는 P-gp 저해제와 병용투여 시작 이전의 용량으로 이 약의 투여를 재개한다. 표7. 이 약의 CYP3A 저해제 및 P-gp 저해제와의 잠재적인 상호작용 관리 (지면 관계상 표의 내용을 기술함) 강력한 CYP3A 저해제 시작 및 용량 증량 기간-신생 림프구성 백혈병: 급기 급성 골수성백혈병: 1일차 10mg/2일차 20mg/3일차 50mg/4일차 100mg 이하, 일일 용량 (용량 증량 기간 이후)—이 약의 용량을 100mg 이하로 줄임. 중등도의 CYP3A 저해제, P-gp 저해제 이 약의 용량을 처음의 50% 줄임. (a 만성 림프구성 백혈병 환자들은, 이 약과 관련된 독성에 따라 권고되는 용량 조절에 대하여, 표4와 표5를 참조한다. 첫 5주 동안의 용량 증량 기간 중 1주 이상 복용 중단했거나 용량 증량 기간 완료 후 2주 이상 복용 중단한 환자의 경우, TLS 위험을 재평가하여 감소된 용량으로 투여를 다시 시작해야 할 필요가 있는지 평가해야 한다(용량 증량 일정의 모든 또는 일부 단계).표4. 만성 림프구성 백혈병에서 독성으로 인한 이 약의 용량 조절(지면 관계상 표의 내용을 기술함) 종양 용해 증후군-혈액학적 수치 변화 또는 TLS를 감소하는 중심. 예번: 다음날의 이 약 투여를 중단한다. 마지막 투여 이후 24-48시간 이내에 재검사 및 권장에는. 동일한 용량으로 이 약의 치료를 다시 시작한다. 해결에 48시간 이상이 필요한 혈액화학 수치 변화가 발생한 경우, 감소된 용량으로 치료를 시작한다 (표5 참조). 임상적 TLS*가 발생한 경우, 해결 후 감소된 용량으로 치료를 시작한다(표5 참조). 비혈액학적 독성.3 또는 4등급의 비혈액학적 독성. 1번째 발생: 이 약을 일시 중단한다. 독성이 1등급 또는 베이스라인 수치로 해결되면, 동일한 용량으로 이 약의 치료를 재개할 수 있다. 용량 조절은 필요하지 않다.2번째 또는 추가 발생: 이 약을 일시 중단한다. 독성을 해결한 후 이 약의 치료를 재개할 때, 표5에 제시된 용량 감소 가이드라인을 따른다. 임상적 제한에 따라 용량이 더 많이 감소될 수 있다. 혈액학적 독성.감염이.나 발열이 있는 3등급의 중성구 감소증, 또는 4등급의 혈액학적

abbvie 한국 애브비㈜ 서울시 강남구 영동대로 421 삼탄빌딩 6층 Tel. 02-3429-9300

KR-VENA-210002-210209

Sanofi Hematology

FOR YOUR OPTIMAL TREATMENT IN HEMATOLOGY

Sanofi will always be with you
in your treatment journey for patients with hematologic disorders

Sanofi-aventis Korea, Ltd
Banpo Hyosung blg., 235, Banpo-daero, Seocho-gu, Seoul. Tel: 02)2136-9000 / Fax: 02)2136-9588
Product information is available on Sanofi-aventis Korea homepage (www.sanofi.co.kr) MAT-KR-2200030-1.0-01/2022

SANOFI

www.yuhan.co.kr 소비자상담실 080-024-1188 **[최신 제품정보 개정일]** 2018.12.03

※ 처방하시기 전, 상세 제품정보를 참조하시기 바랍니다.

JW Pharmaceutical

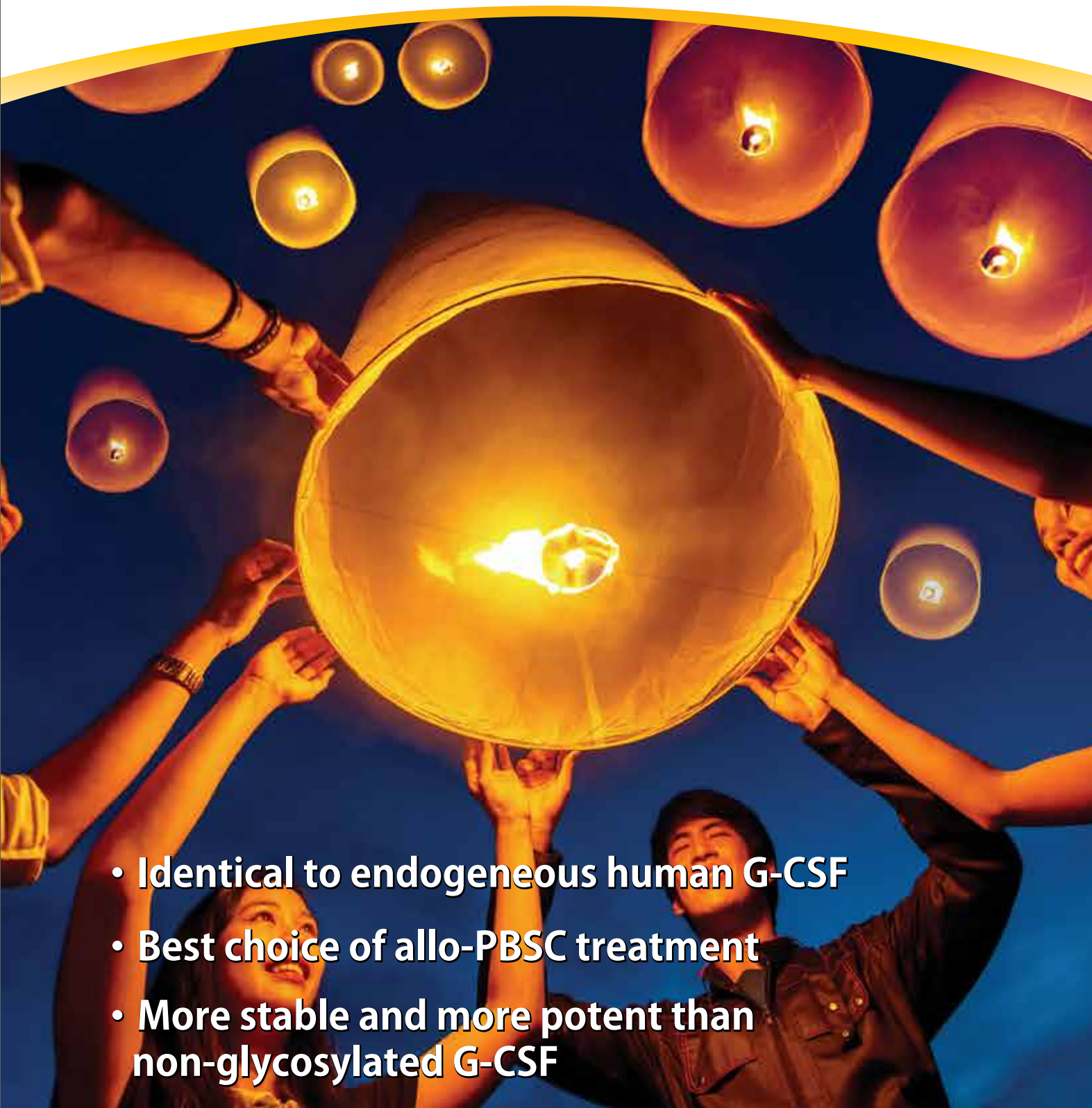
Glycosylation makes all the difference

NEUTROGIN®

50μg
100μg
250μg

Glycosylated rHuG-CSF

lenograstim



- Identical to endogeneous human G-CSF
- Best choice of allo-PBSC treatment
- More stable and more potent than non-glycosylated G-CSF

In CMV prophylaxis

A PATH OF PROTECTION FROM THE START

Start PREVYMIS™ as early as day zero for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).[1-4†]

Not an actual patient

Indication

- PREVYMIS™ is an antiviral drug indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).[1,2]

†[NCCN guideline] Consider letermovir as primary prophylaxis for CMV+ allogeneic HCT recipients.
CMV, cytomegalovirus; **HSCT,** hematopoietic stem cell transplantation; **R+,** recipient positive.

PREVYMIS™ (letermovir)
240 mg, 480 mg tablets
Injection 20 mg/mL

Reference 1. PREVYMIS™_Tab. Prescribing Information. MSD Korea.(Revision date 23 November 2021) **2.** PREVYMIS™_IV. Prescribing Information. MSD Korea. (Revision date 23 November 2021) **3.** Ljungman P, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis.* 2019 Aug;19(8):e260-e272. **4.** 2021, 07/02/21 2021 National Comprehensive Cancer Network(NCCN) ; Prevention and Treatment of Cancer-Related Infections.

XPOVIO®
(selinexor)

THE X FACTOR

in MM and DLBCL

The First
Only FDA Approved
Oral XPO1 Inhibitor

제품명 : 엑스포비오정20밀리그램 원료약품 및 그 분량: 1정(167.2밀리그램) 중 유효성분: 셀리넥서 20.0 밀리그램 성상 파란색의 원형 필름코팅정 효능효과1. 이전에 네 가지의 치료 요법에서 적어도 두 가지 프로테아좀 억제제, 적어도 두 가지 면역조절 이미드 치료제 그리고 적어도 한 가지의 anti-CD38 항체 치료를 받은 경우로, 재발 또는 불응성 다발골수종이 있는 성인환자에 대한 덱사메타손과의 병용요법 2. 두 가지 이상의 전신치료 후 재발 또는 불응성 미만성 거대 B-세포 림프종 성인 환자의 치료 용법·용량 1) 이전에 네 가지의 치료 요법에서 적어도 두 가지 프로테아좀 억제제, 적어도 두 가지 면역조절 이미드 치료제 그리고 적어도 한 가지의 anti-CD38 항체 치료를 받은 경우로, 재발 또는 불응성 다발골수종이 있는 성인환자에 대한 덱사메타손과의 병용요법: 이 약을 매주 첫째 날 및 셋째 날, 80 mg씩 주2회 복용한다. 경구용 덱사메타손은 매주 첫째 날 및 셋째 날, 20mg씩 주2회 이 약과 병용하여 복용한다. 2) 두 가지 이상의 전신치료 후 재발 또는 불응성 미만성 거대 B-세포 림프종 성인 환자의 치료: 이 약을 매주 첫째 날 및 셋째 날, 60mg씩 주2회 복용한다. 다음 환자에는 투여하지 말 것 이 약의 주성분 및 첨가제 성분에 과민증이 있는 환자 이상반응 1) 다발골수종 환자: 다발골수종 환자의 가장 흔한 이상 반응(증상 ≥20%)은 혈소판감소증, 피로, 오심, 빈혈, 식욕저하, 체중 감소, 설사, 구토, 저나트륨혈증, 호중구 감소증, 백혈구 감소증, 변비, 호흡 곤란, 상부 호흡기 감염이다. 2) 미만성 거대 B 세포 림프종 환자: 미만성 거대 B 세포 림프종 환자의 진단 검사 이상을 제외한 가장 일반적인 이상 반응(증상 ≥20%)은 피로, 오심, 설사, 식욕 저하, 체중 감소, 변비, 구토, 발열이다. 등급 3-4의 진단 검사 이상은(≥15%) 혈소판감소증, 림프구 감소증, 호중구 감소증, 빈혈, 저나트륨혈증이다. 일반적 주의 혈소판 감소증, 호중구 감소증, 위장관 독성, 저나트륨혈증, 심각한 감염, 신경 독성, 백내장 임부, 수유부에 대한 투여 이 약은 비임상시험 결과 및 작용 기전에 근거할 때 임신한 여성에게 투여될 경우 태아 독성의 가능성이 있다. 이 약을 임부에게 투여하여 약물 관련 위험성을 평가한 자료는 없다. 이 약 또는 그 대사체가 모유로 이행되는지 여부를 평가한 자료는 없다. 이 약의 투여기간 및 최종 투약 후 1주일 동안은 모유 수유를 중단해야 한다. 보관 및 취급상의 주의사항 1) 어린이의 손이 닿지 않는 곳에 보관하도록 주의한다. 2) 30℃ 이하에서 보관한다.
수입판매원 안텐진제약 주식회사 서울특별시 강남구 테헤란로 152 강남파이낸스센터 41층 디이그제큐티브센터 | 엑스포비오® 환자전화 080-508-3243 팩스(02)2008-4952 | 이메일 safety.korea@antengene.com | 개정년월일: 2021년 10월 25일
*제품을 처방하시기전 상세 제품설명서를 참고하여 주시기 바랍니다.

KR-XPO-CM-2022-001

ANTENGENE

[제품명] 트룩시마주®주 500mg/50mL, Truxima® (리툭시맙) (단클론항체, 유전자재조합) **[원료약품 및 그 분량]** 1 바이알 (50 mL) 중 Rituximab 500 mg **[성상]** 무색 또는 미황색이고 투명에서 탁한 용액이 무색 투명한 바이알에 든 주사제 **[효능・효과]** 1) 림프종 : 재발성 또는 화학요법 내성인 여포형 림프종(B세포 비호지킨 림프종 IWF분류중 B, C, D형) / 이전에 치료받은 적이 없는 여포형 림프종에서 화학요법과 병용투여 / 여포형 림프종에서 유도요법 실시 후 유지요법 / CD20 양성의 미만형 대형 B세포 비호지킨 림프종(DLCL)[CHOP화학요법 (cyclophosphamide, doxorubicin, vincristine, prednisolone 으로 구성, 8주기 투여)과 병용하여 투여해야 한다.] 2) 만성 림프구성 백혈병 3) 류마티스 관절염 4) 베게너육아종증 및 현미경적 다발혈관염 **[용법・용량]** (주입방법) 별도의 전용관을 써서 정맥 점적 주입하며 매회 30~60분전 해열제 및 항히스타민제 투여하여야 하고 비호지킨 림프종 및 만성림프구성 백혈병 환자의 치료계획 중 글루코코르티코이드가 포함되어 있지 않은 경우 전처치를 고려해 보아야 한다. 1차 주입 시 초기 주입 속도는 50 mg/h이 권장되며 30분마다 50 mg/h씩 속도를 높여 최고 400 mg/h까지 증가할 수 있다. 이후 이 약의 주입 속도는 100 mg/h에서 시작하여 30분마다 100 mg/h씩 증가시켜 최고 400 mg/h까지 높일 수 있다. (림프종) 치료기간 중 용량 감량은 비람직하지 않으며 이 약을 표준 화학요법과 병용투여하는 경우 화학요법제의 감량지침을 적용하도록 한다. ① 여포형 비호지킨 림프종 1) 병용요법: 이전에 치료받은 적이 없거나 재발성/불응성인 환자에게 유도요법으로 화학요법과 병용할 경우 권장용량은 375 mg/m²이며 8주기까지 투여한다. 이 약은 글루코코르티코이드 정맥 투여 후(해당되는 경우만), 매 화학요법 투여 주기 제1일에 투여한다. 2)유지요법: 이전에 치료받은 적이 없고 유도요법에 반응하는 환자는 2개월에 한번씩 375 mg/m²(유도요법 최종 투여로부터 2개월 후 유지요법 시작)을 재발성/불응성이고 유도요법에 반응하는 환자는 3개월에 한번씩 375 mg/m²(유도요법 최종 투여로부터 3개월 후 유지요법 시작)을 질환 진행 시까지 또는 최대 2년간 유지요법으로 투여한다. 3)단독요법: 재발성/불응성 환자에서 유도요법으로 투여할 경우 권장용량은 375 mg/m²이며 매주 1회씩 4주에 걸쳐 투여한다. 1차 치료 시 반응했던 환자가 재발한 경우 재투여하였으며 이때 반응률은 처음과 유사하였다. 권장용량은 375 mg/m²이며 매주 1회씩 4주에 걸쳐 투여한다. ② 미만형 대형 B세포 비호지킨 림프종: CHOP 화학요법과 병용투여한다. 권장용량은 375 mg/m²이며 매 화학요법 투여 주기의 제1일에 투여한다. 화학요법 구성약물들은 이 약 주입 후에 투여해야 한다. ※ 만성 림프구성 백혈병, 류마티스 관절염, 베게너육아종증 및 현미경적 다발혈관염의 용법・용량 및 제품에 대한 보다 자세한 정보는 제품설명서를 참조하시거나 아래의 연락처로 문의하여 주시길 바랍니다.

셀트리온제약 CELLTRION
서울시 송파구 중대로 135 IT벤처타워 서관 17층
Tel 080-850-3612 www.celltrionph.com

Truxima® Rituximab

GC 녹십자

A New Paradigm of Immunoglobulin Injection

I.V.-Globulin SN inj. 10%

Convenience

High concentration immunoglobulin

UP

Reduced volume load

Reduced infusion time

High Concentration

I.V.-Globulin SN inj. 10%

Takeda

서울특별시 송파구 올림픽로 300 롯데월드타워 37층 (05551) Tel. 02-3484-0800
• 제품관련 의약정보(학술)문의 Tel: 080 908 0971 / e-mail: medinfoAPAC@takeda.com
• 이상사례보고 AE.SouthKorea@takeda.com
• 더 자세한 제품 정보는 식품의약품안전처 의약품통합정보시스템(https://nedrug.mfds.go.kr)의 제품 허가사항을 참조하시기 바랍니다.

C-APROM/KR/ADCE/0182 Date of Preparation Mar/2022

KRd, Kyprolis® (carfilzomib)+lenalidomide+dexamethasone; **Kd,** Kyprolis® (carfilzomib)+dexamethasone; **KdD,** Kyprolis® (carfilzomib)+daratumumab+dexamethasone; **BIW,** twice-weekly; **QW,** once-weekly.

References 1. Stewart AK, et al. *N Engl J Med.* 2015;372:142-52. **2.** Dimopoulos MA, et al. *Lancet Oncol.* 2016;17:27-38. **3.** Moreau P, et al. *Lancet Oncol.* 2018;19:953-964. **4.** Dimopoulos M, et al. *Lancet.* 2020;396:186–97. **5.** Leleu X, et al. *Leuk Lymphoma.* 2021 Feb;62:358-367.

키프롤리스® 제품요약정보 제품명: 키프롤리스주60밀리그램, 30밀리그램(카르필조밉), **효능효과:** 이전에 한 가지 이상의 치료를 받은 다발성골수종 환자의 치료를 위한 다음약물과의 병용요법: 레날리도마이드 및 덱사메타손 또는 덱사메타손 또는 다라투무맙 및 덱사메타손 **용법용량:** [레날리도마이드 및 덱사메타손과의 병용요법] 3주 동안 매주 2일 연속으로 투여 후 12일간 휴약하여 총 28일을 1 치료주기로 한다. 첫 번째 주기의 1일, 2일에 20 mg/m²의 시작용량으로 투여한다. 13주기부터는 8일과 9일에 투여하지 않으며 18 주기 이후에는 투여를 중단한다. 레날리도마이드는 1-21일에 25 mg을 경구 투여하고, 덱사메타손은 28일 주기의 1일, 8일, 15일, 22일에 40 mg을 경구 또는 정맥투여한다. [덱사메타손과의 병용요법-주2회 20/56 mg/m² 요법] 3주 동안 매주 2일 연속으로 투여 후 12일간 휴약하여 총 28일을 1 치료주기로 한다. 첫 번째 주기의 1일, 2일에 20 mg/m²의 시작용량으로 투여한다. 30분 동안 정맥내 주입으로 투여. 시작용량 투여 후, 첫 번째 주기의 8일에 목표용량 56 mg/m²로 증량한다. 매 28일 주기의 1, 2, 8, 9, 15, 16, 22, 23일에 덱사메타손 20 mg을 경구 또는 정맥투여 한다. [덱사메타손과의 병용요법-주1회 20/70 mg/m² 요법] 3주 동안 매주 1일에 투여 후 13일간 휴약하여 총 28일을 1 치료주기로 한다. 첫 번째 주기의 1일에 20 mg/m²의 시작용량으로 투여한다. 30분 동안 정맥내 주입으로 투여. 시작용량 투여 후 첫 번째 주기의 8일에 목표용량 70 mg/m² 로 증량한다. 모든 주기의 1, 8 및 15일과 1-9주기의 22일에 덱사메타손 40 mg을 경구 또는 정맥투여한다. [다라투무맙(정맥내 주입) 및 덱사메타손과의 병용요법-주2회 20/56 mg/m²] 3주 동안 매주 2일 연속으로 투여 후 12일간 휴약하여 총 28일을 1치료주기로 한다. 첫 번째 주기의 1일, 2일에 20 mg/m²의 시작용량으로 투여한다. 30분 동안 정맥내 주입으로 투여. 시작용량 투여 후 첫 번째 주기의 8일에 목표용량 56 mg/m²로 증량한다. 다라투무맙은 실체중 기준 16 mg/kg 용량을 1주기의 1일과 2일에 8 mg/kg씩의 분할 용량으로 정맥내 주입한다. 16 mg/kg을 매주 1회 1주기의 8, 15 및 22일에 투여하고, 2주기의 1, 8, 15 및 22일에 투여한 후 3-6주기에는 2주간격, 나머지 주기에는 4주 간격으로 투여한다. 16 mg/kg을 매주 1회 1주기의 8, 15 및 22일에 투여한 후 3-6주기에는 2주간격, 나머지 주기에는 4주 간격으로 투여한다. 매 28일 주기의 1, 2, 8, 9, 15 및 16일에 덱사메타손 20 mg, 22일에 40 mg을 경구 또는 정맥투여한다. [다라투무맙(정맥내 주입) 및 덱사메타손과의 병용요법-주1회 20/70 mg/m²] 3주 동안 매주 1일에 투여 후 13일간 휴약하여 총 28일을 1 치료주기로 한다. 첫 번째 주기의 1일에 20 mg/m²의 시작용량으로 투여한다. 30분 동안 정맥내 주입으로 투여. 시작용량 투여 후 첫 번째 주기의 8일에 목표용량 70 mg/m² 로 증량한다. 다라투무맙은 실체중 기준 16 mg/kg 용량을 1주기의 1일과 2일에 8 mg/kg씩의 분할 용량으로 정맥내 주입한다. 16 mg/kg을 매주 1회 1주기의 8, 15 및 22일에 투여하고, 2주기의 1, 8, 15 및 22일에 투여한 후 3-6주기에는 2주간격, 나머지 주기에는 4주 간격으로 투여한다. 1 및 2주기의 1, 2, 8, 9, 15, 16, 22 및 23일에 덱사메타손 20 mg을 경구 투여하거나 정맥내 주입한다. 3-6주기의 1, 2, 15 및 16일에 덱사메타손 20 mg, 8 및 22일에 40 mg을 경구 투여 또는 정맥내 주입한다. 7주기 및 그 이후로 1 및 2일에 덱사메타손 20 mg, 8, 15 및 22일에 40 mg을 경구 투여 또는 정맥내 주입한다. **다음 환자에게는 투여하지 말 것:** 이 약의 주성분 또는 다른 성분에 과민반응이 있는 환자, **이상반응:** [레날리도마이드 및 덱사메타손과의 병용요법] 임상시험에서 10% 이상 보고된 이상반응은 빈혈, 호중구감소증, 혈소판감소증, 설사, 변비, 구역, 피로, 발열, 말초부종, 무력증, 상기도감염, 기관지염, 바이러스성 상기도감염, 폐렴, 저칼륨혈증, 저칼슘혈증, 고혈당증, 근육경련, 요통, 기타 미분류 말초신경병증, 불면증, 기침, 호흡곤란, 발진, 색전증 및 혈전증, 고혈압이었고, 10% 이상 보고된 3-4등급 임상검사치 이상은 림프구, 혈색소증가수, 인, 혈소판, 총 백혈구수, 헤모글로빈, 칼륨 감소 및 당 증가이었다. [덱사메타손과의 병용요법-주2회 20/56 mg/m² 요법] 임상시험에서 10% 이상 보고된 이상반응은 빈혈, 혈소판감소증, 설사, 구역, 변비, 구토, 피로, 발열, 무력증, 말초부종, 기도 감염, 폐렴, 기관지염, 요통, 두통, 불면증, 기침, 호흡곤란, 고혈압이었다. [다라투무맙(정맥내 주입) 및 덱사메타손과의 병용요법-주2회 20/56 mg/m²] 임상시험에서 15% 이상 보고된 이상반응은 주입 관련 반응, 피로, 발열, 기도 감염, 폐렴, 기관지염, 혈소판감소증, 빈혈, 설사, 구역, 고혈압, 기침, 호흡곤란 불면증, 요통이었다. [다라투무맙(정맥내 주입) 및 덱사메타손과의 병용요법-주1회 20/70 mg/m²] 임상시험에서 15%이상 보고된 이상반응은 혈소판감소증, 빈혈, 호중구감소증, 림프구감소증, 피로, 주입 관련 반응, 발열, 기도 감염, 기관지염, 비인두염, 인플루엔자, 구역, 구토, 설사, 변비, 호흡곤란, 기침, 고혈압, 불면증, 두통, 요통, 사지 통증이었다. 시판 후 심근병증, B형 간염 바이러스(HBV) 재활성화, 용혈요독증후군(HUS), 위장관 천공, 심낭염, 대상포진, 착란상태, 거대세포바이러스 감염(맥락망막염, 폐렴, 소장대장염, 바이러스 혈증포함), 장폐색이 자발보고 되었다. **일반적 주의:** 심장독성, 급성신부전, 종양용해증후군, 폐독성, 폐동맥고혈압, 호흡곤란, 고혈압, 정맥혈전증, 주입 관련 반응, 출혈, 혈소판감소증, 간독성 및 간부전, 혈전성 미세혈관병증, 가역성 후두부 뇌병증 증후군(PRES), B형 간염 바이러스(HBV) 재활성화, 진행성 다초점 백질 뇌병증(PML), 새롭게 진단된 이식이 불가능한 다발성골수종 환자에서의 멜팔란 및 프레드니손과의 병용요법에서 치명적이고 중대한 독성의 증가, 배태자독성이 발생할 수 있으므로 모니터링, 용량감량, 투여중지, 중단 등의 필요한 의학적 조치를 취하여야 한다. **임부 및 수유부:** 작용기전과 동물시험 결과로 볼 때, 태아독성을 야기할수 있으므로 적절한 피임 조치를 해야 한다. 임신 중 사용하거나 환자가 투약 중에 임신하게 되면, 환자에게 태아에 위험이 있음을 알려야 한다. **보관 및 취급상의 주의사항:** 차광 냉장(2-8°C) 보관. **정맥 투여를 위한 재구성 및 조제방법:** 과량투여를 막기위해 투여량 계산에 주의해야 하며, 재구성하기 전 조제방법을 숙지하여야 한다. 수입판매원: 암젠코리아유한회사(서울특별시 중구 을지로 5길 19, 20층). (개정일: 2021.05.04) **※제품을 처방하시기 전 상세 제품설명서를 참고하여주시기 바랍니다.**

KR-06617-KYP-2021-Aug

암젠코리아유한회사
대한민국 서울특별시 중구 을지로5길 19 페럼타워 20층 | 수신자 부담: 00798 611 3554

AMGEN®

Celgene | Bristol Myers Squibb™ Company

Pomalyst® (pomalidomide) capsules

Pomalyst®는

RRMM 환자의
치료 성적을 개선시킬 수 있는
Standard of Care 입니다.[1,2]

RRMM, relapsed/refractory multiple myeloma.

Reference

1. Dimopoulos, et al. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010) a phase 3b study in refractory multiple myeloma. *Blood.* 2016 Jul 28;128(4):497-503. **2.** NCCN clinical practice guidelines in oncology ver 4. 2020

포말리스트®캡슐 (포말리도마이드) 1mg / 2mg / 3mg / 4mg

[분류번호: 421] [전문의약품]

[원료약품 및 그 분량] 유효성분 : 포말리스트 1밀리그램 1캡슐 중 포말리도마이드(별규) 1.00mg 포말리스트 2밀리그램 1캡슐 중 포말리도마이드(별규) 2.00mg 포말리스트 3밀리그램 1캡슐 중 포말리도마이드(별규) 3.00mg 포말리스트 4밀리그램 1캡슐 중 포말리도마이드(별규) 4.00mg 첨가제 : 만니톨, 전호화전분, 캡슐, 푸마르산스테아릴나트륨 **[성상]** 포말리스트캡슐 1밀리그램 : 노란색의 가루가 든 상부 어두운 청색, 하부 노란색의 경질캡슐 포말리스트캡슐 2밀리그램 : 노란색의 가루가 든 상부 어두운 청색, 하부 주황색의 경질캡슐 포말리스트캡슐 3밀리그램 : 노란색의 가루가 든 상부 어두운 청색, 하부 녹색의 경질캡슐 포말리스트캡슐 4밀리그램 : 노란색의 가루가 든 상부 어두운 청색, 하부 청색의 경질캡슐 **[효능·효과]** 1) 이전에 레날리도마이드를 포함한 한 가지 이상의 치료를 받은 다발골수종 환자의 치료에 보르테조밋 및 덱사메타손과의 병용요법 2) 이전에 레날리도마이드와 보르테조밉을 포함한 최소 두 가지 치료를 받고, 재발 또는 불응한 다발골수종 환자의 치료에 덱사메타손과 병용요법 **[용법·용량]** 이 약은 위해관리프로그램 (사용상의 주의사항 중 '5. 일반적 주의사항 참조')에 규정된 사항을 따르는 것에 동의한 환자에게만 투여되어야 한다. 또한 이 약은 위해관리프로그램에 등록된 의사들에 의해서만 처방되어야 하고, 등록된 약사들에 의해서만 조제되어야 한다. 임신가능성이 있는 여성에게 처방될 경우, 본 프로그램에서 정하고 있는 일정에 따라 지속적으로 임신테스트의 음성결과를 확인하여야 한다. 1. 이전에 레날리도마이드를 포함한 한 가지 이상의 치료를 받은 다발골수종 환자의 치료에 보르테조밉 및 덱사메타손과의 병용요법 이 약의 초기 권장 용량은 반복되는 21일 주기로 제1일~14일에 1일 1회 4mg을 경구로 투여하는 것이다. 이 약과 보르테조밉 및 덱사메타손 병용요법의 권장투약 일정은 표 1과 같다. 보르테조밉의 초기 권장 용량은 1일 1회 1.3mg/m²의 용량을 정맥 또는 피하주사로 투여하며, 덱사메타손의 초기 권장 용량은 1일 1회 20mg이다. 이 약, 보르테조밉 및 덱사메타손의 병용요법은 질병이 진행되거나, 수용 불가능한 독성이 발생할 때까지 지속한다.

표1. 이 약과 보르테조밉 및 덱사메타손 병용요법의 권장 투약 일정

1~8 주기	일 (21일 주기)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
이 약(4mg)	○	○	○	○	○	○	○	○	○	○	○	○	○	○							
보르테조밉(1.3mg/m²)	○			○				○			○										
덱사메타손(20mg)	○	○		○	○			○	○		○	○									

9 주기 이상	일 (21일 주기)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
이 약(4mg)	○	○	○	○	○	○	○	○	○	○	○	○	○	○							
보르테조밉(1.3mg/m²)	○							○													
덱사메타손(20mg)	○	○						○	○												

2.이전에 레날리도마이드와 보르테조밉을 포함한 최소 2가지 치료를 받고, 재발 또는 불응한 환자의 치료에 덱사메타손과 병용요법 이 약의 초기 권장 용량은 반복되는 28일 주기로 제 1일 ~ 21일에 1일 1회 4mg을 경구로 투여하는 것이다. 덱사메타손의 권장 용량은 각 28일 치료 주기의 제 1일, 8일, 15일 및 22일에 1일 1회 40mg을 경구투여 한다. 이 약과 덱사메타손의 병용요법은 질병이 진행되거나, 수용 불가능한 독성이 발생할 때까지 지속한다. **[사용상의 주의사항]** 1. 경고 1) 배태자 독성 기형유발이 예상되므로, 이 약은 임신 중에 복용해서는 안 된다. 이 약은 구조적으로 탈리도마이드와 관련성이 있다. 탈리도마이드는 인간에게 중증의 치명적인 선천적 기형을 초래하는 기형 유발 물질(teratogen)로 알려져 있다. 주요 기관형성 기간 중에 투여되는 경우, 이 약은 쥐와 토끼 모두에서 발생독성이 있는 것으로 확인되었다. 환자에게 임신 가능성이 없다는 신뢰할만한 증거가 없는 경우에는, 모든 환자들에 대해 임신 예방 프로그램의 조건들이 충족되어야 한다. 2) 이 약의 기형발생 독성 때문에 이 약이 태아에 노출되는 것을 막기 위하여 위해관리프로그램에 등록한 의사와 약사만이 처방 및 조제할 수 있고, 이 프로그램에서 정하고 있는 사항에 동의하고, 서명한 환자에 한하여 처방할 수 있다. 환자들은 이 프로그램을 준수하여야 한다. 제조사로부터 동 프로그램에 대한 자세한 정보를 제공받아야 한다. 3) 혈액학적 독성 재발성/불응성 다발성 골수종 환자에서 가장 흔하게 보고된 등급 3 또는 4의 혈액학적 이상반응은 호중구 감소증이며, 빈혈 및 혈소판 감소증이 그 뒤를 이었다. 환자들의 혈액학적 이상반응, 특히 호중구 감소증에 대해 관찰되어야 한다. 환자들에게는 발열 반응에 대해 즉시 보고하도록 권고되어야 한다. 특히 출혈 위험성을 증가시키는 것으로 알려진 의약품을 동시에 사용하는 경우, 의사들은 비출혈을 포함한 출혈의 징후에 대해 환자들을 관찰해야 한다. 베이스라인, 초기 8주 동안엔 주 1회, 그리고 이후로는 1개월 간격으로 전체 혈구수 측정 결과가 관찰되어야 하며 용량 조절이 필요할 수 있다.(용법용량 참조) 환자들은 혈액제제 및/또는 성장인자(growth factor)의 투여가 필요할 수 있다. 4) 혈전색전성 질환 덱사메타손과 함께 이 약을 투여 받은 환자들에서 정맥 혈전색전성 질환(주로 심부정맥 혈전증과 폐색전증) 및 동맥 혈전성 질환이 발생했다. 혈전증의 기왕력을 포함하여 알려진 혈전색전증의 위험인자들을 가지는 환자들은 철저하게 관찰되어야 한다. 조정 가능한 위험인자들(예. 흡연, 고혈압 및 고지혈증)을 최소화하기 위해 조치가 취해져야 한다. 환자 및 의사는 혈전색전증의 징후 및 증상을 관찰하도록 권고되어진다. 환자들에게는 호흡곤란, 흉통, 팔 또는 다리 부종과 같은 증상이 발생하는 경우 치료를 받도록 지시하여야 한다. 특히 추가적인 혈전성 위험인자를 가진 환자들의 경우, 항응고 치료(금기가 아닌 경우)가 권장된다(아세틸살리실산(acetylsalicylic acid), 와파린 (warfarin), 헤파린(heparin), 또는 클로피도그렐(clopidogrel)). 예방적 조치를 취할 것인지에 대한 결정은 개별 환자의 기저 위험인자들을 주의 깊게 평가한 후에 이루어져야 한다. 임상시험에서, 환자들은 예방목적의 아세틸살리실산 또는 대체 가능한 항혈전 치료를 받았다. 적혈구 생성제의 사용은 혈전색전증을 포함한 혈전성 독성 발생의 위험을 수반한다. 따라서 혈전색전성 질환의 위험을 증가시킬 수 있는 다른 제제들뿐만 아니라 적혈구 생성제(Erythropoietic agent)들은 신중하게 사용되어야 한다. 5) 이차 원발성 악성 종양 이차 원발성 악성종양이 이 약을 투여받고 있는 환자들에서 보고된 바 있다. 의료진은 이차 원발성 악성종양의 발생에 대한 표준 암 검진을 통하여 이 약의 투여 전 및 투여 중 환자들을 주의 깊게 평가하고 지시된 대로 치료를 시작해야 한다. 6) 어지러움 및 혼동 이 약 투여 후 어지러움 및 혼동상태가 보고된 바 있다. 환자들은 어지러움 또는 혼동이 문제가 될 수 있는 상황을 피해야 하며, 먼저 의사의 진찰을 받지 않고 어지럼증 또는 혼동을 초래할 수 있는 다른 의약품을 복용해서는 안 된다. **[사용기한]** 제조일로부터 48개월 **[저장방법]** 기밀용기, 실온(1~30℃)보관 **[포장단위]** 21캡슐/PTP/팩 ※ 기타 자세한 사항은 제품설명서를 참조하시거나 세엘진(유)(전화번호 02-3469-7800)로 문의하시기 바랍니다 **제조자** Celgene International Sàrl Route de Perreux 1, 2017 Boudry, Switzerland **제조자(2차 포장)** Bollore Logistics(Singapore) Pte. Ltd. 101 Alps Avenue #03-01 Singapore 498793 **수입판매원** 세엘진 (유) 서울시 강남구 테헤란로 504, 11층 (대치동, 해성1빌딩) 개정연월일 : 2019년 10월 30일

2003KR21PR000065-01 / Feb.2021

DARZALEX®
daratumumab
concentrate for solution for infusion

다발골수종 치료를 도약시킬 새로운 클래스의 시작

다잘렉스®주 [전문의약품]

[조성·성상] 1. 조성 400mg : 1 바이알 (20 mL) 당 다라투무맙 400mg, 100mg : 1바이알(5mL) 당 다라투무맙 100mg. 2. 성상 무색 내지 노랑색의 액이 무색투명한 바이알에 든 주사제 **[효능·효과] ·새롭게 진단된 조혈모세포이식이 적합하지 않은 다발골수종 환자에 대한 보르테조밉, 멜팔란 및 프레드니솔론과 병용요법 ·새롭게 진단된 조혈모세포이식이 적합한 다발골수종 환자에 대한 보르테조밉, 탈리도마이드 및 덱사메타손과의 병용요법 ·새롭게 진단된 조혈모세포이식이 적합하지 않은 다발골수종 환자 또는 이전에 한 가지 이상의 치료를 받은 다발골수종 환자에서 레날리도마이드 및 덱사메타손과의 병용요법 ·이전에 한 가지 이상의 치료를 받은 다발골수종 환자에서 보르테조밉 및 덱사메타손과의 병용요법 ·프로테아좀억제제와 면역조절제제를 포함하여 적어도 세 가지 치료를 받은 경우로서, 재발 또는 불응성 다발골수종의 치료 [용법·용량]** 주입 전/후 약물을 투여 해야하며, 만일 주입관련반응이 나타나는 경우 적절한 의료처치를 행해야 한다.**1. 전 처치 :** 주입관련반응의 위험을 줄이기 위하여 다음의 약을 매번 주입하기 1-3시간 젼에 모든 환자에게 투여한다. **1) 코르티코스테로이드**(장시간 또는 중간시간 작용형): **[단독요법 시]** 첫 번째 및 두 번째 투여 전, 메틸프레드니솔론 100 mg 또는 이와 동등한 용량을 정맥 투여한다. 세 번째 투여부터 용량을 감량할 수 있다. (경구 또는 정맥주사 메틸프레드니솔론 60 mg) **[병용요법 시]** 덱사메타손 20mg(또는 이와 동등한)을 이 약을 투여하기 전 매번 투여한다. 덱사메타손이 기저요법으로의 코르티코스테로이드인 경우, 이 약의 투여일에는 덱사메타손 치료 용량이 전 처치 약물을 대신한다. 이 약 첫 번째 투여 시에는 투여 전 덱사메타손을 정맥 주사하고, 이후부터는 이 약 투여 전 경구 투여를 고려할 수 있다. 환자가 전 처치 약물로 덱사메타손을 투여받은 경우, 추가적인 기저요법으로의 코르티코스테로이드(예, 프레드니솔론)는 이 약 투여일에 투여해서는 안 된다. **2) 해열제** (경구 아세트아미노펜 650 - 1,000 mg) 3) 항 히스타민제 (경구 또는 정맥투여 디펜히드라민 25 - 50 mg 또는 이와 동등한 약물). **2. 이 약의 투여** 만 18세 이상의 성인에 대한 이 약의 권장용량은 16 mg/kg 이며 스케쥴에 따라 정맥 주입한다. **1) 새로 진단된 다발골수종 : 조혈모세포이식이 적합하지 않은 환자에 대한 보르테조밉, 멜팔란, 프레드니솔론과 병용요법 시 투여일정 (6주 사이클) 1주에서 6주까지** 1주 간격 투여 (총 6회), **7주에서 54주까지** 3주 간격 투여 (총 16회), **55주부터 질병 진행 전까지** 4주 간격 투여. **병용약물의 투여 : 보르테조밉은 제1주기(6주)** 피하주사로 체표면적 당 1.3mg/m^2 용량으로 1, 2, 4, 5주차에 주 2회 투여(8회 투여), 제2~9주기: 1, 2, 4, 5 주차에 주 1회 투여한다.(각 주기당 4회 투여). 멜팔란은 9mg/m^2 용량으로, 프레드니솔론은 60mg/m^2 용량으로 9주기(1 치료주기 당 각 6주) 동안 각각 경구 투여한다(제1~9주기). **조혈모세포이식이 적합한 환자에 대한 보르테조밉, 탈리도마이드, 덱사메타손과 병용요법 시 투여일정 (4주 사이클) [유도요법] 1주에서 8주까지** 1주 간격 투여 (총 8회), **9주에서 16주까지** 2주 간격 투여 (총 4회) **[공고요법] 1주에서 8주까지** 2주 간격 투여 (총 4회) **병용약물의 투여** : 보르테조밉은 체표면적 당 1.3mg/m^2 용량으로 2주 동안 주 2회(1, 4, 8, 11일) 투여하는 28일(4주)을 한 주기로 하여 유도요법(제1~4주기)과, 제 4주기 이후 조혈모세포이식에 이어 두 주기의 공고요법(제5~6주기)을 반복한다. 탈리도마이드는 보르테조밉을 투여하는 6주기 동안 100mg 1일 1회 경구 투여한다. 덱사메타손은 경구 또는 정맥투여로서 제1~2주기의 1,2,8,9,15,16,22,23 일에 40mg을 투여하고, 제 3~4주기의 1,2 일에는 40mg, 그 이후 투약일(8, 9, 15, 16일)에는 20mg을 투여한다. 제 5~6주기에는 1, 2, 8, 9, 15, 16일에 덱사메타손 20mg을 투여한다. **조혈모세포이식이 적합하지 않은 환자에 대한 레날리도마이드/덱사메타손과의 병용요법 (4주 사이클) : 재발/불응성 레날리도마이드/덱사메타손 병용요법과 동일 2) 재발/불응성 다발골수종 : 단독요법 및 레날리도마이드/덱사메타손과의 병용요법 (4주 사이클) 1주에서 8주까지** 1주 간격 투여 (총 8회), **9주에서 24주까지** 2주 간격 투여 (총 8회), **25주부터 질병 진행 전까지** 4주 간격 투여. 병용약물의 투여 레날리도마이드는 28일(4주)을 1 치료주기로 하여 반복 투여하며, 1일~21일까지 25mg 1일 1회 경구 투여하고, 덱사메타손은 40mg/주(75세 초과 혹은 BMI 18.5 미만의 경우 20mg/주로 감량)로 경구투여 또는 정맥투여한다. **보르테조밉/덱사메타손과의 병용요법 (3주 사이클)** 1주에서 9주까지 1주 간격 투여 (총 9회), 10주에서 24주까지 3주 간격 투여 (총 5회), 25주부터 질병 진행 전까지 4주 간격 투여. 보르테조밉은 체표면적 당 1.3mg/m^2 용량으로 2주 동안 주 2회(1, 4, 8, 11일) 투여하는 21일(3주)을 한 주기로 하여 총 8번의 주기를 반복한다. 덱사메타손은 보르테조밉을 투여하는 8주기 동안 1, 2, 4, 5, 8, 9, 11, 12일에 20mg씩 경구 투여하거나(보르테조밉 1 치료주기(3주) 중 2주 간 80mg/주), 75세 초과, BMI 18.5 미만, 당뇨가 잘 조절되지 않거나 이전에 스테로이드 요법에 내약성이 낮았던 경우 20mg/주로 감량하여 투여한다. 3. 주입 후 약물 지연된 주입관련반응의 위험을 줄이기 위하여 주입 후 약물을 다음과 같이 투여한다. 단독요법 시 매번 이 약을 투여한 이후 2일 동안(주입 후 다음 날 부터 시작) 경구 코르티코스테로이드(메틸프레드니솔론 20 mg 또는 이와 동등한 용량의 중간 시간 또는 장시간 작용형 코르티코스테로이드)를 투여한다. 병용요법 시 이 약 투여 다음 날 저용량 경구 메틸프레드니솔론(20mg 이하의 용량) 또는 이와 동등한 약물 투여를 고려한다. 그러나 기저 요법(background regimen)으로 코르티코스테로이드(예, 덱사메타손, 프레드니솔론)를 이 약 투여 다음 날 투여할 경우, 추가적인 주입 후 약물은 필요하지 않을 수 있다. **[사용상의 주의사항] 1. 다음 환자에는 투여하지 말 것** 이 약 또는 이 약의 구성성분에 중증의 과민반응 이력이 있는 환자 **2. 다음 환자에는 신중히 투여할 것.** 1) 이전에 이 약에 대한 주입관련반응 이력이 있는 환자 2) 기저요법으로 인해 유도된 호중구감소증이 있는 환자 3) 기저요법으로 인해 유도된 혈소판감소증이 있는 환자 **3. 이상반응** 이 약을 투여받은 환자에서 가장 빈번하게 관찰된 약물이상반응은 주입관련반응, 피로, 구역, 설사, 변비, 발열, 호흡곤란, 기침, 호중구감소증, 혈소판감소증, 빈혈, 말초부종, 무력증, 말초감각신경병증, 상기도감염이었다. 중대한 약물이상반응은 패혈증, 폐렴, 기관지염, 상기도감염, 폐부종, 독감, 발열, 탈수, 설사, 심방세동이었다. **4. 일반적 주의 1) 주입관련반응. 2) 호중구감소증/혈소판감소증 3) 대상포진 바이러스 재활성화 4) B형간염바이러스 재활성화 5) 간섭 항글로불린검사에서의 간섭(간접쿰스검사).** 이 약은 적혈구의 CD38에 결합하여 항체검사 및 교차시험을 포함한 적합성 시험을 간섭한다. **5. 임부, 수유부 1)임부** 임신 기간 중에 이 약의 사용으로 인한 위험성에 대한 사람 또는 동물실험데이터는 없다. 임신 초기에 IgG1 단클론 항체가 태반을 통과하는 것으로 알려져 있다. 그러므로 이 약은 임부에 대한 치료의 유익성이 태아에 대한 잠재적 위험을 상회한다고 판단되는 경우를 제외하고 임신 중에 투여해서는 안 된다. 만약 환자가 이 약을 투여하는 동안 임신하게 되면 환자에게 태아에 대한 잠재적 위험에 대해 알려야 한다. 태아에 대한 노출을 막기 위해 임신할 가능성이 있는 여성은 약물 투여 기간과 마지막 투여 후 3개월 동안에는 효과적인 피임을 해야 한다. **2)수유부 :**이 약이 모유 중으로 분비되는지의 여부는 알려져 있지 않다. 사람 면역글로불린 G는 모유 중으로 분비되며 신생아에 대한 위해, 흡수가능성이 알려져 있지 않기 때문에 유아에 대한 수유의 유익성과 환자에 대한 치료의 유익성을 고려하여 수유를 중단할지 치료를 중단할지 결정해야 한다. **[수입판매원] ㈜ 한국얀센** * 기타 상세한 내용은 제품설명서를 참고하시기 바랍니다. (최신 허가사항 반영일: 2021.06.07)

janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson
서울특별시 용산구 한강대로 92 LS 용산타워 25층
Tel. 02. 2094. 4500 I www.janssen.com/korea

CP-286784_17/01/2023

TAKE A STAND FOR LONGER SURVAVAL

Median OS[1] (Xospata vs. salvage chemotherapy) 9.3 (95% CI, 7.7-10.7) months
vs. 5.6 (95% CI, 4.7-7.3) months HR=0.64 (95% CI, 0.49-0.83); p<0.001

조스파타®가 2022년 3월 1일, 드디어 건강보험 급여가 적용됩니다.[2]

조스파타®가 건강보험 급여 적용으로
FLT3 변이 양성인 재발 또는 불응성 급성 골수성 백혈병 성인 환자의 치료에
한발 더 가까운 곳에서 도움을 드릴 수 있게 되었습니다.

FLT3, Fms-Like Tyrosine kinase 3

References 1. Perl AE, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML. N Engl J Med. 2019 Oct 31;381(18):1728-1740. **2.** 암환자에게 처방·투여하는 약제에 대한 요양급여의 적용기준 및 방법에 관한 세부사항(건강보험심사평가원 공고 제2022-38호, 2022.2.25.) 시행 2022년 3월 1일

사용상의 주의사항

1. 경고 1) 분화증후군 이 약을 투여받은 환자 319명 중 3%에서 분화증후군이 보고되었다. 분화증후군은 골수 세포의 급격한 증식 및 분화와 관련이 있으며 치료되지 않을 경우 생명을 위협하거나 치명적일 수 있다. 이 약으로 치료된 환자에서 확인된 분화증후군의 증상은 발열, 호흡곤란, 흉막 삼출, 심낭 유출, 폐부종, 저혈압, 빠른 체중 증가, 말초부종, 발진 그리고 신기능 장애였다. 일부의 경우 급성 열성 호중구 피부질환이 동반되어 나타났다. 분화증후군은 이 약물의 투여 후 1일부터 82일 이내에 발생하였고, 백혈구증가증이 동반되거나 또는 동반되지 않은 형태로 나타났다. 분화증후군이 의심되면 증상이 개선될 때까지 코르티코스테로이드와 혈류 동태 모니터링을 시작한다. 증상이 개선된 이후에는 코르티코스테로이드를 점차 감량하고 코르티코스테로이드를 최소 3일 동안 투여한다. 분화증후군의 증상은 코르티코스테로이드치료의 조기중단으로 인해 재발할 수 있다. 코르티코스테로이드 치료를 시작한 이후 심각한 징후 및/또는 증상이 48 시간 이상 지속되는 경우, 징후와 증상이 더 이상 악화되지 않을 때까지 이 약의 투여를 중단한다(용법·용량 및 '4. 이상반응' 참조). **2) 가역적 후두부 뇌병증 증후군(PRES: posterior reversible encephalopathy syndrome)** 이 약을 투여받은 환자들(1%)에서 발작과 정신상태 변화 등의 증상을 동반하는 가역적 후두부 뇌병증 증후군(PRES)이 발생했다는 보고가 있었다. 해당 증상들은 치료 중단 후 소실되었다. PRES의 진단에는 뇌 영상, 가급적이면 자기공명 영상법(MRI)에 의한 확인이 필요하다. PRES가 발생한 환자들에게는 이 약의 사용을 중단하여야 한다(용법·용량 및 '4. 이상반응' 참조). **3) QT 간격의 연장** 이 약을 투여받은 환자 중 1%에서 QTcF가 500 msec를 초과하였고, 7%에서 QTcF가 기저대비 60 msec 이상 증가하였다. 이 약은 심실 재분극의 지연(QT 간격의 연장)과 연관이 있는 것으로 나타났다('4. 이상반응' 참조). 이 약의 치료 전, 치료 첫 주기의 8일째와 15일째, 그리고 이후 두 번의 연속된 투여 주기를 시작하기 전에 심전도(ECG) 검사를 실시한다. QTcF가 500 msec를 초과하는 환자들에 대해서는 이 약의 투여를 중단하거나 투여를 재개할 경우 감량하여 투여한다. 저칼륨혈증이나 저마그네슘혈증이 있으면 QT 간격이 연장될 가능성이 높 아 질 수 있 다 . 이 약의 치료 전과 치료기간 중에 저칼륨혈증이나 저마그네슘혈증을 교정한다(용법·용량 및 '4. 이상반응' 참조). **2. 다음 환자에는 투여하지 말 것** 이 약의 유효성분 또는 이 약의 구성성분에 과민반응이 있는 환자. 아나필락시스 반응이 보고되었다. **3. 다음 환자에는 신중히 투여할 것** 이 약을 투여받은 환자(4%)에서 췌장염이 보고되었다. 췌장염을 시사하는 징후 및 증상이 발생한 환자들을 평가하고 지속적으로 관찰한다. 췌장염 증상이 있을 경우 회복될 때까지 이 약 투여를 중단하고 투여 재개하는 경우 감량하여 투여한다. **4. 이상반응** 이 약 120mg을 적어도 1회 이상 투여 받은 재발 또는 불응성 급성 골수성 백혈병 환자 319명을 대상으로 이 약의 안전성이 평가되었다. 이들에 대한 임상 시험으로 다국가 활성 대조 방식의 3상 시험 1건(2215-CL-0301)과 보조적인 용량 증량 방식의 1/2상 시험 2건(2215-CL-0101과 2215-CL-0102의 120mg 용량군)이 진행되었다. 최종 분석에서 이 약의 노출 기간은 중앙값 기준으로 111일(범위 4 ~ 1,320일)로 확인되었다. 이 약의 사용과 관련하여 가장 빈번하게 발생한 약물이상반응은, 알라닌 아미노전이효소 증가(82.1%), 아스파르테이트 아미노전이효소 증가(80.6%), 혈중 알칼리 인산분해 효소 증가(68.7%), 혈중 크레아티닌 인산활성효소 증가(53.9%), 설사(35.1%), 피로(30.4%), 오심(29.8%), 변비(28.2%), 기침(28.2%), 말초부종 (24.1%), 호흡곤란(24.1%), 어지럼증(20.4%), 저혈압 (17.2%), 사지통증(14.7%), 무력증(13.8%), 관절통(12.5%), 근육통(12.5%) 등이었다. 가장 빈번하게 발생한 중대한 이상반응(2% 이상)으로는 급성 신손상, 설사, 알라닌 아미노전이효소 증가, 호흡곤란, 아스파르테이트 아미노전이효소 증가, 저혈압, 그리고 분화증후군이었다.임상시험 중에 관찰된 이상반응을 아래 표 2에 발생 빈도 별로 구분하여 열거하였다. 발생 빈도는 다음과 같이 구분된다: 매우 흔하게(≥ 1/10); 흔하게(≥ 1/100 ~ <1/10); 흔하지 않게(≥ 1/1,000 ~ <1/100); 드물게(≥ 1/10,000 ~ <1/1,000); 매우 드물게(<1/10,000); 빈도 불명(예측할 수 없음). 각 빈도 범주안에서는 중대성이 감소하는 순서로 나열되었다.

[표 2] 이 약의 임상시험에서 보고된 이상반응

이상반응	이 약 120mg 1일 1회 투여 (N=319)		
	등급 전체 %	3등급 이상 %	빈도 구분
심장계 장애			
심장막 삼출	4.1	0.9	흔하게
심막염	1.6	0	흔하게
심부전	1.3	1.3	흔하게
심전도 QT 연장	8.8	2.5	흔하게
위장관계 장애			
설사	35.1	4.1	매우 흔하게
오심	29.8	1.9	매우 흔하게
변비	28.2	0.6	매우 흔하게
일반적 장애 및 투약 부위 상태			
피로	30.4	3.1	매우 흔하게
말초부종	24.1	0.3	매우 흔하게
무력증	13.8	2.5	매우 흔하게
권태	4.4	0	흔하게
면역계 장애			
아나필락시스 반응	1.3	1.3	흔하게
실험실 검사 소견			
알라닌 아미노전이효소 증가*	82.1	12.9	매우 흔하게
아스파르테이트 아미노전이효소 증가*	80.6	10.3	매우 흔하게
혈중 알칼리 인산분해효소 증가*	68.7	1.6	매우 흔하게
혈중 크레아틴 인산활성효소 증가*	53.9	6.3	매우 흔하게
근골격계 및 결합조직 장애			
사지통증	14.7	0.6	매우 흔하게
관절통	12.5	1.3	매우 흔하게
근육통	12.5	0.3	매우 흔하게
근골격통	4.1	0.3	흔하게
신경계 장애			
어지럼증	20.4	0.3	매우 흔하게
가역적 후두부 뇌병증 증후군	0.6	0.6	흔하지 않게
비뇨기 및 배뇨장애			
급성 신손상	6.6	2.2	흔하게
호흡기, 흉부, 종격동 장애			
기침	28.2	0.3	매우 흔하게
호흡곤란	24.1	4.4	매우 흔하게
분화증후군	3.4	2.2	흔하게
혈관계 장애			
저혈압	17.2	7.2	매우 흔하게

MedDRA(v. 19.1)의 우선 용어(PT) 적용. * 발생 빈도는 중앙 실험실 검사 수치를 기준으로 함.
관심대상 이상반응 1) 분화증후군 이 약의 임상시험에서 319명의 환자 중 11명(3%)이 분화증후군을 경험하였다. 분화증후군을 경험한 11명의 환자 중 9명(82%)는 치료 후 또는 이 약을 감량한 이후에 증상이 개선되었다. 분화증후군이 의심되는 경우에는 용법·용량 및 '1. 경고'를 참조한다. **2) 가역적 후두부 뇌병증 증후군(PRES)** 이 약의 임상시험에서 319명의 환자 중 0.6%가 PRES를 경험하였다. PRES는 드물고 가역적이며, 신경학적 장애로서 고혈압을 동반하거나 동반하지 않은 상태로 발작, 두통, 착란, 시각 및 신경학적 장애를 포함한 증상으로 빠르게 발전할 수 있다. 이 약의 치료를 중단한 이후에는 증상이 소실되었다(용법·용량 및 '1. 경고' 참조). **3) QT 연장** 임상시험에서 319명의 환자 중 이 약 120mg을 투여한 환자에서 4명(1%)이 기저치 이후 QTc 값으로서 QTcF가 500 msec을 초과하였다. 추가로, 모든 용량에 걸쳐 12명의 재발성 불응성 급성 골수성 백혈병 환자(2.3%)에서 최대 기저치 이후 QTcF 간격이 500 msec을 초과하였다(용법·용량 및 '1. 경고', 그리고 '14. 전문가를 위한 정보의 (1) 약력학적 특성' 참조) 문서작성일: 2022년 2월 14일

astellas **한국아스텔라스 제약** (06164) 서울특별시 강남구 테헤란로 521 파르나스타워 7층 Tel.02-3448-0504 Fax. 02-3448-0510 AKR-XSP-202202-05

XOSPATA® gilteritinib

ULTOMIRIS® will be the New Standard of Care for PNH

Selected prescribing information

울토미리스®주 300 mg / 30 ml 라불리주맙 정맥주사용 | 전문의약품

[원료약품 및 그 분량] 1바이알(30mL)중 유효성분 : 라불리주맙(별규)……300mg **[효능·효과]** 성인의 발작성 야간 혈색소뇨증 (PNH)의 치료 **[용법·용량]** 이 약은 환자의 체중에 따라 표1에 정한 용량으로 정맥 내 점적 투여한다. 초기 용량 투여 2주 후부터 8주 마다 한 번씩 유지 용량으로 투여한다. 투여일정은 예정된 투여일의 ±7일까지(이 약의 첫 번째 유지 용량 제외) 때때로 변경될 수 있지만, 그 다음 투여는 원래 일정에 따라 관리해야 한다. 에쿨리주맙 제제에서 이 약으로 바꾸는 경우, 에쿨리주맙 제제 마지막 투여 2주 후에 이 약을 환자의 체중에 따라 표1에 정한 용량(초기용량)을 투여하고, 이후 2주 후부터 8주마다 한 번씩 유지 용량으로 투여한다. (표 1은 제품설명서 전문 참고) **[사용상의 주의사항] 1. 경고** 1) 중대한 수막구균 감염 작용 기전에 의해, 이 약의 사용은 수막구균 감염/패혈증 (*Neisseria meningitidis*)에 대한 환자의 감수성을 증가시킨다. 수막구균성 질환은 어느 혈청군에 의해서도 발생할 수 있다. 감염의 위험성을 낮추기 위하여, 이 약의 투여가 지연됨으로 인한 위험성이 수막구균 감염 발생의 위험성보다 큰 경우를 제외하고는 모든 환자들은 반드시 이 약의 투여를 시작하기 최소한 2주 전에 수막구균 예방접종을 해야만 한다. 수막구균 예방접종을 한 후 2주가 지나기 전에 이 약의 투여를 시작하는 환자는 예방접종 후 2주까지 적절한 예방적 항생요법 치료를 받아야 한다. 흔한 병원성 수막구균 혈청군을 예방하기 위하여 가능하다면 혈청군 A, C, Y, W135 및 B에 대한 백신이 권장된다. 환자들은 백신 사용을 위한 최신의 예방접종 지침에 따라 백신을 접종 혹은 재접종 받아야 한다. 만약 환자가 에쿨리주맙 제제를 투여하다가 이 약으로 바꾸는 경우, 의사는 최신의 예방접종 지침에 따라 수막구균 예방접종이 되었는지 확인해야 한다. 예방접종이 수막구균 감염을 막는데 충분하지 않을 수 있다. 적절한 항생제 사용에 대한 공식적인 지침 제공을 고려해야 한다. 이 약을 투여받은 환자에서 중대한 수막구균 감염/패혈증 사례가 보고된 바 있고, 다른 말단 보체 억제제로 치료받은 환자에서 중대하거나 치명적인 수막구균 감염/패혈증 사례가 보고되었다. 모든 환자에 대하여 수막구균 감염 및 패혈증의 초기 증상이 나타나는지 반드시 모니터링 해야 하며, 감염이 의심되는 경우에는 즉시 평가하고, 적절한 항생제로 치료한다. 환자는 이러한 증상이나 징후에 대해 통보받아, 즉각적인 의학적 조치를 받을 수 있어야 한다. 의료진은 환자에게 환자용 정보 안내서 및 환자용 안전성 카드를 제공해야 한다. 2) 예방접종 예방접종으로 보체가 더욱 활성화 될 수 있다. 결과적으로, 발작성 야간 혈색소뇨증(PNH)를 포함한 보체-매개 질환이 있는 환자의 경우, 용혈과 같은 기저질환의 증상과 징후가 증가할 수 있다. 그러므로, 환자는 권장 예방접종 후 질병 증상을 더욱 면밀히 관찰해야 한다. **2. 다음 환자에는 투여하지 말 것** 1) 이 약의 주성분 또는 첨가제에 과민반응이 있는 환자 2) 치료되지 않은 수막구균 (*Neisseria meningitidis*) 감염 환자 3) 수막구균(*Neisseria meningitidis*) 백신을 현재 접종하지 않은 환자 또는 백신 접종 이후 2주 이내 이 약 투여를 시작한 환자로서 적절한 예방적 항생요법 치료를 받지 않은 환자(단, 이 약 투여 지연에 따른 위험이 수막구균 감염 발생 위험보다 중대한 경우는 제외)(1. 경고 1) 중대한 수막구균 감염 항 참조) **3. 다음 환자에는 신중히 투여할 것 1) 기타 전신 감염** 활성 전신감염이 있는 환자를 이 약으로 치료 시 주의해서 투여해야 한다. 이 약은 말단 보체 활성을 차단하므로 환자들은 감염, 특히 *Neisseria* 균 및 피낭성 세균(encapsulated bacteria) 감염에 대한 감수성이 증가할 수 있다. 기타 말단 보체 억제제를 투여한 환자들에서 파종성 임균 감염을 포함하는 *N. meningitidis* 외의 Neisseria 종에 의한 중대한 감염이 보고되었다. 잠재적인 중대한 감염과 그 증상 및 징후에 대한 인식을 높이기 위하여 환자용 설명서를 제공해야 한다. 임질 예방에 관해 환자에게 조언해야 한다. **4. 약물이상반응** 가장 흔한 약물이상반응은 두통, 상기도감염, 비인두염이었다. 임상시험 환자 중 가장 중대한 약물이상반응은 수막구균 감염 및 수막구균 패혈증이었다. 임상시험에서 관찰된 약물이상반응 (표 1. ≥1% 발생한 이상반응 발췌): 매우 흔하게(≥1/10) - 상기도감염, 비인두염, 두통, 흔하게(≥1/100 - <1/10): 어지러움, 구토, 메스꺼움, 설사, 복부 통증, 소화불량, 발진, 가려움증, 요통, 관절통, 근육통, 근경련, 발열, 인플루엔자 유사 증상, 피로, 오한. 무기력 PNH 임상시험을 포함한 모든 임상시험에서 이 약으로 인한 가장 중대한 약물이상반응은 수막구균성 감염/패혈증이었다. 이 약으로 치료받은 환자에서 수막구균 감염은 수막구균성 패혈증으로 나타났다. 환자는 수막구균성 패혈증의 증상이나 징후에 대해 통보받아, 즉각적인 의학적 조치를 받을 수 있어야 한다. **[제조의뢰자]** Alexion Pharmaceuticals, Inc. **[제조자(원제의약품)]** Alexion Pharma International Operations Unlimited Company **[수입·판매자]** (주)한독 **[최종개정일]** 2020. 05. 21 **※ 보다 자세한 정보는 제품설명서를 참조하시기 바랍니다.**

KR.RAV.201204

HANDOK (주)한독 서울시 강남구 테헤란로 132 T 02-527-5114 F 02-527-5001 www.handok.co.kr ALEXION

GO29365 study

Multicenter, open-label, randomized phase 1b/2 trial to evaluate safety and antitumor activity of polatuzumab in DLBCL in combination with BR.
The phase 2 part of the study randomised 80 patients to receive either BR, or BR in combination with polatuzumab for six 21-day cycles.
Eligible patients had relapsed/refractory DLBCL after ≥1 prior line of therapy and were not candidates for hematopoietic stem cell transplant.
The primary endpoint was complete response (CR) assessed by an independent review committee.

Roche

For previously treated R/R DLBCL who are not eligible for HSCT

POWERED FOR SURVIVAL

References. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2020 Jan 10;38(2):155-165.

CR

40% POLIVY+BR | **17.5%** BR

P=0.026

ORR

45% POLIVY+BR | **17.5%** BR

mPFS

9.5 Months POLIVY+BR | **3.7** Months BR

(HR, 0.36; 95% CI, 0.21 to 0.63; P<.001)[1,*]

Median OS from POLIVY®+BR combination regimen and BR regimen was 12.4 mo and 4.7 mo respectively.

(Exploratory analysis, HR=0.42; 95% CI, 0.24-0.75; P=0.002)[†]

Median observation time: 22 months
* As defined by an IRC.
† Stratification by duration of response to prior therapy (≤12 months vs>12 months).
BR=bendamustine and rituximab; **CI**=confidence interval; **CR**=complete response; **mPFS**=median Progression Free Survival; **HR**=hazard ratio; **ORR**=overall response rate; **OS**=overall survival; **DLBCL**=Diffuse Large B-cell Lyphomal; **HSCT**=Hematopoietic Stem Cell Transplantation; **R/R**=Refractory/Relapse.

POLIVY injection (polatuzumab vedotin)

COMPOSITION
1 vial(448.5mg) contains
Active ingredient: Polatuzumab Vedotin (in-house) 140mg
Excipient(stabilizer): Sucrose 288mg
Other excipients: Sodium Hydroxide, Succinic Acid, Polysorbate 20

APPEARANCE
Colorless vial filled with white to grayish-white lyophilized cake. The reconstituted solution is colorless to slightly brown, clear to slightly opalescent.

INDICATION(S)
POLIVY in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for haematopoietic stem cell transplant and who have failed at least one prior therapy.

DOSAGE AND ADMINISTRATION
The recommended dose of Polivy is 1.8mg/kg given as an intravenous infusion every 21 days in combination with bendamustine and rituximab for 6 cycles. Polivybendamustine, and rituximab can be administered in any order on Day 1 of each cycle. The recommended dose of bendamustine is 90mg/m²/day on Day 1 and 2 when administered with Polivy and rituximab. If not already premedicated, administer premedication with an antihistamine and antipyretic to patients prior to administration of Polivy. The initial dose of Polivy should be administered as a 90-minute intravenous infusion. Patients should be monitored for infusion-related reactions during the infusion and for at least 90 minutes following completion of the initial dose. If the prior infusion was well tolerated, the subsequent dose of Polivy may be administered as a 30-minute infusion and patients should be monitored during the infusion and for at least 30 minutes after completion of the infusion. If a planned dose of Polivy is missed, it should be administered as soon as possible and the schedule of administration should be adjusted to maintain a 21-day interval between doses.
Dose Modifications The infusion rate of Polivy should be slowed or interrupted if the patient develops an infusion-related reaction. Discontinue Polivy immediately and permanently if the patient experiences a life-threatening reaction. For dose modifications for peripheral neuropathy see Table 1.

Table 1 Polivy dose modifications for Peripheral Neuropathy

Severity on Day 1 of any cycle	Dose modification
Grade 2-3	Hold Polivy dosing until improvement to ≤ Grade 1. If recovered to Grade ≤ 1 on or before Day 14, restart Polivy at a permanently reduced dose of 1.4mg/kg. If a prior dose reduction to 1.4mg/kg has occurred, discontinue Polivy. If not recovered to Grade ≤ 1 on or before Day 14, discontinue Polivy.
Grade 4	Discontinue Polivy.

For dose modifications for myelosuppression see Table 2.

Table 2 Polivy, bendamustine, and rituximab dose modifications for myelosuppression

Severity on Day 1 of any cycle	Dose modification[a]
Grade 3-4 Neutropenia	Hold all treatment until ANC recovers to >1000/μL. If ANC recovers to >1000/μL on or before Day 7, resume all treatment without any additional dose reductions. If ANC recovers to >1000/μL after Day 7: restart all treatment, with a dose reduction of bendamustine from 90mg/m² to 70mg/m² or 70mg/m² to 50mg/m². If a bendamustine dose reduction to 50mg/m² has already occurred, discontinue all treatment.
Grade 3-4 Thrombocytopenia	Hold all treatment until platelets recover to>75,000/μL. If platelets recover to>75,000/μL on or before Day 7, resume all treatment without any additional dose reductions. If platelets recover to>75,000/μL after Day 7: restart all treatment, with a dose reduction of bendamustine from 90mg/m² to 70mg/m² or 70mg/m² to 50mg/m². If a bendamustine dose reduction to 50mg/m² has already occurred, discontinue all treatment.

[a] If primary cause is due to lymphoma, the dose of bendamustine may not need to be reduced.

Table 3 Polivy, bendamustine and rituximab dose modifications for Infusion-related reactions (IRRs)

Severity of IRR on Day 1 of any cycle	Dose modification
Grade 1-3 IRR	Interrupt POLIVY infusion and give supportive treatment. For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue Polivy. For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue Polivy. Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50mg/hour every 30 minutes. For the next cycle, infuse Polivy over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.
Grade 4 IRR	Stop Polivy infusion immediately. Give supportive treatment. Permanently discontinue Polivy.

PRECAUTIONS FOR USE
1. WARNINGS
1) Myelosuppression Serious and severe neutropenia and febrile neutropenia have been reported in patients treated with Polivy as early as the first cycle of treatment (see 3. Undesirable Effects). Prophylactic G-CSF administration should be considered. Grade 3 or 4 thrombocytopenia or anemia can also occur with Polivy (see 3. Undesirable Effects). Complete blood counts should be monitored prior to each dose of Polivy. More frequent lab monitoring and/or Polivy delays or discontinuation should be considered in patients with Grade 3 or Grade 4 neutropenia and thrombocytopenia. **2) Peripheral Neuropathy** Peripheral neuropathy has been reported in patients treated with Polivy as early as the first cycle of treatment, and the risk increases with sequential doses (see 3. Undesirable effects). Patients with pre-existing peripheral neuropathy may experience worsening of this condition. Peripheral neuropathy reported with Polivy treatment is predominantly sensory peripheral neuropathy; however, motor and sensorimotor peripheral neuropathy have also been reported. Patients should be monitored for symptoms of peripheral neuropathy such as hypoesthesia, hyperesthesia, paresthesia, dysesthesia, neuropathic pain, burning sensation, weakness, or gait disturbance. Patients experiencing new or worsening peripheral neuropathy may require a delay, dose reduction, or discontinuation of Polivy. **3) Infections** Serious, life threatening, or fatal infections, including opportunistic infections, such as pneumonia (including pneumocystis jirovecii and other fungal pneumonia),bacteremia, sepsis, herpes infection, and cytomegalovirus infection have been reported in patients treated with Polivy (see 3 Undesirable Effects). Patients shouldbe closely monitored during treatment for signs of bacterial, fungal, or viral infections. Anti-infective prophylaxis should be considered. Polivy and any concomitant chemotherapy should be discontinued in patients who develop serious infections. **4) Progressive Multifocal Leukoencephalopathy (PML)** PML has been reported with Polivy treatment (see 3. Undesirable effects). Patients should be monitored closely for new or worsening neurological, cognitive, or behavioral changes suggestive of PML. Polivy and any concomitant chemotherapy should be held if PML is suspected and permanently discontinued if the diagnosis is confirmed. **5) Tumor Lysis Syndrome** Patients with high tumor burden and rapidly proliferative tumor may be at increased risk of tumor lysis syndrome. Appropriate measures in accordance with local guidelines should be taken prior to treatment with Polivy. Patients should be monitored closely for tumor lysis syndrome during treatment with Polivy. **6) Embryo-Fetal Toxicity** Based on the mechanism of action and nonclinical studies, Polivy can be harmful to the fetus when administered to a pregnant woman. (see 6. Pregnancy, Lactation, Childbearing). Advise a pregnant woman of the risk to the fetus. Females of reproductive potential should be advised to use effective contraception during treatment with Polivy and for at least 9 months after the last dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Polivy and for at least 6 months after the last dose. **7) Hepatic Toxicity** Serious cases of hepatic toxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with Polivy. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Liver enzymes and bilirubin level should be monitored.
2. CONTRAINDICATIONS Polivy is contraindicated in patients with a known hypersensitivity to polatuzumab vedotin or any of the excipients.

Polivy-2020-10-27-1.0

*For more detailed product information and product-related AE cases, please contact Korea Roche 02-3451-3600. *The latest product information can be found on the Korea Roche website (www.roche.co.kr).

Roche **Roche Korea Co., Ltd.** 17th fl. GT tower, 411, Seocho-daero, Seocho-gu, Seoul. (po) 06615

POLIVY® polatuzumab vedotin

M-KR-00001027

The 1st FDA approved TPO receptor agonist

로미플레이트® 주
(로미플로스팀)

"I Take Possession of the power to help control ITP"

급여기준 ▶▷▷	
투여대상: 성인 만성 면역성(특발성) 혈소판 감소성 자반증 환자(ITP)	corticosteroid와 immunoglobulin에 불응인 비장절제환자
	corticosteroid와 immunoglobulin에 불응인 비장절제술이 의학적 금기인 환자
투여개시	혈소판수 20,000/㎕ 이하
	또는 20,000/㎕–30,000/㎕ 이더라도 임상적 의의가 있는 출혈 (중추신경계 질환, 위장관 출혈, 안 출혈 등)이 있는 경우
투여기간	치료당 최대 6개월까지 인정함

[원료의약품의 분량] 로미플레이트 250ug 1 바이알 중 (주성분) 로미플로스팀 375ug, (안정제) 수크로스(15mg), 폴리소르베이트20(0.03mg), (부형제) 만니톨 30mg, (첨가제) L–히스티딘, 묽은염산 **[성상]** 흰색의 용해용 분말이 들어있는 유리 바이알 **[효능효과]** 코르티코스테로이드 또는 면역글로불린 또는 비장절제술에 충분한 반응을 보이지 않은 만성 면역성(특발성) 혈소판 감소성 자반증 환자에서의 저혈소판증 치료 **[용법용량]** 이 약은 피하 주사로 주 1회씩 투여하여야 한다. 1) 초기 용량: 로미플로스팀의 초기 용량은 1㎍/kg이며 실제 체중을 기초로 계산한다. 2) 용량 조정: 치료 시작 시에 피험자의 실제 체중을 용량 계산에 사용하여야 한다. 주 1회 투여 로미플로스팀 용량은 환자의 혈소판 수가 ≥ 50 x 10^9/L가 될 때까지 1㎍/kg씩 증량하여야 한다. 혈소판 수가 안정될 때까지(용량 조정 없이 최소 4주간 ≥ 50 x 10^9/L) 혈소판 수를 매주 측정하여야 한다. 이후에는 1개월에 한 번씩 혈소판 수를 측정하여야 한다. 1주 최고 용량인 10㎍/kg을 초과하여서는 안 된다. 3) 치료 중단: 1주 최고 용량인 10㎍/kg로 로미플로스팀 치료를 4주간 실시한 후 혈소판 수가 임상적으로 중요한 출혈을 방지할 수 있는 충분한 수준으로 증가하지 않는 경우 로미플로스팀 치료를 중단하여야 한다.

서울특별시 강남구 논현로 430 역삼동 아세아타워빌딩 11층 (우)06223
TEL:02-3471-4321 FAX:02-3471-4322 http://www.kyowa-kirin-korea.com

Kyowa KIRIN

REWRITING CANCER SURVIVAL

with KYMRIAH®

In R/R DLBCL,

DURABLE EFFICACY

- 2-year PFS rate of 33% & OS rate of 40%[1]
- mDOR not reached at 40.3 months[1]
- ORR 52% (95% CI 41-62) & CR 40%[2]

QUALITY OF SURVIVAL

- Low rates of CRS (1–4.5%) & neurotoxicity (0-5%) in the real world[3,4]
- QoL improvements[5]

CONVENIENCE & FLEXIBILITY

- Simple, 1-time infusion[4]
- Flexible scheduling[7]

Product Information 킴리아주 (티사젠렉류셀)

처방하시기 전 QR 코드 또는 식품의약품안전처 의약품통합정보시스템(https://nedrug.mfds.go.kr)을 통해 상세 제품정보를 참조하시기 바랍니다.

NOW APPROVED

세계 최초의 CAR-T 세포 치료제 KYMRIAH®
2021년 3월 국내 허가 승인[6]

적응증[6]

- 25세 이하의 소아 및 젊은 성인 환자에서의 이식 후 재발 또는 2차재발 및 이후의 재발 또는 불응성 B세포 급성 림프성 백혈병 (B-cell acute lymphoblastic leukemia, ALL)의 치료
- 두가지 이상의 전신 치료 후 재발성 또는 불응성 미만성 거대 B세포 림프종 (diffuse large B-cell lymphoma, DLBCL) 성인 환자의 치료

JULIET Study Design[2]

Single-group, open-label, multicenter, international phase 2 pivotal study of tisagenlecleucel in adults with relapsed or refractory DLBCL. The primary end point was the best overall response rate. Of the enrolled patients, 93 patients received a single infusion (median dose, 3.0 10^8 CAR-positive viable T cells; range, 0.1 10^8 to 6.0 10^8) and were included in the evaluation of efficacy.

R/R, refractory/relapsed; PFS, progression-free survival; OS, overall survival; mDOR, median duration of response; ORR, overall response rate; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; QoL, quality of life; CAR-T, chimeric antigen receptor T-cell

1. Jaeger U, *et al.* Poster presented at the 2020 ASH Annual Meeting & Exposition, held virtually on 5-8 December 2020. Poster 1194. **2.** Schuster SJ, *et al.* N Engl J Med. 2019; 380:45-56. **3.** Pasquini MC, *et al.* Blood Adv. 2020;4(21):5414-5424. **4.** Riedell P, *et al.* Transplantation & Cellular Therapy Annual Meeting; February 19-23, 2020; Orlando, FL. Presentation 52. **5.** Maziarz RT, *et al.* Blood Adv. 2020;4:629-37. **6.** 킴리아주(티사젠렉류셀), 식품의약품안전처 의약품통합정보시스템 (nedrug.mfds.go.kr) **7.** Tyagarajan S, *et al.* Cytotherapy. 2019;21(12):1198-1205.

*Disclaimer : The materials for KYMRIAH contained in this exhibition are approved for use only in Korea. Prescribing information may vary depending on local approval in each country. Therefore, before prescribing any product, always refer to local materials such as the prescribing information and/or the Summary of Product Characteristics (SPC)

KR21071149221

NOVARTIS

KYMRIAH® (tisagenlecleucel) Dispersion for IV infusion

Otsuka

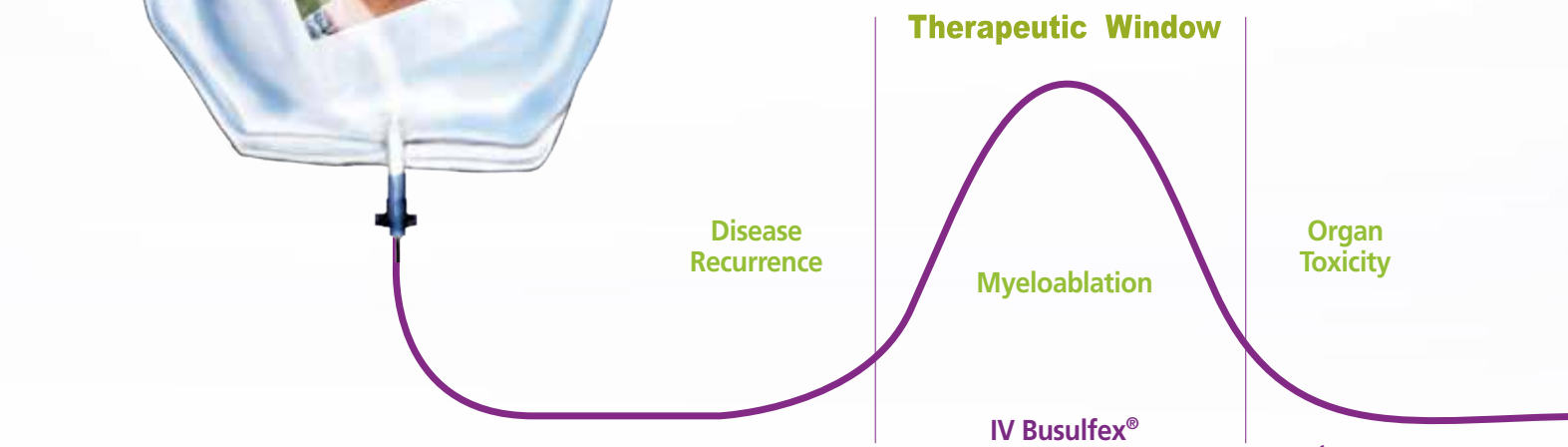
IV Busulfex®
(busulfan) Injection

IV Busulfex (Busulfan)

- **IV Bu** formulation to **achieve absolute dose assurance** associated with its controlled administration[1]
- The combination of Cy with **IV Bu** administration appeared **safer compared with that of oral Bu.**[1]
- Significantly lower incidence of HVOD with **IV Bu** compared with oral Bu and a significantly lower day-100 TRM[1]

- **Cy** : Cyclophosphamide, **Bu** : Busulfan, **HVOD** : Hepatic veno-occlusive disease
  TRM : Treatment-Realted Mortality

Target AUCss with precision



IV Busulfex®
Therapeutic Window = 900-1500 μMol/min[1]
(Target AUC values)

Reference 1. Ciurea SO, et al. *Biol Blood Marrow Transplant.* 2009;15(5):523-536.

INFORMATION

제품명 : 부설펙스 주(바이알)(부설판)(성분명 : Busulfan) 성상 : 이 약은 바이알에 충전된 무색의 액상주사제이다. **성분·함량 :** 이 약 1바이알(10ml)중 (주성분) 부설판(USP) : 60.0mg (첨가제) 폴리에틸렌글리콜400 6.7mL, 디메틸아세트아미드 3.3mL **효능·효과 :** 다음 질환에 대하여 시클로포스파미드 와 병용하여 조혈모세포 이식시 전처치요법으로 사용한다 : 급성 백혈병, 만성 골수성 백혈병, 림프종, 골수 이형성증후군 **용법·용량 :** 1) 성인 0.8 mg/kg으로서 이상 체중 또는 그 보다 낮은 실제 체중을 적용하여 4일간 매 6시간마다 16회를 중심 정맥 카테터를 통하여 2시간 동안 투여한다. 시클로포스파미드는 이 약 16회째 요법이 완료된 6시간 후, 골수이식 개시 3일전에 60 mg/kg용량으로 한시간 동안 이틀간 주입한다. 과체중 혹은 심각한 비만 환자의 경우, 교정 이상 체중(AIBW)에 근거하여 용량을 산정하여야 한다. 이상 체중(IBW)은 다음과 같이 계산된다.(단위 : 신장 cm, 몸무게 kg) IBW(남성) = 50 + 0.91 ×(신장 - 152) IBW(여성) = 45 + 0.91 ×(신장 - 152) 교정 이상 체중(AIBW)은 다음과 같이 계산된다. AIBW = IBW + 0.25 ×(실제체중 - IBW) 이 약은 교정 이상 체중 (AIBW)을 근거로 한 용량을 투여하였을 때 가장 좋은 클리어런스를 예상할 수 있다. 마른환자, 정상 및 비만 환자들의 경우 실제 체중, 이상체중(IBW) 또는 다른 인자들을 근거로 하여 투여했을 경우, 클리어런스에 유의성 있는 차이를 나타낼 수 있다. 이 약은 뇌-혈관 장벽을 통과하여 발작을 일으키는 것으로 알려져 있기 때문에 모든 환자는 페니토인으로 이를 예방하여야 한다. 페니토인은 부설판의 혈중농도- 시간곡선하면적(AUC)를 15% 감소시킨다. 다른 항경련제를 사용하면 부설판의 혈장 AUC가 높아지므로 간정맥 폐쇄성질환(VOD) 또는 발작의 위험성이 높아진다. 다른 항경련제를 사용할 경우에는 혈장 부설판 노출을 모니터해야 한다. 5-HT3계열의 구토억제제를 이 약 초회 사용 이전에 투여하여야 하며, 이 약의 계획된 투여 기간동안 계속 투여하여야 한다. 최적의 치료를 위하여 가능한한 약동학적 모니터링을 실시하는 것이 좋다. 2) 소아 소아(n=24)에 대한 약물동태학적 결과에 근거한 권장용량은 환자의 실제 체중(ABW)을 적용하여 12 kg 이하일 경우 1.1 mg/kg, 12 kg 초과일 경우 0.8 mg/kg를 4일간 매 6시간마다 16회를 중심 정맥 카테터를 통하여 2시간 동안 투여한다. 이 약의 초회 투여 후, 투여용량의 조절 및 치료 약물농도 모니터링(TDM)의 실시가 권장된다. 시클로포스파미드는 이 약 16회째 요법이 완료된 후, 골수이식 개시 5일전부터 50 mg/kg용량으로 1일 1회, 4일간 주입한다. ※ 치료 약물농도 모니터링에 근거한 소아 환자의 투여용량의 조절 초회 투약 후 목표 AUC(1,125 μM·min)에 도달하기 위한 소아 환자의 교정 투여용량은 다음과 같이 계산된다. 교정투여용량(mg) = 실제 투여용량(mg) × 목표 AUC (μM·min) / 실제 AUC (μM·min) 3) 정맥 내 투약을 위한 준비 이 약은 60mg의 부설판을 6mg/ml의 농도로서 함유하고 있는 10ml 무균 용액이며, 일회용 유리 바이알로 공급된다. 이 약은 사용 전 0.9% 생리식염수 주사액 또는 5% 포도당 주사액에 희석되어야 한다. 희석액의 양이 이 약 부피의 10배가 되어야 하며, 최종농도가 약 0.5mg/ml 으로 유지되어야 한다.

KD Code : 649900341 **포장단위 :** 10ml x 1, 8바이알 **저장방법 :** 2~8℃보관, 밀봉용기 **사용기한 :** 제조일로부터 30개월

* 기타 상세한 사항은 최신제품설명서를 참조하시기 바랍니다.

Otsuka
한국오츠카제약
Under license of Otsuka pharmaceutical Co,.Ltd
06227 서울시 강남구 역삼로 226 오츠카비전빌딩
Tel 02. 3287. 9000 | Fax 02. 3287. 9069 | www.otsuka.co.kr

BUS-19-002
Date of approval : 28 June 2019

ICLUSIG®
(ponatinib HCl) tablets

CML/Ph(+)ALL

T315I mutation disease or
After failure of 2nd generation TKIs

Iclusig®(ponatinib)는
☆ Potent pan-BCR-ABL inhibitor 로서
2세대 TKIs로 치료되지 않는 환자들에게 효과적인 약제입니다.[1]

1. Massaro F, et al. *Curr Cancer Drug Targets.* 2018;18(9):847-856.

Product Information

[제품명] 아이클루시그정15밀리그램(포나티닙염산염) 아이클루시그정45밀리그램(포나티닙염산염) **[성상]** 흰색의 양면이 볼록한 원형 필름코팅 정제 **[효능효과]** 1. 다른 티로신 키나제 억제제(TKI)로 치료되지 않는 만성기, 가속기, 급성기 만성 골수성 백혈병(CML) 또는 필라델피아 염색체 양성 급성 림프구성 백혈병(Ph+ ALL) 성인 환자의 치료. 2. T315I 양성 만성기, 가속기, 급성기 만성 골수성 백혈병(CML) 또는 T315I 양성 필라델피아 염색체 양성 급성 림프구성 백혈병(Ph+ ALL) 성인 환자의 치료. **[용법용량]** 1. 권장 용량 권장 시작 용량은 1일 1회 45mg 이다. 주요 세포유전학적 반응에 도달한 만성기 CML 및 가속기 CML 환자에 대해 이 약의 감량을 고려해야 한다. 3개월 (90일)까지 반응이 없다면, 이 약의 중단을 고려해야 한다. 이 약은 음식물에 상관없이 복용할 수 있다. 정제는 통째로 삼켜야 한다. **[사용상주의사항]** 1. 경고 1) 동맥 폐쇄 제 1상 및 제 2상 임상시험에서 이 약을 투여 받은 환자 중 최소 35%에게서 치명적인 심근경색, 뇌졸중, 뇌의 큰 동맥 협착, 중증 말초혈관 질환을 포함한 동맥 폐쇄가 발생하였다. 제2상 임상시험에서 최소 48개월 추적조사 시 치료를 지속중인 환자(N=133)를 포함한 이 약을 투여 받은 환자 중 33%(150/449)가 심혈관(21%), 말초혈관(12%), 또는 뇌혈관(9%) 동맥폐쇄 사례를 경험하였으며, 일부 환자는 1가지 유형 이상의 동맥폐쇄 사례를 경험하였다. 이 약은 치료 시작 후 2주 이내 및 하루 15mg 정도의 낮은 용량에도 치명적이고 생명을 위협하는 동맥 폐쇄를 유발할 수 있다. 또한 이 약은 재발성 또는 다병소성 혈관 폐쇄를 유발할 수 있다. 환자들은 이 약에 의한 혈관 폐쇄로 인해 혈관재개통술 (관상동맥, 뇌혈관 및 말초동맥)을 받아야 했다. 제 2상 임상시험에서, 최초 심혈관, 뇌혈관 및 말초동맥 폐쇄성 사례의 발생 시까지의 기간 중앙값은 각각 193일(범위: 1-1355), 526일(범위: 5-1339), 478일(범위: 3-1344)이었다. 심혈관 위험인자가 있었던 환자와 없었던 환자 모두에서 이러한 사례들을 경험하였으며, 여기에는 50세 이하 환자도 포함되어 있었다. 동맥 폐쇄 사례가 나타난 환자에서 관찰된 가장 흔한 위험인자는 고혈압(62%, 93/150), 고지혈증(61%, 91/150) 및 심장질환 병력(48%, 72/150)이었다. 동맥 폐쇄성 이상사례들은 연령이 증가할수록, 그리고 허혈, 고혈압, 당뇨병 또는 고지혈증의 과거력이 있는 환자일수록 더 흔하게 나타났다. ※기타 상세한 사항은 최신의 제품설명서를 참조하시기 바랍니다.

Otsuka
한국오츠카제약
Under license of Otsuka pharmaceutical Co.,Ltd

06227 서울시 강남구 역삼로 226 오츠카비전빌딩
Tel 02. 3287. 9000 | Fax 02. 3287. 9069 | www.otsuka.co.kr

ICS-20-002 | 20200629 approved

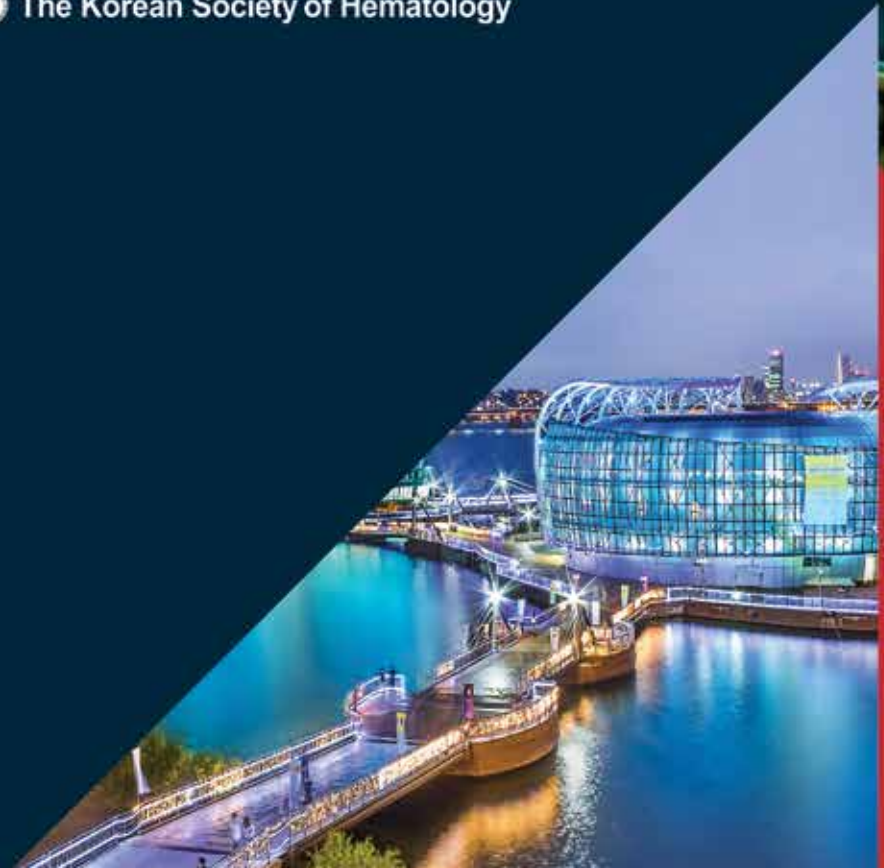
www.icksh.org

iCKSH 2023

2023 KOREAN SOCIETY OF HEMATOLOGY INTERNATIONAL CONFERENCE & 64th ANNUAL MEETING

MARCH 30 - APRIL 1, 2023

The Korean Society of Hematology



The Korean Society of Hematology

ICKSH 2022 Secretariat: PEOPLE-X, Corp.
17, Hanamnum B/D 16, Yeoksam-ro 17-gil,
Yeoksam-dong, Gangnam-gu, Seoul 06246, Korea
Tel. +82-2-566-6031, 6033
Fax. +82-2-566-6087
E-mail. icksh@icksh.org