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BLOOD RESEARCH

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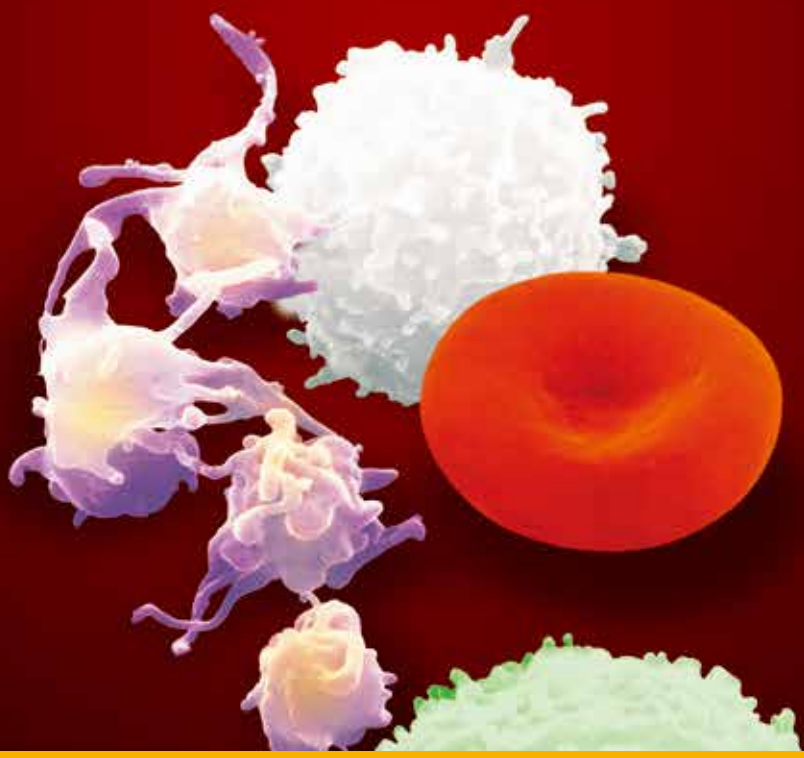
2019 Korean Society of Hematology
International Conference &
60th Annual Meeting

Date : March 14(Thu) - 16(Sat), 2019
Venue : Grand Walkerhill Hotel, Seoul, Korea



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ICKSH 2019

MARCH 14 - 16, 2019

Grand Walkerhill Hotel, Seoul, Korea

2019 KOREAN SOCIETY OF
HEMATOLOGY International Conference
& 60th Annual Meeting

The Korean Society of Hematology

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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.

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Open Access Policy

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

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WELCOME MESSAGE

Dear Colleagues,

On behalf of the Organizing Committee, it is our great honor and pleasure to invite you to the 2019 KSH International Conference & the 60th Annual Meeting, hosted by the Korean Society of Hematology (KSH), which will be held in Seoul, Korea from March 14 to 16, 2019.

The Korean Society of Hematology successfully held the first ICKSH in conjunction with BTG last year, surpassing all expectations. Now, the Organizing Committee is positioning the KSH to lead the field of hematologic diseases through the relationships and cooperation of many countries by sharing our treatment technology with the world. The ICKSH will offer the unique opportunity to learn about the latest findings and research from renowned specialists as well as to exchange ideas and information on the most recent trends.

Our programs will include benign hematologic diseases, various types of hematologic malignancies, coagulation/thrombosis related disorders and transfusion medicine through plenary lectures, as well as scientific and education sessions. In addition, a variety of stimulating social programs has been planned so participants can enjoy the fascinating Korean culture and share our warm spirit of friendship.
We welcome you all and hope you enjoy ICKSH 2019 in Seoul, Korea.

Chan-Jeoung Park, M.D., Ph.D.
Congress Chair
The Korean Society of Hematology

Bin Cho, M.D., Ph.D.
President
The Korean Society of Hematology

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PROGRAM AT A GLANCE Thursday, March 14

Time	VISTA 1	VISTA 2	VISTA 3	GRAND HALL
08:00-09:00	Registration			
09:00	OPENING REMARKS			
09:00-10:30	**JS01** KAI-KSH JOINT SYMPOSIUM Immunotherapeutics in Blood Disease	**SS01** Bone Marrow Failure		
	IL-7-hyFc, a long-acting recombinant IL-7 protein, generates anti-tumor activity by modulating both adaptive and innate immune cells in the tumor microenvironment (Seung-Woo Lee, Korea)	Paroxysmal nocturnal hemoglobinuria in bone marrow failure (Jun Ho Jang, Korea)		
	Towards next-generation CAR-T cell therapy for cancer (Chan Hyuk Kim, Korea)	Germline mutations in inherited bone marrow failure (Jean Soulier, France)		
	Immunotherapeutics in blood disease: Cytotoxic T lymphocyte therapy (Hyewon Lee, Korea)	Telomere length and somatic mutations in aplastic anemia (Dong Soon Lee, Korea)		
	Immune checkpoint inhibitor in lymphoma (Yoon Seok Choi, Korea)			
10:30-10:45	Coffee Break			
10:45-11:45	**PL01** Gene Therapy in Hematology			
	Application of CRISPR/Cas-9 in blood disease (Matthew H. Porteus, USA)			
	Gene therapy for hemophilia-will there be a new era in hemophilia treatment? (Katherine Ann High, USA)			

PROGRAM AT A GLANCE Thursday, March 14

Time	VISTA 1	VISTA 2	VISTA 3	GRAND HALL
11:45-12:45	**PRESIDENTIAL SYMPOSIUM**			
	Stem cells in human AML (Ravi Majeti, USA)			
	Precision medicine in pediatric acute lymphoblastic leukemia (Ching-Hon Pui, USA)			
12:45-13:40	[Luncheon] **LS01** NOVARTIS	[Luncheon] **LS02** AMGEN		[Luncheon] **LS03** Roche
	Treatment free remission in CML: Promise and challenges (Adam Mead, UK)	Optimal treatment sequencing for patients with relapsed/refractory multiple myeloma (Ajai Chari, USA)		Current issues in the treatment of B-cell lymphoma (Seok Jin Kim, Korea)
13:40-14:40	**AS01** Lymphoid	**AS02** Myeloid		
	Treatment of Philadelphia chromosome positive acute lymphoblastic leukemia- Korean perspectives (Young Rok Do, Korea)	CML in Philippines (Priscilla B. Caguioa, Philippines)		
	Hematopoietic stem cell transplantation for adult acute lymphoblastic leukemia in Taiwan – on Behalf of TSBMT (Tran-Der Tan, Taiwan)	Outcome of allogeneic hematopoietic stem cell transplantation for SAA and PNH at Vietnam national institute of haematology and blood transfusion (Binh Thi Thanh Vo, Vietnam)		
	Adult ALL in Malaysia (Sen Mui Tan, Malaysia)	Hemoglobinopathy in Thailand (Duantida Songdej, Thailand)		

PROGRAM AT A GLANCE Thursday, March 14

Time	VISTA 1	VISTA 2	VISTA 3	GRAND HALL
14:40-14:55	Coffee Break			
14:55-16:25	**JS02** KOGO-KSH JOINT SYMPOSIUM Genomics for Precision Hematology	**SS02** Multiple Myeloma	**SS03** Transplantation/ Cell Therapy	**ES01** Iron Metabolism
	Understanding angioimmunoblastic T-cell lymphoma: From genomics to animal pathology (Jaesang Kim, Korea)	Immunological weapons against multiple myeloma (Je-Jung Lee, Korea)	Thymidine kinase cell therapy (Maria Chiara Bonini, Italy)	Iron metabolism in hemoglobinopathies (Vip Viprakasit, Thailand)
	Genomic pathogenesis of Epstein–Barr virus (EBV)-induced diffuse large B cell lymphoma (Sung-Yup Cho, Korea)	Roles of bone marrow microenvironment in clonal evolution and drug resistance of multiple myeloma (Yusuke Furukawa, Japan)	Updates on CAR T cell therapy for multiple myeloma (Jesús G. Berdeja, USA)	Deferasirox for iron overload patients: Preserving organ functions (Norbert Gattermann, Germany)
	Current status of precision hematology (Young-Uk Cho, Korea)	Antigen-mediated regulation in myeloma (Madhav V. Dhodapkar, USA)	Accelerating personalization of immune therapies for blood cancers (Larry W. Kwak, USA)	Management of iron overload in MDS (Heather Alice Leitch, Canada)
	Clinical application of personalized medicine for AML (Joon-ho Moon, Korea)			
16:25-16:40	Break			

PROGRAM AT A GLANCE Thursday, March 14

Time	VISTA 1	VISTA 2	VISTA 3	GRAND HALL
16:40-18:10	**SS04** Myeloproliferative Neoplasm	**SS05** Bleeding Disorder/ Thrombosis	**SS06** Pediatric Disease	**ES02** Indolent Lymphoma: From Genetics to the Clinic
	Genetic causes of myeloproliferative diseases: Stratification of patients and new therapeutic targets (Robert Kralovics, Austria)	Progress in gene therapy for hemophilia A and B (Glenn F. Pierce, USA)	Inherited hematologic malignancies (Lucy Ann Godley, USA)	Mantle cell lymphoma -from the clinic to genetics (Mats Jerkeman, Sweden)
	Molecular mechanism of MPN development by mutant calreticulin (Norio Komatsu, Japan)	Individualized treatment for hemophilia: Population pharmacokinetics approach (Cindy H. T. Yeung, Canada)	GATA2 deficiency: How to make the diagnosis ? How to treat it ? (Jean Donadieu, France)	From genetics to the clinic: Follicular lymphoma (Gilles Salles, France)
	Interferon in myeloproliferative neoplasms (Jean-Jacques Kiladjian, France)	Mechanisms of cancer-associated thrombosis (Nigel Mackman, USA)	Roles of monosomy 7 and SAMD9/SAMD9L mutations in myeloid leukemogenesis (Hirotaka Matsui, Japan)	From genetics to the clinic of chronic lymphocytic leukemia (Wei Xu, China)
18:10-18:30	Break			
18:30-20:00	WELCOME RECEPTION (Re: BAR, Vista Walkerhill Seoul, 1F)			

PROGRAM AT A GLANCE Friday, March 15

Time	VISTA 1	VISTA 2	VISTA 3
08:00-09:00	Registration		
09:00-10:30	**JS03** EHA-KSH JOINT SYMPOSIUM I Multiple Myeloma	**SS07** Benign Hematology	**SS08** Histiocytosis
	Monoclonal antibodies in the treatment of multiple myeloma (Francesca Maria Gay, Italy)	EuroBloodNet: The rare anaemia disorders European epidemiological platform (María del Mar Mañú Pereira, Spain)	Langerhans cell histiocytosis 2019: New insights and opportunities (Carl E. Allen, USA)
	Treatment for advanced multiple myeloma in Korea (Chang-Ki Min, Korea)		
	Experimental therapy except monoclonal antibodies (Francesca Maria Gay, Italy)	Clinical utility of high-throughput sequencing for the diagnosis of hereditary hemolytic anemia (Myungshin Kim, Korea)	Treatment of HLH - today and tomorrow (Jan-Inge Henter, Sweden)
	Clinical outcomes of cytogenetic high-risk multiple myeloma in Korea (Kihyun Kim, Korea)	The molecular spectrum of hemoglobinopathy: Thalassemia and Hb variants (Cornelis Leonard Harteveld, The Netherlands)	Genetic studies on the hemophagocytic lymphohistiocytosis (HLH) in Korea (Jong Jin Seo, Korea)
10:30-10:45	Coffee Break		
10:45-11:45	**PL02** Clinical Hematology		
	Breakthroughs in the treatment of aplastic anemia (Neal Stuart Young, USA)		

PROGRAM AT A GLANCE Friday, March 15

Time	GRAND HALL	WALKER HALL 1	WALKER HALL 2
08:00-09:00	Registration		
09:00-10:30	**ES03** Acute Lymphoblastic Leukemia		
	Pharmacogenetics in patients with childhood acute lymphoblastic leukemia (Yoichi Tanaka, Japan)		
	Recent advances in the treatment of adult ALL (Won Sik Lee, Korea)		
	Mutational landscape of ALL: Next-generation sequencing-based mutations scanning strategy (Seung-Tae Lee, Korea)		
10:30-10:45	Coffee Break		
10:45-11:45			

PROGRAM AT A GLANCE Friday, March 15

<table>
<tr><th>Time</th><th>VISTA 1</th><th>VISTA 2</th><th>VISTA 3</th></tr>
<tr><td>11:45-
12:45</td><td>AS03
Special Report from JSH, CAH, KSH</td><td colspan="2" rowspan="3">POSTER PRESENTATION
(Exhibition Hall, B3)</td></tr>
<tr><td>Developing strategies to improve efficacy and safety of chimeric antigen receptor cell therapy
(Kyung-Nam Koh, Korea)</td></tr>
<tr><td>New insights into poor hematopoietic reconstitution after allo-HSCT
(Yuan Kong, China)</td></tr>
<tr><td>12:45-
13:40</td><td>[Luncheon]
LS04
Bristol-Myers Squibb</td><td colspan="2">[Luncheon]
LS05
Takeda ONCOLOGY</td></tr>
<tr><td></td><td>Advances of CML management and the prospects for the future
(Susanne Saußele, Germany)</td><td colspan="2">A new paradigm shift in frontline treatment of hodgkin lymphoma
(Andrea Gallamini, France)</td></tr>
<tr><td>13:40-
13:50</td><td colspan="3">Coffee Break</td></tr>
</table>

PROGRAM AT A GLANCE Friday, March 15

Time	GRAND HALL	WALKER HALL 1	WALKER HALL 2
11:45-12:45	POSTER PRESENTATION (Exhibition Hall, B3)		
12:45-13:40	[Luncheon] **LS06** KYOWA KIRIN The role of the darbepoetin alfa of the treatment for low-risk of MDS (Jun Ho Jang, Korea)		
13:40-13:50	Coffee Break		

PROGRAM AT A GLANCE Friday, March 15

Time	VISTA 1	VISTA 2	VISTA 3
13:50-15:05	**OP01** AML/MDS	**OP02** ALL	**OP03** Lymphoma
15:05-16:20	**OP07** AML/MDS	**OP08** Multiple Myeloma	**OP09** Lymphoma/Histiocytosis
16:20-16:35	Break		
16:35-18:05	**SS09** Future ICT based Medicine	**SS10** Acute Myeloid Leukemia/ Myelodysplastic Syndromes	**SS11** Chronic Myeloid Leukemia
	Deep learning for CRISPR-Cpf1 research (Sungroh Yoon, Korea)	Genomics of core-binding factor AML (Nicolas Duployez, France)	Is chronic myeloid leukemia a single hit disorder?: Evidence from next-generation sequencing data (Dennis Kim, Canada)
	Precision dinner: Genomes and health records (Ju Han Kim, Korea)	Precision medicine in AML in the era of novel agents (Gail J. Roboz, USA)	NGS-based ABL1 kinase domain mutation detection (Simona Soverini, Italy)
	Connected health and wellness journey (Jack Ahn, USA)	Incorporation of molecular assessments in risk stratification for myelodysplastic syndromes: Ready for prime time? (Amer M. Zeidan, USA)	Precision medicine and immunity in CML (Satu Mustjoki, Finland)
18:05-18:30	Break		
18:30-20:00	GALA DINNER (Walkerhill Theatre, B1)		

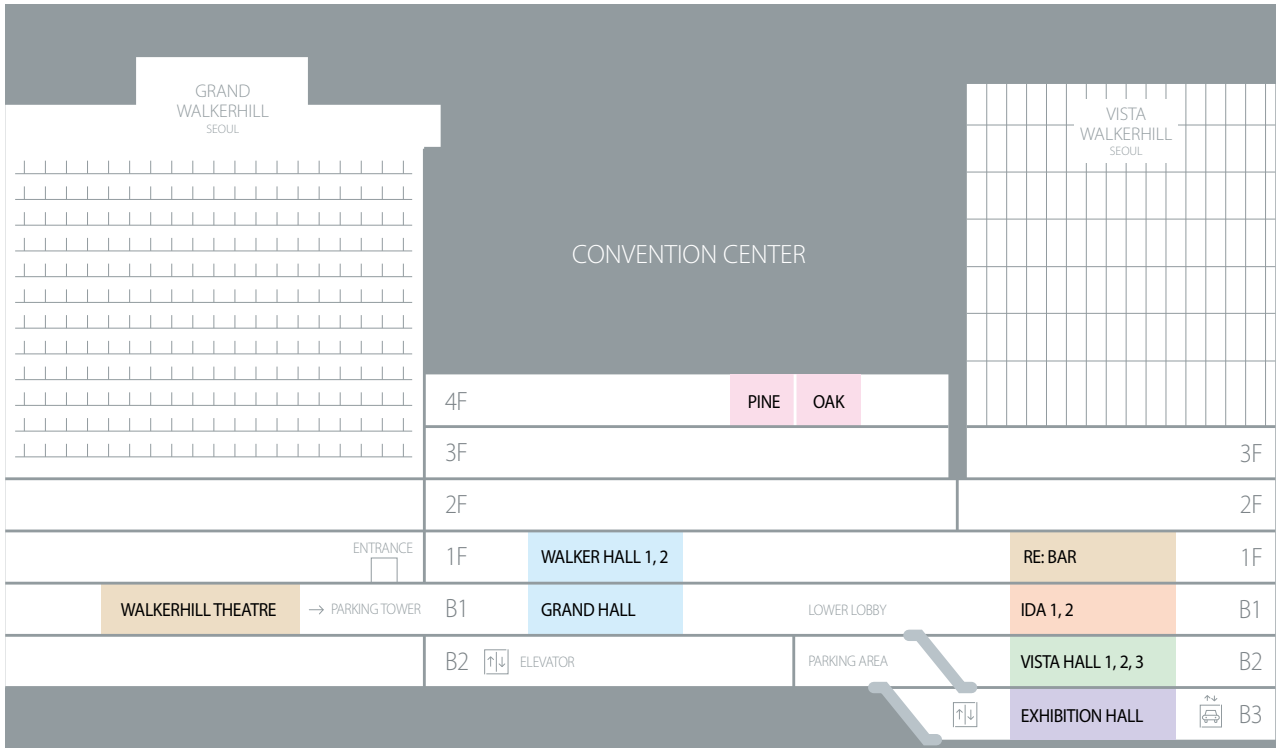
PROGRAM AT A GLANCE Friday, March 15

Time	GRAND HALL	WALKER HALL 1	WALKER HALL 2
13:50-15:05	**OP04** Laboratory Hematology/Cell Therapy/Hematopoiesis Stem Cell Biology/Basic Science	**OP05** Bone Marrow Failure Syndrome/ Anemia/Cytopenia	**OP06** Transplantation
15:05-16:20	**OP10** MPNs/CML	**OP11** Platelet/Hemostasis/ Thrombosis	**OP12** Transplantation
16:20-16:35	Break		
16:35-18:05	**ES04** Coagulation		
	Early "Goal-directed Coagulation Therapy" approaches for the management of acute trauma-hemorrhage and trauma-induced coagulopathy (Marc Guido Maegele, Germany)		
	Clinical application of clot waveform analysis in hemophilia treatment (Keiji Nogami, Japan)		
	Thrombin generation assay (Bas de Laat, The Netherlands)		
18:05-18:30	Break		
18:30-20:00	GALA DINNER (Walkerhill Theatre, B1)		

PROGRAM AT A GLANCE Saturday, March 16

Time	VISTA 1	VISTA 2	VISTA 3	GRAND HALL
07:30-08:30	**BUSINESS MEETING** (Walker Hall 2, 1F)			
08:30-09:00	WORKING PARTY REPORTS			
09:00-10:30	**JS04** EHA-KSH JOINT SYMPOSIUM II Chronic Myelogenous Leukemia	**SS12** Childhood Acute Lymphoblastic Leukemia	**SS13** Lymphoma	**SS14** Advances in Technology
	Europe's experience of treatment-free remission in CML (Susanne Saußele, Germany)	Treatment of childhood ALL with IKZF1 deletion (Malaysia-Singapore ALL 2010 Study) (Allen Yeoh Eng Juh, Singapore)	Pathogenesis of EBV-associated lymphoproliferative disorders (Hiroshi Kimura, Japan)	Droplet microfluidics in antibody discovery, immune repertoire sequencing and personalized cancer therapy (Christoph A. Merten, Germany)
	Korea's experience of treatment-free remission in CML (Hawk Kim, Korea)			
	TKI-related cardiovascular toxicities in Europe (Susanne Saußele, Germany)	Multicenter clinical trial of pediatric acute lymphoblastic leukemia in China: CCLG 2008 study (Chi-kong Li, Hong Kong)	Molecular understanding of peripheral T-cell lymphoma (Javeed Iqbal, USA)	Applications of single-cell mass cytometry in hematologic malignancies (Gregory Behbehani, USA)
	Long-term safety of tyrosine kinase inhibitors in chronic myeloid leukemia patients (Jee Hyun Kong, Korea)	Recent updates of prospective trials for ALL in Japan (Yasuhiro Okamoto, Japan)	Clinical application of cell-free DNA in lymphoma (Seok Jin Kim, Korea)	Prediction of acute myeloid leukemia risk in healthy individuals (Liran I. Shlush, Israel)
10:30-10:45	Coffee Break			
10:45-11:45	**PL03** Genomics in Lymphoid Malignancies			
	The new genomics of acute lymphoblastic leukemia (Charles G. Mullighan, USA)			
	Genetic basis and treatment of high-risk multiple myeloma (Gareth J Morgan, USA)			
11:45-12:30	AWARD CEREMONY & CLOSING (Vista 1, B2)			

FLOOR PLAN Side View



4F PINE, OAK
Meeting Room

1F WALKER HALL 1, 2
Oral Session

Re:Bar
Welcome Reception

B1 WALKERHILL THEATRE
Gala Dinner

GRAND HALL
Scientific Session
Exhibition (Lobby)
Coffee & Tea (Lobby)
Event & Photo Zone (Lobby)
Meeting Room

IDA 1, 2
Organizing Committee
VIP Room
Preview Room
Kit & Cloak Desk (Lobby)

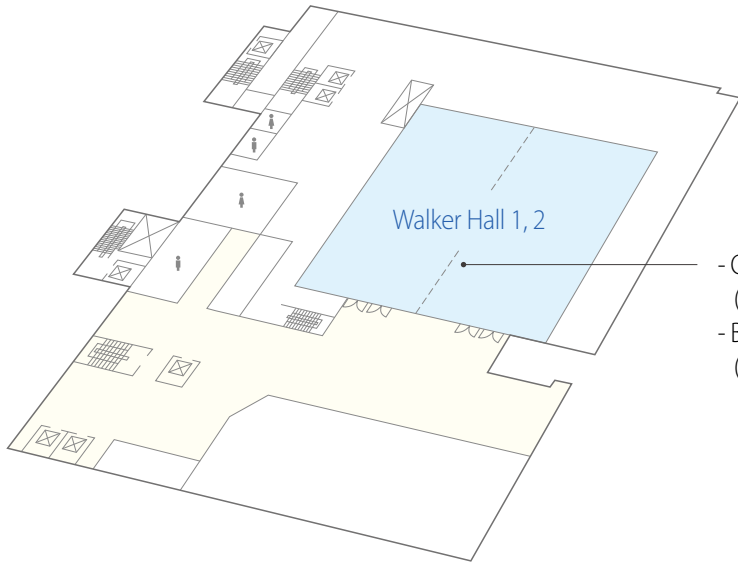
B2 VISTA HALL
Scientific Session
Opening / Closing Ceremony
Plenary Session

VISTA HALL LOBBY
Exhibition
Registration Desk
Coffee Break

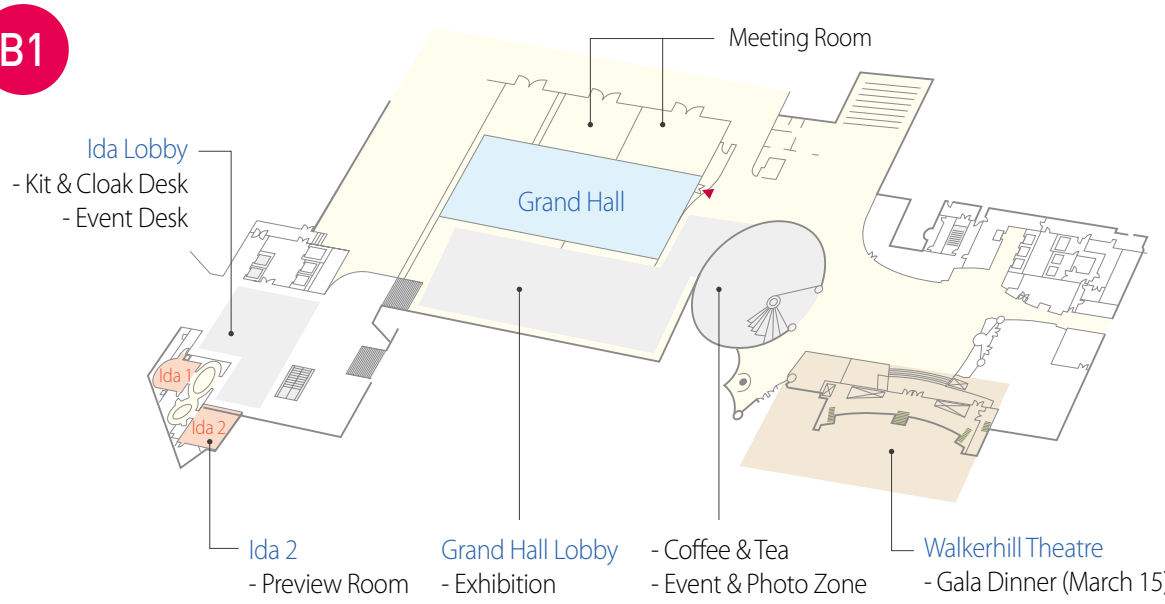
B3 EXHIBITION HALL
Exhibition
Posters
Coffee
Internet Lounge

FLOOR PLAN

1F

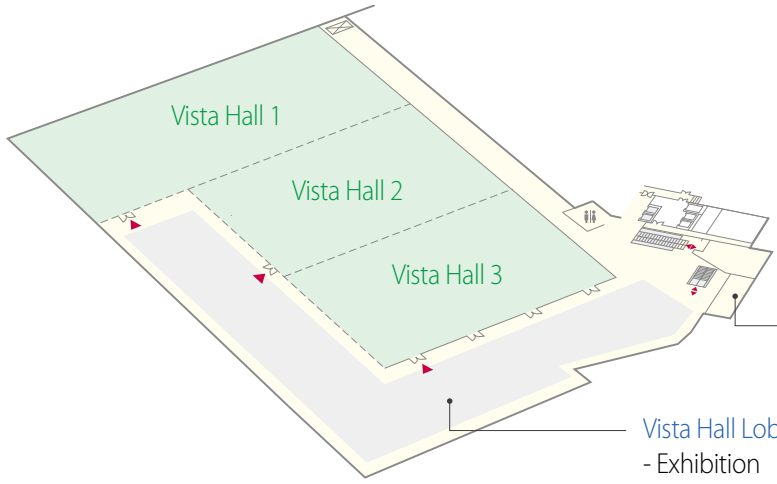


B1

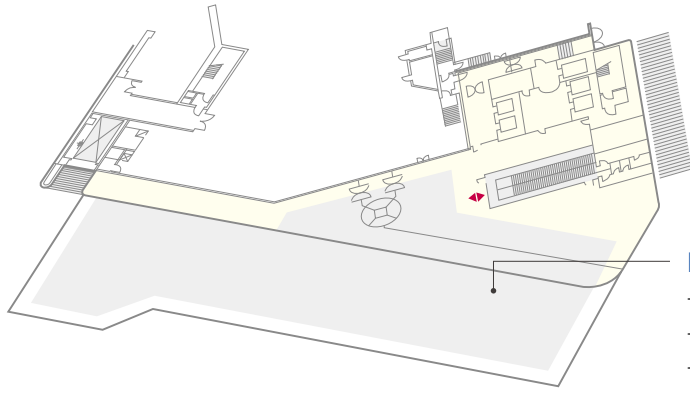


FLOOR PLAN

B2



B3



GENERAL INFORMATION

Registration

All participants are required to check in at the registration desk to pick up their name badge. Badges must be worn during all scientific sessions and social programs.

LOCATION	Vista Lobby (B2)
OPERATION HOURS	March 14 (Thu) 08:00 - 18:00
	March 15 (Fri) 08:00 - 18:00
	March 16 (Sat) 08:00 - 12:30

On-site Registration Fees

General	USD 200
Resident / Trainee / Nurse / Student	USD 100

+ **Registration fees include:**
  Participation in all scientific sessions, exhibition, satellite symposium including lunch, coffee breaks, conference kit, welcome reception and gala dinner.
+ Conference Kit will be distributed with your name badge at the Kit desk (B1). The kit includes a Program book and Abstract book.

Lunch

Lunch boxes will be provided during the satellite symposium. Please bring the lunch coupon in your name badge.

LOCATION	Vista Hall 1 (B2), Vista Hall 2+3 (B2), Grand Hall (B1)
OPERATION HOURS	March 14 (Thu) 12:45 - 13:40
	March 15 (Fri) 12:45 - 13:40

Coffee Break

Coffee will be served at coffee break times in **Vista Hall Lobby (B2).**
Barista coffee and tea will be provided during the conference **at the Grand Hall Lobby (B1) and Exhibition Hall (B3).**

Internet

+ Internet lounge is located in the Exhibition Hall (B3) during the conference.
+ Wifi internet access is available at the all conference venue.

Certificate of Attendance

Participants may receive the certificate of attendance. Please contact the ICKSH 2019 Secretariat after conference via icksh@icksh.org.

GENERAL INFORMATION

Useful Phone Numbers

+ Police 112
+ Fire and Ambulance 119
+ Medical Emergency 1339

Useful Travel Website

+ Seoul City Tourism: http://www.visitseoul.net
+ Seoul Metropolitan Government: http://english.seoul.go.kr
+ Korean Tourism Organization: http://kto.visitkorea.or.kr/eng.kto

ICKSH2019 Secretariat Office

+ Onsite: Besides Cloak room, Vista Hall Lobby (B2)

+ After conference: 1F, Haeoreum Bldg., 16 Yeoksam-ro 17Gil, Gangnam-gu, Seoul, 06246, Korea
  T. +82-2-566-6031
  F. +82-2-566-6087
  E. icksh@icksh.org

SPEAKER INFORMATION

Preview Room

All speakers are requested to visit the preview room no later than 2 hours before their session. They will be assisted by our staff who will help upload the presentation file to the server before the session.

LOCATION	IDA 2 (B1)
OPERATION HOURS	March 14 (Thu) 08:00 - 18:00
	March 15 (Fri) 08:00 - 18:00
	March 16 (Sat) 08:00 - 12:00

Poster Presentation

Pre-selected posters are required to have a presentation time as following schedule.
After onsite reviews, the scientific committee will select Best Posters and the winners should attend the award at Closing Ceremony on March 16 (Sat).

LOCATION	Exhibition Hall (B3)
DATE & TIME	March 15 (Fri) 11:45 - 12:45

SOCIAL PROGRAM

Opening

With the opening address by Chan-Jeoung Park, Congress chairman, ICKSH 2019 will begin.

LOCATION	Vista 1 (B2)
DATE & TIME	March 14 (Thu) 09:00

Welcome Reception

Welcome to ICKSH 2019! The Organizing Committee will prepare welcome reception.

LOCATION	Re:BAR, Vista Walkerhill Seoul (1F)
DATE & TIME	March 14 (Thu) 18:30 - 20:00

Gala Dinner

Please join us to share an unforgettable evening. Enjoy the climax of ICKSH 2019 with an excellent dinner and exciting performance.

LOCATION	Theater (B1)
DATE & TIME	March 15 (Fri) 18:30 - 20:00

SPONSORS (Acknowledgement)

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PLENARY LECTURES

MARCH 14 (Thu.)

PL01-1
10:45 - 11:15 | Vista 1-3 (B2)

Application of CRISPR/Cas-9 in blood disease

Matthew H. Porteus
Stanford Medical School, Stanford University, USA

PL01-2
11:15 - 11:45 | Vista 1-3 (B2)

Gene therapy for hemophilia-will there be a new era in hemophilia treatment?

Katherine Ann High
Spark Therapeutics Inc., USA

MARCH 15 (Fri.)

PL02-1
10:45 - 11:15 | Vista 1-3 (B2)

Breakthroughs in the treatment of aplastic anemia

Neal Stuart Young
National Institutes of Health, USA

MARCH 16 (Sat.)

PL03-1
10:45 - 11:15 | Vista 1-3 (B2)

The new genomics of acute lymphoblastic leukemia

Charles G. Mullighan
St. Jude Children's Research Hospital, USA

PL03-2
11:15 - 11:45 | Vista 1-3 (B2)

Genetic basis and treatment of high-risk multiple myeloma

Gareth J Morgan
NYU Myeloma Centre, USA

PRESIDENTIAL SYMPOSIUM

MARCH 14 (Thu.)

PS-1

11:45 - 12:15 | Vista 1-3 (B2)

Stem cells in human AML

Ravi Majeti
Stanford University, USA

PS-2

12:15 - 12:45 | Vista 1-3 (B2)

Precision medicine in pediatric acute lymphoblastic leukemia

Ching-Hon Pui
St. Jude Children's Research Hospital, USA

DAILY PROGRAM

March 14 (Thurday)

March 15 (Friday)

March 16 (Saturday)

2019 KOREAN SOCIETY OF
HEMATOLOGY INTERNATIONAL CONFERENCE
& 60th ANNUAL MEETING

DAILY PROGRAM Thursday, March 14

08:00- Registration — Lobby

09:00- Opening Remarks — Vista 1

09:00-10:30 **[JS01] KAI-KSH Joint Symposium: Immunotherapeutics in Blood Disease** — Vista 1

Chairs Tae Woo Kim (Korea University College of Medicine, Korea)
Je-Jung Lee (Chonnam National University Medical School, Korea)

JS01-1 IL-7-hyFc, a long-acting recombinant IL-7 protein, generates anti-tumor activity by modulating both adaptive and innate immune cells in the tumor microenvironment
Seung-Woo Lee (POSTECH, Korea)

JS01-2 Towards next-generation CAR-T cell therapy for cancer
Chan Hyuk Kim (KAIST, Korea)

JS01-3 Immunotherapeutics in blood disease: Cytotoxic T lymphocyte therapy
Hyewon Lee (National Cancer Center, Korea)

JS01-4 Immune checkpoint inhibitor in lymphoma
Yoon Seok Choi (Chungnam National University College of Medicine, Korea)

09:00-10:30 **[SS01] Bone Marrow Failure** — Vista 2

Chairs Hoon Kook (Chonnam National University Medical School, Korea)
Jean Soulier (University Paris Diderot, France)

SS01-1 Paroxysmal nocturnal hemoglobinuria in bone marrow failure
Jun Ho Jang (Sungkyunkwan University School of Medicine, Korea)

SS01-2 Germline mutations in inherited bone marrow failure
Jean Soulier (University Paris Diderot, France)

SS01-3 Telomere length and somatic mutations in aplastic anemia
Dong Soon Lee (Seoul National University School of Medicine, Korea)

10:30-10:45 Coffee Break

10:45-11:45 **[PL01] Gene Therapy in Hematology** — Vista 1-3

Chair Chan-Jeoung Park (University of Ulsan College of Medicine, Korea)

PL01-1 Application of CRISPR/Cas-9 in blood disease
Matthew H. Porteus (Stanford Medical School, Stanford University, USA)

PL01-2 Gene therapy for hemophilia-will there be a new era in hemophilia treatment?
Katherine Ann High (Spark Therapeutics Inc., USA)

11:45-12:45 **[PS] Presidential Symposium** — Vista 1-3

Chair Bin Cho (College of Medicine, The Catholic University of Korea, Korea)

PS-1 Stem cells in human AML
Ravi Majeti (Stanford University, USA)

PS-2 Precision medicine in pediatric acute lymphoblastic leukemia
Ching-Hon Pui (St. Jude Children's Research Hospital, USA)

DAILY PROGRAM Thursday, March 14

12:45-13:40 **[LS01]** NOVARTIS — Vista 1

Chair Dong-Wook Kim (College of Medicine, The Catholic University of Korea, Korea)

Treatment free remission in CML: Promise and challenges
Adam Mead (University of Oxford, UK)

12:45-13:40 **[LS02]** AMGEN — Vista 2-3

Chair Chang-Ki Min (College of Medicine, The Catholic University of Korea, Korea)

Optimal treatment sequencing for patients with relapsed/refractory multiple myeloma
Ajai Chari (Mount Sinai Hospital, USA)

12:45-13:40 **[LS03]** Roche — Grand Hall

Chair Hyeon-Seok Eom (Center for Hematologic Malignancy, National Cancer Center, Korea)

Current issues in the treatment of B-cell lymphoma
Seok Jin Kim (Sungkyunkwan University School of Medicine, Korea)

13:40-14:40 **[AS01] Lymphoid** — Vista 1

Chairs Seok Lee (College of Medicine, The Catholic University of Korea, Korea)
Tran-Der Tan (Koo Foundation Sun Yat-Sen Cancer Center, Taiwan)

AS01-1 Treatment of Philadelphia chromosome positive acute lymphoblastic leukemia- Korean perspectives
Young Rok Do (Keimyung University School of Medicine, Korea)

AS01-2 Hematopoietic stem cell transplantation for adult acute lymphoblastic leukemia in Taiwan – on Behalf of TSBMT
Tran-Der Tan (Koo Foundation Sun Yat-Sen Cancer Center, Taiwan)

AS01-3 Adult ALL in Malaysia
Sen Mui Tan (Hospital Ampang, Malaysia)

13:40-14:40 **[AS02] Myeloid** — Vista 2

Chairs Won Sik Lee (Inje University School of Medicine, Korea)
Bach Quoc Khanh (National Institute of Hematology and Blood Transfusion, Vietnam Society of Hematology and Blood Transfusion, Vietnam)

AS02-1 CML in Philippines
Priscilla B. Caguioa (University of Santo Tomas Hospital, St. Luke's Medical Center, Philippines)

AS02-2 Outcome of allogeneic hematopoietic stem cell transplantation for SAA and PNH at Vietnam national institute of haematology and blood transfusion
Binh Thi Thanh VO (National Institute of Hematology and Blood Transfusion, Vietnam)

AS02-3 Hemoglobinopathy in Thailand
Duantida Songdej (Ramathibodi Hospital, Mahidol University, Thailand)

14:40-14:55 Coffee Break

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14:55-16:25 **[JS02] KOGO-KSH Joint Symposium: Genomics for Precision Hematology** Vista 1

Chairs Sanghyuk Lee (Ewha Womans University School of Medicine, Korea)
Sun-Hee Kim (Sungkyunkwan University School of Medicine, Korea)

JS02-1 Understanding angioimmunoblastic T-cell lymphoma: From genomics to animal pathology
Jaesang Kim (Department of Life Science, Ewha Womans University, Korea)

JS02-2 Genomic pathogenesis of Epstein–Barr Virus (EBV)-induced diffuse large B cell lymphoma
Sung-Yup Cho (Seoul National University College of Medicine, Korea)

JS02-3 Current status of precision hematology
Young-Uk Cho (University of Ulsan College of Medicine, Korea)

JS02-4 Clinical application of personalized medicine for AML
Joon-ho Moon (Kyungpook National University Hospital, Korea)

14:55-16:25 **[SS02] Multiple Myeloma-How is Multiple Myeloma Developed and Progressed? From 3 Different Viewpoint** Vista 2

Chairs Chang-Ki Min (College of Medicine, The Catholic University of Korea, Korea)
Yusuke Furukawa (Jichi Medical University, Japan)

SS02-1 Immunological weapons against multiple myeloma
Je-Jung Lee (Chonnam National University Medical School, Korea)

SS02-2 Roles of bone marrow microenvironment in clonal evolution and drug resistance of multiple myeloma
Yusuke Furukawa (Jichi Medical University, Japan)

SS02-3 Antigen-mediated regulation in myeloma
Madhav V. Dhodapkar (Emory University, USA)

14:55-16:25 **[SS03] Transplantation/Cell Therapy** Vista 3

Chairs Hyeon-Seok Eom (Center for Hematologic Malignancy, National Cancer Center, Korea)
Maria Chiara Bonini (Università Vita-Salute San Raffaele, Italy)

SS03-1 Thymidine kinase cell therapy
Maria Chiara Bonini (Università Vita-Salute San Raffaele, School of Medicine, Italy)

SS03-2 Updates on CAR T cell therapy for multiple myeloma
Jesús G. Berdeja (Sarah Cannon Research Institute, USA)

SS03-3 Accelerating personalization of immune therapies for blood cancers
Larry W. Kwak (City of Hope Comprehensive Cancer Center, USA)

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14:55-16:25 **[ES01] Iron Metabolism** Grand Hall

Chairs Joon Seong Park (Ajou University School of Medicine, Korea)
Heather Alice Leitch (University of British Columbia, Canada)

ES01-1 Iron metabolism in hemoglobinopathies
Vip Viprakasit (Medicine Siriraj Hospital, Mahidol University, Thailand)

ES01-2 Deferasirox for iron overload patients: Preserving organ functions
Norbert Gattermann (Heinrich Heine University, Düsseldorf, Germany)

ES01-3 Management of iron overload in MDS
Heather Alice Leitch (University of British Columbia, Canada)

16:25-16:40 Break

16:40-18:10 **[SS04] Myeloproliferative Neoplasm** Vista 1

Chairs Chul Won Choi (Korea University Guro Hospital, Korea)
Robert Kralovics (CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Austria)

SS04-1 Genetic causes of myeloproliferative diseases: Stratification of patients and new therapeutic targets
Robert Kralovics (CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Austria)

SS04-2 Molecular mechanism of MPN development by mutant calreticulin
Norio Komatsu (Juntendo University School of Medicine, Japan)

SS04-3 Interferon in myeloproliferative neoplasms
Jean-Jacques Kiladjian (Saint-Louis Hospital and Paris 7 University, France)

16:40-18:10 **[SS05] Bleeding Disorder/Thrombosis** Vista 2

Chairs Sung-Hyun Kim (Dong-A University College of Medicine, Korea)
Glenn F. Pierce (World Federation of Hemophilia, USA)

SS05-1 Progress in gene therapy for hemophilia A and B
Glenn F. Pierce (World Federation of Hemophilia, USA)

SS05-2 Individualized treatment for hemophilia: Population pharmacokinetics approach
Cindy H. T. Yeung (McMaster University, Canada)

SS05-3 Mechanisms of cancer-associated thrombosis
Nigel Mackman (University of North Carolina, USA)

16:40-18:10 **[SS06] Pediatric Disease: Inherited Hematologic Malignancies** Vista 3

Chairs Nack Gyun Chung (College of Medicine, The Catholic University of Korea, Korea)
Lucy Ann Godley (The University of Chicago, USA)

SS06-1 Inherited hematologic malignancies
Lucy Ann Godley (The University of Chicago, USA)

SS06-2 GATA2 deficiency: How to make the diagnosis? how to treat it?
Jean Donadieu (Hopital Trousseau, France)

SS06-3 Roles of monosomy 7 and SAMD9/SAMD9L mutations in myeloid leukemogenesis
Hirotaka Matsui (Kumamoto University, Japan)

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16:40-18:10 **[ES02] Indolent Lymphoma: From Genetics to the Clinic** — Grand Hall

Chairs: Inho Kim (Seoul National University College of Medicine, Korea); Mats Jerkeman (Lund University, Sweden)

ES02-1 Mantle cell lymphoma -from the clinic to genetics
Mats Jerkeman (Lund University, Sweden)

ES02-2 From genetics to the clinic: Follicular lymphoma
Gilles Salles (Université Claude Bernard Lyon—1 (UCBL), France)

ES02-3 From genetics to the clinic of chronic lymphocytic leukemia
Wei Xu (First Affiliated Hospital of Nanjing Medical University, China)

18:10-18:30 Break

18:30-20:00 **Welcome Reception** — Re:BAR, Vista Walkerhill Seoul (1F)

DAILY PROGRAM Friday, March 15

09:00-10:30 **[JS03] EHA-KSH Joint Symposium I: Multiple Myeloma** Vista 1

Chairs Jae-Yong Kwak (Chonbuk National University Medical School, Korea)
Francesca Maria Gay (AOU Città della Salute e della Scienza, Italy)

JS03-1 Monoclonal antibodies in the treatment of multiple myeloma
Francesca Maria Gay (AOU Città della Salute e della Scienza, Italy)

JS03-2 Treatment for advanced multiple myeloma in Korea
Chang-Ki Min (College of Medicine, The Catholic University of Korea, Korea)

JS03-3 Experimental therapy except monoclonal antibodies
Francesca Maria Gay (AOU Città della Salute e della Scienza, Italy)

JS03-4 Clinical outcomes of cytogenetic high-risk multiple myeloma in Korea
Kihyun Kim (Sungkyunkwan University School of Medicine, Korea)

09:00-10:30 **[SS07] Benign Hematology: Hereditary Red Blood Cell Defect** Vista 2

Chairs Jin Yeong Han (Dong-A University College of Medicine, Korea)
Cornelis Leonard Harteveld (Leiden University Medical Center, The Netherlands)

SS07-1 EuroBloodNet: The rare anaemia disorders European epidemiological platform
María del Mar Mañú Pereira (University Hospital Vall d'Hebron, Vall d'Hebron Research Institute, Spain)

SS07-2 Clinical utility of high-throughput sequencing for the diagnosis of hereditary hemolytic anemia
Myungshin Kim (College of Medicine, The Catholic University of Korea, Korea)

SS07-3 The molecular spectrum of hemoglobinopathy: Thalassemia and Hb variants
Cornelis Leonard Harteveld (Leiden University Medical Center, The Netherlands)

09:00-10:30 **[SS08] Histiocytosis** Vista 3

Chairs Chuhl Joo Lyu (Yonsei University College of Medicine, Korea)
Ho Joon Im (University of Ulsan College of Medicine, Korea)

SS08-1 Langerhans cell histiocytosis 2019: New insights and opportunities
Carl E. Allen (Baylor College of Medicine, USA)

SS08-2 Treatment of hemophagocytic lymphohistiocytosis - today and tomorrow
Jan-Inge Henter (Karolinska Institute, Sweden)

SS08-3 Genetic studies on the hemophagocytic lymphohistiocytosis (HLH) in Korea
Jong Jin Seo (University of Ulsan College of Medicine, Korea)

09:00-10:30 **[ES03] Acute Lymphoblastic Leukemia** Grand Hall

Chairs Dae Young Zang (Hallym University College of Medicine, Korea)
Chi-kong Li (The Chinese University of Hong Kong, Hong Kong)

ES03-1 Pharmacogenetics in patients with childhood acute lymphoblastic leukemia
Yoichi Tanaka (Kitasato University, Japan)

ES03-2 Recent advances in the treatment of adult ALL
Won Sik Lee (Inje University School of Medicine, Korea)

ES03-3 Mutational landscape of ALL: Next-generation sequencing-based mutations scanning strategy
Seung-Tae Lee (Yonsei University College of Medicine, Korea)

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10:30-10:45 Coffee Break

10:45-11:45 **[PL02] Clinical Hematology** — Vista 1-3

Chair Hwi-Joong Yoon (Kyung Hee University College of Medicine, Korea)

PL02-1 Breakthroughs in the treatment of aplastic anemia
Neal Stuart Young (National Institutes of Health, USA)

11:45-12:45 **[AS03] Special Report from JSH, CAH, KSH** — Vista 1

Chairs Hee-Je Kim (College of Medicine, The Catholic University of Korea, Korea)
Shigeru Chiba (University of Tsukuba, Japan)

AS03-1 Developing strategies to improve efficacy and safety of chimeric antigen receptor cell therapy
Kyung-Nam Koh (University of Ulsan College of Medicine, Korea)

AS03-2 New insights into poor hematopoietic reconstitution after allo-HSCT
Yuan Kong (Peking University People's Hospital, China)

AS03-3 Targeting hotspot RHOA mutation in angioimmunoblastic T-cell lymphoma
Shigeru Chiba (University of Tsukuba, Japan)

11:45-12:45 **Poster Presentation** — Exhibition Hall, B3

12:45-13:40 **[LS04]** Bristol-Myers Squibb — Vista 1

Chair Dong-Wook Kim (College of Medicine, The Catholic University of Korea, Korea)

Advances of CML management and the prospects for the future
Susanne Saußele (University of Mannheim, Germany)

12:45-13:40 **[LS05]** Takeda ONCOLOGY — Vista 2-3

Chair Won Seog Kim (Sungkyunkwan University School of Medicine, Korea)

A new paradigm shift in frontline treatment of hodgkin lymphoma
Andrea Gallamini (Medical Innovation & Statistics A. Lacassagne Cancer Center, France)

12:45-13:40 **[LS06]** KYOWA KIRIN — Grand Hall

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

The role of the darbepoetin alfa of the treatment for low-risk of MDS
Jun Ho Jang (Sungkyunkwan University School of Medicine, Korea)

13:40-13:50 Coffee Break

13:50-15:05 **[OP01] Acute Myeloid Leukemia/Myelodysplastic Syndrome** — Vista I

Chairs Jeong Yeal Ahn (Gachon University Gil Hospital, Korea)
June-Won Cheong (Yonsei University College of Medicine, Korea)

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OP01-1 RNA sequencing as an alternative tool for detecting measurable residual disease in core binding factor acute myeloid leukemia
Taehyung Kim (University of Toronto, Canada)

OP01-2 Different predictive roles of risk group and WT1 expression in elderly AML treated by intensive chemotherapy or hypomethylating agent
Seung-Hwan Shin (The Catholic University of Korea Yeouido St. Mary's Hospital, Korea)

OP01-3 Role of plasma gelsolin protein in the final stage of erythropoiesis and in correction of myelodysplasia
Eun Jung Baek (Hanyang University Guri Hospital, Korea)

OP01-4 Research use only and cell population data items from DxH800 analyzer is useful in discriminating MDS patients from those with cytopenia without MDS
Sang Hyuk Park (University of Ulsan College of Medicine, Korea)

OP01-5 Androgen therapy for lower-risk myelodysplastic syndrome
Eun-Ji Choi (University of Ulsan College of Medicine, Korea)

OP01-6 Lenalidomide as a second-line therapy after failure of hypomethylating agents in patients with myelodysplastic syndrome (VIOLTET study)
Hawk Kim (Gachon University Gil Medical Center, Korea)

13:50-15:05 **[OP02] Acute Lymphoblastic Leukemia** Vista 2

Chairs Eun Sil Park (Gyeongsang National University College of Medicine, Korea)
Sung Hwa Bae (Catholic University of Daegu School of Medicine, Korea)

OP02-1 A pragmatic, non-interventional study to evaluate effectiveness and safety of clofarabine in Korean pediatric patients with refractory or relapsed acute lymphoblastic leukemia
Jung Yoon Choi (Seoul National University College of Medicine, Korea)

OP02-2 The genotype distribution and pharmacogenetic effect on mercaptopurine dose of NUDT15 and TPMT in Korean children with acute lymphoblastic leukemia
Hyery Kim (University of Ulsan College of Medicine, Korea)

OP02-3 Mutational profiling through exome sequencing along with MYD88 L265P analysis could facilitate the diagnosis of vitreoretinal lymphoma
Borahm Kim (Yonsei University College of Medicine, Korea)

OP02-4 Utility of MLPA as a cost effective diagnostic and prognostic method in hematological malignancies: Experience of a tertiary care centre from India
Prateek Bhatia (Post Graduate Institute of Medical Education and Research, India)

OP02-5 Genetic characteristics and long-term outcomes of Korean adult patients with Ph-Like ALL versus non-Ph-Like ALL
Jae-Ho Yoon (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

OP02-6 Outcomes after second allogeneic hematopoietic cell transplantation in relapsed acute lymphoblastic leukemia: A single-center experience
Seug Yun Yoon (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

13:50-15:05 **[OP03] Lymphoma** Vista 3

Chairs Sung-yong Oh (Dong-A University College of Medicine, Korea)
Deok Hwan Yang (Chonnam National University Medical School, Korea)

OP03-1 Diffuse large B-cell lymphomas carrying chromosomal abnormalities showed a poor prognosis despite aggressive treatment
Gi June Min (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

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OP03-2 Telomere length and its correlation with gene mutations in chronic lymphocytic leukemia in a Korean population
Da Young Song (Seoul National University Hospital, Korea)

OP03-3 International prognostic index improves prognostic value of interim PET-CT scans in diffuse large B-cell lymphoma
Ho-Young Yhim (Chonbuk National University Hospital, Korea)

OP03-4 Screening for monoclonal B-lymphocytes expansions in a hospital-based Chinese population with lymphocytosis
Jiadai Xu (Zhongshan Hospital, Fudan University, China)

OP03-5 Peripheral T cell lymphoma - Demographic profile and outcomes : 17 years experience from tertiary cancer centre, India
Siva Sree Kesana (Cancer Institute (WIA), India)

OP03-6 A multicenter retrospective analysis of clinicopathologic features of monomorphic epitheliotropic intestinal T-cell lymphoma
Jun Ho Yi (Chung-Ang University, Korea)

13:50-15:05 **[OP04] Laboratory Hematology/Cell Therapy/ Hematopoiesis Stem Cell Biology/Basic Science** Grand Hall

Chairs Myung Geun Shin (Chonnam National University Medical School, Korea)
Hyun Kyung Kim (Seoul National University College of Medicine, Korea)

OP04-1 Autophagy and unfolded protein response as the regulatory mechanism for the sensitivity of leukemia stem cells to G9a inhibitor
Ji Eun Jang (Yonsei University College of Medicine, Korea)

OP04-2 3-methyladenine potentiates bortezomib-induced apoptosis of myeloma cell via increasing mitochondrial ROS through autophagy inhibition
Chu Myong Seong (Ehwa Womans University Mokdong Hospital, Korea)

OP04-3 Adoptive transfer of type 1-regulatory T cell ameliorates GVHD by partial differentiation into Foxp3+CD4+T cell with CTLA-4 and ICOS dependent manner
Young-Woo Jeon (Catholic Hematology Hospital, Korea)

OP04-4 Understanding thrombocytopenia: Role of MicroRNA in neonatal and adult megakaryopoiesis
Ravi Kumar Gutti (University of Hyderabad, India)

OP04-5 The expression level of prohibitin 2 as mitochondrial autophage receptor matches the prognostic chromosomal aberrations of hematological malignancies
Jun Hyung Lee (Chonnam National University Hwasun Hospital, Korea)

OP04-6 Epigallocatechin gallate suppresses interleukin-1β Secretion by inhibition of NLRP3 inflammasome
Cheng Zhang (Qilu Hospital, Shandong University, China)

13:50-15:05 **[OP05] Bone Marrow Failure Syndrome/Anemia/ Cytopenia** Walker Hall 1

Chairs Deog-Yeon Jo (Chungnam National University College of Medicine, Korea)
Hye Lim Jung (Sungkyunkwan University School of Medicine, Korea)

OP05-1 HLA-G-ILT2 interaction contribute to suppression of marrow B-cell growth in acquired aplastic anemia
Peng Chen (Qilu Hospital of Shandong University, China)

OP05-2 A phase 3, multicenter, noninferiority study of ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors
Jong Wook Lee (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

OP05-3 Prediction of thrombosis risk in patients with paroxysmal nocturnal hemoglobinuria
Yuzhou Huang (Peking Union Hospital, China)

OP05-4 High prevalence of anemia in elderly in South Korea: Urgent health-care problem before post-aged society- base on data from the KNHANES
Hee Won Chueh (Dong-A University College of Medicine, Korea)

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OP05-5 Vitamin-D and biochemical status in young children with beta-thalassemia major
Uet Yu (Shenzhen Children's Hospital, China)

OP05-6 Application of rapamycin up-regulating treg cell ratio in children with chronic refractory immune cytopenia - A single-center case series
Hao Gu (Beijing Children Hospital, Capital Medical University, China)

13:50-15:05 **[OP06] Transplantation** Walker Hall 2

Chairs Hyeon Jin Park (National Cancer Center, Korea)
Seong Kyu Park (SoonChunHyang University College of Medicine, Korea)

OP06-1 Predictive role of circulating immune cell subtypes early after allogeneic hematopoietic stem cell transplantation in patients with acute leukemia
Sung-Soo Park (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

OP06-3 The outcome of hematopoietic stem cell transplantation (HSCT) in pediatric patients with hemophagocytic lymphohistiocytosis (HLH) in Korea
Jun Eun Park (Ajou University School of Medicine, Korea)

OP06-4 HLA-haploidentical transplantation for thalassemia major using NF-08-TM haploid regimen
Xiaoling Zhang (Shenzhen Children's Hospital, China)

OP06-5 Comparison of haploidentical and umbilical cord blood transplantation using targeted busulfan in children and adolescent with hematologic malignancies
Kyung Taek Hong (Seoul National University Hospital, Korea)

OP06-6 Different circulating T cells are associated with early relapse after autologous HSCT in patients with multiple myeloma and classical hodgkin lymphoma
Egor Batorov (Research Institute of Fundamental and Clinical Immunology, Russia)

15:05-16:20 **[OP07] Acute Myeloid Leukemia/ Myelodysplastic Syndrome** Vista 1

Chairs Eul-Ju Seo (University of Ulsan College of Medicine, Korea)
Keon Hee Yoo (Sungkyunkwan University School of Medicine, Korea)

OP07-1 Molecular abnormalities and their correlation with the prognosis of younger Indian patients with de novo myelodysplastic syndromes: AIIMS study
Rekha Chaubey (All India Institute Of Medical Science, India)

OP07-2 Immunogenic cell death in acute myeloid leukemia: Synergy with venetoclax
Marc Diederich (Seoul National University, Korea)

OP07-3 Prediction of clinical outcomes with assessment of sarcopenia and adipopenia by computed tomography in adult patients with acute myeloid leukemia
Jongheon Jung (National Cancer Center, Korea)

OP07-4 Hyperleukocytosis at initial diagnosis of AML: Cytogenetic and molecular feature and prognostic implication in patients undergoing allogeneic-HSCT
Silvia Park (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

OP07-5 Germline predisposition gene mutations in pediatric acute myeloid leukemia
Dajeong Jeong (Seoul National University College of Medicine, Korea)

OP07-6 HSCT is an effective method to improve the prognosis of AML in children with c-Kit mutationanalysis of 131 cases
Li Gao (Children's Hospital of Soochow University, China)

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15:05-16:20 **[OP08] Multiple Myeloma** Vista 2

Chairs Hyo Jung Kim (Hallym University College of Medicine, Korea)
Sukjoong Oh (Sungkyunkwan University School of Medicine, Korea)

OP08-1 Next-generation sequencing study of V(D)J rearrangements on non-CR patients showing MRD negativity by next-generation flow
Naery Yang (Seoul National University College of Medicine, Korea)

OP08-2 Bone marrow tracer uptake pattern of PET/CT in multiple myeloma: Image interpretation criteria and prognostic value
Jing Li (Zhongshan Hospital, Fudan University, China)

OP08-3 Real world experience of carfilzomib, and dexamethasone versus pomalidomide-based combination chemotherapy after a 2nd-Line therapy in RRMM
Ji Hyun Lee (Dong-A University Hospital, Korea)

OP08-4 PD-1 blockade reinvigorates bone marrow CD8+ T cells from multiple myeloma patients in the presence of TGF-B inhibition
Yoon Seok Choi (Chungnam National University College of Medicine, Korea)

OP08-5 A multicenter, phase II study of response-adapted lenalidomide-based therapy for elderly patients with newly diagnosed multiple myeloma in Korea
Kwai Han Yoo (Gachon University Gil Medical Center, Korea)

OP08-6 Preclinical and clinical results of combination immunotherapy; Cancer vaccine with immune modulator, checkpoint inhibitors and epigenetic regulator
Jooeun Bae (Harvard Medical School, USA)

15:05-16:20 **[OP09] Lymphoma/Histiocytosis** Vista 3

Chairs Seong Hyun Jeong (Ajou University School of Medicine, Korea)
Hyoung Soo Choi (Seoul National University College of Medicine, Korea)

OP09-1 Clinical features and treatment outcomes of hodgkin lymphoma: A retrospective review in a Malaysian tertiary centre
Yang Liang Boo (Hospital Sultanah Aminah, Malaysia)

OP09-2 Primary central nervous system lymphoma : An institutional experience from India with uniform chemotherapy protocol
Pooja Gogia (Sarvodaya Hospital and Research Centre, India)

OP09-3 Busulfan, etoposide, cytarabine and melphalan (BuEAM) as a conditioning regimen for autologous stem cell transplantation in patients with non-Hodgkin
Jae-Cheol Jo (Ulsan University Hospital, University of Ulsan College of Medicine, Korea)

OP09-4 Predictive parameters for neutropenia after R-CHOP chemotherapy with prophylactic peg G-CSF in patients with diffuse large B-cell lymphoma
Do Young Kim (Pusan National University Hospital, Korea)

OP09-5 Clinical characteristics of childhood hemophagocytic syndrome and analysis of underlying genetic deficiency
Huirong Mai (Shenzhen Children's Hospital, China)

OP09-6 Identification of genetic mutation in pediatric patients with HLH : The study of Korean clinical research network for histiocytosis
Hyery Kim (University of Ulsan College of Medicine, Korea)

15:05-16:20 **[OP10] Myeloproliferative Neoplasm/ Chronic Myeloid Leukemia** Grand Hall

Chairs Ki-Seong Eom (College of Medicine, The Catholic University of Korea, Korea)
Min Kyoung Kim (Yeungnam University College of Medicine, Korea)

OP10-1 An epidemiologic study for disease transformation and second cancers in Korean patients with myeloproliferative neoplasms
Junshik Hong (Seoul National University Hospital, Korea)

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OP10-2 The temporal sequence and the differences of somatic mutation acquisition determines clinical behaviors of JAK2 positive myeloproliferative neoplasms
Ja Min Byun (Seoul National University Boramae Medical Center, Korea)

OP10-3 Retrospective screening for myeloproliferative neoplasms in patients with cerebral infarctions as revealed using the revised 2016 WHO criteria
Ik-Chan Song (Chungnam National University Hospital, Korea)

OP10-4 Clinical characteristics and risk groups of chronic myeloid leukemia in children
Quoc Thanh Nguyen (University of Medicine and Pharmacy, Vietnam)

OP10-5 Expression and clinical significance of PTEN gene in chronic myeloid leukemia (CML) patient in Indian population
Asgar Ali (All India Institute of Medical Sciences Patna, Bihar, India)

OP10-6 Pilot prospective phase II study of Nilotinib combined by chemotherapy for myeloid blastic phase of chronic myeloid leukemia or bcr-Abl positive acute
Hawk Kim (Gachon University Gil Medical Center, Korea)

15:05-16:20 **[OP11] Platelet/Hemostasis/Thrombosis** Walker Hall 1

Chairs Sun-Young Kong (National Cancer Center, Korea)
Soo-Mee Bang (Seoul National University College of Medicine, Korea)

OP11-1 Single-center clinical data analysis of hereditary thrombocytopenia in children with chronic thrombocytopenia
Jingyao Ma (Beijing Children's Hospital, Capital Medical University, National Center of Children's Health, China)

OP11-2 Developing a diagnostic predictive model for immune thrombocytopenic purpura based on immature platelet fraction
Min Ji Jeon (Korea University Guro Hospital, Korea)

OP11-3 Insufficient receptor editing leads to B cell central intolerance and subsequent autoantibodies accumulation in primary immune thrombocytopenia
Zi Sheng (Qilu Hospital, Shandong University, China)

OP11-4 ROTEM parameters as predicting factors for bleeding in immune thrombocytopenic purpura
Huu Tuan Nguyen (Cho Ray Hospital, Vietnam)

OP11-5 Increased pathogenic Th17 cells in primary immune thrombocytopenia
Ju Li (Qilu Hospital, Shandong University, China)

OP11-6 Prediction value of risk assessment model deep vein thrombosis with padua prediction score
Iswandi Darwis (Faculty of Medicine, Lampung University, Indonesia)

15:05-16:20 **[OP12] Transplantation** Walker Hall 2

Chairs Byung-Su Kim (Hallym University College of Medicine, Korea)
Eun Sun Yoo (Ewha Womans University School of Medicine, Korea)

OP12-1 Cytoprotective autophagy in bone marrow endothelial cells enhance hematopoietic stem cells in poor graft function patients after allo-transplant
Xie-Na Cao (Peking University People's Hospital, China)

OP12-2 Aberrant bone marrow M1/M2 macrophage polarization may contribute to prolonged isolated thrombocytopenia after allotransplantation
Hong-Yan Zhao (Peking University, China)

OP12-3 G-CSF-induced macrophage polarization may prevent acute graft-versus-host disease after allogeneic hematopoietic stem cell transplant
Qi Wen (Peking University People's Hospital, China)

DAILY PROGRAM Friday, March 15

OP12-4 Early transplantation-related mortality within 50 days after allogeneic hematopoietic stem cell transplantation in patients with acute leukemia
Seom Gim Kong (Kosin University Gospel Hospital, Korea)

OP12-5 Incidence of anicteric veno-occlusive disease/sinusoidal obstruction syndrome and defibrotide efficacy following hematopoietic stem cell transplant
Richard Martin (Jazz Pharmaceuticals, UK)

OP12-6 Phase I trial of repeated infusions of bone-marrow derived mesenchymal stem cells in steroidrefractory chronic graft-versus-host disease patients
Nayoun Kim (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

16:20-16:35 Break

16:35-18:05 **[SS09] Future Information and Communications Technologies (ICT) based Medicine** Vista 1

Chairs Dae-Young Kim (Philip Morris International, Korea)
Ju Han Kim (Seoul National University College of Medicine, Korea)

SS09-1 Deep learning for CRISPR-Cpf1 research
Sungroh Yoon (Seoul National University, College of Engineering, Korea)

SS09-2 Precision dinner: Genomes and health records
Ju Han Kim (Seoul National University College of Medicine, Korea)

SS09-3 Connected health and wellness journey
Jack Ahn (Samsung Electronics, USA)

16:35-18:05 **[SS10] Acute Myeloid Leukemia/ Myelodysplastic Syndromes** Vista 2

Chairs Je-Hwan Lee (University of Ulsan College of Medicine, Korea)
Amer M. Zeidan (Yale University, USA)

SS10-1 Genomics of core-binding factor AML
Nicolas Duployez (Lille University Hospital, France)

SS10-2 Precision medicine in AML in the era of novel agents
Gail J. Roboz (Weill Medical College of Cornell University, USA)

SS10-3 Incorporation of molecular assessments in risk stratification for myelodysplastic syndromes: Ready for prime time?
Amer M. Zeidan (Yale University, USA)

16:35-18:05 **[SS11] Chronic Myeloid Leukemia** Vista 3

Chairs Sang Kyun Sohn (Kyungpook National University School of Medicine, Korea)
Simona Soverini (University of Bologna, Italy)

SS11-1 Is chronic myeloid leukemia a single hit disorder?: Evidence from next-generation sequencing data
Dennis Kim (University of Toronto, Princess Margaret Cancer Centre, Canada)

SS11-2 NGS-based ABL1 kinase domain mutation detection
Simona Soverini (University of Bologna, Italy)

SS11-3 Precision medicine and immunity in CML
Satu Mustjoki (University of Helsinki, Finland)

DAILY PROGRAM Friday, March 15

16:35-18:05 **[ES04] Coagulation: Global Assay of Hemostasis** Grand Hall

Chairs Jaewoo Song (Yonsei University College of Medicine, Korea)
Sung-Hyun Kim (Dong-A University College of Medicine, Korea)

ES04-1 Early "Goal-directed Coagulation Therapy" approaches for the management of acute trauma-hemorrhage and trauma-induced coagulopathy
Marc Guido Maegele (Witten/Herdecke University, Germany)

ES04-2 Clinical application of clot waveform analysis in hemophilia treatment
Keiji Nogami (Nara Medical University, Japan)

ES04-3 Thrombin generation assay
Bas de Laat (Synapse Research Institute, The Netherlands)

18:05-18:30 Break

18:30-20:00 **Gala Dinner** Walkerhill Theater, B1

DAILY PROGRAM Saturday, March 16

07:30-08:30 **Business Meeting** — Walker Hall 2

08:30-09:00 **Working Party Reports** — Vista 1

09:00-10:30 **[JS04] EHA-KSH Joint Symposium II - Chronic Myelogenous Leukemia** — Vista 1

Chairs: Chul Won Jung (Sungkyunkwan University School of Medicine, Korea); Susanne Saußele (University of Mannheim, Germany)

JS04-1 Europe's experience of treatment-free remission in CML
Susanne Saußele (University of Mannheim, Germany)

JS04-2 Korea's experience of treatment-free remission in CML
Hawk Kim (Gachon University College of Medicine, Korea)

JS04-3 TKI-related cardiovascular toxicities in Europe
Susanne Saußele (University of Mannheim, Germany)

JS04-4 Long-term safety of tyrosine kinase inhibitors in chronic myeloid leukemia patients
Jee Hyun Kong (Yonsei University College of Medicine, Korea)

09:00-10:30 **[SS12] Childhood Acute Lymphoblastic Leukemia : Recent Updates of Prospective Trial of Pediatric ALL in Asia** — Vista 2

Chairs: Young Tak Lim (Pusan National University College of Medicine, Korea); Allen Yeoh Eng Juh (National University of Singapore, Singapore)

SS12-1 Treatment of childhood ALL with IKZF1 deletion (Malaysia-Singapore ALL 2010 Study)
Allen Yeoh Eng Juh (National University of Singapore, Singapore)

SS12-2 Multicenter clinical trial of pediatric acute lymphoblastic leukemia in China: CCLG 2008 study
Chi-kong Li (The Chinese University of Hong Kong, Hong Kong)

SS12-3 Recent updates of prospective trials for ALL in Japan
Yasuhiro Okamoto (Kagoshima University Graduate School of Medical and Dental Sciences, Japan)

09:00-10:30 **[SS13] Lymphoma** — Vista 3

Chairs: Seok-Goo Cho (College of Medicine, The Catholic University of Korea, Korea); Javeed Iqbal (University of Nebraska Medical Center, USA)

SS13-1 Pathogenesis of EBV-associated lymphoproliferative disorders
Hiroshi Kimura (Nagoya University Graduate School of Medicine, Japan)

SS13-2 Molecular understanding of peripheral T-cell lymphoma
Javeed Iqbal (University of Nebraska Medical Center, USA)

SS13-3 Clinical application of cell-free DNA in lymphoma
Seok Jin Kim (Sungkyunkwan University School of Medicine, Korea)

DAILY PROGRAM Saturday, March 16

09:00-10:30 **[SS14] Advances in Technology** Grand Hall

Chairs Yonggoo Kim (College of Medicine, The Catholic University of Korea, Korea)
Christoph A. Merten (European Molecular Biology Laboratory (EMBL), Germany)

SS14-1 Droplet microfluidics in antibody discovery, immune repertoire sequencing and personalized cancer therapy
Christoph A. Merten (European Molecular Biology Laboratory (EMBL), Germany)

SS14-2 Applications of single-cell mass cytometry in hematologic malignancies
Gregory Behbehani (The Ohio State University– the James Cancer Center, USA)

SS14-3 Prediction of acute myeloid leukemia risk in healthy individuals
Liran I. Shlush (Weizmann Institute of Science, Israel)

10:30-10:45 Coffee Break

10:45-11:45 **[PL03] Genomics in Lymphoid Malignancies** Vista 1-3

Chair Hyeoung-Joon Kim (Chonnam National University Medical School, Korea)

PL03-1 The new genomics of acute lymphoblastic leukemia
Charles G. Mullighan (St. Jude Children's Research Hospital, USA)

PL03-2 Genetic basis and treatment of high-risk multiple myeloma
Gareth J Morgan (NYU Myeloma Centre, USA)

11:45-12:30 Award Ceremony & Closing Vista 1-3

POSTER LIST

2019 KOREAN SOCIETY OF
HEMATOLOGY INTERNATIONAL CONFERENCE
& 60th ANNUAL MEETING

POSTER LIST

PP-001 Inhibition of Unc-51-Like kinase 1 (ULK1) preferentially induces apoptosis and autophagy in FLT3-ITD- mutated acute myeloid leukemia cells

Ji Eun Jang[1], Ju-In Eom[2], Hoi-Kyung Jeung[2], Haerim Chung[1], Yu Ri Kim[1], June-Won Cheong[1], Yoo Hong Min*[1]
[1] Department of Internal Medicine, Yonsei University College of Medicine, Korea
[2] Avison Biomedical Research Center, Yonsei University College of Medicine, Korea

PP-002 RNA CRISPR-Cas9 efficiently down regulates pCrKL signalling in K562 BCR-ABL cell line: Insights from in-vitro experiments with gene editing

Prateek Bhatia*, Aditya Singh
Pediatric Hematology-Oncology Unit, Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh, India

PP-003 HTLV-1 bZIP factor modulates p53 pathway by stabilizing PICT1 complex

Takayuki Ohshima*, Rio Yamada, Risa Mukai, Kanata Yoshimoto, Yu Maruoka
Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, Japan

PP-004 Prognostic impact of interim and post-treatment positron emission tomography status in mantle cell lymphoma patients treated with frontline R-CHOP

Young-Woo Jeon[1,2,3], Seugyun Yoon[1], Ki-Joon Min[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], Hee-Je Kim[1], Seok Lee[1], Chang-Ki Min[1], Jong Wook Lee[1], Seok-Goo Cho*[1,2,3]
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[2] Hematology, Institute for Translational Research and Molecular Imaging, Catholic Institutes of Medical Science, Korea
[3] Hematology, Laboratory of Immune Regulation, Convergent Research Consortium for Immunologic Disease, Korea

PP-005 Genetic alterations and their clinical implications in langerhans cell histiocytosis

Kyung-Nam Koh[1], Sung Min Chun[2], Jong Jae Kim[2], So Yoon Min[1], Jin Kyung Suh[1], Hyery Kim[1], Ho Joon Im[1], Jong Jin Seo*[1]
[1] Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea
[2] Pathology, Asan Medical Center, University of Ulsan College of Medicine, Korea

PP-006 Predictive role of circulating microRNA-29c-3p expression for autologous stem cell transplantation in patients with newly diagnosed multiple myeloma

Sung-Soo Park[1], Tae Woo Kim[1], Seug Yun Yoon[1], Gi June Min[1], Silvia Park[1], Young-Woo Jeon[1,2], Seung-Ah Yahng[3], Seung-Hwan Shin[4], Sung-Eun Lee[1,2], Jae-Ho Yoon[1,2], Byung-Sik Cho[1,2], Ki-Seong Eom[1,2], Yoo-Jin Kim[1,2], Seok Lee[1,2], Hee-Je Kim[1,2], Seok-Goo Cho[1], Chang-Ki Min*[1,2]
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PP-007 Incidence, prevalence, mortality, and causes of death associated with Waldenström macroglobulinemia in Korea: A nationwide, population-based study

Seri Jeong[1], Seom Gim Kong[2], Da Jung Kim[3], Sangjin Lee[4], Ho Sup Lee*[3]
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[2] Pediatrics, Kosin University College of Medicine, Korea
[3] Hematology-Oncology, Kosin University College of Medicine, Korea
[4] Statistics, Pusan National University, Korea

PP-008 Nationwide epidemiologic study for disease transformation and secondary cancers in Korean children and young adults with myeloproliferative neoplasms

Hyoung Soo Choi[1], Junshik Hong[2], Ju Hyun Lee[3], Soo Mee Bang*[3]
[1] Pediatrics, Seoul National University Bundang Hospital, Korea
[2] Internal Medicine, Seoul National University Hospital, Korea
[3] Internal Medicine, Seoul National University Bundang Hospital, Korea

PP-009 Distribution chemotherapy response modulating genetic polymorphisms in Armenian population

Yervand Hakobyan, Arsen Arakelyan*
Adults' Department, Hematology Center after Prof. Yeolyan MH RA, Armenia
Institute of Molecular Biology NAS RA, Armenia

POSTER LIST

PP-010 Twenty years' experiences of exchange transfusion in Korea
Min-Sun Kim, Dae-Hyun Ko*, Sang-Hyun Hwang, Heung-Bum Oh
Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea

PP-011 Antileukemic activity of Thiazole-Pyrazole conjugates against human leukemic cell via inhibition of epidermal growth factor receptor (EGFR)
Udaya Pratap Singh*[1], Hans Raj Bhat[2]
[1] *Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology & Sciences, India*
[2] *Department of Pharmaceutical Sciences, Dibrugarh University, India*

PP-012 2-Phenylpyrimidine coumarin induces apoptosis via activation of caspase and inhibition of PI3K/Akt/mTOR-Kinase in human leukemic cell
S. Singh
Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology & Sciences, India

PP-013 Impact of the immuno-microenvironmental changes in AML by blocking both CXCR4 and dual immune checkpoints
Hee-Sun Hwang[1], A-Reum Han[1], Ji Yoon Lee[1], Hee-Je Kim*[1,2]
[1] *Leukemia Research Institute, The Catholic University of Korea Seoul St. Mary's Hospital, Korea*
[2] *Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea Seoul St. Mary's Hospital, Korea*

PP-014 A case of jumping translocation of 1q42 in acute myeloid leukemia patient
Cheongang Park, Seon-Ho Mun, A-Jin Lee, Chang-Ho Jeon, Hun Suk Suh, Sang-Gyung Kim*
Laboratory Medicine, Daegu Catholic University Medical Center, Korea

PP-015 Flow cytometric characteristics of distinct population in acute basophilic leukemia
Seon-Ho Mun, Sang-Gyung Kim*, A-Jin Lee, Hun Suk Suh, Chang-Ho Jeon, Cheongang Park
Laboratory Medicine, Daegu Catholic University Medical Center, Korea

PP-016 PTEN/AKT signaling mediates chemoresistance in refractory acute myeloid leukemia through enhanced glycolysis
Min Jeong Ryu[1,2], Jeongsu Han[1,2,4], Soo Jeong Kim[1,4], Min Joung Lee[1,3,4], Xianshu Ju[1,3,4], Yu Lim Lee[1,3,4], Jeong Hwan Son[3], Jianchen Cui[1,3,4], Yunseon Jang[1,3,4], Woosuk Chung[5,6], Ik-Chan Song[7], Gi Ryang Kweon[1,2,3], Jun Young Heo*[1,3,4,5]
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PP-017 A genome-wide CRISPR screen identifies PTEN critical for NL101 sensitivity in acute myeloid leukemia
Liming Lin, Shu Li, Feiqiong Gao, Jiawei Zhang, Yang Xu*
Department of Hematology, The Second Affiliated Hospital of Zhejiang University School of Medicine, China

PP-018 Efficacy and safety of lenalidomide as monotherapy and multitherapy in the management of acute myeloid leukemia: A meta-analysis
Md Sarfaraj Hussain*[1], Abul Kalam Najmi[2]
[1] *Department of Pharmacognosy, Integral University, India*
[2] *Department of Pharmacology, Jamia Hamdard, India*

PP-019 Decitabine efficacy and safety in the management of acute myeloid leukemia: A meta analysis of observational studies
Md Salman Hussain*[1], Abul Kalam Najmi[2]
[1] *Department of Pharmaceutical Medicine, Jamia Hamdard, India*
[2] *Department of Pharmacology, Jamia Hamdard, India*

PP-020 Acute promyelocytic leukemia - retrospective analysis from a tertiary care oncology centre from South India
Perraju Bhaskar Bhuvan Lagudu[1], Venkatraman Radhakrishnan*[1], Prashanth Ganesan[2], Ganesan T S[1], Manikandan Dhanushkodi[1], Nikita Mehra[1], Jayachandran Perumal[1], Kripa Sankar[1], Gnana Sagar Tenali[1], Krishna Rathinam[1]
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POSTER LIST

PP-021 Impact of treatment and transplantation on survival in a phase 3 study of CPX-351 vs 7+3 in older adults with newly diagnosed, high-risk/secondary AML

Tara L. Lin[1], Jorge E. Cortes[2], Laura F. Newell[3], Donna Hogge[4], Richard M. Stone[5], Jonathan E. E. Kolitz[6], Gary J. Schiller[7], Matthew J. Wieduwilt[8], Daniel H. Ryan[9], Richard Martin*[10], Robert J. Ryan[11], Michael Chiarella[11], Arthur C. Louie11
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PP-022 CPX-351 Vs 7+3 in older adults with newly diagnosed acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) enrolled in a phase 3 study

Daniel H. Ryan[1], Jorge E. Cortes[2], Laura F. Newell[3], Robert K. Stuart[4], Donna Hogge[5], Jonathan E. Kolitz[6], Gary J. Schiller[7], Matthew J. Wieduwilt[8], Richard Martin*[9], Robert J. Ryan[10], Arthur C. Louie[10]
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PP-023 Genetic mutation profiling of acute myeloid leukemia using targeted next generation sequencing

Ha Jin Lim[1], Jun Hyung Lee[1], Seung Yeob Lee[1], Sejong Chun[1], Seung-Jung Kee[1], Soo-Hyun Kim[1], Jong-Hee Shin[1], Seo-Yeon Ahn[2], Hyeoung-Joon Kim[2], Myung Geun Shin*[1,3]
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PP-024 Beyond hypomethylating agent (HMA) failure in elderly acute myeloid leukemia (AML) patients

Silvia Park[1], Hee-Je Kim*[1], Dong-Wook Kim[1], Yoo-Jin Kim[1], Jong Wook Lee[1], Seok Lee[1], Ki-Seong Eom[1], Seok-Goo Cho[1], Chang-Ki Min[1], Byung Sik Cho[1], Jae-Ho Yoon[1], Young-Woo Jeon[1], Sung-Soo Park[1], Gi June Min[1], Seug Yun Yoon[1], Seung-Hwan Shin[2], Sung-Eun Lee[1], Seung-Ah Yahng[3]
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PP-025 Dialkyl resorcinol stemphol disrupts calcium homeostasis triggering immunogenic necroptosis in acute myeloid leukemia

Jin-Young Lee, Marc Diederich*
Department of Pharmacy, College of Pharmacy, Seoul National University, Korea

PP-026 Evaluation of the ion torrent oncomineTM myeloid research assay for clinical applications in hematologic malignancy

Jae Won Yun[1], Heyjin Kim[1,2], Jung Yoon[1], Jong Eun Park[1], Hee-Jin Kim[1], Sun-Hee Kim[1], Jong Won Kim*[1]
[1] *Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*
[2] *Department of Laboratory Medicine, Myongji Hospital, Hanyang University Medical Center, Korea*

PP-027 Role of allogeneic hematopoietic cell transplantation in acute myeloid leukemia patients with NPM1wt and FLT3-ITD negative group

Ju-Hyung Kim[1,2], Jungmin Lee[1,2], Ji-Yeon Ham[2,3], Jang Soo Suh[2,3], Joon-Ho Moon*[1,2], Sang Kyun Sohn[1,2]
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POSTER LIST

PP-028 Gene amplification and chromothripsis in acute myeloid leukemia with complex chromosomal abnormalities

Chang Ahn Seol[1], Chan-Jeoung Park[1], Seongsoo Jang[1], Young-Uk Cho[1], Jung-Hee Lee[2], Je-Hwan Lee[2], Kyoo-Hyung Lee[2], Jin-Ok Lee[3], Eul-Ju Seo*[1]
[1] *Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea*
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[3] *Asan Institute for Life Sciences, University of Ulsan College of Medicine and Asan Medical Center, Korea*

PP-030 Clinical application of next-generation sequencing in diagnostic work-up of patients with acute myeloid leukemia and myelodysplastic syndrome

Min Young Lee[1, 2], Young-Uk Cho*[1], Chan-Jeoung Park[1], Seongsoo Jang[1], Ari Ahn[1]
[1] *Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea*
[2] *Department of Laboratory Medicine, Kyung Hee University School of Medicine, Kyung Hee University Hospital at Gangdong, Korea*

PP-031 Reclassifying acute myeloid leukemia according to the revised 2016 WHO classification in a large patient group

Min-Young Lee, Young-Uk Cho*, Seongsoo Jang, Eul-Ju Seo, Chan-Jeoung Park
Department of Laboratory Medicine, University of Ulsan, College of Medicine and Asan Medical Center, Korea

PP-032 Predictive role of geriatric assessment for early events in elderly AML fit for intensive chemotherapy; Interim data of a prospective cohort study

Gi June Min[1], Byung Sik Cho*[1], Seug Yun Yoon[1], Silvia Park[1], Seung-Ah Yahng[2], Young-Woo Jeon[1], Seung-Hwan Shin[3], Jae-Ho Yoon[1], Sung-Eun Lee[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Seok Lee[1], Heeje Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Dong-Wook Kim[1], Jong Wook Lee[1]
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PP-033 Stable disease has survival benefit after hypomethylating agent in myelodysplastic syndrome

Hawk Kim*[1], Jae Sook Ahn[2], Young-Rok Do[3], Ho Jin Shin[4], Won Sik Lee[5], Sung-Nam Lim[6], Joon Ho Moon[7], Ho Sup Lee[8], Sung Hwa Bae[9], Yunsuk Choi[10]
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PP-034 Red blood cell and platelet indices: Could it predict survival of patients with myelodysplastic syndrome?

Jieun Uhm*[1], Moo-Kon Song[2], Young Woong Won[3], Byeong Bae Park[1], Jung Hye Choi[3], Young Yiul Lee[1]
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PP-035 Monocyte subset for the screening of chronic myelomonocytic leukemia

Sang Mee Hwang*, Jun Park, Seung-Ah Jeon
Laboratory Medicine, Seoul National University Bundang Hospital, Korea

PP-036 Polymorphism of TPMT and ITPA and their adverse effects of chemotherapy for acute lymphoblastic leukemia children in Bangladesh

Sanjana Zaman*[1, 2] Hiroko Fukushima[3], Ryoko Suzuki[3], Shoji Yoshimatsu[3, 4], Mohammad Delwer Hossain Hawlader[1], Nobutaka Kiyokawa[5], Takashi Fukushima[2]
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[5] *Department of Pediatric Hematology and Oncology Research, National Research Institute for Child Health and Development, Tokyo, Japan*

PP-037 Customised superparamagnetic iron-oxide polymeric nanocarriers for targeted and controlled delivery of anti-tumor drug in acute lymphoblastic leukemia

Anas Ahmad
Nano-Therapeutics, Institute of Nano Science and Technology (INST), India

POSTER LIST

PP-038 Immuno phenotypes and the value of cluster of differentation in acute leukemia at National Children's Hospital, Vietnam
Thi Ha Dang[1], Thanh Binh Nguyen*[2], Thi Nghiem Luong[1], Thi Duyen Nguyen[1], Hong Ha Tran Thi[1], Thi Thoa Ta[1], Thu Giang Phan[2]
[1] *Hematology Laboratory Department, National Children's Hospital, Vietnam*
[2] *Faculty of Immunology, Hanoi Medical University, Vietnam*

PP-039 Temporal trends in nutritional status of children with acute lymphoblastic leukemia during intensive phase of treatment
Venkatraman Radhakrishnan
Medical Oncology, Cancer Institute, India

PP-040 Preliminary experience at a single centre in India with a collaborative multicentre risk stratified and response adapted protocol for treating pediatric ALL
Venkatraman Radhakrishnan
Medical Oncology, Cancer Institute, India

PP-041 Homozygous TCF3 mutation is associated with severe hypogammaglobulinemia and acute lymphoblastic leukemia
Ridha Barbouche*[1], Lamia Aissaoui[2], Yu-Lung Lau[3], Meriem Ben-Ali[1]
[1] *Immunology, Pasteur Institute of Tunis, Tunisia*
[2] *Hematology, Aziza Othmana Hospital,, Tunisia*
[3] *Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong*

PP-042 A comparative study of palmar and digital dermatoglyphic patterns among leukemic patients & non-leukemic Individuals: A meta-analysis
Ameet Kumar Jha*[1], Sujatha D'costa[2]
[1] *Preclinical Sciences, Texila American University, Guyana*
[2] *Anatomy, American University of Antigua, Antigua&Barbuda*

PP-043 The effect of GATA3 rs3824662 gene polymorphism on children with pre-B-cell acute lymphoblastic leukemia treated by CCLG-ALL 2008 protocol
Xinran Chu[1], Dong Wu[2], Jing Gao[1], Shaoyan Hu*[1]
[1] *Department of Hematology and Oncology, Children's Hospital of Soochow University, China*
[2] *Department of Pediatric, Qiyuan People's Hospital, China*

PP-044 Comparision of parental perception on "Health Related Quality of Life (hrqol)" in children with acute lymphoblastic leukemia (on treatment) and normal
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PP-045 Detecting diplotype of NUDT15 variants and 6-Mercaptopurine sensitivity by target sequence cDNA of NUDT15
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PP-046 Sociodemographic, clinical and laboratory profile of acute leukemia patient in Sanglah General Hospital, Bali
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PP-047 Two cases of burkitt leukemia with IGH-MYC rearrangement associated with precursor B-cell phenotype
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PP-048 Chymeric antigen receptor (CAR) T-cell immunotherapy : A new promising therapy for patients with relapsed B-cell acute lymphoblastic leukemia
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PP-049 Anti-leukemic effect of ajwain oil against DMBA induced leukemic rat model: Possible mechanism of action
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PP-050 Chemo-protective effect of lemon oil against the benzene induced leukemia via regulation of growth factors and inflammatory mediators
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PP-051 Detection of complex variant t(9;22) chromosome translocations in newly diagnosed cases of chronic myeloid leukaemia. A single institute experience
Noorulain Fareed*, Noor Muhammad Somroo, M. Saeed Quraishy, Sana Rafiq
Oncology/ Hematology, Dr. Ruth K. M. Pfau, Civil Hospital, Karachi, Pakistan

PP-052 Optimal time points for BCR-ABL1 tyrosine kinase domain mutation analysis based on European LeukemiaNet recommendations in chronic myeloid leukemia
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PP-053 A retrospective study of paediatric chronic myeloid leukemia from a tertiary cancer centre, India
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PP-054 Population pharmacokinetic and dose-response analyses of dasatinib to support dosage in Asian pediatric patients with chronic myeloid leukemia
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PP-055 A study of treatment-free remission evaluation in real-world chronic myeloid leukemia; Estimated cost-effectiveness analysis (ASTER-C)
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PP-056 Highly sensitive detection of BCR-ABL in clinical samples by QXDx BCR-ABL %IS digital droplet PCR
Hee-Jung Chung, Mina Hur*, Hannah Kim, Sumi Yoon, Hee-Won Moon, Yeo-Min Yun
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PP-057 Survival outcomes with addition of methotrexate and cytarabine onto standard treatment for diffused large B-cell lymphoma (DLBCL): 3-year follow-up
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PP-058 High serum glucose during chemotherapy is associated with inferior survival outcome in patients with non-Hodgkin lymphoma
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PP-059 Follicular lymphoma with leukemic presentation
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PP-060 Milk- alkali syndrome with pulmonary calcification in diffused large B cell lymphoma: A case report
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PP-061 Asian variant of intravascular large B-cell lymphoma
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PP-062 Clinical impact of prognostic nutritional index in diffuse large B cell lymphoma
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PP-063 Clinical characteristics and outcome of acquired immune deficiency syndrome (AIDS) related lymphomas (ARL) in Hospital Ampang
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PP-064 Necropotosis was restored in chronic lymphocytic leukemia by inhibiting LTB-NF-KB-LEF1 pathway
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PP-065 Prevalence and immunophenotypic characteristics of monoclonal B-cell lymphocytosis in Korea
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PP-066 Event free survival at 24 months is a surrogate end point for subsequent overall survival in peripheral T-cell lymphoma
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PP-067 Prurigo nodularis and hodgkin's Lymphoma – A rare association
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PP-068 The protection effect of moringa extract from lymphoma cell metastasis through decreasing ICAM-1 in Internal carotid artery of metabolic syndrome rats
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PP-069 Ibrutinib vs real-world (RW) treatment outcomes in chronic lymphocytic leukemia by Del11q status: Adjusted comparison of clinical trial and RW data

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PP-070 A case of EBV-Positive NK/T cell lymphoma progressed from severe mosquito bite allergy

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PP-071 Efficacy of Ibrutinib-Rituximab versus Real-World (RW) regimens for waldenström's macroglobulinemia: Adjusted comparison of clinical trial and RW data

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PP-072 Treatment outcomes of adult primary mediastinal B-cell lymphoma (PMBCL) treated with dose-adjusted R-EPOCH as frontline therapy in tertiary hospital

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PP-073 Triple improvement in the clinical, laboratory, and radiologic manifestations of multicentric castleman disease after treatment with siltuximab

Gi June Min[1], Seok-Goo Cho*[1], Seug Yun Yoon[1], Silvia Park[1], Seung-Ah Yahng[2], Seung-Hwan Shin[3], 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], Dong-Wook Kim[1], Jong Wook Lee[1]
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PP-074 A 15-year-old male diagnosed with mantle cell lymphoma, presenting with mediastinal mass

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PP-075 Treatment abandonment amongst patients with hematological malignancy in TYA age group

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PP-076 Effect of the dose of rituximab on survival outcomes of the DLBCL treated with rituximab-CHOP; Based on the national health information database

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PP-077 Clinical impact of ibrutinib in refractory or relapsed mantle cell lymphoma: Single-Center experience in clinical practice

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PP-078 Results and prospects for the treatment of anaplastic cell lymphoma in adult patients

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PP-079 Genetic and non-genetic risk factors of bleomycin-Induced pulmonary toxicity in south indian patients with hodgkin lymphoma

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PP-080 A rare case of high grade nodal marginal zone B cell lymphoma with diffuse bone marrow involvement and igm-type monoclonal paraproteinemia

Sang Hyuk Park[1], Jaewook Kim[1], Joseph Jeong[1], Seon-Ho Lee[1], Hee Jeong Cha[2], Seol Hoon Park[3], Yunsuk Choi[4], Jae-Cheol Jo[4], Ji-Hun Lim*[1]
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PP-081 9-year-old boy diagnosed with X-linked lymphoproliferative disease type 1 - Case report

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PP-082 Multi-gene sequencing of hemophagocytic lymphohistiocytosis in pediatric patients: Gene profiles and its correlation with bone marrow findings

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PP-083 Isolated splenic Rosai-Dorfman disease presenting as a fever of unknown origin in a 10-months-old child

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PP-084 Multiple myeloma in teenage patient: A case report

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PP-085 Multiple myeloma patients on novel agents: Effect of pneumococcal vaccination on incidence of infectious complications

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PP-086 Detection of chromosome 13 (13q14) deletion among Sudanese patients with multiple myeloma using a molecular genetics fluorescent in situ hybridization

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PP-087 MGUS predicts worse prognosis in patients with coronary artery disease
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PP-088 The value of abdominal fat aspiration and labial salivary gland biopsy in diagnosing immunoglobulin light chain amyloidosis
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PP-089 Megakaryocytic expression of GATA-1, IL-6, and IL-8 in plasma cell neoplasm with dysmegakaryopoiesis
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PP-090 Bortezomib-based first line treatment for AL amyloidosis patients who are not candidate for stem cell transplantation
Joon Young Hur[1], Kang Kook Lee[1], Sang Eun Yoon[1], Sehhoon Park[1], Jangho Cho[1], Youjin Kim[1], Gayeon Lee[2], Jinoh Choi[2], Eunseok Jeon[2], Ju Hong Min[3], Byungjun Kim[3], Jung Sun Kim[4], Jung Eun Lee[5], Joon Young Choi[6], Seok Jin Kim[1], Jun Ho Jang[1], Won-Seog Kim[1], Chul Won Jung[1], Kihyun Kim*[1]
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PP-091 Health-related quality of life in relapsed/refractory multiple myeloma: Systematic review of randomized control trials
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PP-092 Prognostic impact of frailty in transplant-ineligible multiple myeloma patients treated with first-Line bortezomib-based chemotherapy
Ji Hyun Lee[1], Sung-Hyun Kim[1], Seok Jae Huh[1], Jae-Cheol Jo[2], Ho-Jin Shin[3], Won-Sik Lee[4], Yoo Jin Lee[5], Ho Sup Lee*[6]
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PP-093 Comparison of conventional cytogenetic analysis and fluorescence in situ hybridization in survival of newly diagnosed myeloma patients
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PP-094 Orthotopic heart transplant facilitated autologous hematopoietic stem cell transplantation for light-chain amyloidosis
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PP-095 Changes in blood viscosity and yield stress before and after phlebotomy
Mikyoung Park, Mina Hur*, Sumi Yoon, Hanah Kim, Hee-Jung Chung, Hee-Won Moon, Yeo-Min Yun
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PP-096 Do we need the revised 2016 WHO polycythemia vera diagnostic criteria for better diagnosis of posttransplantation erythrocytosis?
Myung-Won Lee[1], Hyewon Ryu[1], Yoon-Seok Choi[1], Ik-Chan Song[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1], Deog-Yeon Jo*[1], Dae Eun Choi[2], Ki-Ryang Na[2], Kang Wook Lee[2]
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PP-097 Characteristics and survival of atypical chronic myeloid leukemia; Based on national health information database
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PP-098 Clinical application of next-generation sequencing in myeloproliferative neoplasms: Genetic profiles and prognostic significance
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PP-099 Clinical effect of haploidentical hematopoietic stem cell transplantation combined with post-transplant cyclophosphamide for children with severe aplastic anemia
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PP-100 The outcome of immunotherapy by antithymocyte globulin and cyclosporine a for acquired aplastic anaemia during 10 years in Vietnam
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PP-101 The incidence of severe chronic neutropenia in Korea and related clinical manifestations: A national health insurance database study
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PP-102 CD3/CD45RA depleted haploidentical transplant for SCID: First case in Vietnam
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PP-103 Label-free and high-sensitive detection of pseudomonas aeruginosa from bacteremia using a surface plasmon resonance DNA-based biosensor
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PP-104 Detection of staphylococcal bacteremia virulence factors using novel isothermal amplification with SPR biosensor methodology
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PP-105 Diagnostics under sky: Mitigation of gap in global health point-of-care diagnosis in extremely poor hematology laboratory linking frugal science
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PP-106 Acute kidney disease as a 90-day mortality predictor in hemato-oncologic patients with persistent acute kidney injury and vancomycin treatment
Ahram Yi[1], Mina Hur*[1], Hyeong Nyeon Kim[2], Hanah Kim[1], Hee-Jung Chung[1], Hee-Won Moon[1], Yeo-Min Yun[1], Sung-Yong Kim[3], Mark Hong Lee[3]
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PP-107 Pattern of hematological disorders on bone marrow examination: A tertiary care hospital experience
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PP-108 Flow cytometry quantitation of acridine orange-Stained malaria parasites
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PP-109 Platelet counting in thrombocytopenic samples using mindray BC-6800 plus
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PP-110 Evaluation of neutrophil gelatinase-associated lipocalin (NGAL), compared with IL-1β, IL-6, TNF-A and CRP in hematologic malignancy
Jung Yoon[1], Ji-Youn Lim[2], Eun-Ah Chang[1], Deok-Su Kim[1], Shin-Jong Kim[1], Myung-Hyun Nam[1], Donggeun Sul[2], Hwa Jung Sung[4], Ji Seon Choi[3], Se Ryeon Lee[4], Chi-Hyun Cho*[1]
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PP-111 Cell population data of automated hematology analyzer Sysmex XN for Sepsis
Mikyoung Park, Mina Hur*, Hanah Kim, Hee-Jung Chung, Hee-Won Moon, Yeo-Min Yun
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PP-112 The effect of oral administration corticosteroid toward leukocytes number and differential count in mice (Mus Musculus) based on its duration
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PP-113 Hematologic scoring system for detection of neonatal sepsis
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PP-114 Screening of dysplastic neutrophils using cell population data using Sysmex XN-1000 analyzer
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PP-115 A case of spurious white blood cell count from automated Sysmex XN hematology analyzer: Difference between WNR and WDF channels
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PP-116 Atypical chronic lymphocytic leukemia has a worse prognosis than CLL and clinically and laboratory different from B-cell prolymphocytic leukemia
Ari Ahn[1], Chan-Jeoung Park*[1], Eul-Ju Seo[1], Seongsoo Jang[1], Young-Uk Cho[1], Misuk Ji[2], Youn Mi Choi[2], Kyoo-Hyung Lee[3], Jae-Hwan Lee[3], Jung-Hee Lee[3], Dok Hyun Yoon[3], Cheol Won Suh[3]
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PP-117 Participation in the external quality assurance for international normalised ratio: Our experience
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PP-118 HDAC inhibitor martinostat-induced immunogenic cell death in chronic myeloid leukemia
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PP-119 Optimization of high resolution melting assays for detection of candidate SNPs associated with anemia: The nutrigenomics unit, FNRI-DOST experience
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PP-120 Comparison of gene expression profile in myeloid, lymphoblastic and mixed phenotype acute leukemia sharing minor BCR/ABL1 fusion using RNA sequencing
Jaewoong Lee[1,2], Eunhee Han[1,2], Kyungja Han[1], Seong-Eui Hong[3], Byung-Sik Cho[4], Hee-Je Kim[4], Myungshin Kim[1,2], Yonggoo Kim[1,2]
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PP-121 Synergistic apoptosis induced by a targeted combination treatment with midostaurin and ABT199 in the FLT3-ITD-Positive and BCL2-overexpressing MV4-11
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PP-122 TMQ0153, a synthetic hydroquinone, induces autophagy followed by controlled necroptosis via mitochondrial dysfunction in chronic myelogenous leukemia
Sungmi Song[1], Barbora Orlikova[1,2], Claudia Cerella[1,2], Ali Al-Mourabit[3], Marc Diederich*[1]
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PP-123 Burden and associated factors of anemia among pregnant women attending antenatal care in southern Ethiopia: Cross sectional study
Amare Desalegn Wolide
Medical Physiology Department, Jimma University, Ethiopia

PP-124 Molecular genetic modifier of glucose-6-phosphate dehydrogenase gene
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PP-125 Macrocytic anemia associated infantile tremor syndrome and vitamin D
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PP-126 Smartphone-based diagnosis in glucose-6-phosphate dehydrogenase deficiency
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PP-127 Microparticles-derived miRNAs serves as a novel diagnosis marker for glucose-6-phosphate dehydrogenase deficiency
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PP-128 Association of hematologic parameters with TMPRSS6 gene variations in iron deficiency anemia patients
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PP-129 The effect of moringa seeds extract as anti anemia of chronic disease through decreasing IL-6 expression in liver tissue of metabolic syndrome rats
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PP-130 Thalassemia major patients presenting with raised HbF and a fast moving Hb
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PP-131 Exploring the β-thalassaemia mutations in western rajasthan with clinical expression
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PP-132 A case of δ-thalassemia in Korea
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PP-133 Parvovirus B19-associated neutropenia and thrombocytopenia without anemia
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PP-134 Attenuation of anemia by retnla in LPS-induced inflammatory response
Mi-Ran Lee*, Seon-Hye Lee, Min-Ju Jeung, Yoon-Hee Hwang, Nam-Hee Kim, Yoon-Jin Park
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PP-135 Glucose-6-phosphate dehydrogenase deficiency in newborns in Birjand, Iran
Mohammad Sadegh Kamali[1], Mohammad Hossein Motahari Nasab[1], Seyed Mehdi Sajjadi*[2]
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PP-136 Screening of α-thalassemia using cord blood in Bangladesh
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PP-137 Knowledge trend of anemia in adolescents in Indonesia
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PP-138 Successful sirolimus treatment of pure red cell aplasia in patients with renal insufficiency
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PP-139 Local wisdom and anemia prevention: Study of the use of herbs as an alternative treatment for rural communities in West Sulawesi, Indonesia
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PP-140 The influence of socio-economic factors on prevelence of anemia among women of reproductive age in ASEAN-5
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PP-141 The problem of identification of population objects during the unification of data from multiple sources when working with a hemophilia register
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PP-142 Prevalence of anaemia in western region of Nepal: A hospital based study
Mukunda Raj Kalouni, Saroj Pokhrel*
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PP-144 Chlorophyll as a considerable treatment for anemia through increases hemoglobin levels in anemia white rat model
Indah Sagitaisna Putri*, Faisal Hafidh
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PP-145 Effect of carica papaya leaf extract on platelet counts in patient of dengue
Jay Karan*[1], Pankaj Bhardwaj[2], Jagdish Goyal[3]
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PP-146 Platelet indices and their value in differentiating the causes of thrombocytopenia
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PP-147 Perioperative management and outcomes in children with congenital bleeding disorders: A retrospective review at a single hemophilia treatment center
Ha Nuel Chon, Seoin Kim, Jinjoo Kim, Young Shil Park*
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PP-148 Reference intervals for platelet dense granules using whole mount electron microscopy
Jin-Yeong Han*[1], In-Hwa Jeong[1], Hee-Won Chueh[2], Sang-Soo Park[3], Seo-Hee Rha[3]
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PP-149 Platelet parameters and inflammation in anemic and non-anemic patients with type 2 diabetes and early CKD
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PP-150 Parameters of coagulation and fibrinolysis in patients with diabetes type 2 and chronic kidney disease
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PP-151 The prognostic value of mean platelet volume in venous thromboembolism
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PP-152 The prognostic role of red cell distribution width in venous thromboembolism and related mortality

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PP-153 Long-term expansion of Gata1^{low} Meg-erythroid cells increased cell division while maintained differentiation potential

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PP-154 Analysis of genetic factors in Korean adult patients with atypical hemolytic uremic syndrome

Jae Won Yun[1], Ki-O Lee[2], Jung Oh Kim[4], Nam Keun Kim[4], Jin Seok Kim[5], Junshik Hong[6], Youngil Koh[6], Sung-Soo Yoon[6], Ho-Young Yhim[7], Yong Park[8], Ki Young Kwon[9], Jinny Park[10], Jong Wook Lee[11], Hee-Jin Kim[1], Doyeun Oh*[3]
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PP-155 Hereditary platelet function disorder from RASGRP2 mutations identified by whole exome sequencing

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PP-156 Cryopreservation of peripheral blood stem cell using mechanical freezers : Initial experience from an Indian tertiary care hospital

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PP-157 Modified post-transplant cyclophosphamide allogeneic HSCT combined with decitabine-based reduction, busulfan and melphalan conditioning regimen in children with juvenile myelomonocytic leukemia

Xiaodong Shi, Yan Yue*
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PP-158 The correlation and predictive value of immature platelet fraction to plasma platelet recovery in patients receiving autoSCT

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PP-159 Survival by time to start of defibrotide in veno-occlusive disease/sinusoidal obstruction syndrome post hematopoietic stem cell transplant in adults

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PP-160 Initial evaluation of the efficacy of autologous stem cell transplantation in non-Hodgkin lymphoma at HCMC Blood Transfusion Hematology Hospital
Nam Duy Hoang*, Thu Hanh Nguyen, Phu Duc Vinh Huynh, Man Van Huynh, Dung Chi Phu
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PP-161 Evaluation of the bacterial and fungal infection status in HSCT patients in HCMC Blood Transfusion and Hematology Hospital
Hanh Thu Nguyen*, Van Man Huynh, Duc Vinh Phu Huynh, Duy Nam Hoang, Thien Ngon Huynh, Xuan Tuan Ma, Chi Dung Phu
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PP-162 Recovery of specific subsets of NK and T cells highly associated with GVHD after haploidentical stem cell transplantation in acute leukemia
Haerim Chung[1], Ji Eun Jang[1], Yu Ri Kim[1], Hoi-Kyung Jeung[2], Ju-In Eom[2], Soo-Jeong Kim[1], Jin Seok Kim[1], June-Won Cheong[1], Yoo Hong Min*[1]
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PP-163 Autologous hematopoietic stem cell transplantation in acute myeloid leukaemia: Long-term outcome
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PP-164 Impact of CMV prophylaxis on rates of rehospitalization in adult CMV seropositive allogeneic HSCT recipients: Experience from the letermovir phase 3 clinical trial
Shahrul Mt-Isa*, Hong Wan, Cyrus Badshah, Valerie Teal, Randi Leavitt, Jonathan Schelfhout, Eungeol Sim
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PP-166 Lkb1 modulates regulatory T cell homeostasis during acute GVHD
Xiuhua Su, Erlie Jiang*
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PP-167 Phase II study of imatinib mesylate and mycophenolate mofetil in children with steroid-refractory sclerotic type chronic graft-versus-host disease
Jung Yoon Choi[1,2], Hyery Kim[3], Hyoung Jin Kang*[1,2], Hee Jo Baek[4], Hoon Kook[4], Jae Min Lee[5], Hong Yul An[1,2], Kyung Taek Hong[1,2], Hee Young Shin[1,2]
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PP-168 Role of platelet-rich plasma in healing diabetic and leprosy foot ulcers in resource poor setting
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PP-169 Curative effect and optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome of higher risk groups
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PP-170 Renal parameters and their associations with clinical severity score among adult Sudanese patients with sickle cell anemia
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PP-171 Autonomic activity and haemodynamic characteristics in relation to clinical severity of sickle cell anaemia among steady state adults
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PP-172 A somatic cell nuclear transfer methodology for replacement of hematological malignant cells population in the myeloproliferative disorders
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PP-173 Adipose-derived stem cells therapy in diabetic osteoarthritis
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PP-174 Adipose tissue derived stromal-vascular-fraction enriched platelet-rich-plasma therapy reverses the effects of androgenetic alopecia
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PP-175 To determine the frequency and types of RBC alloimmunization in multitransfused oncology patients at a teaching hospital in Lahore, Pakistan
Aisha Mahesar*, Ayisha Imran, Nauman Malik, Mansoor Mazari
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PP-176 An attempt to tailor wastage of blood products in the form of returned units
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PP-177 Inappropriate use of fresh frozen plasma in a tertiary care hospital
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PP-178 Post donation notification, counseling and response rate of reactive blood donor:
An important step to prevent reactive donor from re-donating blood
Sidra Asad Ali*, Syed Usama, Mariam Mirza
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PP-179 Therapeutic plasma exchange in rat killer (Yellow Phosphorus) poisoning: Experience from South India
Deepti Sachan*[1], Ilankumaran Kaliamoorthy[2], Akila Rajakumar[2], Dinesh Jothimani[2], Mettu S Reddy[2], Kulaseharan Vh[2], Mukul Vij[3], Mohamed Rela[2]
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PP-180 Correlation between the IgG subclasses with occurrence and severity of haemolytic disease of foetus and newborn
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Maternal and Reproductive Health, Sanjay Gandhi Postgraduate Institute of Medical Sciences, India

PP-181 Overview of antibodies implicated in delayed hemolytic transfusion reaction
Rahul Katharia*, Rajendra Chaudhary
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PP-182 Retrospection of anti-blood group antibody proficiency testing data using geometric mean and standard deviation
John Jeongseok Yang, Dae-Hyun Ko*, Sang-Hyun Hwang, Heung-Bum Oh
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PP-183 Ensuring standard transfusion practices amidst staff nurses by implicating a framework of knowledge gap analysis and subsequent reformatory measures
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PP-184 Knowledge, attitudes and practices on blood transfusion of medical residents in a tertiary hospital: A questionnaire-based study
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PP-185 Correlation between packed red cells hematocrit with post-transfusion hemoglobin level in anemic patient at Badung mangusada district hospital, Bali
Ni Gusti Ayu Arini Junita Putri Kardinal*[1], Ni Made Renny Anggreni Rena[2], Wayan Losen Adnyana[2], Tjokorda Gde Dharmayudha[2], Ketut Suega[2], I Made Bakta[2], Anak Agung Wiradewi Lestari[3]
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PP-186 Impact of voluntary non-remunerated blood donation: How the community responses in developing country
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PP-187 Development of deep vein thrombosis after achieving remission in a patient with acquired hemophilia A
Camille Ariadne Tanchanco*[1], Valerie Ramiro[2], Johannes Paolo Cerrado[3], John Mark Torres[3], Teresita Dumagay[1], Angelina Mirasol[1], Teresa Abola[2]
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PP-188 Successful management and delivery in a pregnancy with secondary evans syndrome from systemic lupus erythematosus and antiphospholipid syndrome
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PP-189 On-demand versus low dose factor VIII prophylaxis treatment in hemophilia A patients: Differences in outcome and factor concentrates utilization
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PP-190 Evaluation of bone marrow study in patients with ewing sarcoma/primitive neuroectodermal tumors at a tertiary-care hospital
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PP-191 Bone marrow findings of IgG4-related disease; A case of bone marrow involvement of IgG4-related disease
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PP-192 Etiology, sensitivity profiles, clinical course of bloodstream infections in patients with hematological and oncological diseases
Senmin Chen, Sixi Liu, Xiuli Yuan, Huirong Mai, Shilin Liu, Junrong Lin, Feiqiu Wen*
Hematology and Oncology Department, Shenzhen Children's Hospital, China

PP-193 Evaluation of neutrophil extracellular traps as the circulating marker for patients with cardiocerebrovascular diseases
Hyeonho Lim[1], Inhwa Jeong[1], Gyudae An[1], Kwangsook Woo[1], Kyeonghee Kim[1], Jeongman Kim[1], Jaekwan Cha[2], Moohyun Kim[3], Jin-Yeong Han*[1]
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POSTER LIST

PP-194 Current status of Korea Leukemia Bank
Soo-Hyun Kim[1, 2], Mi-Young Lee[1, 2], Soo-Young Choi[2], Hea-Lyun Yoo[2], Kyung-Mi Kee[2], Ji-Hyung Suh[2], Seon Young Yang[2], Suna Park[2], Sa-Hee Park[2], Dong-Wook Kim*[1, 2, 3]
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PP-195 A report of a new NFKB1 frameshift mutation contributing to primary immunodeficiency diseases
Yan Liu, Anli Liu, Jun Peng*
Department of Hematology, Qilu Hospital, Shandong University, China

PP-196 A case of occult macrophage activation syndrome that mimics of refeactory kawasaki disease
Sang Hyun Joo, Kwang Nam Kim*
Pediatrics, Hallym University Sacred Heart Hospital, Korea

PP-197 Cutaneous manifestation among transfusion patients
Mandeep Joshi
Public Health, Community Health and Environmental Society, Nepal

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Anand Krishna Singh
Biotechnology, Devi Ahilya University Indore, India

PP-200 Production of a chemotherapeutic enzyme drug for acute myeloid leukemia and acute lymphoblastic leukemia: L- asparaginase
Girish Pendharkar*, Sujata Umrane, Dhanashree Patil, Shweta Patil
School of Life Sciences, Kavayitri Bahinabai Chaudhari North Maharashtra University, India

PP-201 Factors associated with quality of life in patients with leukemia
Elaheh Alizargar, Azadeh Alizargar*
Community Health Research Center, Khorasgan Azad University, Iran

PP-202 Systematic literature review and assessment of health-related quality of life in aggressive non-Hodgkin lymphoma survivors
Md Azharuddin*[1], Mohammad Adil[2], Pinaki Ghosh[3], Manju Sharma[1, 2]
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PP-203 Psychosocial counseling for prevention of sickle cell in a tribal population
Suresh Gemawat
Genaral Medical Laboratory, Madan Mohan Medical and Counselling Centre, India

PP-204 Incidence of cancer incidence in India: A analysis from cancer registries
Abul Kalam Najmi*[1], Md Salman Hussain[2], Md Sarfaraj Hussain[3]
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PLENARY LECTURE
& PRESIDENTIAL SYMPOSIUM

2019 KOREAN SOCIETY OF
HEMATOLOGY INTERNATIONAL CONFERENCE
& 60th ANNUAL MEETING

PL01-1

Application of CRISPR/Cas-9 in blood disease

Matthew H. Porteus

Stanford Medical School, Stanford University, USA

Genome editing provides a method to change the genomic DNA sequence of a cell with single nucleotide precision. While ZFNs, TALENs and other nuclease systems can work well, the ease of design, high activity, and high specificity of the CRISPR/Cas9 nuclease system has accelerated the translation of the concept of genome editing to the clinic. We have had to optimize the use of the CRISPR/Cas9 system to achieve high frequencies of editing in primary human cells such as hematopoietic stem cells and T-cells. These optimizations include delivering the system as a ribonucleoprotein complex (RNP) with purified Cas9 and synthetic gRNAs with end-modifications, using AAV6 to transduce cells to deliver donor DNA for homologous recombination, and to using specific high-fidelity variant of Cas9 to maintain high on-target activity while minimizing off-target effects. Using this system, we now routinely achieve genome editing by homologous recombination in hematopoietic stem cells of 40-70%. We are now translating this system to engineer the blood system to treat genetic red blood cell diseases like sickle cell disease and genetic metabolic diseases such as mucopolysacchroidosis type I.

PL01-2

Gene therapy for hemophilia-will there be a new era in hemophilia treatment?

Katherine A. High

Spark Therapeutics, Philadelphia, USA

Gene therapy has entered an exciting phase, with products now licensed in both the US and Europe, and investigational products for a number of diseases, including hemophilia, now in late phase testing. After a brief review of the two "waves" of gene therapy trials for hemophilia, the first wave beginning in the late 1990's, and involving a range of different vectors and routes of administration, and the second beginning in 2010, and focused on intravenous administration of AAV vectors, the talk will review the most recent published clinical studies in gene therapy for hemophilia. Basic information on AAV vector design and manufacture will be reviewed. Safety data in clinical trials will be discussed, and relevant data from animal studies will also be considered. The presentation will also cover considerations for defining endpoints for efficacy, durability, and predictability.

PL02-1

Breakthroughs in the treatment of aplastic anemia

Neal Stuart Young

National Institutes of Health, USA

Understanding and treatment of severe aplastic anemia, historically a uniformly and rapidly fatal disease affecting mainly young persons, have markedly improved over the last several decades. Aplastic anemia was one of the first diseases to be cured by allogeneic transplant. Hematopoietic stem cell transplantation has become increasingly available due to better prophylaxis and treatment of infectious complications and graft-versus-host disease. BMT is now undertaken in older and even elderly patients, and the donor pool has been greatly expanded by large registries of unrelated histocompatible volunteers, and the success of strategies that allow successful engraftment of haploidentical donor cells from family members. Immunosuppression directed against the immune pathophysiology of aplastic anemia is a good alternative to transplant, but there has been little improvement on results with the standard regimen of horse anti-thymocyte globulin and cyclosporine, despite many well designed and innovative research approaches. Hematopoietic growth factors are generally ineffective in bone marrow failure, but eltrombopag, a thrombopoietin synthetic mimetic, was surprisingly effective as monotherapy in patients with refractory disease, producing robust trilineage responses in about 50% of cases. Eltrombopag administered with standard immunosuppression increases the overall and especially the complete hematologic response rates in treatment-naïve severe aplastic anemia; the combination is now FDA-approved for this indication in the United States. Results with combination therapy have inspired a range of novel strategies to treat aplastic anemia and related syndromes: limiting toxicities by eliminating ATG, early introduction of oral low risk therapy, and broadening of the indications to moderate aplastic anemia and overlap syndromes such as hypoplastic myelodysplastic syndrome. Results from the clinic also have inspired new hypotheses related to stem cell biology; the role of the immune system in marrow failure; and mechanisms of genomic instability and "clonal evolution".

PL03-1

The new genomics of acute lymphoblastic leukemia

Charles G. Mullighan

Hematological Malignancies Program, St Jude Children's Research Hospital, USA

Recent studies have used integrative genomic analysis of over 2000 samples of acute lymphoblastic leukemia in children and adults to provide subclassification of all cases, define constellations of genomic lesions defining each subtype, examine the associations of germline and somatic genomic alterations driving leukemogenesis, and identify genetic determinants of outcome. These studies have identified unexpectedly broad diversity of subtypes with over 23 driven by aneuploidy, transcription factor alterations and kinase driving lesions. Many such subtypes were cryptic on cytogenetic analysis and require genomic sequencing to identify all lesions due to heterogeneity of founding alteration. Moreover, many founding lesions are now appreciated to be diverse rearrangements, structural variations or sequence mutations, also indicating the need for molecular analysis for accurate ALL classification. This talk will review the current state of the art of ALL genomic pathogenesis, classification and diagnosis, and describe new opportunities for risk stratification and therapeutic intervention.

PL03-2

Genetic basis and treatment of high-risk multiple myeloma

Gareth J Morgan

NYU Myeloma Centre, USA

While we have significantly impacted the survival of low risk multiple myeloma (MM) we have been significantly less successful in improving outcomes for high-risk (HR) disease. To effectively make progress we need to address the definitions and biology of high-risk status. HR status is the end result of the evolutionary transformation of a normal plasma cell driven by the adaptation of the myeloma-propagating cell to the microenvironment which comes to dominate by a clonal sweep. HR disease is enriched for extra-medullary disease and plasma cell leukaemia, is less dependent on the microenvironment and has more proliferative features than the earlier stages of disease.

The genetic features that define HR include amp1q, P53 mutation and the adverse translocation t(4;14) and t(14;16). We have recently defined a extremely high risk group, "double hit" myeloma defined by the biallelic inactivation of P53 and/or ISSIII and amp 1q. This group constitutes approximately 8% of NDMM and has a median PFS and OS that is extremely poor, similar to that seen in RRMM and so could be used to do studies at presentation. This is a robust definition with easily identifiable DNA based variants.

The GEP 70 in contrast is more difficult to measure but identifies 15% of patients at diagnosis that contains the double hit group but the outcome is more variable. In an attempt to find the full extent of HR at presentation we have carried out a segmentation analysis based on machine learning approaches applied to gene expression profiles. This approach identified a HR cluster with distinct molecular features that has poor clinical outcome that could be used to target specific treatment strategies.

Interestingly recent analysis of the bone marrow microenviroment has identified that the cellular content becomes increasingly modified as the disease progresses and a HR microenvironment exists that contributes over and above the genetic features acquired by the tumor cells. This opens the potentially for targeting immunotherapy and interventions to the microenvironment.

Currently we are not in a position to target therapy based on our biological knowledge other than to utilize chemotherapy approaches to target the proliferative nature of the myeloma-propagating cells responsible for these late disease stages. In order to exploit this concept we have conducted a clinical trial utilizing high dose sequential therapy with the addition of daratumumab. This combination has succeeded in getting most patients to the maintenance phase of treatment, which has previously been difficult because of relapse between blocks of high dose therapy.

PS1

Stem cells in human AML

Ravi Majeti

Department of Medicine, Division of Hematology, Cancer Institute, and Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, USA

AML develops from the sequential acquisition of multiple mutations in a single lineage of cells. These mutations initially occur in HSCs, termed pre-leukemic HSCs, and are enriched in genes involved in regulation of the epigenome. The pre-leukemic cells acquire additional mutations, often in genes involved in proliferation, resulting in development of AML. Stratification of a cohort of AML patients into high or low pre-leukemic HSC groups demonstrated that the high group had much worse overall and relapse-free survival, indicating that the presence of pre-leukemic HSC may be critical for clinical outcomes. In bulk AML, sequencing studies demonstrated that most cases harbor multiple subclones with a complex evolutionary structure. These subclones potentially exhibit distinct features including leukemia stem cell properties, clonal dominance, and responses to chemotherapy and targeted agents. Isolating and investigating these subclones is essential to understanding their properties, and is facilitated by a novel humanized ossicle xenotransplantation model, single cell methods, and CRISPR/Cas9 engineering of normal and leukemic cells. Eventually, all subclones must be targeted in order to improve long-term outcomes and for potential cures in AML. Notably, mutation-specific targeted agents have the potential to improve outcomes in AML. Several approaches were employed to identify mutation-specific vulnerabilities including epigenomic profiling, computational approaches, and metabolomic profiling. Several targets were validated through genetic and/or pharmacologic modulation in primary AML cells and xenograft models, making them strong candidates for therapeutic development.

PS2

Precision medicine in pediatric acute lymphoblastic leukemia

Ching-Hon Pui

St. Jude Children's Research Hospital, USA

Next-generation high-throughput sequencing technology, especially transcriptome sequencing, has identified additional novel genetic subtypes of acute lymphoblastic leukemia (ALL) with prognostic and therapeutic implications, as well as cooperative mutations that account for much of the heterogeneity in clinical response among patients with specific genetic subtypes. Virtually all patients can now be classified by their specific driver genetic mutations, some of which are amendable to available targeted therapeutics. Several new subtypes of B-ALL have been identified: Ph-like, iAMP21, DUX4-rearranged, MEF2D-rearranged, ZNF384-rearrangement, ETV6-RUNX1-like and PAX5 ALL. T-ALL is genetically more diverse than B-ALL, and no genetic alterations have been identified that reproducibly and independently predict outcome. In a recent comprehensive genomic analysis, 106 putative driver genes were identified among 264 children and young adults with T-ALL. ABL1 tyrosine kinase inhibitors promise to improve outcome of some subtypes of Ph-like ALL and T-cell ALL. Risk-adapted treatment based on clinical and genetic features as well as minimal residual disease (MRD) measurement has improved the cure rate of childhood ALL to approximately 90%. The optimal use of MRD information should take into consideration of the level and the timing of measurement, the germline and leukemia genetics, and treatment efficacy. Negative MRD after the first two weeks of remission induction helps to identify very low-risk patients with ETV6-RUNX1-positive or hyperdiploidy>50 ALL for treatment reduction. By contrast, positive MRD at latter time points is useful to identify patients who require more intensive or novel therapy. Increasing number of inherited polymorphisms and mutations of host germline genetic variants have been associated not only with the drug response, resistance and toxicity, but also with the risk of leukemic transformation. For example, polymorphism of *NUDT15* strongly predisposed patients to mercaptopurine-related toxicity, especially among Asian patients. Germline TP53 alterations was associated with the development of childhood low-hypodiploid ALL and increased the risk of relapse and development of second cancer. Up to 5% of children with ALL have inherited cancer susceptibility genes that have important implications not only for the patients but also their family members in terms of genetic counseling, testing and monitoring for early detection of cancer and management.

JOINT SYMPOSIUM

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JS01-1

IL-7-hyFc, a long-acting recombinant IL-7 protein, generates anti-tumor activity by modulating both adaptive and innate immune cells in the tumor microenvironment

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Interleukine-7 (IL-7), a strong candidate for a novel immunotherapeutic agent, plays important roles in the development and homeostasis of T lymphocytes. Recombinant IL-7 has shown positive effects in various models by increasing T cells in both mice and humans; however, the short half-life and stability of recombinant IL-7 has remained a challenge for its clinical application to cancer immunotherapy. Here, we investigated anti-tumor effects of a long-acting form of recombinant human IL-7 fused with hybrid Fc (rhIL-7-hyFc; Hyleukin-7) in mice. rhIL-7-hyFc administration in tumor-free mice generated the cytokine-induced $CD8^+$ T cell proliferation, which altering $CD8^+$ T cell homeostasis by expanding largely the TCM-phenotype $CD8^+$ T cells displaying activation-induced attributes, such as Eomes, Granzyme B, CXCR3, and IFN-□. When injected into mice with syngeneic tumor graft, rhIL-7-hyFc induced anti-tumor activity in a dose-dependent manner. rhIL-7-hyFc dramatically expands $CD8^+$ T cells in the periphery and recruits effector $CD8^+$ T cells in the tumor, yielding a high $CD8^+$ T/Treg cell ratio in the tumor microenvironment (TME). rhIL-7-hyFc increases Ki-67 and granzyme-B expression but decreases expression levels of immune checkpoint molecules on $CD8^+$ tumor-infiltrating lymphocytes (TILs). Surprisingly, rhIL-7-hyFc reduced myeloid-derived suppressor cells (MDSCs) in the TME, yielding the high $CD8^+$ T/MDSC ratio. Collectively, rhIL-7-hyFc treatment confers anti-cancer activity by inducing a "$CD8^+$ T cell infiltrated-inflamed-immune favorable" TME. The combination treatment of rhIL-7-hyFc with cyclophosphamide and immune checkpoint blockades showed enhanced anti-tumor efficacy in an advanced tumor model. Furthermore, we found that the anti-tumor activity of rhIL-7-hyFc was achieved under lymphopenic conditions by normalizing $CD8^+$ T cell homeostasis. In sum, rhIL-7-hyFc generates an effective anti-tumor response through reconstructing $CD8^+$ T lymphocytes; this activity was highly enhanced by combination therapies with the chemotherapeutics and immune checkpoint blockades. Our data suggests that rhIL-7-hyFc can be applied to various cancer immunotherapy regimens as a monotherapy or in combination partner with conventional and other immunotherapies.

JS01-2

Towards next-generation CAR-T cell therapy for cancer

Chan Hyuk Kim

KAIST, Korea

Due to its ability to recognize antigens in an MHC-independent manner, T cells that are engineered to express chimeric antigen receptor (CAR) can be a viable option for the tumors with low mutational burden. Indeed, the second-generation CD19-targeting CAR-T cells with an engineered signaling domain demonstrated unprecedented anti-leukemic responses in patients with refractory B-cell cancer, and became the first approved gene therapy for cancer last year. In light of their clinical success, there has been an explosion of interest in CAR-T cells for cancer immunotherapy. However, the inability to control the activity of this potent live drug has resulted in severe treatment related toxicities and the constraint in targeting more than one antigen have limited its general application. Furthermore, various immune-suppressive mechanisms present in the tumor microenvironment often severely limits the anti-tumor activity of CAR-T cells against solid tumors, posing a major obstacle for more widespread application of this innovative therapy. In this talk, I will discuss our recent research efforts focusing on addressing these limitations of current CAR-T therapy.

JS01-3

Immunotherapeutics in blood disease: Cytotoxic T lymphocyte therapy

Hyewon Lee

National Cancer Center, Korea

Clinical application of the immune system against cancer cells has been revolutionally increased. The first practical use of immune cells in the management of cancer was an allogeneic hematopoietic stem cell transplantation (HSCT) with a graft-versus-tumor (GVT) effect by donor T cells. More recently, increasing number of immunotherapies such as adoptive T cell therapies, immune checkpoint inhibitors, cancer vaccinations, and chimeric antigen receptor (CAR) T cells are emerging both in hematology and oncology. Adoptive T cell therapy refers to the administration of tumor antigen-reactive T cells which can detect tumor cells and induce their cell-death. Cytotoxic T cell therapy is a special form of adoptive cell therapies and it has been a promising treatment strategy for various hematologic diseases, especially in Epstein-Barr virus (EBV)-associated diseases. However, responses may be variable and often not durable according to affecting factors such as the type of target antigens, quality of T cell products, underlying hematologic diseases and the patient's immune status. Engineered T cells may be more potent against tumor than non-engineered T cells, but associated with increased toxicities. To optimize adoptive T cell therapy, careful selection of target antigens and defining immunologically sensitive patient subgroups is imperative. Recent technical advances in immune genomics and proteomics may helpful when designing optimal T cell therapies. Here, we will review the latest research in the field of non-engineered, adoptive cytotoxic T cells in therapy of hematologic malignancies. Efforts to optimize adoptive immunotherapy and to overcome resistance to immunotherapy will also be discussed.

JS01-4

Immune checkpoint inhibitor in lymphoma

Yoon Seok Choi

Chungnam National University College of Medicine, Korea

Lymphoma is a clonal disorder of lymphocytes that can typically infiltrate the sites of disease, including the secondary lymphoid organs, bone marrow and extranodal sites. In addition to the presence of malignant lymphocytes, many immune cells are also observed within the tumor microenvironment. Recent works have documented the cellular and molecular mechanism underlying the suppressed anti-tumor immune response in the lymphoma microenvironment and have developed the therapeutic strategies to overcome such impairment in eradicating tumor cells. In fact, trials of monoclonal antibody drugs blocking immune checkpoint receptors that downregulate T cell function have achieved noteworthy clinical benefit in several types of malignant lymphoma.

Of note, anti-programmed death-1 (PD-1) antibody monotherapy has been effective and safe in patients with relapsed/refractory Hodgkin lymphoma, with more than two third of patients experiencing an objective response of impressive duration. The responsiveness to the treatment is associated with expression of programmed death ligand 1 (PD-L1) on tumor cells resulting from genetic alteration if the *PD-L1/PD-L2* locus on chromosome 9p24.1. As immune checkpoint inhibitors have been actively studied also in the treatment of non-Hodgkin lymphoma, the clinical benefit has been reported in several subtypes, including primary mediastinal large B-cell lymphoma. However, response rates reported from the study of immune checkpoint inhibitor monotherapy in hematologic malignancies are not satisfactory. In addition to the clinical data of the overall treatment outcome and safety in the prospective clinical trials, therefore, the current studies of immune checkpoint inhibitors are also focusing on the biomarkers that predict who will get benefit from the treatment. Also, to maximize the efficacy outcome of immune checkpoint inhibitor, combination approaches have been also actively studied by adding cytotoxic agents or other immune checkpoint modulating agents.

In this presentation, the recent results reported from the clinical trials in the treatment of lymphoid malignancies will be briefly introduced. Current status of efforts to improve the clinical outcomes of immune checkpoint modulation will be also discussed in terms of biomarker development and combination approaches.

JS02-1

Understanding angioimmunoblastic T-cell lymphoma: From genomics to animal pathology

Jaesang Kim

Department of Life Science, Ewha Womans University, Korea

Angioimmunoblastic T-cell lymphoma (AITL) is a rare and distinct subtype of peripheral T-cell lymphoma, specifically of follicular helper T (Tfh) cells, mostly affecting elderly people in their 6th and 7th decades. AITL is marked by a high rate of lymphadenopathy, hepatosplenomegaly and bone marrow involvement; hypergammaglobulinemia, hemolytic anemia and skin rash are also observed although less frequently. The 5-year overall survival is only 33%, indicative of the aggressive nature of AITL and lack of effective therapy currently. We have previously reported that a missense mutation in RHOA encoding p.Gly17Val occurs frequently in AITL indicating that this is a "driver" oncogenic mutation. We now describe a murine model which expresses the human RHOA mutant gene product in a T-cell specific manner and develops AITL-like symptoms. Most transgenic mice feature with latency one or two enlarged lymph nodes characterized by aberrant lymph node architecture, extensive lymphocytic infiltration, extrafollicular meshwork of follicular dendritic cells and arborized endothelial venules characteristic of AITL. We also provide evidence for expansion of B-cells leading to hypergammaglobulinemia and the presence of dominant T cell clonal populations. Transcriptomic profiling revealed that the gene expression pattern within affected lymph nodes of the mice most points to expansion of Tfh cells and closely simulates that of AITL patients with the identical p.Gly17Val mutation. The murine model should therefore be useful in dissecting pathogenesis of AITL at the molecular level particularly for the cases with the p.Gly17Val mutation.

JS02-2

Genomic pathogenesis of Epstein–Barr Virus (EBV)-induced diffuse large B cell lymphoma

Sung-Yup Cho

Seoul National University College of Medicine, Korea

Epstein-Barr virus (EBV)-positive diffuse large B cell lymphomas (EBV$^+$-DLBLs) tend to occur in immune com promised patients, such as the elderly or those undergoing solid organ transplantation. The pathogenesis and genomic characteristics of EBV$^+$-DLBLs are largely unknown because of the limited availability of human samples and lack of experimental animal models. We observed the development of 25 human EBV$^+$-DLBLs during the engraftment of gastric adenocarcinomas into immune deficient mice. An integrated genomic analysis of the human-derived EBV$^+$-DLBLs revealed enrichment of mutations in Rho pathway genes, including *RHPN2*, and Rho pathway transcriptomic activation. Targeting the Rho pathway using a ROCK inhibitor, fasudil, markedly decreased tumor growth in EBV$^+$-DLBL patient-derived xenograft (PDX) models. Thus, alterations in the Rho pathway appear to contribute to EBV-induced lymphomagenesis in immune suppressed environments.

JS02-3

Current status of precision hematology

Young-Uk Cho

University of Ulsan College of Medicine, Korea

The diverse genetic characteristics of hematologic malignancies have been critical for defining genetic biomarkers that classifying disease subtype of both myeloid and lymphoid malignancies. Many of these characteristics are now incorporated into the revised WHO classification for diagnostic assessment. From a hemopathologist's point of view, it is most important that we diagnose the disease correctly based on WHO-defined criteria. However, there are a number of geneticabnormalities that are not routinely evaluated in clinical laboratories using standard technique but can be defined as specific disease entities due to their relevance to prognosis and/or potential therapeutic implication. As the number of these changes increases, massively parallel sequencing has replaced conventional methods over the last decade due to its comprehensiveness and high throughput, and finally integrated into clinical services in Korea.
In this talk, I have focused on genetic changes essential to establishing a diagnosis of hematologic malignancies and/or determining standard clinical care. New examples of genomic lesions identified in ongoing studies and their clinical relevance will also be reviewed.

JS02-4

Clinical application of personalized medicine for AML

Joon-ho Moon

Kyungpook National University Hospital, Korea

Survival rates have improved for patients with acute myeloid leukemia (AML) over the past thirty years, despite the lack of major improvements in AML therapy, often attributed to improvements in supportive care. Outcomes are still suboptimal and it may be a consequence of our insufficient understanding of the biology of AML

Over the past decade, the advances in genetic sequencing technology and interpretation have revolutionized our understanding of the molecular events leading to AML. This molecular information allows for improved classification of AML, a better understanding of the molecular mechanisms that underlie the development of leukemia, an expanded ability to monitor for minimal residual disease, and also presents an opportunity to find aberrant molecular targets. This information now has progress on the targeted therapies from typical intensive AML treatment remaining the 40-year-old cytotoxic combinations.

In this talk, recent progress on the classification of AML, high sensitive measurements of minimal residual disease, and recent progress targeted therapy to patient-specific somatic mutations will be discussed.

JS03-1

Monoclonal antibodies in the treatment of multiple myeloma

Francesca Maria Gay

AOU Città della Salute e della Scienza, Italy

Monoclonal Antibodies (MoABs) directed against plasmacell antigents have been recently included in the treatment armamentarium against multiple myeloma (MM). These include MoAbs against CD38 and against SLAMF7. Anti-CD38 MoABs (daratumumab, isatuximab, TAK-079, and MOR202) have pleiotropic mechanism of action: Fc-dependent immune effector mechanisms such as complement-dependent cytotoxicity (CDC), antibody- dependent cellular cytotoxicity (ADCP) and antibody-dependent cellular phagocytosis (ADCP); they also eliminate immune suppressor cells such as regulatory T cells and myeloid-derived suppressor cells. Anti-SLAMF7 MoAB elotuzumab activates NK cells and has direct anti-MM effect inducing ADCC. Both Daratumumab and Elotuzumab have synergistic activity with immunomodulatory drugs (IMIDs). Daratumumab plus lenalidomide-dexamethasone (DRd) improved progression-free survival (PFS) over lenalidomide-dexamethasone (Rd) in the relapse setting; Daratumumab plus bortezomib-dexamethasone (DVd) also improved PFS vs bortezomib-dexamethasone (Vd). Both DRd and DVd have been now approved by EMA and FDA as treatment options for relapsed-refractory MM. Daratumumab proved to be effective also has single agent in heavily pretreated patients, and other combination with second generation proteasome inhibitor Carfizomib and second generation IMID pomalidomide are under evaluation in clinical trials. More recently Daratumumab combinations proved to be superior to current standards of care also in the upfront setting: Daratumumab-bortezomib-melphalan prednisone (DVMP) and daratumumab-Rd were superior to VMP and Rd in randomized phase III studies. Isatuximab is also currently under evaluation in several trials in the upfront and relapse setting. Elotuzumb plus Rd (ERd) showed improved PFS vs Rd, and is another option approved by EMA and FDA at relapse. Elotuzumab plus pomalidomide-dexamethasone also improved PFS in a phase II trial in comparison with pomalidomide-dexamethasone.

Other monoclonal antibodies with a different mechanism of action are currently under development in the relapse setting. These include antibody drug conjugates directed anti- B cell maturation antigen (BCMA) (GSK2857916 conjugated with monomethyl auristatin-F) and bi-specific MoAbs (AMG-420).

JS03-2

Treatment for advanced multiple myeloma in Korea

Chang-Ki Min

College of Medicine, The Catholic University of Korea, Korea

The use of the proteasome inhibitor (PI), bortezomib and immunomodulator (IMiD), thalidomide or lenalidomide for the treatment of multiple myeloma (MM) has contributed to significant improvements in patient outcomes over the last 2 decades. Bortezomib and 2nd generation IMiD lenalidomide form the backbone of many preferred regimens in the frontline or relapsed settings, and they have contributed to a doubling in the average life expectancy for MM patients. However, despite these novel therapies, MM remains an incurable disease, and resistance to both agents is increasingly on the rise. Several phase 2 and phase 3 trials have demonstrated the efficacy of approved agents for the patients who failed bortezomib and lenalidomide treatment. IMiD pomalidomide, the histone deacetylase inhibitor panobinostat and the PIs carfilzomib and ixazomib, as well as the monoclonal antibodies daratumumab and elotuzumab, and new classes of agents in early-stage development may add to the treatment strategies available for patients with advanced MM. With each drug with differing mechanisms of action and efficacy and safety profiles, it can be difficult for physicians to decide upon the most appropriate agent to use. While there is no standard treatment for these patients, improving the outcomes of patients in this setting represents a significant clinical challenge, and is an area of intense research focus.
In Korea, carfilzomib and dexamethasone (Kd) and pomalidomide and dexamethasone with or without cyclophosphamide (Pd or PCd) are options for treatment of double failed MM. Daratumumab is indicated as a single agent. In preliminary analyses including Korean MM patients, significant differences in terms of overall response, progression-free survival or overall survival were not observed between Kd and Pd/PCd regimens. Acceptable outcomes of daratumumab monotherapy on advanced MM patients were also observed despite relatively frequent infectious adverse events. Investigations are underway on the latest treatment experiences for Korean patients using KMMWP registry and the results will be provided.

JS03-3

Experimental therapy except monoclonal antibodies

Francesca Gay

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In the last two decades, several new agents have been introduced in the treatment of multiple myeloma (MM) patients. Proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs) were the first drugs that proved to be able to significantly improve progression-free survival (PFS) and overall survival (OS). For many years, bortezomib-dexamethasone (Vd) and lenalidomide-dexamethasone (Rd), followed by pomalidomide-dexamethasone (Pd), have been the cornerstones of the treatment of relapsed/refractory MM. In recent times, second generation PIs (carfilzomib and ixazomib) have been combined with lenalidomide in the relapsed setting: Carfilzomib plus Rd (KRd) significantly improved PFS and OS vs Rd alone; ixazomib plus Rd (IRd) significantly improved PFS. Carfilzomib plus dexamethasone (Kd) significantly improved PFS and OS vs Vd. The combination of Pd plus bortezomib has been also evaluated in an early relapse setting, showing an improved PFS in comparison with Vd. Most of the treatment recommendations for relapsing MM patients suggest using these novel combos in the early phases of the disease (first and second relapse). The major challenge for clinicians will be how to choose the best option for each patient, in order to maximize the efficacy and minimize toxicities and costs, in the context of the several options available including monoclonal antibodies. Newer agents, with a different mechanism of actions, have shown their efficacy as single drugs in later lines of therapy, in patients heavily pretreated. These agents include novel alkylating agents (melflufen), bcl2 inhibitor (venetoclax), and selective inhibitor of nuclear export (selinexor). The efficacy and safety in heavily pretreated patients provide the rationale to combine these drugs with backbone treatments and to move these combinations in the early-line setting. In the treatment scenario with drugs that target a single mechanism of the tumor cell, the identification of biomarkers that can predict tumor response is extremely important. For instance venetoclax showed a marked activity as single agent in patients harboring t(11;14)and in patients with high-bcl2 levels in combination with bortezomib. Another field of development, besides monoclonal antibodies, are CAR-T cells, currently under evaluation in the heavily pretreated setting, with promising preliminary results.

JS03-4

Clinical outcomes of cytogenetic high-risk multiple myeloma in Korea

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Introduction of novel agents including proteasome inhibitors, immune modulating drugs and monoclonal antibodies improved the survival of multiple myelomas. However the outcome of high risk myeloma is still poor. The International Myeloma Working Group consensus recently updated the definition for high-risk multiple myeloma based on cytogenetic abnormalities. Novel therapeutic agents and changes in insurance policies were introduced in recent years in Korea: however, the clinical courses and prognosis in cytogenetic high-risk multiple myeloma patients in Korea have not reported according to the change of the treatment. We evaluated clinical outcomes in patients with FISH confirmed status for at least one of the three cytogenetic abnormality types [t(4;14), t(14;16) and del(17p)]. We used the Korean Myeloma Registry, the web-based multicenter patient registry system established by the Korean Multiple Myeloma Working Party. In the extracted sub-dataset including 448 patients Detailed analysis of the data will be presented at the conference and will be compared with data from other multicenter trials from other countries. Further research of high-risk multiple myeloma is warranted, which might provide a better understanding therapy options and improve survival.

Keyword:
Multiple Myeloma, Cytogenetic Abnormality, High-Risk Patients, Korean Myeloma Registry

JS04-1

Europe's experience of treatment-free remission in CML

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With the introduction of tyrosine kinase inhibitors (TKI) to the treatment of chronic myeloid leukemia (CML), the disease has changed from a fatal one to a chronic disease in the majority of patients. The life expectancy of patients with CML receiving TKI treatment is nearly comparable now to that of the general population. A significant proportion of patients with CML in chronic phase achieve a deep molecular response (DMR) determined via BCR-ABL1 transcript measurement including BCR-ABL1 levels of 0.01% on the international scale (IS) or deeper. Treatment strategies not only comprise overall survival anymore but achievement of DMR with even the possibility of a successful attempt to stop therapy (treatment-free remission, TFR). The first prospective proof of concept for stopping TKI was the Stop Imatinib (STIM1) trial where 38 % of the patients maintained a molecular remission (in this study defined as undetectable BCR-ABL1 transcripts) after five years of imatinib discontinuation. Since then multiple trials were conducted or are still ongoing. Each of these trials used different entry criteria and different triggers for restarting the TKI treatment. Meanwhile, loss of major molecular remission (MMR) is accepted as a trigger for restarting therapy. TFR rates within all TKI stopping studies were between 38% and 60% after 12 months with about 80-90% of patients losing molecular response within the first 6 months thereby confirming data of the STIM trial.

On the basis of the results of the diverse stopping trials several CML management recommendations have included TFR as a possible treatment option under special conditions. In addition, the prescribing information of nilotinib has detailed when to stop nilotinib in CML patients on the basis of the nilotinib stopping trials ENEStop and ENESTfreedom.

However, it is estimated that only 20% of CML patients can be off treatment in the long run.

The fact that around 50% of patients going into a TFR approach fail to stop the TKI treatment is not satisfying. There is a need for better identification of patients who can successfully stop therapy on the one hand, but also to guide patients from the time of diagnosis to a TFR approach.

The search for prognostic markers is absolutely important. Within all studies prognostic analysis were performed. Mostly TKI duration was important in prediction of a successful TFR. In the EURO-SKI trial, main prognostic marker was the duration of DMR before stopping treatment besides TKI duration and interferon pre-treatment. A steady increase in TFR success per year in DMR before stopping could be detected.

On a biological background it seems that two major mechanisms for unsuccessful TFR are important: the leukemic stem cell and the immune surveillance of the CML disease.

A primary goal in CML management is to better guide patients on their therapeutic journey towards the goal of performing a TFR attempt.

JS04-2

Korea's experience of treatment-free remission in CML

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The ultimate goal of treatment in chronic myeloid leukemia (CML) is getting normal survival without any harmful effect of the treatment. More hopeful goal is restoring normal life without CML. Curing CML can be achieved only by allogeneic hematopoietic cell transplantation (alloHCT). However, alloHCT is not desirable treatment option in these tyrosine kinase inhibitors (TKIs) era not only because of high mortality but also because of high morbidity. Treatment-free remission (TFR) by TKIs is an emerging alternative of alloHCT. More and more data reveals that TFR can be performed as a real-practice although current recommendations guided TFR under strict clinical trial settings. We will review the cost-effectiveness of various TKIs under consideration of TFR possibility and Korean CML physicians' current concept and persepectives on TFR in real-practice. Also we will review the Korean TFR data.

JS04-3

TKI-related cardiovascular toxicities in Europe

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Chronic myeloid leukemia (CML) is a model for cancer disease due to the fact that a unique translocation determines the disease. With the introduction of tyrosine kinase inhibitors (TKI) to treatment, the disease has changed from a fatal one to a chronic disease in the majority of patients. The life expectancy of patients with CML receiving TKI treatment is nearly comparable now to that of the general population. A significant proportion of patients with CML in chronic phase achieve a deep molecular response determined via BCR-ABL1 transcript levels measured with real-time quantitative polymerase chain reaction (RQ-PCR) to evaluate residual disease.Treatment strategies not only comprise overall survival anymore but achievement of deep molecular remission (DMR) with even the possibility of successful attempt to stop therapy (treatment-free remission, TFR). However, most reports on treatment in CML focus on efficacy. In contrast, adverse events (AEs) are often reported as infrequent, and manageable, but they are increasingly important as therapy is lifelong and multiple TKIs are available. For this reason, it is important to understand, manage and prevent adverse events also not to jeopardize the achievemnt of treatment goals. In this context, attention must be given to comorbidities and drug interactions. Especially cardiovascular toxicities which came up with the introduction of 2nd generation TKI, are of great importance as they can hamper outcome in CML patients. The lecture will discuss actual data and results of CML studies with the focus on cardiovascular toxicities.

JS04-4

Long-term safety of tyrosine kinase inhibitors in chronic myeloid leukemia patients

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Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment and outcomes of chronic myeloid leukemia (CML), changing it from a life-threatening disease to one with life expectancies similar to the general population. Although these treatments have dramatically changed the natural course of CML, they may result in cardiovascular and/or metabolic complications. Now, to avoid these long-term complications, the focus of treatment has shifted to TKI discontinuation.
Here, we will review the long-term complication of currently available TKIs, and present incidence of long-term complication of TKIs in Korean CML patients using National Health Information Database.

ASIAN HEMATOLOGY SYMPOSIUM

2019 KOREAN SOCIETY OF
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AS01-1

Treatment of Philadelphia chromosome positive acute lymphoblastic leukemia - Korean perspectives

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Around 1,300 case of ALL case developed in Korea in a year. Most cases of ALL occur in children, but most deaths from ALL (about 4 out of 5) occur in adults. Children may do better than adults because of differences in the nature of childhood and adult ALL, differences in treatment, or some combination of these. About 20-30% of adult ALL case has Philadelphia chromosome, this could explain the poor outcome of adult ALL. The incorporation of tyrosine kinase inhibitors (TKIs) into the frontline treatment regimens has demonstrated significant improvements in complete remission (CR) and long-term survival rates in adults with Ph-positive ALL. Unfortunately, substantial portion of patient succumb to death because of disease progression. Therefore, an improved strategy to induce more effective leukemic cell clearance is needed. There is unmet needs in how to best treat Ph-positive ALL. In this session, speakers from Asian countries(Taiwan, Malaysia) will talk about current treatment strategy for their country's adult ALL treatment. I will briefly review current adult Ph-positive ALL induction with TKI, consolidation treatment and maintenance in Korea. Recently, adult Korean hematologists are more interested in prognostic significance of minimal residual disease (MRD) and trying to set up MRD monitoring. Some new agents in relapsed and refractory setting will be available in the near future in Korea.

AS01-2

Hematopoietic stem cell transplantation for adult acute lymphoblastic leukemia in Taiwan – on behalf of TSBMT

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Background: Acute lymphoblast leukemia in adult has relative inferior response to chemotherapy and more easier to relapse as compared in children. Therefore, after induction chemotherapy, especially in first complete remission, high dose chemotherapy plus allogeneic stem cell transplantation is the curative treatment for adult patients. For induction failure or relapsed refractory patients, HDC/Allo-SCT is also an option of salvage treatment.

Method: This is a retrospectively study from the data base of Taiwan Society of Blood and Marrow Transplant Registry, collected patients between June 1995 and September 2017. We investigated a variety of immunophenotypes, specific cytogenetics, types of transplant, and overall survival in our patients cohort. We also investigated the outcome of limited patients to undergo second transplant.

Result: We totally have 526 patients in our cohort, including 13 (2.4%) patients with hyperdiplod cytogenetic, 93 (17.7%) with t(9; 22) [Ph(+)], 9 (1.7%) with t(4; 11), 67 (12.7%) with complex cytogenetic (>3 abnormalities), 71 (13.5%) with other cytogenetic abnormalities, 188 (35.7%) with normal cytogenetic, and 85 (16.2%) were unknown of cytogenetics. Fifty patients had extramedullary involvement including 25 (4.75%) had mediastinal tumor, 24 (4.56%) had leptomeningeal involvement, 1 (0.19%) had testis involvement, and none had brain parenchymal involvement.

Conclusion: We will present overall survival of these 526 patients in our cohort and compare the outcome of Ph(+) versus Ph(-) paients and in different pre-transplant disease status (CR1, CR2 and beyond, induction failure, or relapsed refractory) and the limited patients undergoing second allogeneic stem cell transplantation.

AS01-3

Adult ALL in Malaysia

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Background: Acute lymphoblastic leukaemia (ALL) represents an uncommon and devastating malignancy among adult patients. Various treatment protocols comprise multi-agent chemotherapy with stem cell transplantation for eligible candidates remain the core of management for this group of patients. Over the years, advancement in novel targeted agents and immunotherapies have significantly created a paradigm shift in the treatment outcomes. Similarly, various laboratory methods have been innovated for more accurate diagnosis and better treatment response assessment. Here, we aimed to investigate the treatment outcome of our adult ALL patients in the tertiary national referral centre.

Materials and Methods: Patients were identified through our centre registry and data was retrospectively collected for all adolescent and adult ALL patients (≥ 12 years) presented to us from 2006 till 2018.

Results: A total of 402 ALL patients with a median age of 30 years were identified, of which more than 2/3 were B lineage ALL (83%) as opposed to T lineage ALL (17%), with males preponderance (57%), Our patients mainly were Malays (58.2%) follow by Chinese (27.1%), and Indian (12.4%) in accordance with our nation ethnic group distribution. About half of the population fell into the high risk group (49%) and one quarter of our B-ALL patients have Ph+ chromosome (25%). Ninety four percent of patients received induction chemotherapy with induction death of 8.6%. The German study group protocols (GMALL) are the most frequent used in our centre for B-ALL as compared to hyper-CVAD or BFM protocol for T-ALL. TKI in combination with hyper-CVAD regimen is routine for Ph+ ALL. The overall remission post induction was 86.5% but such remission was not sustained with a relapse rate of 34.5%. About one third of our patients (28.4%) proceeded to allogeneic stem cell transplantation (alloSCT). In the last 2 years, we have some patients received Blinatumumab to deepen the remission prior alloSCT or salvaged with CAR-T cell therapy after relapse post alloSCT. The overall survival (OS) for all assessable patients was poor with 34.1% at 2 years and 26.7% at 3 years respectively. The event free survival (EFS) was 26.6% at 2 years and 21% at 3 years respectively. The main cause for such dismal outcome was disease relapse and progression (68%). In general, intensive chemotherapy follow by alloSCT improved overall response significantly; with 3 years OS of 53% among transplant candidate versus 12.3% for non alloSCT patients respectively. For the last few years, our centre also have embarked in evaluating treatment response according to minimal residual disease (MRD) by flow cytometry analysis as supplement to the routine bone marrow study for better treatment decision. Such measure enable us to better select our alloSCT candidates and significantly improved in the transplant outcomes whereby the 3 years OS from 2012-2018 was 57.7% versus 44.6% from 2006-2011 respectively in addition to the availability of TKI and better supportive care and in general.

Conclusion: Majority of our adult ALL patients fell into the high-risk group that warrant further investigations to look for any genetic predisposition as more novel targeted agents and immunotherapies are available.Better treatment outcome could be achieved with improvement in patient's awareness and treatment adherence. Simultaneously, advancement in laboratory aspects in term of monitoring MRD might guide us in tailoring treatment decisions and further improve the outcome as a whole.

AS02-1

CML in Philippines

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Leukemia is the 8th most common cancer in the Philippines (Globocan 2017). These data encompasses all leukemias including chronic Myelogenous leukemia. Imatinib is the first line tyrosine kinase inhibitor still widely used in the Philippines. Imatinib and Nilotinib availability to patients are made possible by the support of Novartis Pharmaceutical and it's Foundation. Most CML patients are seen in the tertiary Hospitals in the cities, mostly in the National Capital Region. Most patients present without symptoms but with elevated white blood cell count and splenomegaly, anemia is mild to moderate, platelet count is normal or increased. Bone marrow aspiration and biopsy is routinely done and sent for cytogenetics, flow cytometry, fluorescent-in-situ hybridization (FISH) for BCR-ABL. Peripheral blood is also sent for FISH. Cytogenetic studies are done only in one Center while FISH is done in a few Tertiary Hospitals in Metropolitan Manila. Molecular monitoring using the NCCN guidelines and Leukiemia Net is usually followed, the method is the real time quantitative reverse transcription polymerase chain reaction. This is ideally done every 3 months but because of the prohibitive amount, patients are able to do it every 6 months or once a year. In cases of resistance to the first line treatment, mutation analysis is unavailable in the Philippines. For the occasional patient who can afford to send specimens to other countries like Singapore, Hongkong or the United States for testing before shifting to a new regimen. For most patients with unknown mutation analysis the dose of Imatinib is just escalated or switched to Nilotinib. Dasatinib, Bosutinib, Ponatinib, Radotinib, Homoharringtonine are not approved by the Philippine FDA and not available. There some patients who take these new drugs procured from abroad. For those who have sustained molecular remission, there are a few who have stopped TKI's and remained in CR.

AS02-2

Outcome of allogeneic hematopoietic stem cell transplantation for SAA and PNH at Vietnam national institute of haematology and blood transfusion

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Objective: Allogeneic stem cell transplantation (SCT) remains the best curative option for patients with benign hematologic disorders, including SAA and PNH. We summarized our results for benign hematologic conditions and suggest recommendations for doing in our condition.

Patients: A total of 42 patients (median age of 23.7 ± 10.2 years, range 5-42 years old) with severe aplastic anemia (n=32), PNH (n=7) or SAA/PNH (n=3) have undergone allogeneic SCT between November 2010 and Nov 2018 at the NIHBT in Hanoi, Vietnam. All most patients were transplanted from peripheral blood stem cell (PBSC) (n=37), only 2 patients from unrelated cord blood (UCB), one case received bone marrow grafts; one patient combined related cord blood and bone marrow stem cell (BMSC) and the last case was haploidentical and unrelated CB transplant. There was one graft rejection SAA patient who was did success the 2nd transplant from the same donor. The conditioning regimens consited of Cy/Flu/+/-hATG in 41 patients and cyclophosphamide post transplant in one haploidentical transplant patient. Regarding the GVHD prophylaxis, all most patients were used CSA and short course of MTX, only one haploidentical patient was given Tacrolimus and MMF.

Results: The incidence of engraftment at day 30 was 92.9%. The estimated 3-year overall survival (OS) and disease-free survival (DFS) were 76.6% and 72.1% respectively. Acute graft-versus-host disease (GVHD) of grade I–II occurred in 21.4% and chronic GVHD in 30.9%. CMV reactivation was observed in 30.3% of patients. The incidence of one hundred days post transplant related mortality was 7.1%. The incidence of one-year mortality was 14.2%.

Conclusions: Based on these results, we recognized that allogeneic hematopoietic stem cell transplantation for patients with severe aplastic anemia and PNH is an effective and safe treatment method if they had HLA matched sibling donor. Haplo-cord transplant represents a promising approach for SAA and PNH patients who lacked an HLA-identical related donor or unrelated donors.

Keywords: Hematopoietic Stem-Cell Transplantation, Non-malignant Diseases, Severe Alpalstic Anemia, PNH, Matched Sibling Donor, Cord Blood Transplantation

AS02-3

Hemoglobinopathy in Thailand

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Thalassemia is a major public health problem in Thailand. Overall carrier rate is approximately 30-40% throughout the country. These comprise 20-30% of deletional α-, 1-8% of α^{CS} -, 3-9% of β- and 10-50% of HbE-thalassemia carriers. Despite decreasing numbers of affected patients, owing to a national policy for pre-natal screening of severe diseases, up to 4,000 patients were born each year. The majority of these patients being β-thalassemia/HbE, and the remaining being homozygous β-thalassemia and HbBart's hydrops fetalis syndrome. The vast majority of the patients received standard care, including regular blood transfusion, iron chelation and folic acid supplementation, all of which are sponsored by the national health coverage.

Hematopoietic stem cell transplantation (HSCT) were first performed in Thailand for a cure of thalassemia since 1988 and the outcomes have been continuously improved. In 2014, our group from Ramathibodi Hospital reported a novel reduce-toxicity conditioning regimen (RTC) for HSCT in a group with very high risk thalassemia, including age > 10 years with hepatomegaly, who underwent matched-related and unrelated donor (MRD & MUD) HSCT. The results showed thalassemia-free survival (TFS) of 93% (n=22), which was comparable to the remaining patients receiving myeloablative conditioning regimen (n=76). Recently, we also initiated haploidentical HSCT for thalassemia, whose MRD and MUD were not available. Integration of pre-transplant immunosuppression, RTC and post-transplantation cyclophosphamide resulted in a 3-year TFS of 95% (n=78). Viral hemorrhagic cystitis being the most common complication, accounting for 30% of the patients.

Although the outcomes of HSCT for a cure of thalassemia has been improved, only approaching 400 patients have undergone HSCT nationwide. This resulted from limitation of resources and donors. Therefore, regular transfusion and iron chelation remain the mainstay of treatment for thalassemia in Thailand. The best clinical practice will not only promote growth and quality of life for patients with thalassemia, but will also prepare them for the best results of upcoming curative therapies available in the future.

AS03-1

Developing strategies to improve efficacy and safety of chimeric antigen receptor cell therapy

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For decades, cancers have been treated with standard treatments, including surgery, radiation, and chemotherapy. However, patients with refractory or recurrent cancers require novel therapeutic modalities. Immunotherapy, an emerging therapeutic option, can harness the components of immune system to fight disease. It represents the future of cancer treatment and its efficacy has been shown even in aggressive types of cancer.

Recent technological advances have made it possible to efficiently transduce transgenes in immune effector cells such as T and NK cells, allowing them to be redirected to target tumor antigens. Genetic engineering of T or NK cells to be armed with chimeric antigen receptors (CARs) have been shown to successfully redirect the specificity of those cells against tumor cells.

Studies on treatment with CAR T or NK cells are growing rapidly. Currently, most clinical success has been achieved using CAR-T cells, especially for hematological malignancies. In 2017, two CD19 CAR T-cell therapies were approved by the FDA, one for the treatments of children with ALL, and the other for adults with advanced lymphoma. However, CAR ¬T-cell therapy has several limitations such as severe cytokine release syndrome, prolonged in-vivo persistence, and relapse due to target antigen loss, and the hassle of producing patient-specific products. Therefore, strategies to improve the efficacy and safety of CAR T-cell therapy are required.

Another target antigens have been studied to develop an approach to prevent and treat CD19-loss escapes in ALL. The interleukin-3 receptor α chain (CD123) is one such antigen that is highly expressed on myeloid and B-cell leukemia cells. Thus, CAR therapy targeting CD123 can be a potential alternative approach to treat CD19-loss relapse. In addition, dual CD19 and CD123 targeting CAR-T cell therapy is expected to further enhance the efficacy of CAR-T cell therapy to prevent antigen-loss relapse.

A potential strategy to improve the safety of CAR cell therapy is to use another immune effector cells such as NK cells, other than T cells. NK cells are potential effector cells in cell-based cancer immunotherapy. Human primary NK cells and the NK cell lines have been successfully transduced to express CARs against cancer cells in several pre-clinical trials. NK cells have several advantages as effector cells to carry CARs. First, CAR NK cells might be safer than CAR T cells in clinical use. Second, NK cells can spontaneously kill tumors by recognizing diverse ligands via a variety of activating receptors such as CD16, NKG2D, and NKp30, in addition to killing target cells through a CAR specific mechanism. Third, NK cells have no risk of GVHD, so there is an opportunity to produce "off-the-shelf" products.

This lecture will review the recent effort to develop strategies to improve efficacy and safety of CAR cell therapy.

AS03-2

New insights into poor hematopoietic reconstitution after allo-HSCT

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for malignant hematopoietic diseases. Although most patients achieve rapid and stable hematopoietic recovery after allo-HSCT, poor hematopoietic reconstitution, including poor graftfunction (PGF) and prolonged isolated thrombocytopenia(PT), remains a life-threatening complication after allo-HSCT.

In particular, with the increasing use of haploidenticalallo-HSCT (haplo-HSCT) in the past ten years, PGF and PT have become growing obstacles contributing to the high morbidity and mortality after allo-HSCT. Due to the limited mechanistic studies, the clinical management of PGF and PT is challenging. Therefore, a better understanding of the pathogenesis of PGF and PT will help guide effective treatments and eventually improve prognosis.

Emerging evidence demonstrates that the bone marrow (BM) micro environment plays a crucial role in maintaining and regulating hematopoiesis. In this regard, we have recently reported that although the transplanted donor HSCs of PGF patients are quantitatively and functionally normal pre-HSCT, the frequency of BM HSCs is dramatically reduced in PGF patients post-HSCT. Moreover, our prospective case-control studies demonstrated that the BM endosteal, vascular and immunemicro environment are impaired in PGF patients following allo-HSCT.

Moreover, in vitro treatment with N-acetyl-L-cysteine, a reactive oxygen species (ROS) scavenger, could enhance the defective HSCs by repairing the dysfunctional BM microenvironment of PGF patients.

Here, based on new insights into the BM microenvironment in PGF and PT patients, I will provide an overview of our recent progress about the pathogenesis and promising treatment strategies for PGF and PT patients postallo-HSCT.

AS03-3

Targeting hotspot *RHOA* mutation in angioimmunoblastic T-cell lymphoma

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Angioimmunoblastic T-cell lymphoma (AITL) is a representative subtype of peripheral T-cell lymphomas, being placed into a group of follicular helper T-cell lymphomas in the latest WHO classification. AITL is highly associated with a spectrum of immune deregulation. Recent genetic studies have identified frequent and disease-specific hotspot (G17V) mutations in *RHOA*, encoding a small GTPase. We previously demonstrated that RHOA(G17V) mutant hyperactivates T-cell receptor (TCR) signaling through aberrant binding to VAV1, a component of the TCR pathway. The next question therefore was whether inhibition of VAV1 phosphorylation could help treat AITL. To find an answer, we first established a mouse model of AITL, with which the question raised could be experimentally challenged. Mice expressing RHOA(G17V) mutant in T cells developed AITL-like lymphomas under the *Tet2*-null background. The tumors were transplantable to *nu/nu* mice, and thus evaluation of an inhibitor of VAV1-targeting tyrosine kinases, dasatinib, was possible. Increased VAV1 phosphorylation and hyper-cytokinemia were evident in the recipient mice. Dasatinib reduced such conditions *in vivo* and prolonged their survival. Based on this POC experiment, we performed a phase I clinical trial of dasatinib monotherapy in relapsed/refractory AITL patients. All the evaluable AITL patients had response to dasatinib. AITL is highly dependent on TCR signaling, and dasatinib appears to be a promising candidate as therapeutics for AITL.

EDUCATION SESSION

2019 KOREAN SOCIETY OF
HEMATOLOGY INTERNATIONAL CONFERENCE
& 60th ANNUAL MEETING

ES01-1

Iron metabolism in hemoglobinopathies

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Thalassemia is one of the most common genetic diseases in man. Due to a very high allele frequency of this autosomal recessive disorder throughout the 'malarial belt' regions expanding; Asia, Southeast Asia, South Asia, Middle East and the Mediterranean countries, over one million new cases are expected each year. With population migration to several other part of the world, the problem related to thalassemia and hemoglobinopathy has become a global problem and health burden in many countries. Due to a primary defect on globin and hemoglobin synthesis, thalassemia syndromes (with two abnormal globin mutations) result in general in chronic hemolytic anemia. Around 1/3 of the patients require regular blood transfusion to survive and this group is known as transfusion dependent thalassemia (TDT) while the rest can live with occasional or infrequent blood transfusion as non-transfusion dependent thalassemia (NTDT). Both conditions demand for a life long medical intension and lead to several complication such as hyperbilirubinemia (due to chronic hemolysis), bony dysmorphic, extramedullary hematopoiesis (due to compensation to chronic anemia) and iron dysregulation.

Iron overload is an unavoidable consequence of regular blood transfusion in patients with TDT. This leads to several complications secondary to iron toxicity including cardiac dysfunction, liver cirrhosis endocrinopathies and growth disturbances. Due to human have no mechanism to excrete this extra iron out; the only measure is by the use of iron chelation therapy. However, clinical efficacy of iron chelation therapy (ICT) in transfusion TDT can be variable due to several factors. These include; baseline (existing) iron status, continuous transfusion iron influx, type, dose and mode of administration of iron chelators, compliance and putative genetic background that might underlie biological response to iron overload and its treatment.

However, even with less blood transfusion, iron overload can occur also in NTDT. Chronic anemia in thalassemia patients will trigger hypoxia inducible factor (HIF2-α) and erythropoietin (Epo) to stimulate erythron mass for increase erythroid production. This would result in a markedly increase of erythroferrone (Erfe) expression from thalassemic erythroid progenitor cells. The Erfe has been shown to supress the production of the key 'hormonal like' peptide; hepcidin mainly secrets from hepatocytes. Hepcidin plays a key role on regulating iron metabolism in normal physiology and several pathology including anemia of chronic inflammation (AI) and hereditary hemochromatosis (HH) by directly interact with a protein called 'ferroportin' (FPP) to block function of this iron channel at duodenal enterocytes (reduced iron absorption) and macrophages (decreased iron recycling from nascent red blood cells). Therefore, the main function of hepcidin is to lowering the body level of iron under a certain threshold in order to minimise damages since iron can induce oxidative stress and reactive iron species. Therefore, a down regulation of hepcidin in thalassemia patients is the by far major pathological derangement in iron metabolism. This leads to chronic iron overload due to increased intestinal absorption and iron stagnant in macrophages in bone marrow and reticuloendothelial system causing ineffective erythropoiesis. Several synthetic hepcidin such as minihepcidin, hepcidin mimic molecules and its related compounds are being developed and some have been analysed in healthy volunteers and patients with iron overload in Phase I and II studies. Modulating iron metabolism in thalassemia patients provides a novel-targeted like modality to manage patients with thalassemia in the era of precision medicine.

ES01-2

Deferasirox for iron overload patients: Preserving organ functions

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While the benefit of iron chelation therapy (ICT) is dramatic for patients with beta thalassemia major, it is less clear for transfusion-dependent patients with MDS, who often do not live long enough to develop clinical complications of iron overload (Gattermann 2018). Nevertheless, registry studies consistently suggested that iron overload shortens and ICT prolongs the survival of transfusion-dependent patients with lower-risk MDS. Prospective clinical trials also showed that ICT can improve bone marrow function in about 10-20% of such patients ***(List et al. 2012, Gattermann et al. 2012, Angelucci et al. 2014).***

In the past, some of the registry studies were probably biased because patients with better overall performance status and/or fewer comorbidities may have been more likely to receive iron chelation therapy. This problem was addressed by a careful matched-pair analysis in the Canadian MDS Registry, which meticulously documents performance status and comorbidities. In this prospective, nonrandomized analysis, receiving ICT was associated with superior OS in lower IPSS risk MDS, adjusting for age, frailty, comorbidity, disability, revised IPSS, severity of transfusion dependency (TD), time to TD, and receiving disease-modifying agents ***(Leitch et al., 2017).***

Another thorough analysis is based on the European LeukemiaNet MDS (EUMDS) Registry, demonstrating that overall survival of chelated patients is significantly better when compared with a large control group of non-chelated patients. When the EUMDS data was last updated at the ASH meeting in 2017, iron chelation was associated with a hazard ratio of 0.66, or 0.75 when adjusted for age, sex, comorbidity, performance status, and number of red blood cell (RBC) units transfused ***(Hoeks et al. 2017).***

At ASH 2018, the results of the only randomized, placebo-controlled clinical trial of the safety and efficacy of ICT with Deferasirox (DFX) in iron-overloaded patients with lower-risk MDS (the Telesto study) were presented ***(Angelucci et al., 2018)***. Study participants were required to have a transfusion history of receiving between 15 and 75 RBC units, have a serum ferritin of >1000 ng/mL, and be free from cardiac, liver, and renal abnormalities. Following a 2:1 randomization protocol, patients received either DFX 10 to 40 mg/kg per day (n=149) or placebo (n=76). The primary objective of the study, event-free survival (EFS), was assessed by a composite primary endpoint of time to first non-fatal event associated with cardiac or liver function or transformation to AML or death, whichever occurred first. Participants in the DFX group experienced a significantly longer median EFS, compared with the placebo group: 1,440 days versus 1,091 days (hazard ratio [HR] = 0.64; 95% CI 0.42-0.96; p=0.015). The 3-year estimated rate of EFS also was greater with DFX (61.5% vs. 47.3%). The most common events in the DFX and placebo arms included worsening cardiac function (1.3% with DFX vs. 2.6% with placebo), hospitalization for congestive heart failure (0.7% vs. 3.9%), liver function impairment (0.7% vs. 1.3%), progression to AML (6.7% vs. 7.9%), and death (32.2% vs 32.9%). Overall survival was not different, but possible differences in OS between the treatment groups may have been shrouded by the effects of ICT given in 52% of patients in the placebo arm after discontinuation of study treatment. In conclusion, the results of this randomized clinical trial clearly support the use of ICT in transfusion-dependent patients with lower-risk MDS. A decrease in cardiac complications appears to be the most important contributor to improved event-free survival.

Gattermann N. Iron overload in myelodysplastic syndromes (MDS). Int J Hematol. 2018 Jan;107(1):55-63

List AF, Baer MR, Steensma DP, et al. Deferasirox reduces serum ferritin and labile plasma iron in RBC transfusion-dependent patients with myelodysplastic syndrome. J Clin Oncol. 2012 Jun 10;30(17):2134-9

Gattermann N, Finelli C, Della Porta M, et al. Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes. Haematologica. 2012 Sep;97(9):1364-71

Angelucci E, Santini V, Di Tucci AA, et al. Deferasirox for transfusion-dependent patients with myelodysplastic syndromes: safety, efficacy, and beyond (GIMEMA MDS0306 Trial). Eur J Haematol. 2014 Jun;92(6):527-36

Leitch HA, Parmar A, Wells RA, et al. Overall survival in lower IPSS risk MDS by receipt of iron chelation therapy, adjusting for patient-related factors and measuring from time of first red blood cell transfusion dependence: an MDS-CAN analysis. Br J Haematol. 2017 Oct;179(1):83-97

Hoeks M et al. Impact of treatment with iron chelators in lower-risk MDS patients participating in the European LeukemiaNet MDS (EUMDS) Registry. ASH 2017, abstract 425.

Angelucci E, Li J, Greenberg PL, et al. Safety and efficacy, including event-free survival, of deferasirox versus placebo in iron-overloaded patients with low- and int-1-risk myelodysplastic syndromes (MDS): outcomes from the randomized, double-blind Telesto study. Abstract 234. Presented at the 2018 ASH Annual Meeting, December 1, 2018; San Diego, CA.

While the survival benefit of iron chelation therapy (ICT) is dramatic for transfusion-dependent patients with beta thalassemia major, the benefit is less clear for transfusion-dependent patients with MDS ***(Gattermann 2018)***. Many patients with MDS do not live long enough to develop clinical complications of iron overload. Nevertheless, registry studies consistently suggested that iron overload shortens and ICT prolongs the survival of transfusion-dependent MDS patients. Prospective clinical trials also showed that ICT can improve erythropoietic output in about 10-20% of patients with lower-risk MDS (***List et al. 2012, Gattermann et al. 2012, Angelucci et al. 2014)***.

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Another thorough analysis is provided by the European LeukemiaNet MDS (EUMDS) Registry, showing that overall survival of chelated patients is significantly better when compared with a large control group of non-chelated patients, even after adjustment for all relevant prognostic facors, i.e. age, sex, comorbidity, performance status, and number of RBC units transfused prior to start of chelation. Importantly, this study looks at survival from the point in time when patients reach the eligibility criteria for chelation therapy. Therefore, long-lasting stable intervals between diagnosis and onset of transfusion-dependency are not counted and not mis¬interpreted as prolonged survival due to iron chelation. When the EUMDS data were last updated at the ASH meeting in 2017, iron chelation was associated with a hazard ratio of 0.66, or 0.75 when adjusted by age, sex, comorbidity, performance status and number of units transfused ***(Hoeks et al. 2017)***.

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Future perspective

It remains an open question whether iron chelation therapy should be started earlier than recommended by current guidelines, considering that suppression of iron-related oxidative stress is the major goal of ICT. An early start of ICT may be convenient for patients because it would allow iron chelators to be used at lower doses, which are better tolerated and, as recent research demonstrated for DFX, may be particularly suitable for supporting the growth of erythroid precursor cells ***(Meunier et al. 2017)***.
A further possibility is to combine ICT with other drugs. The combination with erythro¬poietin was recently tested in the KALLISTO trial and not shown to be better than Epo alone ***(Gattermann et al., 2018)***. Such a trial should perhaps be repeated using DFX at a very low dosage (5 mg/kg/d), equivalent to the in-vitro concentration of 3 µM that was effective in the experiments conducted by Meunier et al.
Finally, another attractive combination partner would be Luspatercept, a ligand trapping molecule that binds and inactivates GDF11, thereby relieving erythropoietic cells from a suppressive signaling cascade and improving erythropoietic output, especially in lower-risk MDS with ring sideroblasts. This effect may be augmented by ICT, which can diminish harmful oxidative stress in the marrow microenvironment.

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Meunier M, Ancelet S, Lefebvre C, et al. Reactive oxygen species levels control NF-κB activation by low dose deferasirox in erythroid progenitors of low risk myelodysplastic syndromes. Oncotarget. 2017 Nov 6;8(62):105510-105524

*Gattermann N, Coll R, Jacobasch L, Allameddine A, Azmon A, DeBonnett L, Bruederle A, Jin J; KALLISTO study investigators. Effect of deferasirox + erythropoietin vs erythropoietin on erythroid response in Low/Int-1-risk MDS patients: Results of the phase II KALLISTO trial.
Eur J Haematol. 2018 May 19. doi: 10.1111/ejh.13096. [Epub ahead of print]*

ES01-3

Management of iron overload in MDS

Heather Alice Leitch

University of British Columbia, Canada

The myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders that lead to bone marrow failure and an increased risk of progression to acute myelogenous leukemia (AML). The incidence of MDS increases with age, with 0.5, 5.3, 15, 49, and 89 cases per 100,000 in the age groups <50, 50-59, 60-69, 70-79, and 80 or more years, respectively, and as many as one in 1000 Canadians over the age of 65 years may be affected. The prevalence of MDS is also increasing as effective therapies become available which extend patient survival. Anemia is present in about 80% of MDS patients at diagnosis; about 40% of patients with International Prognostic Scoring System (IPSS) low risk MDS and 80% with high risk disease are red blood cell (RBC) transfusion dependent. Although new therapies reduce or delay the need for transfusion, the majority of patients will eventually develop RBC transfusion dependence; this has implications for survival and has a marked impact on quality of life. Secondary iron overload (IOL) from blood transfusion is a common complication of MDS. It is widely thought that IOL is physiologically important and that the use of iron chelation therapy (ICT) to prevent or reduce IOL is a key consideration in MDS management, although this is not universally accepted. Although the results of a randomized controlled trial of ICT in lower risk MDS are awaited, this trial enrolled slowly, the sample size was reduced by two thirds, and it may no longer be powered to be informative on many of the clinical endpoints relevant to ICT in this patient population. In this presentation, an overview of the available evidence supporting a clinical benefit of ICT in MDS is provided. This includes background on transfusion dependence, IOL and survival in MDS; data on survival with ICT in MDS; other evidence for clinical benefit of ICT in MDS which may impact on survival (organ function, hematologic improvement, infection reduction, progression to AML, outcomes around hematopoietic stem cell transplantation); and current recommendations for ICT in MDS. Mechanisms by which these clinical endpoints may be impacted are reviewed. Areas for future research and clarification are summarized. Data from the randomized controlled trial of ICT in MDS will be reviewed. ICT dosing, dose adjustments and side effect management are reviewed.

ES02-1

Mantle cell lymphoma -from the clinic to genetics

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Mantle cell lymphoma (MCL) is a relatively uncommon lymphoma subtype, constituting around 5% of all lymphomas, and usually with a very aggressive clinical course. Younger patients receive intensive chemotherapy with consolidation with autologous stem cell transplant, aiming for long term remission and possibly cure, whereas older patients receive less intensive therapy, for which no standard has been identified.

Here, we will present the work by the Nordic Lymphoma Group, in developing treatment strategies for MCL, in younger and elderly patients, as well as in the relapsed situation. We will also discuss the importance of translational studies within clinical trials, on the RNA and DNA level, to identify subgroups of patients that require specific management. Lastly, we will discuss novel agents and future developments in the treatment of MCL.

ES02-2

From genetics to the clinic: Follicular lymphoma

Gilles Salles

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Follicular lymphoma is an intriguing tumor, that may develop after many years of clinically occult circulation of cells carrying the translocation hallmark of this disease, the t(14;18)(q32;q21). In recent years, new insights on the tumor biology of this lymphoma have been discovered (Huet, Nat Rev Cancer, 2018). The mutation landscape is dominated by alterations of genes involved in epigenetic control that appear to occur early during the disease development; some of those, as well as other mutations, were recently shown to remodel the tumor microenvironment, allowing lymphoma cells to escape to immune control. Despite these advances and the description of several biological based prognostic indexes, patients prognosis is still usually assessed using standard clinical variables, such as tumor burden, FLIPI indexes of more recently the PRIMA-PI index (Bachy, Blood 2018)

The treatment of patients with follicular lymphoma has been profoundly modified with the emergence of anti-CD20 antibodies 20 years ago. Patients with a low tumor burden can still be safely watched, even if rituximab single agent allows a clinical response in 3 out of 4 patients. When patients present with a high tumor burden or symptoms, immunochemotherapy is usually indicated since this approach has shown to improve patients overall survival. Different chemotherapy backbones can be used, with different safety and efficacy profiles. Recently, obinutuzumab, when substituted to rituximab, was also shown to improve the outcome of patients receiving immunochemotherapy. Chemotherapy free regimens have been also developed, and the combination of rituximab and lenalidomide appears to have a similar efficacy profile as compared to immunochemotherapy in the first line setting (Morschhauser, NEJM 2018). When patients experience disease progression after their initial management, many options can be discussed, ranging from other immunotherapy approaches to stem cell transplant.

Despite the dramatic improvement of survival expectancy for patients with follicular lymphoma in last 2 decades, lymphoma still represents the leading cause of death (Sarkozy et al.) and new personalized treatment approaches still need to be developed.

ES02-3

From genetics to the clinic of chronic lymphocytic leukemia

Wei Xu

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Chronic lymphocytic leukemia (CLL) is characterized by the clonal proliferation and accumulation of mature and typically CD5-positive B-cells within the blood, bone marrow, lymph nodes, and spleen. CLL is a heterogeneous disease with a variable clinical course. Genomic markers are among the strongest prognostic factors in CLL.

Chromosomal aberrations, *IGHV* and TP53 mutation status are well-established and essential to discriminate between a more indolent course of disease and a high-risk CLL, which requires an alternative treatment regimen. Approximately 80% of CLL patients carry chromosomal alterations. The initiating chromosomal aberrations comprise del(13q) in about 55% of cases, and trisomy 12 in 10–20% of cases. Del(11q) is seen in about 10% of cases and del(17p) in about 5–8% of cases, but these aberrations are usually acquired at late stages of the disease. Del(13q) causes the loss of miRNAs (miR-15a and miR-16-1), which initiates leukemogenesis. Del(11q) causes the loss of the *ATM* gene, which encodes a DNA damage response kinase *ATM*. Del(17p) typically deletes the tumour suppressor gene *TP53*. More than 80% of cases with a del(17p) also carry mutations in the remaining *TP53* allele, resulting in a functional disruption of the TP53 pathway. *TP53* mutations and del(17p) are therefore collectively categorized as genetic *TP53* aberrations.

IGHV mutation status is a strong prognostic factor: Early-stage CLL cases with unmutated *IGHV* show shorter time to first treatment and decreased overall survival (OS) in multivariate analysis. Intriguingly, stimulation also occurs in specific *IGHV* subsets via recognition of epitopes on the BCR molecule itself by the heavy chain complementarity-determining region HCDR3. In addition to the number of mutations, the usage of a specific VH gene is also prognostic for outcome. V3–21 usage was shown to be a prognostic factor independently of mutation status.

Additional recurrent somatic gene mutations have been identified in *NOTCH1, ATM, BIRC3, MYD88, and SF3B1. SF3B1, ATM,* and *BIRC3* may describe CLL with adverse outcome, whereas *NOTCH1* is predictive for resistance against CD20 antibodies. Integration of novel drivers into a small set of key pathways forms the basis for future pathogenetic and therapeutic implications.

The survival of CLL cells also depends on a permissive microenvironment of cellular components. Macrophages, T cells, or stromal follicular dendritic cells stimulate crucial survival and pro-proliferative signalling pathways in leukaemic cells by secreting chemokines, cytokines, and angiogenic factors or by expressing distinct surface receptors or adhesion molecules.

ES03-1

Pharmacogenetics in patients with childhood acute lymphoblastic leukemia

Yoichi Tanaka

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Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. In the past few decades, the therapeutic outcome of ALL has achieved remarkable progression, with 5-year overall survival reaching >90%. Despite this improvement in therapeutic outcome, treatment-related severe toxicity results in interruption of therapy consequently compromising efficacy. Therefore, the prediction of response to therapy and appropriate adjustment of therapeutic dose is important to further improve the therapeutic outcome. Host inherited genetic variant may be a predictive factor of therapeutic response.

The agent 6-mercaptopurine (6-MP) is the main component of ALL therapy. However, a proportion of ALL patients experience severe toxicity and require interruption of therapy. Established factors of 6-MP sensitivity include a germline genetic variation and low expression of a drug metabolite enzyme termed thiopurine S-methyl transferase (*TPMT*). However, the frequency of *TPMT* deficiency among Asian patients is lower than that observed among European patients. Therefore, *TPMT* genotyping has not been useful in the Asian population for the adjustment of the therapeutic dose. Recently, a genome-wide association study revealed that the variant of nudix hydrolase 15 (*NUDT15*) was a risk factor of 6-MP intolerability. Thereafter, studies reported the association between the *NUDT15* genotype and 6-MP tolerability or therapeutic outcome in mainly Asian patients with childhood ALL. *NUDT15* codes the *NUDT15* enzyme, which dephosphorylates thioguanosine triphosphate to monophosphate. Patients with the *NUDT15* variant are highly sensitive to 6-MP. In particular, patients with the homozygous variant require reduction of the 6-MP dose to <10 mg/m2/day during maintenance therapy. Notably, the tolerable dose of 6-MP for patients with the *NUDT15* homozygous variant was different than that reported in those with the *NUDT15* diplotype. Furthermore, 6-MP tolerability is influenced by the interaction with other risk variants, such as transporters. In Asia, in the near future, the initial dose of 6-MP will be adjusted according to the patient's *NUDT15* genotype.

In this lecture, I will discuss the pharmacogenetics of childhood ALL, especially 6-MP tolerability associated with germline *NUDT15* variant.

ES03-2

Recent advances in the treatment of adult ALL

Won Sik Lee

Inje University School of Medicine, Korea

The management of acute lymphoblastic leukemia (ALL) in adult patients has traditionally depended on combination chemotherapy, but the outcome was inferior compared to childhood counterpart. Recently, monoclonal antibodies, antibody-drug conjugates and bispecific antibody constructs showed us considerable promise in improving the outcome in these adult patients especially in the salvage setting. The representatives of this group are rituximab, inotuzumab ozogamicin, and blinatumomab. Furthermore, recent study showed more than 80% of ALL patients in complete remission with evidence of minimal residual disease (MRD) achieved a complete MRD response following treatment with blinatumomab. On the other hand, adoptive cellular therapies such as chimeric antigen receptor (CAR) T cells achieved another successful result in children and young adult patients with multiply relapsed/refractory disease. Early results in adult trials have also shown significant responses, and strategies aimed at mitigating toxicities associated with the therapy have improved tolerability. Therefore, if available, CAR T-cell therapy deserves consideration for salvage of adults with B-lineage ALL who are multiply relapsed, refractory, or relapsed after a previous allogeneic transplantation. Finally, the effort to find the optimal sequencing of the available antibodies in the relapsed or even frontline setting as well as their integration with stem cell transplant and CAR T-cell therapy is ongoing. Herein, I review updated data for such recent advance of treatment in adult patients with ALL especially focused on immune based approach.

ES03-3

Mutational landscape of ALL: Next-generation sequencing-based mutations scanning strategy

Seung-Tae Lee

Yonsei University College of Medicine, Korea

Over the past decade, next-generation sequencing (NGS) has led to an exponential increase in our understanding of the genetic basis of hematologic malignancies. Introduction of NGS methods into clinical diagnostic laboratories has created an opportunity to profile the multiple actionable driver genes in patients with known and/or suspected hematologic malignancies. NGS technologies have been applied to hematological disorders in a variety of contexts: guiding diagnosis, subclassification, prognosis, and minimal residual disease (MRD) testing, often allowing the identification of novel mutations.

Lymphoblastic leukemias are genetically heterogeneous and distinct genetic subtypes show different phenotypic, prognostic and therapeutic implications. Furthermore, many gene alterations can be candidates for targeted agents. Somatic mutations in several genes are present in B-cell precursor acute lymphoblastic leukemia (BCP-ALL). These mutations have identified in genes which are involved in RAS signaling, B-cell differentiation and development, JAK/STAT signaling, TP53/RB1 tumor suppressor and noncanonical pathways and in other/unknown genes. Moreover, copy number changes involving *IKZF1, CRLF2, PAX5* and *EBF1* have been implicated in BCP-ALL with clinical significance. T-cell acute lymphoblastic leukemia has been associated with four different classes of mutations: (i) Affecting the cell cycle (*CDKN2A/CDKN2B*); (ii) Impairing differentiation (*HOX* genes, *MLL, LYL1, TAL1/2* and *LMO1/2*); (iii) Providing a proliferative and survival advantage (*LCK* and *ABL1*); (iv) Providing self-renewal capacity (*NOTCH1*).

Understanding the mutational landscape of lymphoblastic leukemias will expand our option for patient diagnosis and care. NGS testing is a promising option for clinical testing and personalized medicine in lymphoblastic leukemias, which will be enhanced by intensive bioinformatics analysis and comprehensive interpretation.

ES04-1

Early "Goal-directed coagulation therapy" approaches for the management of acute trauma-hemorrhage and trauma-induced coagulopathy

Marc Guido Maegele

Witten/Herdecke University, Germany

Uncontrolled hemorrhage and trauma-induced coagulopathy (TIC) remain the major causes for preventable death after trauma. One out of four severely injured patients admitted to the trauma bay is bleeding with variable degrees of laboratory coagulopathy and early detection and management have been associated with improved outcomes. In the acute phase, the clinical strategies for treatment follow the „Damage Control Resuscitation" (DCR)-concept which advocates the empiric administration of blood products in predefined ratios. However, the optimum ratio is still under debate, no universal standard for the composition of these transfusion packages has yet been established and storage time may considerably affect the hemostatic competence of these products. As an alternative, several European but also a few US trauma centers have instituted the concept of „Goal-directed Coagulation Therapy" (GDCT) based upon results from early point-of-care (POC) viscoelastic testing assays.

The technology of blood viscoelastic testing was first described by Hartert, a German physician, back in 1948. These tests provide real time, point of care (POC) information on the dynamics of clot development, stability and dissolution thereby reflecting in-vivo hemostasis. While previous devices needed to be operated manually, the novel ROTEM® Sigma runs fully automated and test results, even if devices are located remotely, can be transferred to connected screens throughout the local IT infrastructure for direct clinical-decision making.

The concept of GDCT based upon results from early POC viscoelastic testing assays is intriguing, primarily driven by physiological understanding and thereby promoting individualized care for bleeding trauma patients. The concept has been shown to reduce bleeding, transfusions of RBC, plasma and platelet concentrates, and also mortality in mixed surgical populations. Moreover, early viscoelastic variables of clot firmness have been shown to be good predictors for the need of massive transfusion and mortality. A recent Cochrane review provided, apart from known reductions in transfusion requirement, for the first time, a survival benefit with the use of viscoelastic testing in bleeding patients.

It is not surprising that viscoelastic testing is increasingly being recognized for its potential to diagnose TIC as well as for the guidance of treatment to augment damage control resuscitation (DCR) during the acute care of bleeding trauma patients. Current guidelines advocate that monitoring and measures to support coagulation should be initiated immediately upon arrival of the patient to the trauma bay and that routine practice in coagulation monitoring in bleeding trauma patients should include the early and repeated monitoring of coagulation using viscoelastic testing assays. Further resuscitation measures should be continued using a goal-directed approach guided either by standard laboratory coagulation assays and/or POC viscoelastic testing assays, such as ROTEM®.

A number of individualized clinical algorithms based upon POC viscoelastic testing assays to guide hemostatic therapies in severe trauma-hemorrhage and TIC have been suggested mostly based upon retrospective registry data or expert opinion. Current trauma guidelines recommend the local implementation of algorithms for the management of bleeding trauma patients including clinical and safety management systems that include parameters to assess key measures of bleeding control and outcome. If key interventions and measures formulated in guidelines or algorithms are implemented, outcomes from trauma including hemorrhage are likely to be improved and death and other complications reduced. However, local algorithms can only consider products, measures and actions that are locally available and not all resources which would compose an optimal clinical pathway may be available anywhere at any time. Therefore, algorithms need to be adopted to local infrastructures and logistics.

ES04-2

Clinical application of clot waveform analysis in hemophilia treatment

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Hemophilia is a congenital bleeding disorder, occurred by genetic abnormalities of factor (F)VIII and FIX, resulting in the frequently repeated intra-muscular and joints bleeding. Due to disturbance of FX activation in the intrinsic complex during the blood coagulation process, severe bleeding symptoms mainly in the joints and muscles are exhibited. For the hemophilia therapy, FVIII and FIX activity by a PTT-based assay is generally measured to evaluate clinical severities and hemostatic effects by administration of clotting factor products. We have experienced, however, that there are some cases in which clinical phenotypes in the patients are discrepant from clinical severities based on the activity. Furthermore, in the recent years, the remarkable development of hemophilia treatment such as extended half-life products and non-factor product (emicizumab), we are entering a new ear as a paradigm shift of hemophilia treatment, resulting in further improving quality of life for patients. However, for some hemostatic monitoring of these new therapeutic products, it is difficult to assess using conventional a PTT-based assay, as a consequence, we may be embarrassed in the clinical setting. The coagulation mechanism is considered as the cell-based coagulation model. Therefore, for the hemophilia treatment, not only evaluation of a PTT-based FVIII or FIX activity, but also a measurement method evaluating comprehensively coagulation potentials trends to be recently utilized. Clotwave form analysis (CWA)is a recently developed global coagulation technique based on the continuous observation of changes in light transmittance that occur as fibrin is formed in plasma during the performance of routine clotting tests including a PTT and PT. Recommendations on the standardization and clinical application of CWA from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis have recently been published. We have already reported many clinical applications on the use of CWA in hemophilia patients with or without inhibitors, in addition the hemostatic monitoring of new hemophilia products such as non-factor product (emicizumab). In the lecture, I would like to talk about the clinical application for hemostatic monitoring in hemophilia treatment using CWA.

ES04-3

Thrombin generation assay

Bas de Laat

Synapse Research Institute, The Netherlands

Thrombin is the central enzyme in blood coagulation by converting fibrinogen into fibrin thereby transforming liquid blood into a clot. The amount and activity of thrombin have shown to predict both a prothrombotic and bleeding phenotype better than existing coagulation assays, due to the increased sensitivity of the thrombin generation assay compared to other assays: The more thrombin the more thrombosis but the less bleeding, the less thrombin the more bleeding but the less thrombosis". Thrombin generation assay as it is now on the market (Calibrated Automated Thrombography) not only detects coagulation but it is also able to detect the interaction between coagulation and platelets by testing platelet rich plasma. Recently we have also shown that thrombin generation can be applied to whole blood taking all cells into account. Besides detecting both thrombosis and bleeding, almost all anticoagulant treatments affect thrombin generation making it an ideal assay for both the detection and monitoring of both the classic and new anticoagulants. Methods to detect thrombin generation in flowing whole blood are being investigated and it is to be expected that in the future point of care methods become available to dedicated to certain diseases such as bleeding during trauma and surgery.

SCIENTIFIC SESSION

2019 KOREAN SOCIETY OF
HEMATOLOGY INTERNATIONAL CONFERENCE
& 60th ANNUAL MEETING

SS01-1

Paroxysmal nocturnal hemoglobinuria in bone marrow failure

Jun Ho Jang

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, progressive, and life-threatening disease driven by chronic hemolysis leading to thrombosis, renal impairment, pain, severe fatigue, poor quality of life, and death. Because immune-mediated bone marrow (BM) failure is essential for the evolution of PNH, patients frequently have an element of BM failure such as aplastic anemia (AA) either before or after the diagnosis of PNH. Approximately half of all patients with AA have detectable populations of PNH clones although in general, the clone size is smaller in patients with AA than in patients with classic PNH.

Treatment of PNH in BM failure is similar to classic PNH if it is not severe AA. Currently eculizumab, a monoclonal antibody to complement protein 5 (C5), can be effective in controlling intravascular hemolysis in both classic PNH and PNH-BM failure, it does not improve underlying cytopenias related to BM failure. Therefore PNH-SAA may require additional treatment such as immune suppressive therapy or allogeneic hematopoietic stem cell transplantation.

Ravulizumab, a humanized monoclonal antibody, is a complement C5 inhibitor for the treatment of PNH. Like the first-generation C5 inhibitor, eculizumab, ravulizumab binds specifically and with high affinity to the complement progein C5. Ravulizumab was approved by US FDA in Dec. 2018. Several other complement inhibitors are now in clinical trials for the treatment of PNH.

SS01-2

Germline mutations in inherited bone marrow failure

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Bone marrow failure (BMF) syndromes are a heterogeneous group of hematological disorders that may either be acquired or inherited (IBMF). Overlap between BMF and myelodysplastic syndromes (MDS) has long been recognized, BMF being intrinsically a situation that favours the expansion of clones with somatic mutations or chromosomal abnormalities such as monosomy 7/del(7q). While Fanconi anemia, dyskeratosis congenital, RUNX1-deficient disorders and others are well-recognized IBMF causes, the underlying genetic diagnosis can remain uncertain in many IBMF cases. However, recognizing the inherited nature of BMF and MDS is crucial to avoid immunosupressive therapy and adapt treatment such as HSCT, including donor choice. It also enables MDS/AML risk monitoring and family counselling. For translational research, identifying causal germline mutations in BMF and MDS can illuminate crucial biological pathways that are involved directly or indirectly in homeostasis and oncogenesis in the bone marrow.

We have systematically collected over 15 years the clinical data and primary samples from patients with BMF seen for diagnosis evaluation at the "French National Center of Bone Marrow Failure Syndromes" (Saint-Louis and Robert Debré Hospitals, Paris, France). In many patients, a "likely-inherited" nature of BMF was suspected based on familial history, physical signs, and/or a very young age (<2 yo), despite that no clear cause could be identified at initial diagnosis evaluation (Fanconi anemia being excluded). Using whole exome sequencing (WES) in non-hematopoietic (fibroblast) DNA on the resulting "unresolved" patient cohort of 179 patients, we were able to identify causal or likely-causal mutations in almost half the patients, and therefore to draw a broad molecular and clinical portrait of this heterogeneous group of patients with "likely-inherited" BMF (with or without MDS features).

Germline mutated genes included genes of familial hematopoietic disorders (*GATA2, RUNX1*), telomeropathies (*TERC, TERT, RTEL1*), ribosome disorders (*SBDS, DNAJC21, RPL5*), and DNA repair deficiency (*LIG4*). Many patients had an atypical presentation, and the mutated gene was often not clinically suspected. We also found mutations in *SAMD9* and *SAMD9L*, *MECOM/EVI1*, and *ERCC6L2*, each of which was associated with a distinct natural history; SAMD9 and SAMD9L patients often experienced transient aplasia and monosomy 7, whereas MECOM patients presented early-onset severe aplastic anemia, and ERCC6L2 patients, mild pancytopenia with myelodysplasia.

In conclusion, this and other recent studies have broadened the molecular and clinical portrait of IBMF syndromes and shed light on newly recognized IBMF/MDS disorders. Importantly, NGS systematic screen help to implement precision medicine at diagnosis and can improve patient management and family counselling.

SS01-3

Telomere length and somatic mutations in aplastic anemia

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Aplastic anemia (AA) is a group of heterogenous disease. Aplastic anemia with somatic mutations or cytogenetic aberrations are considered as clonal disease either as pre-malignant stage or malignant disease and differential treatment approach from idiopathic AA need to set. The presence of clonality in aplastic anemia could be a determining point for the choice of treatment among bone marrow transplantation or immunosuppressive therapy, and the detection method of clonality could be conventional cytogenetics (CG), molecular cytogenetics or molecular genetic test. Detection sensitivity is 5% by CG, 20-30% by Sanger sequencing, and 0.5-1.0% by next generation sequencing (NGS). We aimed to investigate the frequencies of clonal changes including cytogenetic aberrations and somatic mutations and their correlation with clinical prognosis in aplastic anemia.

We reviewed clinical data of the 437 patients (mean age 38 years, M:F ratio 1.1) who were diagnosed with AA from 1997 to 2013. Results of G-banding were available in 277 patients and in all them, fluorescent in situ hybridization (FISH) for -5/5q-, -7/7q-, +8, -20/20q-, and 1q gain was performed. Target capture sequencing for 88 hematopoiesis related genes was performed in patients. Mutations were selected by running algorithms including SIFT, Polyphen2, and CADD, and normal variant was filtered by 1000Gp, ESP6500, and the in-house Korean database (n=250). We assessed disease progression, survival and response to treatment in 248 patients.

Of 437 patients, 21(4.8%) showed disease progression: MDS in 14 (68.2%), AML in 4 (18.2%), PMF in 2 (9.1%) and plasma cell myeloma in 1 (4.5%). Mean duration of transformation to MDS was months (1- month). Among, only 2 patients showed cytogenetic aberrations (CA) at initial diagnosis, but 9 patients showed cytogenetic evolution at the time of disease transformation: monosomy 7(%), trisomy 8(%), and 1q gain (%). Among 277 patients in whom both G-banding and FISH panel were performed, (7.%) showed cytogenetic aberrations; G-banding revealed numerical abnormality (9/17, 52.9%), structural abnormality (5/17, 29.4%), combined abnormality (3/17, 17.6%). FISH revealed trisomy 8 in %, complex ≥ abnormality in Patients with aberrant FISH result for MDS was associated with disease progression (p=0.012). Median percentage of FISH+ clonal cells were smaller (5.5%), compared to those of MDS (51.0%) and AML (86.5%). The number of mutated genes and frequently mutated genes was *NOTCH1 (3/%), MED12 (%), SCRIB (2/%), BCOR (2/%), DNMT3A (8%), CDKN2A (1/%), LRP1B (1/%), NPM1 (1/%), NFKBIE (1/%), LAMB4 (1/%), SMARCA2 (1/%), JAK2 (1/%), RB1 (1/%), POLG (1/%), RUNX1 (1/%), U2AF1 (1/%), DDX3X* (1/ In patients with somatic mutations, % showed disease progression. But patients with somatic mutation did not any difference in survival, treatment response and disease progression. When the patients were divided by clonal (cytogenetic aberration by G-banding or FISH or somatic mutation by NGS, 14.3%), and non-clonal (85.7%) in IST treatment group, the clonal group showed adverse response compared to non-clonal group (p=0.048) while BMT treatment showed similar response between two groups.

Five percent of among AA patients in Korea revealed disease progression and about half of AA patients harboring clonalities showed at the time of disease transformation. CA was strongly associated with adverse prognosis or treatment response, while somatic mutation was not. Increased sensitivity of detection for clonality could reveal the hidden clonality in AA, but significance of molecular clonal hematopoiesis in AA need to be further investigated.

SS02-1

Immunological weapons against multiple myeloma

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Multiple myeloma (MM) suppresses the immune response as a whole by releasing immune suppressive molecules and cytokines, leading to the tumor's escape from the effector immune response. The goal of cancer immunotherapy is to activate, re¬store, and augment cytotoxic effector cells at the tumor site to effectively kill the tumor, all of which rely on the safe induction of cytotoxic cells that recognize and kill tumor cells. An ideal immunotherapy should overcome the effects of an immunosuppressive micro¬environment, train and recruit immune cells to elimi¬nate all cancer cells, improve patient outcome without affecting healthy cells, and remain active in the event of recurrence. Dendritic cell (DC) vaccination and adoptive cell immunotherapy with chimeric antigen receptor (CAR) T-cells, T-cell receptor (TCR)-engineered T-cells, and natural killer (NK) cells are emerging as promising forms of cellular immunotherapy in patients with MM. In this presentation, I will focus on the efficacy and safety of recent preclinical and clinical trials in the development of DC vaccines, genetically engineered effector T-cells, and NK cell therapies for MM.

SS02-2

Roles of bone marrow microenvironment in clonal evolution and drug resistance of multiple myeloma

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Recent studies with next generation sequencing have revealed the complex genomic architecture of multiple myeloma. A model combining "Big Bang" dynamics and Darwinian type of branching evolution has been put forward to explain the development and progression of the disease. As a result of branching evolution, multiple clones emerge with distinct characteristics in terms of growth advantage and drug sensitivity. It is widely believed that the interaction with bone marrow microenvironment accelerates clonal heterogeneity of myeloma cells. The bone marrow microenvironment also confers drug resistance to myeloma cells via at least two overlapping mechanisms. First, bone marrow stromal cells (BMSCs) produce soluble factors, such as interleukin-6 and insulin-like growth factor-1, to activate signal transduction pathways leading to drug resistance (soluble factor-mediated drug resistance). Second, BMSCs up-regulate the expression of cell cycle inhibitors, anti-apoptotic members of the Bcl-2 family, and ABC drug transporters in myeloma cells upon direct contact (cell adhesion-mediated drug resistance). Elucidation of the mechanisms underlying drug resistance may greatly contribute to the advancement of multiple myeloma therapies. We have demonstrated that epigenetic alterations play important roles in drug resistance of myeloma cells, especially cell adhesion-mediated drug resistance (CAM-DR). We found that class I histone deacetylases (HDACs) are up-regulated in myeloma cells via VLA-4-mediated adhesion to BMSCs and determine the sensitivity of myeloma cells to proteasome inhibitors (Oncogene 28: 231, 2009; Blood 116: 406, 2010). The histone H3-K27 methyltransferase EZH2 regulates the transcription of several anti-apoptotic genes and drug transporters in an Ikaros-dependent manner, rendering the acquisition of CAM-DR and stemness by immature myeloma cells, including myeloma stem cells (J. Clin. Invest. 125: 4375, 2015; Cancer Res. 78: 1766, 2018). In addition, another histone methyltransferase, MMSET, was shown to confer drug resistance to myeloma cells by facilitating DNA repair (Leukemia, submitted for publication). These findings provide a rationale for the inclusion of epigenetic drugs, such as HDAC inhibitors and histone methylation modifiers, in combination chemotherapy for myeloma patients to increase the therapeutic index.

SS02-3

Antigen-mediated regulation in myeloma

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Myeloma is a common plasma cell malignancy wherein all cases are preceded by a precursor state called monoclonal gammopathy of undetermined significance (MGUS). The mechanisms underlying the development of MGUS are not known. Clinical observations of increased risk of MGUS and myeloma in patients with Gaucher disease (GD), an inherited lipid-storage disorder led us to examine the possible link between lipid-mediated immune activation and development of gammopathies. These studies led to the discovery of Lyso-glucosphingosine-reactive CD1d-restricted type II NKT cells that exhibit a T follicular helper (TFH) phenotype and help the induction of lipid-reactive plasma cells and antibodies. Accordingly, reduction of antigenic-lipids led to reduction of the risk of gammopathy in mouse models of Gaucher disease. In addition to GD-asociated gammopathy, a proportion of patients with sporadic gammopathies also have lipid-reactive immunoglobulins (Igs) secreted by clonal plasma cells. This was validated by single-cell cloning of clonal B cell receptor and production of recombinant Igs. Patients with such closes were enriched for non-hyperdiploid clones. Interestingly, following growth of these tumor cells in mice, injection of lipid antigens led to not only increase in clonal plasma cells, but also increased growth of polyclonal plasma cells in vivo. These studies support a model wherein chronic antigen-mediated stimulation leads to increase in polyclonal plasma cells followed by evolution of monoclonal disease. Even in the setting of established clones, the clones remain sensitive to antigenic stimulation. Therefore these data support the possibility that targeting the antigenic triggers underlying B/plasma cell clones may allow prevention of MGUS and MM.

SS03-1

Thymidine kinase cell therapy

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Cellular immunotherapy, and in particular T-cell therapy, have recently produced impressive clinical results. Expanded tumor specific T cells, genetically engineered T cells are rapidly entering the clinical arena. The most effective and consolidated cell therapy approach is allogeneic haematopoietic stem cell transplantation (HSCT), the only cure for several patients with high-risk haematological malignancies. The potential of allogeneic HSCT is strictly dependent on the donor immune system, particularly on alloreactive T lymphocytes, that promote the beneficial graft-versus-tumour effect (GvT), but may also trigger the detrimental graft-versus-host-disease (GvHD). Gene transfer technologies allow to manipulate donor T cells to enforce GvT and foster immune reconstitution, while avoiding or controlling GvHD. The suicide gene approach is based on the transfer of a suicide gene into donor lymphocytes, for a safe infusion of a wide T cell repertoire, that might be selectively controlled in vivo in case of GvHD. The herpes simplex virus thymidine kinase (TK) is the suicide gene most extensively tested in humans. Its expression in donor lymphocytes confers to the cells (TK-cells) lethal sensitivity to the anti-herpes drug, ganciclovir. Progressive improvements in suicide genes, vector technology and transduction protocols have allowed to overcome the toxicity of GvHD while preserving the antitumor efficacy of allogeneic HSCT. Several phase I-II-III clinical trials documented the safety and the efficacy of the TK-cell approach. The activation of the suicide machinery prooved highly effective in abrogating acute GVHD in all reported trials, resulting in conditional approval by the European Medicines Agency (EMA) of a gene therapy medicinal product consisting of TK-engineered allogeneic T lymphocytes. The experience gained through the preclinical and clinical development of TK-cells have been also instrumental for shaping innovative, genetically engineered cellular products, for cancer immunotherapy. Challenges and opportunities will be discussed.

SS03-2

Updates on CAR T cell therapy for multiple myeloma

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Allogeneic bone marrow transplantation and donor lymphocyte infusions have been the most successful examples of adoptive cellar therapy for most hematologic malignancies but have had a limited role in multiple myeloma for various reasons. The recognition and ability to harness autologous tumor infiltrating lymphocytes and/or marrow infiltrating lymphocytes have led to ongoing clinical research in the adoptive transfer of these more anti-myeloma specific lymphocytes. (ref Noonan et al, Sci Trans med 2015) Autologous peripheral t cells can also be genetically modified to create affinity-enhanced T cell receptor T cells (TCR T cells) or chimeric antigen receptor T cells (CAR T cells). Thus far, the biggest advance has been in the field of CAR T cell therapy. CAR T cells are T cells that are genetically engineered to express a chimeric antigen receptor (CAR). A CAR usually contains an antigen binding domain, a costimulatory domain and a signaling domain. In MM, CARs have been constructed to recognize several antigens though B cell maturation antigen (BCMA) is the most active target to date. There are several clinical trials ongoing with BCMA-directed CAR T cells. Clinical data from various trial have shown impressive activity with responses rates of 50-100% in heavily pretreated relapsed/refractory patients with MM. (refs: Brudno et al, JCO 2018; Cohen et al, ASH 2017; Berdeja et al, EHA 2018; Zhang et al, EHA 2017; Smith et al, ASH 2017). The current data of CART therapy in MM will be reviewed. Novel constructs, vectors, armoured CARTs, allogeneic CARTs, ACTRs and other advances will be discussed.

SS03-3

Accelerating personalization of immune therapies for blood cancers

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Cancer patients responding to immune checkpoint blockade usually bear tumors that are heavily infiltrated by T cells and express a high load of neoantigens, indicating that the immune system is involved in the therapeutic effect of these agents, and strongly supports the renewed interest in cancer vaccine strategies. Idiotypic determinants of a lymphoma surface Ig, formed by the interaction of the variable regions of heavy and light chains, can be used as a tumor-specific antigen, and effective vaccination using idiotype proteins was demonstrated recently in a positive controlled Phase III clinical trial (Schuster [Kwak] et al. ***J Clin Oncol 2011***). These variable region genes can also be cloned and used as a DNA vaccine, a delivery system holding tremendous potential for streamlining vaccine production. To increase vaccination potency, we are targeting the vaccine to antigen-presenting cells (APCs) by fusion of the antigen with a sequence encoding a chemokine (MIP-3α), which binds an endocytic surface receptor on APCs. Lymphoplasmacytic lymphoma (LPL) is a low grade, incurable disease featuring an abnormal proliferation of Immunoglobulin (Ig)-producing malignant cells. Asymptomatic patients are currently managed by a "watchful waiting" approach, as available therapies provide no survival advantage if started before symptoms develop. LPL is an excellent model to test our vaccine since patients have both an intact immune function and low tumor burden. We are evaluating the safety and feasibility of this next-generation DNA vaccine in ***a first-in-human clinical trial currently enrolling*** asymptomatic LPL patients (Thomas ST et al. [Kwak] ***BMC Cancer 2018*** Feb 13;18(1):187.
doi: 10.1186/s12885-018-4094-2). This vaccine could shift the current paradigm of clinical management for patients with asymptomatic LPL and inform development of other personalized approaches.

Another personalized therapy, chimeric antigen receptor (CAR) T-cells, have the potential to revolutionize the treatment of cancers. Particularly in hematological malignancies, there are reports of promising clinical outcomes in advanced non-Hodgkin lymphomas (NHLs) with CD19-CAR T-cell therapy. However, disease relapse is problematic, and is thought to be caused by poor long-term persistence of the CAR T-cells, and loss of the CD19 target on tumors. Thus, there is an urgent need for improved novel CAR T-cell therapies directed at alternative targets.

The CAR T-cell platform relies on antibody-derived single chain fragments (scFv), which are genetically engineered into chimeric T-cell receptors, and that recognize target cell surface proteins on tumors. One potential target is B-cell activating factor receptor (BAFF-R), a tumor necrosis factor receptor superfamily protein (TNFRSF13C) specifically involved in B lymphocyte development and mature B-cell survival, that is primarily expressed on B cells and various subtypes of B-cell NHLs and ALL. We have recently developed a humanized therapeutic BAFF-R antibody with strong anti B-cell tumor activity (Qin H. et al. ***Clin Cancer Res 2018***).

Specifically, we adapted a scFv based on our humanized anti-BAFF-R antibody onto a second generation CAR platform containing CD3ζ and 4-1BB intracellular signaling domains. In response to BAFF-R-expressing malignant human B cells (NHLs, acute lymphoblastic leukemias, and chronic lymphocytic leukemias), our CAR T cells readily proliferated and secreted cytotoxic cytokines. We demonstrated both significant levels of BAFF-R CAR T-cell activation and malignant B-cell killing in vitro.
Established human NHL tumors in xenogeneic models were eliminated following BAFF-R CAR T-cell treatments in vivo. Remarkable tumor-free survival was repeatedly observed in human lymphoma xenograft models including JeKo-1 (mantle cell lymphoma) and Raji (Burkitt lymphoma) in NSG mice. We pursued optimization of CAR T-cell persistence by comparing three subsets of early stage T cells (central memory, TCM; memory stem, TSCM; and naïve, TN) as potential starting material for CAR T cell generation. Our in vivo studies show CAR T cells from the TN population retained highest potency eradicating established tumors at a minimal therapeutic dose compared to

other subtypes. We also observed the long term anti-tumor effects conferred by CD8+ CAR T cells required the addition of CD4+ CAR T cells. Finally, we performed a head-to-head comparison of BAFF-R CAR T cells with CD19 CAR T cells in the Raji model. BAFF-R CAR T-cell treatment demonstrated long-term tumor free survival in all treated mice compared to the CD19 CAR T-cell treated cohort, which only showed delayed tumor growth ($P<0.01$).

Thus, BAFF-R CAR T cells demonstrate remarkable efficacy against B-cell malignancies. Targeting BAFF-R potentially addresses unmet clinical needs in B-cell NHLs and ALL, particularly in the setting of CD19 CAR-T-resistance or CD19-negative relapse.

SS04-1

Genetic causes of myeloproliferative diseases: Stratification of patients and new therapeutic targets

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Myeloproliferative neoplasms (MPN) are characterized by clonal overproduction of terminally differentiated myeloid cells, increased risk of thrombosis, bleeding and leukemic transformation. Both acquired and constitutional genetic alterations contribute to the MPN pathogenesis. An overview of genomic data generated over the past decade using SNP microarray analysis and exome sequencing will be provided. The genetic defects associated with MPN are classified into the following categories: 1) germline genetic predispositions, 2) disease initiating mutations (JAK2, MPL, CALR) and 3) mutations driving disease progression. The germline genetic predispositions include a variety of factors with weak and strong effect that predispose carriers to acquisition of somatic mutations that initiate MPN. The disease initiating mutations are targeting the JAK/STAT signaling pathway. Three genes (JAK2, CALR, MPL) are mutated in a mutually exclusive manner in more than 95% of MPN cases. JAK2 mutations are present most frequently in all three MPN subtypes while the less frequent CALR and MPL mutations are present only in primary myelofibrosis and essential thrombocythemia and have not been seen in polycythemia vera. JAK2, CALR, and MPL induce overlapping phenotypes but also influence the clinical course specifically. A fraction of MPN patients that are negative for the common JAK2, CALR, and MPL mutations often carry unusual JAK2 and MPL mutations. The last group of mutations associated with disease progression is the most diverse. Both somatic point mutations and chromosomal aberrations are identified that strongly influence leukemic transformation and in each patient both types of defects are often detected in complex mono- or bi-clonal hierarchies. At the leukemic stage, each patient seems to be a unique transformation event and patient stratification at this stage of the disease will be challenging. The clinical utility of somatic mutations will be discussed focusing on their predictive power and monitoring of minimal residual disease. Emerging new therapeutic targets and treatment strategies will be summarized.

SS04-2

Molecular mechanism of MPN development by mutant calreticulin

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Somatic mutations of the calreticulin (CALR) gene, which encodes a molecular chaperone, have been previously reported in patients with JAK2- and MPL-unmutated essential thrombocythemia and primary myelofibrosis, a subcategory of myeloproliferative neoplasms (MPNs). Previously, our group and others have shown that expression of mutant CALR results in transformation of cells through interaction and activation of the thrombopoietin receptor, MPL (Blood 2016). We recently reported that mutant but not wild-type CALR forms a homomultimeric complex, and demonstrated that the interaction between mutant CALR molecules within the homomultimeric complex was required for the binding and activation of MPL (Leukemia 2018). Since it is generally known that simultaneous cytokine binding to two extracellular receptor domains is critical for receptor activation, we proposed a model in which a multimer of mutant CALR simultaneously interacts with two MPL molecules and thus induces the activation of JAK2 bound to MPL. Although we have demonstrated that mutant CALR serves as a "fake" ligand for MPL, mutant CALR did not have the capability to activate MPL in a paracrine fashion. Rather, mutant CALR only cell-autonomously activated MPL, leaving the molecular mechanism of MPL activation through CALR and MPL engagement elusive. In my talk, I would like to present data to answer this question.

SS04-3

Interferon in myeloproliferative neoplasms

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Interferon alfa (IFN-α) has been used for over 30 years to treat myeloproliferative neoplasms (MPN), including polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF).(1, 2) IFN-α was shown to induce clinical, hematological, molecular and histopathological responses in small clinical studies.(3, 4) Such combined efficacy has never been achieved with any other drug to date in a significant proportion of patients. However, toxicity remains a limitation to its broader use, but the development of pegylated forms with better tolerance has increased the proportion of patients being treated with IFN-α. Several phase 3 studies of peg-IFN-α are in progress, and the results of the PROUD-PV and CONTINUATION-PV studies comparing hydroxyurea to ropeginterferon(5) have been presented at ASH 2018 (Gisslinger et al., Blood 2018 132:579; doi: https://doi.org/10.1182/blood-2018-99-118715). These results show that ropeginterferon induces similar hematological response (control of hematocrit, leucocytes and platelets) rates than hydroxyurea after 12 months in PV patients, with a good tolerance. However, during the second and third years of treatment, superiority of ropeginterferon over standard therapy is significant in terms of hematological and also molecular response. This study prompted the first approval by EMA of an IFN-α in Philadelphia-negative MPN. In addition, sustained clinical, molecular, and morphological responses after IFN-α discontinuation raise the hope that this drug could eradicate MPN malignant cells in selected patients.

Several combinations based on IFN-α are also in development. We have shown the results of the first part of the RUXOPEG study, a multi-center Bayesian Phase 1/2 adaptive trial of pegylated-IFN-α 2a and ruxolitinib in patients with MPN-related myelofibrosis (Kiladjian et al., Blood 2018 132:581; doi: https://doi.org/10.1182/blood-2018-99-110785). Phase 1 included 6 cohorts of 3 pts with increasing doses of both drugs, to a maximum of 20 mg BID of ruxolitinib combined with 135 mcg/week of pegylated-IFN-α 2a. Indeed, no dose limiting toxicity at 45 days was observed at any dose combination, and the trial will now enter the phase 2 that will compare two different combinations (20 mg BID and 15 mg BID of ruxolitinib, respectively, with 135 mcg/week of pegylated-IFN-α 2a). Preliminary results of efficacy in phase 1 are encouraging. The spleen size rapidly diminished (from a mean of 9.7 cm below costal margin by palpation; to 4.7 cm after 6 months), and the mean JAK2V617F allele burden decreased from 74% to 46% after 12 months. In addition, in this population of patients at high molecular risk (75% of patients had at least on additional non-driver mutation, including mutations in ASXL1, TP53, EZH2) it was promising to observe a decrease not only in the JAK2V617F mutant allele burden but also in clones harboring additional mutations. Finally, sequential bone marrow biopsies could also show a reduction in cellularity and in the degree of fibrosis in selected patients.

In a preclinical model we have also tested the combination of IFN-α and arsenic (AS). Indeed, the promyelocytic leukemia protein (PML) is a transcriptional target of IFN-α, resulting in TP53 or RB activation leading to apoptosis, cell cycle arrest or senescence (Maslah et al., Blood 2018 132:52; doi: https://doi.org/10.1182/blood-2018-99-112518). We hypothesized that PML, the key organizer of the PML-nuclear bodies (NB), is an important component of IFN efficacy that can be further enhanced by its combination with AS. We have developed chimeric animals transplanted with a mixture of bone marrow (BM) from wild type (WT) mice and conditional JAK2VF KI/vavCre/UbiGFP mice to analyze the effect of drugs on cell number and JAK2VF allele burden (GFP). Animals, suffering from a PV-like disease, were treated by IFN, AS or IFN+AS for 8 to 14 weeks and blood was analyzed every 2 weeks. IFN reduced the leukocytosis (from wk2), the platelet number (from wk2), the erythrocytosis (from wk6) and the JAK2VF allele burden in granulocytes (from wk4), platelets (from wk2) and RBC (from wk8). The addition of arsenic significantly improved the efficacy of IFN for reducing the leukocytosis ($p<0.03$) and the polycythemia ($p=0.02$) on the short term (weeks 4-6) without toxicity on the platelet number. The effect of the IFN+AS combination was particularly sticking in improving the reduction of JAK2 mutant allele burden compared to IFN alone in granulocytes ($p=0.005$), platelets ($p=0.001$) and RBC ($p=0.001$). Improvement of IFN treatment by the addition of AS was also observed on splenomegaly and allele burden in early bone marrow cells (SLAM). Furthermore, the IFN/AS combination induced less disease relapse (48%,) than IFN alone (73%) as assessed on blood cell counts, allele burden and splenomegaly 9 weeks after treatment discontinuation. Strikingly, none of the secondary mice transplanted with the bone marrow of mice treated with IFN+AS combination developed a disease compared with ≈70% of the mice transplanted with bone

marrow treated with IFN alone showing a dramatic effect of the combination on disease initiating cells. All these in vivo data demonstrated that AS greatly improved the hematological and molecular remission induced by IFN alone.

To better understand the underlying mechanism, in vitro data showed a significantly greater number and size of PML-nuclear bodies in JAK2VF vs. WT UT-7 cells at baseline. Interestingly, IFN + AS significantly increased PML-nuclear bodies in both cell types but more importantly in JAK2VF cells. IFN+AS also had a synergistic impact on JAK2VF cell proliferation. A cell cycle arrest was induced by IFN+AS in UT-7 JAK2VF cells while no significant change was observed in UT-7 WT cells. IFN+AS combination clearly induced senescence in JAK2VF cells as shown by a significantly higher increase of the proportion of S-βgal+ cells in JAK2VF compared to WT cells. The IFN+AS efficacy appeared to be PML dependent since the knockdown of PML by shRNA in the JAK2VF positive HEL cell line, significantly reduced the anti-proliferative effect and pro-senescent activity of IFN+AS. Similar results were found using normal CD34+ cells compared to JAK2VF positive CD34+ primary cells from PV patients regarding increased PML-nuclear bodies formation in the presence of IFN+AS, decreased proliferation and enhanced senescence. Moreover, IFNa+AS had a drastic effect on the clonogenic potential of BFU-E progenitors derived from 10 PV patients with a specific targeting of JAK2VF colonies (reduced from 67% to 32%).

Altogether these results strongly suggest the involvement of PML in the mechanism of action of IFN in MPN therapy and the utility of AS to greatly improve its efficacy. Such results could provide rationale for a phase 1 study in patients with JAK2V617F-positive MPN resistant or intolerant to currently available therapies.

1. Kiladjian JJ, Giraudier S, Cassinat B. Interferon-alpha for the therapy of myeloproliferative neoplasms: targeting the malignant clone. Leukemia. 2016;30(4):776-81.
2. iladjian JJ, Mesa RA, Hoffman R. The renaissance of interferon therapy for the treatment of myeloid malignancies. Blood. 2011;117(18):4706-15.
3. Kiladjian JJ, Cassinat B, Chevret S, Turlure P, Cambier N, Roussel M, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood. 2008;112(8):3065-72.
4. Masarova L, Patel KP, Newberry KJ, Cortes J, Borthakur G, Konopleva M, et al. Pegylated interferon alfa-2a in patients with essential thrombocythaemia or polycythaemia vera: a post-hoc, median 83 month follow-up of an open-label, phase 2 trial. Lancet Haematol. 2017;4(4):e165-e75.
5. Gisslinger H, Zagrijtschuk O, Buxhofer-Ausch V, Thaler J, Schloegl E, Gastl GA, et al. Ropeginterferon alfa-2b, a novel IFNα-2b, induces high response rates with low toxicity in patients with polycythemia vera. Blood. 2015.

SS05-1

Progress in gene therapy for hemophilia A and B

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For 35 years, since the Factor VIII and Factor IX genes were cloned, the dream of curing hemophilia via inserting normal genes into affected individuals has remained just out of reach, despite positive results in animal models for more than 20 years. The initial human trials in the 1990s-early 2000s identified adeno-associated virus (AAV) as the preferred vector system, and encouraging but transient results were obtained using AAV2-FIX. The transgene was lost via a T-cytotoxic cellular response toward hepatocytes containing the FIX gene recognized AAV capsid peptides displayed in the context of HLA class 1, the typical response in a viral infection. A subsequent trial employed steroids to manage the T-cell response, preserving hepatocytes containing the FIX transgene, resulting in an average ~5% FIX activity in 10 subjects. Subsequent studies have employed the Padua mutant of FIX, R338L, a natural mutation conferring 6-8-fold higher specific activity, to enable FIX expression following IV administration in the ~30% range. For years, B-domain deleted FVIII has been difficult to package in AAV vectors, resulting in low hepatic expression in animal models. More recently, a promoter/enhancer-BDD-FVIII construct has been developed that, when packaged in AAV5, has yielded ~100% FVIII activity at 1 year and ~50% activity at 2 years. These remarkable Phase 1/2 results for both FIX and FVIII have led to 2 HemB and 2 HemA Phase 3 trials, ongoing at present. Despite these promising results, many questions remain, including the duration of transgene expression, long term safety, managing the short term immune response, assessing direct hepatocyte toxicity, and what level of expression is sufficient. Further understanding of AAV transduction biology and exploration of more efficient and cell type specific AAV vectors, as well as alternative vector systems, will offer the continued advancement of the field, to the benefit of those affected by bleeding disorders.

SS05-2

Individualized treatment for hemophilia: Population pharmacokinetics approach

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Hemophilia A and B are rare bleeding disorders, caused by mutations in the factor VIII (FVIII) and factor IX (FIX) genes, respectively. Hemophilia A affects 1 in 5000 male live births, while hemophilia B affects 1 in 30,000. The current mainstay of hemophilia treatment is factor replacement therapy with plasma-derived or recombinant concentrates at regular intervals as primary prophylaxis to prevent bleeding and joint damage.

Tailoring prophylaxis to individual patient characteristics has been suggested as an effective strategy to increase the net clinical benefit of hemophilia treatment. However, in order to optimally tailor prophylaxis, the estimation of the pharmacokinetic (PK) disposition of FVIII/FIX at the individual level is required and may pose as a barrier. Typically, multiple blood sampling is required over 24 to 72 hours (i.e., 11 points for the classical approach), which can be burdensome for the hemophilia patient. Additionally, the clinician treating the patient may be inconvenienced with performing the needed complication calculations that are beyond the expertise of most hemophilia treaters.

Although in theory population pharmacokinetics (popPK) has enabled a more reliable approach to estimating individual parameters using reduced data points from individual patients, there are only few readily accessible hemophilia popPK applications available to clinicians, and none providing a one-stop-shop for most available concentrates.

The Web-Accessible Population Pharmacokinetic Service – Hemophilia (WAPPS-Hemo) project has been developed to address this gap and provide a comprehensive popPK application for hemophilia health care providers (www.wapps-hemo.org). WAPPS-Hemo is a centralized, dedicated, web-accessible, and actively moderated database that allows the input of certified hemophilia patient PK data.

WAPPS-Hemo has the potential to provide PK-tailoring to individual patients. In a recently conducted study by Stemberger et al., treatment tailoring based on individual PK profiles on limited sampling data was performed in 36 patients using WAPPS-Hemo. The study demonstrated accurately predicted post-infusion factor activity level in >90% of cases, including for critical levels. In 25 patients, 138 FVIII activity levels were analyzed after tailoring treatment, where only nine cases were predicted to be above >15% while the observed was between 3-15%, and one case predicted at above 3% instead of below. The study presents an example of adopting PK-tailored prophylactic treatment in routine clinical practice using WAPPS-Hemo. The potential of WAPPS-Hemo in the individualized treatment for hemophilia using popPK is to be further explored.

SS05-3

Mechanisms of cancer-associated thrombosis

Nigel Mackman

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Cancer patients have a 4-7 fold increased risk of venous thrombosis. There is a range of incidence of thrombosis associated with different cancer types with pancreatic cancer having one of the highest rates. Risk scores have been developed to identify ambulatory cancer patients at risk for venous thrombosis. However, guidelines do not recommend thromboprophylaxis for patients expect for multiple myeloma patients. We are attempting to elucidate prothrombotic pathways and biomarkers in pancreatic cancer patients that can be used to identify patients that would benefit from thromboprophylaxis. We have found that levels of tumor-derived, tissue factor-positive microvesicles are associated with venous thrombosis in pancreatic cancer patients. Moreover, tumor-derived, human tissue factor-positive microvesicles are incorporated into venous thrombi in mice, and inhibition of human tissue factor reduced thrombus size. In other studies, levels of the neutrophil extracellular trap (NET) biomarker citrullinated histone H3 were associated with venous thrombosis in pancreatic cancer patients. We found that mice bearing human pancreatic tumors had increased levels of circulating neutrophils. In addition, thrombi from tumor bearing mice had increased levels of neutrophils and citrullinated histone H3. DNase I treatment of mice reduced thrombus size in tumor bearing mice but not in control mice. Our studies suggest that both tumor-derived, tissue factor-positive microvesicles and neutrophils and NETs contribute to venous thrombosis in pancreatic cancer patients.

SS06-1

Inherited hematologic malignancies

Lucy Ann Godley

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Familial predisposition to myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) is likely more common than generally appreciated. We are using several approaches to address how germline mutations drive leukemogenesis in patients. First, we are measuring the frequency at which a germline mutation is found within patients with myeloid malignancies, focusing initially on patients diagnosed with myelodysplastic syndromes diagnosed between the ages of 18-40 years old. To answer this question, we are analyzing germline DNA using a next-generation sequencing panel, which is capable of identifying both single nucleotide variants as well as gene deletion/duplication events.

In many cases, we have obtained germline DNA by growing primary mesenchymal stromal cells (MSCs) from frozen bone marrow aspirates. Second, we are testing whether germline mutations within the MSCs themselves might contribute to leukemogenesis by performing in vitrodifferentiation assaysto assess whether the germline mutations block normal adipocyte, chondrocytes, and/or osteocyte differentiation in these cells.

Third, we want to understand the molecular progression and clonal evolution that occurs within individuals as they develop leukemia. To do this, we are measuring clonal hematopoiesis in peripheral blood samples from germline mutation carriers who have not been diagnosed with overt malignancies. Through these studies, we hope to dissect how germline mutations alter cellular function and drive leukemia development, with the ultimate goal of developing intervention strategies that could delay or block cancer development in at-risk individuals.

SS06-2

GATA2 deficiency: How to make the diagnosis? how to treat it ?

Jean Donadieu

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Germline heterozygous mutations of hematopoietic transcription factor GATA2 have been reported to cause several diseases: i.e., familial myelodysplasia (MDS), myeloid leukemia (AML), monocytopenia mycobacterial infections/dendritic cell, monocyte, B and NK deficiency (MonoMAC/DMLC), and Emberger's syndrome (primary lymphedema with MDS). GATA2 is a transcription factor involved in early hematopoiesis and germline mutations predisposed to familial MDS and/or AML, such as RUNX1 and CEBPA, and germ line pathogenic variant (class 3 and 4) are transmitted dominantly.

We will present an update of the literature, which involved 4 distinct cohorts (NIH[1], UK[2], Germany[3] and France[4]) and numerous cases reports. The total reported cases since the initial description in 2011 involved about 300 cases worldwide. Several aspects should be emphasized.

First, the presentation of the diseases is extremely heterogeneous. Mild neutropenia, mild thrombocytopenia, aplastic anemia, pulmonary proteinosis, dermatologic lesions like profuse warts and panniculitis, lymphoedema, deafness, bacterial infections but also atypical mycobacterial have been described as part of the phenotype. Leukemia and myelodysplasia which frequently bore monosomy 7 or trisomy 18 can be observed. Overall, 91% of patients were symptomatic by the age of 40, with life-threatening manifestations. The unification of so many phenotypes under one gene reveals the complex regulation network linked to this transcription factor and suggests that more phenotypes may be identified.

Secondly, the mutational spectrum of *GATA2* is highly heterogeneous with no mutational hotspot. Molecular defects are distinct mutations and consist of amino-acid substitutions within the highly conserved C-terminal zinc finger domain, truncating mutations spread over the entire coding region, regulatory mutations in the 9.5-kb regulatory region, and, more rarely, whole-gene deletion. No correlation between the type or location of the *GATA2* mutation and the clinical phenotype has been established, with exception of an association between lymphedema and a nonsense and deletion mutation.

Thirdly, germline *GATA2* mutations are strongly linked with leukemia and about 80% of *GATA2* patients should be diagnosed before age of 40 years with malignancies. A revised IPSS score allowed classification between a stable disease and hematological transformation.

Fourtly, mortality in historical cohort is high (up to 45% by the age of 40 years). And so far, hematopoietic stem-cell transplantation (HSCT) remained the sole curative therapy in cases of infectious complications and clonal evolution. The timing of HSCT remains difficult to determine, but the earlier it was performed, the better is the outcome.

Reference List

1. Spinner MA, Sanchez LA, Hsu AP et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. Blood 2014;123:809-821.
2. Dickinson RE, Milne P, Jardine L et al. The evolution of cellular deficiency in GATA2 mutation. Blood 2014;123:863-874.
3. Wlodarski MW, Hirabayashi S, Pastor V et al. Prevalence, clinical characteristics and prognosis of GATA2-related myelodysplastic syndromes (MDS) in children and adolescents. Blood 2016;127:1387-1397.
4. Donadieu J, Lamant M, Fieschi C et al. Natural history of GATA2 deficiency in a survey of 79 French and Belgian patients. Haematologica 2018;103:1278-1287.

SS06-3

Roles of monosomy 7 and SAMD9/SAMD9L mutations in myeloid leukemogenesis

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Pediatric myelodysplastic syndrome (MDS) is a rare hematological disorder which account for less than 5% of hematological malignancies in children. *GATA2* and *SAMD9/SAMD9L* genes, the latter of which locates on the long arm of chromosome 7, have been recently shown to be mutated in the disease with or without preceding clinical manifestations. In addition, *GATA2* mutation in pediatric MDS is often accompanied by monosomy 7, thus functional analysis of candidate responsible genes on chromosome 7 including *SAMD9/SAMD9L* is underway in many laboratories.

More than 15 years ago, we undertook isolation of responsible genes from 21.7 Mb region within 7q21.2–7q31.1. Array CGH was performed on Juvenile Myelomonocytic Leukemia specimens that show no apparent deletion on chromosome 7 by conventional chromosome analysis, and we identified around 200Kb common micro deletionin 7q21.3. There are three genes in this region, namely *SAMD9, SAMD9L* and *MIKI(HEPACAM2)*, whose function had not been extensively investigated.

Among which, *SAMD9* and *SAMD9L* are derived from a common ancestral gene and encode proteins with 60% similarity. Both *SAMD9L* heterozygote and homozygote mice naturally developed MDS at advanced age. *SAMD9L* protein is localized in early endosomes, and mechanistically, the downregulation of the protein inhibits the fusion of early endosomes, which gives rise to sustained cytokine signals due to the delayed disassembly of cytokine receptors incorporated into the endosomal fraction. Based on these observations, we concluded *SAMD9/SAMD9L* as promising myeloid tumor suppressor genes.

SAMD9 was recently identified as the responsible gene for MIRAGE syndrome, which exhibitsvarious symptoms including myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy. *SAMD9L* missense mutation was also reported to cause Ataxia Pancytopenia syndrome, a disease showing ataxia due to the atrophy of cerebellum and pancytopenia that sometimes progress into MDS. The mutations in these syndromes are supposed to be gain-of-function mutations, in which expression of mutant protein suppresses growth of hematopoietic cells, and this is consistent with our view that *SAMD9/SAMD9L* are tumor suppressor genes. It is noteworthy that the loss of chromosome 7 occurs always in mutant-containing allele when cells acquire growth advantage to evolve into malignant clones.

In this presentation, I would like to discuss the recent findings on how monosomy 7 contributes to the development of myeloid malignancies.

SS07-1

EuroBloodNet: The rare anaemia disorders European epidemiological platform

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On the light of the Directive 2011/24/EU on patients' rights in crossborder healthcare and with the objective to concentrate highly specialized treatment, knowledge and resources, the European Reference Networks (ERNs) were defined based on Centres of Expertise recognized at the national level. The first 24 ERNs covering 24 different medical specialties started their activity in March 2017, the ERN-EuroBloodNet, www.eurobloodnet.com, is one of them.

This means that ERN-EuroBloodNet is a collaborative network of 66 medical centres from 15 countries; it brings together individuals and institutions committed to improve healthcare services in rare, oncological and non-oncological, hematologic diseases (RHD). Its main goal is to promote excellence for best health care in RHDs based on cutting-edge diagnosis procedures and therapies while removing barriers for making them available at the European level. In line with this goal, to foster European surveillance on RHDs, the creation of a European patient registry on rare haematological diseases has been supported. It'll promote access to clinical trials, facilitate the provision of –omics platforms and new technologies and foster research projects i.e. drug-gable targets identification, gene therapy and pathophysiology.

In line with the ERN-Eurobloodnet goal RADeep, Rare Anaemia Disorders European Epidemiological Platform, https://www.eurobloodnet.eu/radeep, is a joint venture conceived in the core of ERN-EuroBloodNet, as an umbrella for both new and already existing European patients' registries in Rare anaemia disorders (RADs). Ensuring interoperability with European structures fostering research, RADeep will allow mapping at the European level the diagnosis methods, demography, survival rate, main clinical features and treatments of those patients.

RADeep is implemented in different phases through disease specific arms i.e. pyruvate kinase deficiency, sickle cell disease, thalassaemia, etc. For each disease specific arm, a scientific committee will be established including experts on prevention, diagnosis and clinical care, researchers, and national coordinators for data collection, while the RADeep steering committee is in charge of all the common and transverse tasks for RADeep coordination and implementation of the different disease specific arms. The first phase of implementation has been designed for pyruvate kinase deficiency. Next phases will include sickle cell disease, thalassaemia, congenital dyserythropoietic anaemia and hereditary xerocytosis.

RADeep principle is to maximize public benefit from data on RAs opened-up through the platform with the only restriction needed to guarantee patient's rights and confidentially in agreement with EU regulations for cross-border sharing of clinical data. Accordingly, a legal frame for RADeep secure sharing and re-use of data on patients affected by RAs has been established from the outset.

A common data set between different specific disease arms is essential to gather harmonized and interoperable data from national registries. It will enable the trends and burden of the disease at the EU level to be analysed and to allow access to controlled data in the context of research projects. In liaisons with research community and industry for the re-use of data, the up-to-date and continuous mapping of services and patients across Europe that RADeep will allow to promote development of clinical trials and –OMICS based research on drug-able targets, especially in those countries with limited access to drugs. In addition, exploratory study population queries aiming at identify adequate target populations and amount of patients to be included in clinical trials will be feasible.

SS07-2

Clinical utility of high-throughput sequencing for the diagnosis of hereditary hemolytic anemia

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Hereditary hemolytic anemias (HHAs) are genetic diseases that present with anemia due to the increased destruction of circulating abnormal RBCs. The RBC abnormalities are classified into the three major disorders of membranopathies, hemoglobinopathies, and enzymopathies. Traditional diagnosis of HHA has been performed via a step-wise process combining clinical and laboratory findings. Nowadays, the etiology of IHA accounts for germline mutations of the responsible genes coding for the structural components of RBCs. Genetic testing has been used for the confirmatory diagnosis of HHA. Sanger sequencing is primarily performed in order to identify the causative mutations in single gene disorders. It is very lucky to identify mutation(s) in the disease-associated gene in the initial trial. If not, a gene-by-gene approach is required. In these cases, patients may undergo multiple rounds of testing for different genes, a pathway to diagnosis, which can be costly and time-consuming. Additionally, the usefulness of Sanger sequencing is limited for the diagnoses of complex, multi-gene disorders or those with locus heterogeneity. Recent advances in molecular technologies, including next-generation sequencing (NGS), inspire us to apply these technologies as a first-line approach for the identification of potential mutations and to determine the novel causative genes in patients with HHAs. NGS panels consisting of common disease-causing genes have been developed and applied to routine molecular diagnosis for undiagnosed IHA patients and their families. In particular, patients with the co-presence of membranopathy, enzymopathy, and/or hemoglobinopathy can be effectively diagnosed using this new technology. Causal gene identification can be deduced through an efficient and reliable strategy to impute and analyze NGS data. The expanded implementation of the new technology will increase our knowledge of the genetic and genomic differences among individuals, gradually leading to a shift in the clinical management and the therapeutic plan from a population-based approach to a personalized therapy for individual patients. In this talk, I review the concept and strategy for the genetic diagnosis of HHAs and provide an overview of the preparations for clinical applications of the new molecular technologies.

References

1. Kim Y, Park J, Kim M. Diagnostic approaches for inherited hemolytic anemia in the genetic era. Blood Res 2017;52:84-94.
2. Haley K. Congenital hemolytic anemia. Med Clin North Am 2017;101:361-74.
3. Park J, Deong DC, Yoo J et al. Mutational characteristics of ANK1 and SPTB genes in hereditary spherocytosis. Clin Genet 2016;90:69-78.
4. Agarwal AM, Nussenzveig RH, Reading NS et al. Clinical utility of next-generation sequencing in the diagnosis of hereditary haemolytic anemias. Br J Haematol 2016;174:806-14.
5. Lin PC, Chiou SS, Lin CY et al. Whole-exome sequencing for the genetic diagnosis of congenital red blood cell membrane disorders in Taiwan. Clin Chem Acta 2018;487:311-17.

SS07-3

The molecular spectrum of hemoglobinopathy; Thalassemia and Hb variants

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The hemoglobinopathies constitute the most common recessive monogenic disorders worldwide [1, 2]. Over 1700 different mutations have been reported which either affect the synthesis of globin chains (causing thalassemia) or alter the structure and properties of the hemoglobintetramer (hemoglobin variants or abnormal hemoglobins) [3]. Hemoglobinopathies are mostly autosomal recessive disorders and heterozygotes are symptom-free but present various hematological characteristics which are used for their identification in carrier screening programs. The homozygous states andcompound-heterozygous states result in four main groups of clinically significant conditions, each witha variable degree of phenotypic severity: the- thalassemias,-thalassemias, sickle cell syndromes, and Hb E syndromes [4]. The heterogeneity of the hemoglobinopathies is caused by the numerous types of thalassemia and abnormal hemoglobin genotypes which can interact when co-inherited, creating a complex range of hematological phenotypes that often cause difficultiesin interpretation. Moreover, some phenotypes can arise from several different genotypes, such as heterozygous alpha zero thalassemia and homozygous alpha plus thalassemia, and the genotypes cannot be distinguished by simple hematological parameters. Finally, the electrophoresis or chromatography techniques used to screen for abnormal hemoglobins only provide a presumed diagnosis for the variant, and further tests are required for a definitive diagnosis. Thus in many cases of carrier screening, an accurate diagnosis requires expertise in the interpretation of the hematological results and confirmation of the genotypes by DNA analysis [1].
The presentation will highlight some unexpected molecular mechanisms showing interesting genotype-phenotype correlations, either ameliorating or deteriorating the clinical presentation of hemoglobinopathy.

[1] John Old, Cornelis Harteveld, Carrier Screening for the Haemoglobinopathies: Past, Present and Future, https://www.lidsen.com/journals/genetics/genetics-01-03-005
[2] Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bulletin of the World Health Organization. 2008;86(6):480-7.
[3]Giardine B, Borg J, Viennas E, Pavlidis C, Moradkhani K, Joly P, et al. Updates of the HbVar database of human hemoglobin variants and thalassemia mutations. Nucleic acids research. 2014;42(Database issue):D1063-9.
[4] Weatherall DJ, Clegg JB. The thalassaemia syndromes: John Wiley & Sons; 2008.

SS08-1

Langerhans cell histiocytosis 2019: New insights and opportunities

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Children with Langerhans cell histiocytosis (LCH) develop granulomatous lesions with characteristic clonal CD207+ dendritic cells (DCs) that can arise as single lesions or life-threatening disseminated disease. Despite the wide range of clinical presentations, LCH lesions are histologically indistinguishable based on disease severity. Historically, incomplete understanding of pathogenic mechanisms has challenged development of optimal clinical strategies for patients with LCH. Recently, activating somatic mutations in MAPK pathway genes, most notably the *BRAFV600E* mutation, have been discovered in almost all cases of LCH. Further, the stage of myeloid differentiation in which the mutation arises defines the extent of disease. MAPK activation in LCH precursor cells drives myeloid differentiation, blocks migration, and inhibits apoptosis, resulting in accumulation of resilient pathologic DCs that recruit and activate T cells. These new insights support reclassification of LCH as a myeloid neoplastic disorder. Early phase trials in adults with LCH and the related Erdheim-Chester disease and emerging case studies demonstrate promising responses to MAPK pathway inhibitors, though potential for cure and safety in children remain to be defined. While we now understand the framework for mechanisms of LCH pathogenesis, continued research will uncover opportunities to identify additional targets and inform personalized therapeutic strategies based on cell of origin, somatic mutation, inherited risk factors and residual disease.

SS08-2

Treatment of hemophagocytic lymphohistiocytosis - today and tomorrow

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Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome with two major forms; primary (familial; FHL) and secondary (acquired) HLH (sHLH). FHL is due to genetic abberations causing defect lymphocyte cytotoxicity, while sHLH in adults commonly is triggered by infections malignancies and autoimmune conditions.

In FHL, functional studies of lymphocyte cytotoxicity are diagnostically valuable, In addition, >90% can get genetic diagnoses. Diagnosis of sHLH is less well defined, and the HLH-2004 diagnostic criteria are recommended but not validated.

Survival in FHL has increased dramatically with around 60% 5-yr survival in HLH-2004. This etoposide/dexamethasone combination is beneficial also in sHLH, including infection-associated HLH, such as severe EBV-HLH, and malignancy-associated HLH (in particular malignancy-triggered HLH). In autoimmune-associated HLH (macrophage activation syndrome, MAS-HLH), etoposide is often a second/third line option.

In severe presumed sHLH we suggest individualized etoposide/corticosteroid-based therapy with 1) etoposide typically once weekly, 2) weekly decisions on etoposide continuation, and 3) lower etoposide dose than in FHL, in particular in adolescents and adults (50-100 mg/m^2 according to age, severity of symptoms, and response to therapy). More intensive therapy, as the full HLH-94/HLH-2004 protocols, may be required in severe EBV-HLH. Biologically, etoposide results in selective deletion of activated T-cells and efficient suppression of inflammatory cytokine production.

Finally, there is still much to learn on sHLH diagnosis and treatment. In the future, we may combine etoposide/corticosteroid with biological treatment (as inhibitors to JAK1/JAK2, IL-1, and/or IFN-gamma) to increase efficacy and reduce side effects. Moreover, the role of SCT in refractory/relapsing sHLH needs to be determined.

SS08-3

Genetic studies on the Hemophagocytic Lymphohistiocytosis (HLH) in Korea

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The first study on the genotype of Korean patients with HLH was carried out in 2009, and *UNC13D* was found to be the predominant causative gene with recurrent splicing mutations. Further study using haplotype analyses identified significantly shared haplotypes in 2 predominant UNC13D mutations, indicating the presence of founder effect which explains the unusual predominance of FHL3 in Korea.
After the identification of *STXBP2* mutation in 2009, *STXBP2* was investigated by conventional sequencing analysis in 50Korean patients who lacked mutations in *PRF1*, *UNC13D*, or *STX11*. One patient with 2 novel mutations of *STXBP2* was found, and the prevalence of FHL5 was estimated to be ~1% in Korea.
Recently the genotype of patients in Korean HLH Registry with no definite HLH-associated gene mutations were reanalyzed using HLH-related 14-gene targeted panel test. This revealed 26 patients (36.1%) of them having at least 1 HLH-associated mutation. Among them, 10 patients (13.9%) were genetically confirmed as pHLH; 1 FHL2, 1 FHL3, 1 XLP type 1, 1 XLP type 2, and 6 with heterozygous mutations in 2 HLH-associated genes (3 *AP3B1/LYST*, 1 *PRF1/BLOC1S6*, 1 *UNC13D/ITK*, and 1 *STX11/SLC7A7*). These findings suggest the need for comprehensive genetic testing for the accurate diagnosis and proper treatment of pHLH.
Recent nationwide retrospective survey on a total of 48 pHLH patients with proven HLH-associated gene mutations revealed *7 PRF1*(14.3%), *36 UNC13D*(75.5%), 1 *STX11*, 2 *STXBP2*, and 2 *SH2D*1A mutations. Median age at diagnosis was 3.2 months, and 75.5% of the patients were diagnosed before 1 year of age. There was no statistical difference in the clinical presentations and laboratory findings at diagnosis among genotype groups. Eight patients died before hematopoietic stem cell transplantation (HSCT). The 5-yr overall survival rate of 36 transplanted patients was 74.8%, whereas that of 13 who didn't receive HSCT was 26.9% (P<0.001). Four patients are alive in complete remission without HSCT for a median duration of 10 months (range 5.7~20.1 months). There was no difference in overall survival rate according to genotype. Among the 25 FHL3 patients, 5 with biallelic splicing mutations showed significantly lower overall survival rate (20% vs. 71.1%, P=0.012) and lower reactivation free survival rates (0% vs. 65.7%;P=0.011) compared to FHL3 patients with other types of mutation.

SS09-1

Deeplearning for CRISPR-Cpf1 research

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Targeted genome editing using CRISPR-Cas (clustered, regularly interspaced, short palindromic repeats and CRISPR-associated proteins) system has rapidly become a mainstream method in molecular biology. Cpf1, a recently reported effector endonuclease protein of class 2 CRISPR-Cas system, has several different characteristics from the predominant Cas9 nuclease. Although Cpf1 has broadened our options to efficiently modify genes in various species and cell types, we still have limited knowledge on Cpf1, especially regarding its target sequence dependent activity profiles. Determination of CRISPR nuclease activities is one of the key initial steps for genome editing. Several computational approaches have been proposed for the in silico prediction of CRISPR nuclease activities. However, they rely on manual feature extraction, which inevitably limits the efficiency, robustness, and generalization performance. To address the limitations of existing approaches, in this talk I will present an end-to-end deep learning framework for CRISPR-Cpf1 guide RNA activity prediction, dubbed as DeepCpf1. Leveraged by (1) a convolutional neural network for feature learning from target sequence composition and (2) multi-modal architecture for seamless integration of an epigenetic factor (i.e., chromatin accessibility), the proposed method significantly outperforms the conventional approaches with an unprecedented level of high accuracy.

This presentation is based on the following publication:
Hui Kwon Kim#, Seonwoo Min#, Myungjae Song, Soobin Jung, Jae Woo Choi, Younggwang Kim, Sangeun Lee, Sungroh Yoon*, Hyongbum (Henry) Kim*, Deep learning improves prediction of CRISPR–Cpf1 guide RNA activity, Nature Biotechnology, vol. 36, no. 3, pp. 239-241, March 2018 [#: co-first authors; *: co-corresponding authors].

SS09-2

Precision dinner: Genomes and health records

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Did personalized genome sequencing help me? 'Fast caffeine and alcohol metabolizer' was not impressive. I found a LoF (Loss of Function) mutation in Coagulation Factor X (F10).It was fortunate that it was heterozygous, as homozygosity might have prevented my birth. My factor assay revealed that my F10 functional activity was at 67%, which is below normal, along with delayed BT, PT and aPTT. Although I am a medically proven F10 deficiency patient, I have no bleeding tendency. Perhaps I am more evolved in this era of hypercoagulability due to our civilization progressing faster than evolution. The problem is that tens of millions of people are prescribed anticoagulants to prevent cerebrovascular accident. Equipped with the knowledge of my genome and its mutations, I know that I should not take anticoagulants. However, the main indication of F10 inhibitors has nothing to do with coagulopathy nor clotting. The prescription of anticoagulants for atrial fibrillation is common, and doctors without the knowledge that I have a LoF variant that would make my response to the drug dangerous would not hesitate to prescribe them to me, or to other patients like me. There is no rationale for prescribing an inhibitor for a target that has already been inhibited by LoF variants. More than 300,000 Koreans (1/167) are at risk due to this specific mutation. Xantine Dehydrogenase (XDH) inhibitors are treatments of choice for gout but may be useless for me due to another LoF variant present on my XDH. Distal tubule reuptake inhibitors may be alternatives for the one in ten patients with this variant, such as myself. LoF's can sometimes protect us in mysterious ways, as well. Despite my very mild symptoms, I am self-medicating myself with an endogenous substance with no metabolite nor side effects. I will eventually lose my sight due to a LCAT deficiency, which is causing cholesterol deposits in my lens, and a GALK1 deficiency which is causing cataracts. I have to enjoy my current sight and see all the beautiful things I can on Earth. This kind of information is not outlined in current medical textbooks. Conventional medicine focuses on the average, and considers us all as average folks. Mere "idiosyncrasies" cannot prevent doctors from prescribing potentially harmful medications without guilty in virtue of medial utilitarianism. Will this approach still hold in this era of digital genomes? We all are minorities in some conditions and against some drugs. One does not fit all, we are all different in some aspects. Medicine has not just been fully personalized yet. Shall we take a walk for precision dinner?

SS09-3

Connected health and wellness journey

Jack Ahn

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IoT, AI, 5G, Digital Health – Much about them have been discussed, reported, demonstrated, and commercialized. With the advent of these technologies, one common thread of user scenarios, namely connected health, has rapidly emerged over a short period of time.
Moreover, IoT, AI, 5G, Digital Health are further enabling the new ecosystem to thrive as it explores more reliable ways to connect and provide seamless user experience across disparate systems, devices, and processes.
In its Progressions series, EY posits that "health is being reimagined as a result of scientific and technological change"[1]. The mentioned scientific and technological change also enables technology providers to reimagine how the health and wellness related products and services are delivered to consumers. In fact, to the technology providers, consumers are no longer mere endpoints of their products and services. Rather, consumers are very much in the center of the new ecosystem more so for the health and wellness related products and services.
Each of us embarks on a very unique health and wellness journey. The advancement in technologies, along with the confluence of a few other factors such as user acceptance, economics, legislative and regulatory changes, and 360° data, allows the technology providers to be an authentic companion throughout each individual's unique health and wellness journey, providing meaningful insights and individualized services at the right time, to the right channel or medium.
"Connected Health and Wellness Journey" discusses a number of health and wellness related user scenarios in the context of these technologies while exploring what they are and what challenges may lie ahead.

[1] Life Sciences 4.0, Ernst & Young Progressions series, ey.com/lifesciences

SS10-1

Genomics of core-binding factor AML

Nicolas Duployez

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RUNX1 and *CBFB* encode subunits of the core binding factor (CBF), a heterodimeric transcription factor required for the establishment of definitive hematopoiesis. Acute myeloid leukemia (AML) with t(8;21)/*RUNX1-RUNX1T1* fusion and AML with inv(16)/*CBFB-MYH11* fusion, reported together as CBF AML, account for approximately 25% of pediatric and 15% of adult de novo AML patients. Since the first description of t(8;21) and inv(16) AML in 1973 and 1983 respectively, a great deal has been learned about the molecular consequences of both rearrangements. Experience from murine models as well as clinical observations have demonstrated that the CBF disruption alone is insufficient to induce AML. CBF AML is largely considered as a model of multistep leukemogenes is requiring additional genetic aberrations. Recently, our group reported the comprehensive genetic profiling in CBF AML patients enrolled in the French trials ELAM02 (0-18 years) and CBF2006 (18-60 years) using both high-throughput sequencing and single nucleotide polymorphism-array1,2. We demonstrated that mutations in genes activating kinase signaling were frequent in both subtypes, as previously described by others. Co-occurrence of multiples signaling lesions in independent subclones, named clonal interference, was frequent and conveyed inferior event-free survival[3]. By contrast, we found mutations in genes encoding chromatin modifiers or members of the cohesin complex with high frequencies in t(8;21) AML (41% and 18% respectively) while they were nearly absent in inv(16) AML1. Interestingly, such mutations were associated with a higher cumulative incidence of relapse in patients with signaling mutations suggesting synergic cooperation between these events. Other events included *ZBTB7A* and *DHX15* mutations in t(8;21) AML (20% and 6% respectively), *FOXP1* deletions or truncating mutations in inv(16) AML (7%) and CCDC26 disruption as a possible new lesion associated with aberrant TK signaling in this particular subtype of leukemia (4.5% of CBF AML)2. Overall, these findings suggest important pathways that distinguish t(8;21) AML from inv(16) AML leukemogenesis with potential biological and clinical significance4.

1. Duployez N, Marceau-Renaut A, Boissel N, et al. Comprehensive mutational profiling of core binding factor acute myeloid leukemia. Blood 2016;127(20):2451–2459.
2. Duployez N, Boudry-Labis E, Roumier C, et al. SNP-array lesions in core binding factor acute myeloid leukemia. Oncotarget 2018;9(5):6478–6489.
3. Itzykson R, Duployez N, Fasan A, et al. Clonal interference of signaling mutations holds prognostic relevance in core binding factor acute myeloid leukemia. Blood 2018;blood-2018-03-837781.
4. Kuykendall A, Duployez N, Boissel N, Lancet JE, Welch JS. Acute Myeloid Leukemia: The Good, the Bad, and the Ugly. Am Soc Clin Oncol Educ Book 2018;(38):555–573.

SS10-2

Precision medicine in AML in the era of novel agents

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For decades, acute myeloid leukemia (AML) has lagged behind other hematological malignancies with respect to improvements in treatments and outcomes. The majority of AML patients relapse and die from their disease despite initial remission, and long-term survival for older patients is rare. During the last few years, increased understanding of the pathobiology of AML has led to refinements in prognostic models, as well as the developed of targeted therapies. The application of next-generation sequencing (NGS) technologies to identify somatic mutations is now part of the standard of care for both newly diagnosed and relapsed AML patients. The presence of several mutations has been incorporated, along with cytogenetics, into the European LeukemiaNet and other prognostic scoring systems for AML. Also, targeted inhibitors of FLT3 (midostaurin, gilteritinib), IDH1 (ivosidenib) and IDH2 (enasidenib) have become commercially available in the United States and are pending approval in other parts of the world. The term "precision medicine" has been increasingly applied in AML as risk-adapted and biology-adapted treatments have evolved. In addition to molecularly targeted approaches, other subgroups of AML patients have been identified, including those with secondary AML, who may benefit from a liposomal combination of cytarabine and daunorubicin (CPX-351), and those with core-binding factor AML, who may benefit from the addition of the calicheamicin-conjugated CD33 antibody gemtuzumab ozogamicin to standard chemotherapy. Finally, the addition of the BLC-2 inhibitor venetoclax to hypomethylating agents or low-dose cytarabine has emerged as the new standard of care for older patients with AML. Early data suggest that venetoclax combinations have significant activity across molecular and cytogenetic subgroups of patients, but more data are needed to optimize its use. Improved techniques of NGS and flow cytometry have resulted in rapid evolution of the field of measurable residual disease (MRD) in AML. MRD-negative complete remission is the goal of AML therapy and significant work is underway to determine which of the novel agents and combinations will result in the highest rates of MRD negativity. A major challenge for the next few years will be to determine a) how to best "mix and match" the agents described above, as well as other emerging novel agents, and b) how to select which AML patients should undergo allogeneic stem cell transplantation in the era of novel therapeutics.

SS10-3

Incorporation of molecular assessments in risk stratification for myelodysplastic syndromes: Ready for prime time?

Amer M. Zeidan

Yale University, USA

Myelodysplastic syndromes (MDS) are characterized by a high degree of heterogeneity in the clinical course, and the outcomes of individual patients are very variable. Dr. Zeidan will overview the epidemiology and the diagnostic approach for MDS. As the management strategies can range all the way from observation to recommendation of allogeneic hematopoietic stem cell transplantation, accurate risk stratification is very important in MDS. Dr. Zeidan will discuss the approach for risk stratification using clinical, pathological, and cytogenetic data that are used in the most widely used prognostic instruments. He will review the progress achieved so far in understanding the molecular pathogenesis of MDS and how does the better understanding of the genetic landscape of MDS is offering opportunities to improve the diagnostic and prognostic evaluation of MDS as well as unravel novel targets for therapeutic interventions. Dr. Zeidan will final discuss why the incorporation of molecular assessment in routine clinical practice remains challenging and discuss future directions for improvement of individualized outcome prediction.

SS11-1

Is chronic myeloid leukemia a single hit disorder?: Evidence from next-generation sequencing data

Dennis Kim

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Chronic myeloid leukemia (CML) is a clonal disease of the hematopoietic stem cells (HSCs) due to the occurrence of the BCR-ABL1 gene rearrangement, which is traditionally thought to be a single hit event in the leukemogenesis of CML. However, there are many evidence suggesting that it is not the case: 1) transient detection of BCR-ABL1 fusion transcripts was reported repeatedly in healthy individual, which disappeared 6-12 months after with repeated test, 2) Transduction of *BCR-ABL1* gene rearrangement itself is not enough to establish CML disorder in mouse models.

Recent advances in next-generation sequencing (NGS) has revealed that the presence of clonal hematopoiesis of indeterminate potential (CHIP) in diverse subtypes of myeloid disorders. It was thought to be very important in the development of pre-leukemic and leukemic clone in myeloid neoplasms. However, it has never been extensively investigated in CML. Our studies(Blood 2017 & Leuk Res 2017) reported that 1) 37% of CML patients carries somatic mutation during course of tyrosine kinase inhibitor (TKI) therapy from diagnosis of CML; 2) those carrying mutation in epigenetic regulation pathways such as *ASXL1, DNMT3A or TET2*, has a lower response rate and poor long-term outcomes following imatinib therapy; 3) 10-20% of CML patients carries mutation in T-cell fraction, suggesting the involvement of CHIP in the leukemogenesis of CML.

In my presentation, recent advances in somatic mutation profiles and genomics will be discussed in the context of its role as a biomarker for response to TKI therapy. Also, clonal evolution of therapy-resistant dormant clones will be discussed. Integrative overview on application of precision medicine in future CML management will be discussed.

SS11-2

NGS-based ABL1 kinase domain mutation detection

Simona Soverini

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Despite the striking efficacy of tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML), a proportion of patients do not achieve an optimal response and require treatment optimization. To this purpose, three generations of molecules are nowadays available: imatinib (first generation) ; dasatinib, nilotinib and bosutinib (second generation) ; ponatinib (third generation). A variety of mechanisms may underlie lack or loss of response to TKIs, but acquisition of point mutations in the BCR-ABL1 kinase domain (KD) is, at present, the only actionable one4. Each first- and second-generation TKI is known to have a well-defined spectrum of sensitive and resistant mutants. Failure to turn off BCR-ABL1 activity and achieve a rapid and deep clearance of mutant cells not only would result in unsatisfactory clinical response, but would also fuel the acquisition of additional mutations. This, in some patients, would result in a clonal complexity (the so called 'compound mutants') that has been shown to be much more difficult to address therapeutically. Screening for mutations is thus recommended both by the European LeukemiaNet (ELN) and by the National Comprehensive Cancer Network (NCCN) in case of failure and warning, that is, whenever a change of therapy is necessary or is to be considered. Capillary (Sanger) sequencing is the current gold standard for diagnostic BCR-ABL1 KD mutation screening. In recent years, however, next-generation sequencing (NGS) has entered routine diagnostic workflows in hematology and oncology as it has proven a powerful and robust technology. In my presentation, I will review the retrospective studies on the use of NGS for BCR-ABL1 KD mutation screening and I will present the results of the first, prospective study ('NEXT-in-CML').

SS11-3

Precision medicine and immunity in CML

Satu Mustjoki

Hematology Research Unit Helsinki, Department of Clinical Chemistry and Hematology, University of Helsinki and Helsinki University Hospital Comprehensive Cancer Center, Finland

The detailed knowledge of molecular pathobiology behind hematological malignancies has pioneered cancer research and resulted in new effective and non-toxic targeted therapies in selected disorders such as tyrosine kinase inhibitor (TKI) therapy in chronic myeloid leukemia (CML). However, persistent minimal residual disease (MRD) due to inherent resistance of the leukemic stem cells remains challenging, and in the majority of the patients the therapy is still not considered curative. Interestingly though, recent results suggest that 40-50% of optimally responding CML patients are able to stop the treatment without disease relapse. Our recent results suggest that the active immune system is crucial when we aim for the curative treatment outcome. Patients who are able to stop the anti-cancer treatment (TKI therapy) and stay in remission have higher number of NK-cells and also the function of the NK-cells has shown to be better than in patients who relapse after therapy discontinuation. However, the immune system is complex and the role of other immune cell subsets is still unclear. In addition, at the time of diagnosis more immunosuppressive environment exists in the CML bone marrow compared to normal controls and this is partly reverted during TKI therapy.

Although with the TKI therapy, the life expectancy of chronic phase CML patients is close to age matched healthy controls, the treatment results in advanced phase CML patients are not optimal, and many patients are still dying due to their disease. Novel sequencing and high-throughput drug screening techniques allow more detailed understanding of the biological heterogeneity of leukemia cells and provide novel therapy targets. Already now, important driver mutations in addition to *BCR-ABL1* fusion gene have been discovered both in advanced phase and chronic phase CML patients. Future studies will show, whether additional genetic analysis will be included in the routine diagnostic set-up in CML to allow individualized treatment tailoring.

SS12-1

Treatment of childhood ALL with IKZF1 deletion (Malaysia-Singapore ALL 2010 Study)

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Mullighan et al found that deletion of *IKZF1* gene (*IKZF1*^{del}), which encodes for the lymphoid transcription protein IKAROS, confers a significantly worse outcome for ALL. *IKZF1*^{del} is seen in 2 out of 3 cases of BCR-ABL1-positive and ~15% of BCR-ABL1-negative childhood ALL. The availability of the multiplex ligation-dependent probe amplification (MLPA) assay allows for a rapid, affordable method to determine *IKZF1*^{del} status, enabling its incorporation into contemporary ALL trials.

Although *IKZF1*^{del} confers a higher risk of relapse in childhood B-lymphoblastic leukemia (B-ALL), it is uncertain whether treatment intensification will reverse this risk and improve outcome. Clappieret al in the retrospective analysis of BFM-based EORTC protocol 58951 study, reported that vincristine-dexamethasone/prednisolone pulses during maintenance therapy reduced the cumulative risk of relapse in *IKZF1*^{del} patients in average risk BCR-ABL1-negative patients. However, Hinze et al reported that similar vincristine/dexamethasone pulses in ALL BFM-95 study actually worsen the outcome. Specifically, patients with *IKZF1*^{del} had 5-yr EFS 57% with pulses compared to 74% without pulse due to increased relapse and non-relapse mortality.

Malaysia-Singapore ALL 2010 (MS2010) study prospectively upgraded the risk assignment of patients with *IKZF1*^{del} to the next higher level and added imatinib to all patients with BCR-ABL1 fusion. A total of 823 B-ALL patients treated on MS2003 (n=507) and MS2010 (n=316) were screened for *IKZF1*^{del} using multiplex ligation-dependent probe amplification (MLPA) assay.

In MS2003 where *IKZF1*^{del} was not used in risk assignment, *IKZF1*^{del} conferred a significantly higher 5-yr CIR (30.4% vs. 8.1%, p=8.7×10-^{7}), particularly in intermediate risk (IR) group who lacked high-risk features (25.0% vs. 7.5%, p=.01). For BCR-ABL1-negative patients, *IKZF1*^{del} conferred a higher 5-yr CIR (20.5% vs 8.0%, p=.01). In MS2010 the 5-yr CIR of patients with *IKZF1*^{del} significantly dropped to 13.5% (p=.05) and no longer showed a significant difference in BCR-ABL1-negative patients (11.4% vs. 4.4%, p=.09). The 5-yr overall survival (OS) for patients with *IKZF1*^{del} improved from 69.6% in MS2003 to 91.6% in MS2010 (p=.007).

The Ma-Spore ALL 2010 study showed that intensifying therapy for childhood B-ALL with *IKZF1*^{del} significantly reduced the risk of relapse and improved overall survival. Incorporating *IKZF1* deletion screening significantly improved treatment outcome in contemporary ALL therapy.

SS12-2

Multicenter clinical trial of pediatric acute lymphoblastic leukemia in China: CCLG 2008 Study

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Acute lymphoblastic leukemia (ALL) is the commonest childhood malignancy and the treatment outcome has improved to about 90% long term survival in most developed countries. China had not started any large scale clinical trials for childhood ALL before 2000 because of medical and economic constraints. Small scale multicenter clinical trial firstly started in south China on a city base in Guangzhou in early 2000. The first large scale multicenter study across the country started in 2008, the Chinese Children Leukemia Group (CCLG) ALL 2008 Study. A total of 2231 patients were recruited from 10 hospitals in 8 cities in China from April 2008 to December 2012. Patients were treated with a modified BFM based protocol, and high risk patients received more intensive maintenance treatment. Cranial irradiation was not applied except central nervous system (CNS) leukemia at diagnosis. Two hospitals piloted minimal residual disease (MRD) monitoring with treatment adjustment. Complete remission (CR) was achieved in 94.1% of evaluable patients. Induction death happened in 1.6% and another 2.9% died due to non-relapse causes after achieving CR, and 4% of patients abandoned treatment. At 5 years, overall survival (OS) and event-free survival (EFS) of the whole group was 85.2% and 79.9%, respectively. The cumulative incidence of relapse (CIR) was 15.3% at 5 years. The outcome of MRD group is better than the non-MRD group (5y-EFS: 82.4% vs 78.3%, $P = 0.038$; 5y-CIR: 10.7% vs 18.0%, $P < 0.001$). With the good result of this multicenter clinical trial in China, further multicenter clinical trials are now ongoing. The two largest clinical trials are China Children Cancer Group (CCCG) 2015 ALL Study and the South China Children Cancer Group (SCCCG) 2016 ALL Study, both are targeting at 5000 subject recruitment. MRD by Flow cytometry is now becoming a standard monitoring tool for ALL studies in China. There are still areas for improvement including trial structure, conduct of clinical trials, shortage of essential medications and long term follow-up of patients.

SS12-3

Recent updates of prospective trials for ALL in Japan

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Before 2003, there were four study groups for pediatric leukemia in Japan. These were formed into one group, JPLSG, in 2003. We started a trial for infant ALL, MLL03, in 2003, followed by a trial for Ph+ ALL, Ph04, in 2004. In 2011, a trial for T-ALL was opened and, finally a trial for BCP-ALL, ALL B12, was opened in 2012. This was largest leukemia trial in Japan and recruited 1,816 patients and closed in 2017. The results of T11 / B12 have not been reported yet, but these seem to be OK. Currently new trials, T19 and B19 are going to be opened this year. One of aims of B19 trial is the optimization of duration of maintenance therapy. Based on the results of the previous study of the Tokyo Children Cancer Study Group, maintenance treatment periods of 18, 24, and 30 months are randomly tested in certain parts of the patient. Another challenge of B19 is, with collaboration with adult study group, extension of the upper limit of age to 65 years. Blinatumomab is going to be incorporated into treatment for patients with high risk features. Simultaneously, trials for infant ALL and Ph+ ALL are going to be open this year.

SS13-1

Pathogenesis of EBV-associated lymphoproliferative disorders

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Nagoya University Graduate School of Medicine, Japan

Ubiquitous Epstein-Barr virus (EBV) infects lymphocytes, and is associated with various lymphoid malignancies. Since EBV preferentially infects B cells, it has a strong association with B-lineage lymphoproliferative diseases or lymphomas such as post-transplant lymphoproliferative disorder, Burkitt lymphoma, and EBV-positive diffuse large B-cell lymphoma (DLBCL) of the elderly. However, it also transforms T- or natural killer (NK)-lineage cells at lesser frequency and is associated with T or NK cell malignancies such as extranodal NK/T cell lymphoma, nasal type (ENKTL) and aggressive NK cell leukemia (ANKL). Chronic active EBV infection (CAEBV), which occurs most often in children and young adults in East Asia, is classified as one of EBV-positive T/NK-cell lymphoproliferative diseases in the 2017 WHO lymphoma classification. CAEBV has an indolent clinical course with highly variable clinical presentations, including fever, lymphadenopathy, hepatosplenomegaly, hypersensitivity to mosquito bites, and skin lesions resembling hydroa vacciniforme. Patients with CAEBV often progress into overt lymphoma (ENKTL) or leukemia (ANKL) in the long-standing clinical course. EBV's transforming capacity in B cells is well characterized, but the molecular pathogenesis of clonal expansion caused by EBV in T/NK cells has not yet been clarified. To clarify the neoplastic nature and pathogenesis of CAEBV, we performed comprehensive genetic analysis in patients with CAEBV. The study revealed that somatic driver mutations (DDX3X and KMT2D) were found in EBV-infected cells, suggesting a unique role of these mutations in neoplastic proliferation of EBV-infected cells. Interestingly, the EBV genome harbored frequent intragenic deletions that were common in various EBV-associated lymphomas, such as DLBCL and ENKTL. Our findings highlight a pathogenic link between intragenic EBV deletions and EBV-associated lymphomagenesis.

SS13-2

Molecular understanding of peripheral T-cell lymphoma

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Peripheral T-cell lymphoma (PTCL) is a complex group of diseases with great heterogeneity in morphology, immunophenotypic characteristics, and clinical features. They represent ~12-15% of all Non-Hodgkin lymphoma (NHL) in the western world with at least 29 distinct entities defined in current WHO classification. PTCL in general have dismal prognosis compared to their B-cell counterparts, partly due to lack of understanding of complex T-cell immunobiology with numerous functional subsets and plasticity. PTCLs are currently diagnosed using a complex and often fragmented combination of clinical, morphological and molecular analyses. More than one-third of these cases cannot be classified further and are designated as **PTCL-not otherwise specified (PTCL-NOS)**. Through extensive gene expression profiling (GEP) studies, robust gene signatures for molecular classification have been identified, which also reflect the pathobiology and demonstrated cell-of- origin of major entities. Remarkably, two novel major molecular subgroups in PTCL-NOS with distinct clinical and biological features were delineated. One subgroup (PTCL-GATA3) is characterized by high expression of GATA3, a master regulator of T helper2 (TH2) differentiation, and its target genes, whereas the other subgroup (PTCL-TBX21) is characterized by high expression of TBX21, master regulator of TH1 differentiation, and its target genes, with the former showing significantly worse clinical outcome. The genetic characterization show distinct patterns of chromosomal copy number abnormalities (CNAs), substantiated by significant enrichment of distinct oncogenic pathways in these subgroups. The comprehensive genomic characterization using next generation sequencing techniques led to identification of recurrent mutation targeting epigenome (TET2, IDH2 and DNMT3A), T-cell activation, and oncogenic pathways (STAT3, NF-kB) in multiple PTCL entities. Such functional integrative functional genomic approaches indicated two major cooperative oncogenic mechanisms in Angioimmunoblastic T-cell lymphoma (AITL) with initial epigenomic dysregulation in CD4+ T cells, followed by aberrant activation of T-cell receptor (TCR) signaling. In summary, genomic characterization has deciphered several novel insights at the genetic and molecular level, which may eventually lead to identify better treatment options. These genetic events are now being explored in mouse models and could provide a deeper understanding of the disease pathogenesis and potential therapeutic targets in future investigation.

SS13-3

Clinical application of cell-free DNA in lymphoma

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Targeted deep sequencing of cell-free DNA was recently used to investigate tumor mutations in relatively broad genomic regions including many cancer-associated target genes in a particular subtype of non-Hodgkin lymphomas (NHLs), such as diffuse large B cell lymphoma and angioimmunoblastic T cell lymphoma. However, the immense heterogeneity of genetic landscapes across lymphoma subtypes with a limited number of commonly and frequently mutated genes poise a hurdle to design a gene panel applicable for diverse subtypes of NHLs. Since 2017, our institute has performed a prospective single-center cohort study for T-cell lymphoma to analyze the feasibility and clinical relevance of circulating cell-free DNA. We designed a panel targeting 66 genes associated with NHLs and performed targeted deep sequencing to analyze circulating tumor DNA in plasma cell-free DNA samples from patients with NHLs across a wide variety of subtypes. In this session, I introduce the progress of our studies and the results of interim analyses.

SS14-1

Droplet microfluidics in antibody discovery, immune repertoire sequencing and personalized cancer therapy

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We have developed fully integrated droplet-based microfluidic platforms for the screening of therapeutic antibodies[1, 2]. In these systems tiny aqueous droplets (picoliter volumes) surrounded by oil serve as independent assay vessels. The technology allows the direct screening of several hundred thousand primary, non-immortalized murine or even human B-cells for the secretion of antibodies that do not just bind to a drug target, but functionally inhibit it. Furthermore, the technology can be used for genotypic and phenotypic characterization of blood cells at the single cell level[3]. We believe this opens the way for many new approaches in drug discovery, including personalized immunotherapy or the use of antibodies to control cellular pathways at will.
In parallel to this we have developed screening platforms enabling rapid identification of optimal drug cocktails for personalized cancer therapy[4]. Results are available within 24h after surgery at consumables costs of less than 150 US$ per screen. The power of this platform has been demonstrated using cancer cell lines, mouse models and even human tumor biopsies. We now envisage first clinical trials and assess further application fields, e.g. for the efficient stratification of patients for immunotherapies.

1. B. El Debs, R. Utharala, I. V. Balyasnikova, A. D. Griffiths and C. A. Merten, Proc Natl Acad Sci U S A, 2012, 109, 11570-11575.
2. N. Shembekar, H. Hu, D. Eustace and C. A. Merten, Cell Rep, 22, 2206-2215.
3. N. Shembekar, C. Chaipan, R. Utharala and C. A. Merten, Lab on a Chip, 2016, 16, 1314-1331.
4. F. Eduati, R. Utharala, D. Madhavan, U. P. Neumann, T. Longerich, T. Cramer, J. Saez-Rodriguez and C. A. Merten, Nat Commun, 2018, 9, 2434.

SS14-2

Applications of single-cell mass cytometry in hematologic malignancies

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Mass cytometry is a novel technology similar to flow cytometry in which antigen-specific antibodies are tagged with heavy metal molecules, rather than fluorophores, and then detected with time of flight mass spectrometry. This enables measurement of up to 50 simultaneous parameters with no auto-fluorescent background and little or no spillover or required compensation. Mass cytometry has tremendous potential for the analysis of highly complex clinical samples, particularly in the diagnosis and monitoring of hematologic malignancies. This presentation will review the basic workings of a mass cytometer, provide an introduction to the bioinformatic algorithms commonly used to analyze the data generated, and the new types of experiments that are enabled by the technology. Examples of potential applications for the use of mass cytometry in the characterization of human malignancies will be presented. Finally, some of the unique challenges associated with the clinical use of mass cytometry will be discussed.

SS14-3

Prediction of acute myeloid leukemia risk in healthy individuals

Liran I. Shlush

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Acute myeloid leukemia (AML) is a devastating disease especially among the elderly. Most AML cases present after a chronic latent phase of age-related clonal hematopoiesis (ARCH), yet while the prevalence of ARCH among the elderly is high (~30%), AML remains a rare event. Recently, we succeeded to predict pre-AML cases seven years prior to diagnosis with a sensitivity of ~40% and a specificity of 98.5%. The most accurate early diagnosis was for cases with mutations in the spliceosome. For these patients we have several drugs that might be useful in AML prevention and clinica trials for AML prevention are under preparation. The future of AML prevention will rely on continues improvement in sensitivity and specificity of the careening assays that will take into account not just somatic mutation data. Future studies on AML prevention should focus not only on the intrinsic properties of the preleukemic mutations but also on the differentiation problem and the changes in the bone marrow microenviroment.

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LS01

Treatment free remission in CML: Promise and challenges

Adam Mead

University of Oxford, UK

Tyrosine kinase inhibitors (TKI) have revolutionised the treatment of patients with chronic myeloid leukaemia (CML). Indeed, recent studies now suggest that survival of patients with CML is similar to that of the normal population. However, challenges remain in the management of CML. Although TKIs are highly-effective treatments, until recently the conventional wisdom was that therapy needed to be 'lifelong', an important consideration as TKIs are not without side effects. Over recent years, large prospective clinical trials, including with the 2nd generation TKI nilotinib, have shown that it is possible to successfully stop TKI therapy without disease recurrence in approximately half of patients achieving sustained a deep molecular remission (DMR), leading to nilotinib receiving the first licence for 'treatment-free remission' (TFR). Today, one of the key goals of therapy is now to achieve deep molecular remission so that TFR and 'cure' might be a reality for many patients in routine clinical practice. However, a number of challenges remain in the development of optimal approaches to maximize the opportunity for TFR across CML patients. In this symposium, Professor Mead will review recent findings from TFR studies, discuss strategies to maximise DMR and discuss new laboratory research approaches that are improving our understanding of treatment resistant CML stem cells so that possibility of successful TFR might be further improved.

LS02

Optimal treatment sequencing for patients with relapsed/refractory multiple myeloma

Ajai Chari

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LS03

Current issues in the treatment of B-cell lymphoma

Seok Jin Kim

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Rituximab, a chimeric anti-CD20 monoclonal antibody improved the treatment outcome of patients with various CD20-expressing B-cell lymphomas, including indolent and aggressive forms of B-cell non-Hodgkin lymphoma. Thus, the intravenous administration of rituximab has revolutionized the treatment of B-cell lymphomas and has become a standard component of care for B-cell lymphomas, including follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia, and mantle cell lymphoma. The proven clinical efficacy of rituximab has led to the development of other anti-CD20 monoclonal antibodies such as obinutuzumab as well as other monoclonal antibodies targeting different antigens of B-cell such as polatuzumab vedotin. Furthermore, the development of a subcutaneous formulation of rituximab has changed the pattern of treatment in clinical practice, thus it has been approved both in the EU and in the USA for the treatment of B-cell lymphomas. In this session, I address current issues related with the treatment of B-cell lymphoma, and introduce the progress of recent studies with novel antibodies targeting B-cells.

LS04

Advances of CML management and the prospects for the future

Susanne Saußele

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With the introduction of tyrosine kinase inhibitors (TKI) to CML treatment, the disease has changed from a fatal one to a chronic disease in the majority of patients. The life expectancy of patients with CML receiving TKI treatment is nearly comparable now to that of the general population. A significant proportion of patients with CML in chronic phase achieve a deep molecular response determined via BCR-ABL1 transcript levels. Treatment strategies not only comprise overall survival anymore but achievement of deep molecular remission (DMR) with even the possibility of successful attempt to stop therapy (treatment-free remission, TFR). The first proof of concept for stopping TKI was the Stop Imatinib 1 (STIM1) trial where 38 % of the patients maintained a molecular remission (defined as negative PCR) after five years of imatinib discontinuation. In the thus far largest CML TKI discontinuation trial (EURO-SKI clinical trial), prognostic markers have been defined, whereas the duration of DMR seems to be the most important. Accurate definition of DMR is therefore increasingly important for optimal patient management and comparison of independent data sets. In addition, in the EURO-SKI study, also the role of the immune system was investigated and found to be of relevance for successful TFR.
An individualized treatment plan from the time point of diagnosis for each patient seems to be the future of CML therapy. This compromises also the choice of the first line-TKI in order to increase the number of patients in TFR.

LS05

A new paradigm shift in frontline treatment of hodgkin lymphoma

Andrea Gallamini

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Background: Hodgkin lymphoma (HL) is one of the success stories of modern oncology, with more than 90% of patients alive and 80% considered cured after long-term follow-up. Improved outcome is the result of numerous factors including more accurate staging, more effective chemo and chemo-radiotherapy, and newer targeted agents. More recently risk-adapted strategies using PET-CT have further enhanced outcomes for high-risk patients, while reducing toxicities for low risk patients. In advanced-stage disease, even after a PET adapted strategy, approximately 15-20% of patients fail primary treatment for primary chemo-refractoriness or relapse following frontline ABVD treatment. Brentuximab vedotin is a CD30-directed antibody-drug conjugate approved for classical HL after failure of autologous stem cell transplantation (ASCT) or ≥2 prior chemotherapy regimens and as consolidation post-ASCT for increased risk HL.

Echelon-1 Trial In 2012, a open-label, randomized, multicenter, phase 3 study, the Echelon-1 trial, was launched to compare the effectiveness, in terms of 2-y modified PFS (mPFS), of AVD plus Brentuximab-Vedotin (A+AVD) versus standard ABVD as frontline therapy in previously untreated stage III and IV HL in 218 oncology/Hematology institutions all over the world (Echelon-1 trial).

Thirteen-hundred-thirty-four Stage III (36%) or IV (64%) HL patients were randomized (58% male; median age 36 y [range 18-83]; ≥45 y, 34%; ≥60 y, 14%). The primary endpoint of modified PFS (mPFS) per IRF was met (HR 0.770 [95% CI 0.603-0.982]; p=0.035), with 117 events in the A+AVD arm and 146 events in the ABVD arm, and was consistent with investigator (INV)-reported modified PFS (HR 0.725 [95% CI 0.574-0.916]; p=0.007). Modified PFS events per IRF were attributed to disease progression (90 vs 102); death (18 vs 22) or receipt of additional anticancer therapy for incomplete response (9 vs 22) after A+AVD or ABVD, respectively. The 2-y mPFS per IRF was 82.1% (95% CI 78.7-85.0) with A+AVD vs 77.2% (95% CI 73.7-80.4) with ABVD. Pre-specified subgroup analysis of mPFS per IRF demonstrated a consistent benefit of the experimental treatment over standard ABVD in patients with stage IV and ≥1 extranodal site. A subset analysis on 186 elderly patients (≥ 60) enrolled in Echelon-1 trial, accounting for 14% of the entire enrolled population, showed no difference in terms of 2-Y mPFS per IRF of the experimental arm over the standard arm in the overall elderly population and only a slight, non-significant benefit for stage iv patients (2-Y mPFS: 71.3 Vs. 66 1%; p= 0.5069. after a mean follow-up of 30 months 15 patients in A+AVD, 8 of them with stage IV and 17 patients in ABVD arm, 13 of them with stage IV had an event. 66/83 patients in the experimental arm and 70/98 in the standard arm had dose modification of treatment and the most frequent dose modification were due to BV (mean 92.35% DI) or Bleomycin (mean 88.7% DI) dose reduction, respectively. The emergence of grade ≥3 AEs were higher in elderly compared to younger patients, febrile neutropenia (FN) and pulmonary toxicity being the most frequents SAEs in experimental and standard treatment, respectively. G-CSF prophylaxis was able to reduce significantly the in cadence of FN in the experimental arm.

Conclusions: the Echelon-1 trial showed a significantly superior modified PFS of A-AVD over ABVD per Independent review, with a 23% reduction in risk of progression, death or need for additional anticancer therapy, and a 2-year modified PFS of 82% Vs. 77% of the standard ABVD arm. These results will be compared with those obtained in the recently published PET-adapted clinical trials in advanced HL.

LS06

The role of the darbepoetin alfa of the treatment for low-risk of MDS

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Many lower-risk myelodysplastic syndrome (MDS) cannot maintain normal hemoglobin level and are therefore anemia. Median hemoglobin in this population was found to be 9.1 g/dL and more than 50% had moderate (8 – 9.1 g/dL) to severe (< 8 g/dL) anemia. For patients with MDS, anemia has particularly negative consequences, such as chronic fatigue, bleeding and low iron levels, and although bold transfusions can temporarily reduce anemia symptoms, they can also lead to transfusion dependency and iron overload, which are associated with reduced survival and worse quality of life.

Erythropoiesis-stimulating agents (ESA) are used to treat anemia in MDS and currently, darbepoetin alfa is commonly used and recommended by clinical guidelines. ESAs showed consistent improvement in erythroid response rate and duration of response. Comparative studies demonstrated similar progression to acute myeloid leukemia and several showed improved overall survival and OoL. Therefore ESA therapy should be the foremost first-line therapy of anemia in most paitent with lower-risk MDS.

ORAL PRESENTATION

2019 KOREAN SOCIETY OF
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OP01-1

RNA sequencing as an alternative tool for detecting measurable residual disease in core binding factor acute myeloid leukemia

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Background: Although core binding factor acute myeloid leukemia (CBF-AML) is considered to have favorable prognosis, its relapse incidence reaches up to 40%. DNA-seq-based measurable residual disease (MRD) detection has shown to be clinically relevant in AML. However, same method cannot be applied to fusion-driven subtypes of AML such as CBF-AML. Instead, quantitative PCR (qPCR) has been used to monitor the levels of RUNX1-RUNX1T1 and CBFB-MYH11. While qPCR is highly sensitive, its results can be highly inconsistent and variable due to confounding factors. In addition, standardization procedures make it challenging to compare qPCR results from different laboratories. RNA-seq, on the other hand is more robust against those factors. In addition, it can quantify transcript expression, discover novel fusion transcripts, and detect somatic mutations. Here in this study we evaluate the effectiveness and feasibility in using DNA and RNA-seq as tools for MRD detection in CBF-AML.

Methods: Fifty-three patients (pts) were enrolled in this study and all samples were collected after obtaining informed consent. In addition to diagnostic samples, samples taken at complete remission (CR) were also sequenced. Targeted gene panel was constructed, covering exonic regions of 84 genes, commonly mutated in myeloid neoplasms (Agilent SureSelect custom probe set). Targeted RNA-seq (Illumina TruSight RNA Pan-Cancer Panel) was additionally performed (n=42/53). Overall, 159 samples including CD3+ T-cells were subjected to DNA-seq and of which 42 diagnosis-CR pairs were further subjected to RNA-seq. After DNA or RNA extraction and library preparation, both DNA and RNA samples were sequenced using an Illumina HiSeq 2500. Variant calling, fusion detection, and monitoring procedures were performed using our in-house algorithms.

Result: At diagnosis, 99 mutations from 49 pts (n = 49/53, 92%) were detected. Consistent with literature, KIT, NRAS, KRAS, ASXL2 were commonly mutated. Among mutations detected at diagnosis, cKIT-D816 mutation and mutations in genes in DNA methylation pathway (DNMT3A and TET2) were associated with higher risk of relapse (HR 5.29, [1.89 - 14.87], P=0.002 and HR 3.15 [1.07 – 9.26], P=0.037). At CR, 46 mutations were still detectable (46/99, 46%). However, we did not find association between mutation clearance at 0.3% (MC03) with OS (P=0.43) and relapse risk (P=0.8). Among MRD-positive pts measured by qPCR, MC03 did not affect OS (p = 0.69) and relapse incidence (P=0.86). Complete clearance of KIT-D816 mutation also did not affect OS and relapse incidence (P=0.94 and P=0.40). Using RNA-seq, we could detect RUNX1-RUNX1T1 and CBFB-MYH11 in all 42 diagnostic samples. By monitoring expressed transcripts at diagnosis in CR samples, we were able to quantify the reduction levels of RUNX1-RUNX1T1 and CBFB-MYH11 (P<6.3e-05 and P<2.2e-13). The reduction level of RUNX1-RUNX1T1 as measured by RNA-seq and qPCR were highly correlated (R2=0.74, P<5.4e-05). High risk mutations were also detectable in RNA-seq. Using information from RNA-seq, a decision tree analysis stratified RUNX1-RUNX1T1 AML pts into three subgroups based on 3-log reduction of RUNX1-RUNX1T1 and cKIT-D816 mutation at diagnosis. These three subgroups had 2-year OS rates at 87%, 74%, and 33% (P<0.08) and 2-year relapse incidence rates at 13%, 42%, and 67% (P<0.05).

Conclusions: Our study demonstrates that RNA-seq can be utilized to monitor fusion transcript during CR and serves as a proof-of-concept study for RNA-seq-based MRD detection in fusion-driven hematologic malignancies.

Keyword: Core Binding Factor, Measurable Residual Disease, RNA Sequencing

OP01-2

Different predictive roles of risk group and WT1 expression in elderly AML treated by intensive chemotherapy or hypomethylating agent

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Background: Hypomethylating agents, including decitabine (DAC), are widely accepted as a frontline treatment for elderly (age ≥ 65 years) acute myeloid leukemia (eAML) patients. However, there are only a few studies directly comparing the results of intensive chemotherapy (IC) and DAC therapy. Moreover, predictive markers for the outcomes of DAC treatment have been scarcely investigated.

Methods: To address this issue, we compared the composite complete response (cCR) and overall survival (OS) rates of eAML patients who received decitabine (DAC group; 86 patients) and intensive treatment (IC group; 49 patients) strategies between Jan 2013 and March 2018 at our institution.

Result: Except a higher patients' age of the DAC group (> 70 yrs; 65.7% vs. 7.4%; P < 0.01), other baseline characteristics, including performance status, were not different between two groups (P > 0.10). Toxicities, including grade III-IV neutropenic fever, pneumonia, and invasive aspergillosis, were more frequently observed in the IC group compared to the DAC group. The cCR (59.3% vs. 18.4%; P < 0.01) and OS (24.6% vs. 6.2%; P = 0.02) rates of the IC group were significantly higher compared to those of the DAC group. In multivariate analysis, therapeutic strategies (IC vs. DAC) was an only significant factor affecting cCR (OR 6.50, 95% CI 2.96–14.20; P < 0.01) and OS (HR 0.63, 95% CI 0.41–0.96; P = 0.03) rates. Of the IC group patients, 20 (41.4%) received allogeneic stem cell transplantation (SCT) on CR (17 patients) or non-CR states (3 patients) showed the long-term OS of 37.9% (95% CI, 9.8–66.6). In further sub-group analysis, disease-risk group (favorable /intermediate vs. poor risk) was a significant factor affecting cCR (66.7% vs. 33.3%; P = 0.02) and OS (28.8% vs 11.1%; P = 0.01) rates in the IC group, whereas it was not significant factor affecting cCR (29.0% vs. 23.5%; P = 0.88) and OS (7.3% vs. 5.9%; P = 0.34) rates in the DAC group. On the other hand, WT1 expression (< 0.45 vs ≥ 0.45) was a significant factor affecting OS rate not in the IC group (18.4% vs. 25.0%; P = 0.94), but in the DAC (11.3% vs. 0%; P = 0.02) group.

Conclusions: Our data showed better results of the IC group compared to those of the DAC group. However, a significant difference of the outcomes between two therapeutic modalities was not observed in the poor risk group. The association of lower WT1 expression at diagnosis with poorer outcomes, not in the IC group but in the DAC group, suggests a relevance of WT1 with methylation status and a possible role of WT1 as surrogate marker for eAML patients treated by DAC. Therefore, DAC might be a preferable therapeutic option for eAML patients with poor disease risk, particularly with high WT1 expression, irrespective of the fitness to intensive treatment strategy. However, for long-term survival, intensive consolidative strategies, such as allogeneic SCT, should be considered at achieving CR after DAC treatment.

OP01-3

Role of plasma gelsolin protein in the final stage of erythropoiesis and in correction of myelodysplasia

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Background: Gelsolin (GSN), an actin-remodeling protein, is involved in cell motility, cytoskeletal remodeling, and cytokinesis. Mature erythroblasts undergo dramatic changes in their cytoskeletal network to become red blood cells (RBCs). In this study, we evaluated the role of human plasma-type gelsolin (pGSN) in terminal erythropoiesis prior to enucleation and in myelodysplastic syndrome (MDS).

Methods: Late erythroblasts differentiated from human cord blood (CB) CD34+ cells, and human bone marrow (BM) cells derived from patients with MDS, were cultured in serum-free medium containing recombinant human pGSN protein. Changes in terminal erythropoiesis were assessed by mRNA expression, cell

maturation, enucleation counting, nuclear dysplasia rate, and cell size measurements, and effects on erythroid dysplasia, apoptosis, and cytoskeleton were evaluated. GSN transcript levels in MDS patients and corrective effects of pGSN on MDS cells were also evaluated.

Result: With pGSN treatment, terminal erythropoiesis at the stage of poly- and ortho-chromatic erythroblasts was enhanced, with higher numbers of mature erythroblasts and enucleated RBCs. pGSN also significantly decreased dysplastic features of cell morphology. The cytoplasm and nuclei of CB erythroblasts cultured in the presence of pGSN were also smaller than those of control cells. We found that patients with MDS, but not with MDS with increased blasts, showed significantly decreased expression of GSN mRNA in their PB and BM buffy coat. When BM erythroblasts of MDS patients were cultured with pGSN, levels of mRNA transcripts related to terminal erythropoiesis and enucleation were markedly increased, with significantly decreased erythroid dysplasia, and better-preserved mitochondrial transmembrane potential than in untreated cells.

Conclusions: Together, our findings demonstrate a key role for pGSN in erythropoiesis in serum-free culture and in pGSN-depleted MDS patients, and indicate a therapeutic value in that pGSN administration may promote erythropoiesis in myelodysplasia.

Keyword: Plasma Gelsolin, Myelodysplastic Syndrome, Erythropoiesis, In Vitro Cell Culture, Erythrocytes, Pharmaceutical Therapeutics

OP01-4

Research use only and cell population data items from DxH800 analyzer is useful in discriminating MDS patients from those with cytopenia without MDS

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Background: Discrimination of patients with myelodysplastic syndrome (MDS) from those with cytopenia without MDS using research use only (RUO) and cell population data (CPD) items obtained from automated hematologic analyzer enables not only fast and appropriate diagnostic approach, but also can reduce implementation of unnecessary invasive procedure such as bone marrow (BM) examination in cytopenic patients. We investigated the performance of RUO/CPD items obtained from DxH800 automated hematologic analyzer (Beckman Coulter, Miami, FL, USA) in the discrimination of MDS patients from cytopenic patients without MDS.

Methods: We retrospectively obtained routine CBC, RUO, and CPD item data at diagnosis from 94 patients with MDS and 100 cytopenic patients without MDS. Total 13 routine CBC, 18 research use only (RUO) items, and 70 CPD items were obtained and results were compared between two subgroups by Mann-Whitney U test. In items with statistically significant differences, receiver operating characteristic (ROC) analysis were performed and both area-under the curve (AUC) scores and best-cutoff values were obtained, and results were compared.

Result: Total seven (53.8%), thirteen (72.2%), and fifteen (21.4%) items showed statistically significant differences between two subgroups in routine CBC, RUO, and CPD items, respectively. Among them, four CBC and RUO items [red cell distribution width-standard deviation (RDW-SD), immature reticulocyte fraction (IRF), mean sphered cell volume (RSCV), high light scatter reticulocytes (HLR)] and two CPD items [mean volume of neutrophils (NE-V-Mean) and mean volume of early granulated cells (EGC-V-Mean)] showed AUC scores > 0.750 and notably, MSCV > 81.4, HLR > 0.15%, NE-V-Mean > 145 and EGC-V-Mean > 156 showed sensitivity of 91.9%, 93.6%, 88.1% and 90.2% in the discrimination of MDS patients from cytopenic patients without MDS. Using previously defined best-cutoff values in six items with AUC > 0.750, scoring system which is defined as +1 score when each item is more than its best-cutoff values and all six results are combined, were developed and decision criteria of scores ≥ 4 showed AUC scores of 0.891 and sensitivity 87.3% and specificity of 79.0% in the discrimination of MDS patients from cytopenic patients without MDS..

Conclusions: Two routine CBC items and four RUO/CPD items showed satisfactory AUC scores, and four RUO/CPD items showed high sensitivity in the discrimination of MDS patients from cytopenic patients without MDS. Scoring system using these six items showed high AUC scores, sensitivity, and specificity in the discrimination of MDS patients from cytopenic patients without MDS. Therefore, RUO/CPD items obtained from DxH800 automated hematology analyzer would be useful in the screening MDS patients from cytopenic patients without MDS.

Keyword: Beckman Coulter DxH800, Cell Population Data, Myelodysplastic Syndrome, Research Use Only, Screening

OP01-5

Androgen therapy for lower-risk myelodysplastic syndrome

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Background: Improvement of cytopenia is one of the primary treatment purposes for patients with the lower-risk myelodysplastic syndrome (MDS). Androgens showed some benefit in telomere diseases including MDS. In this retrospective study, we aimed to evaluate the efficacy of androgen in lower-risk MDS.

Methods: We analyzed the data of 139 patients who received androgens (danazol or oxymetholone) for treatment of cytopenia between March 2001 and June 2018. All patients had the international prognostic scoring system low or intermediate-1 risk at the time of androgen therapy. The assessment of hematologic improvement (HI) was based on the international working group response criteria for MDS.

Result: Androgens (oxymetholone for 83 patients and danazol for 56) were given as first (n=108, 77.7%) or over second (n=31, 22.3%)-line treatment for MDS. The time interval between diagnosis and androgen treatment was median 1.3 months (range, 0–240.6), and 75 patients (54.0%) were red blood cell (RBC) transfusion-dependent before treatment. The dose intensity of oxymetholone and danazol was 50 and 385 mg/day respectively, and the median treatment duration was 5.8 months (range, 0.9–92.2). Eighty-two patients (59.0%) achieved HI at any lineage: 29.0% for erythroid (HI-E), 51.9% for platelet (HI-P), and 60.5% for neutrophil (HI-N). The median time to HI following androgen therapy was 1.8 months (range, 0.2–124.5) for any HI, 4.1 months (range, 0.6–124.5) for HI-E, 1.7 months (range, 0.4–40.4) for HI-P, and 1.8 months (range, 0.2–8.4) for HI-N. In univariate analysis, presence of RBC transfusion-dependence (49.3% vs. 70.3%, P=.012) and pre-treatment low hemoglobin (<9.0 g/dL, 45.8% vs. 65.9%, P=.003) were associated with lower HI rate. During the median follow-up duration of survivors of 40.8 months (95% confidence interval [CI], 38.0–67.5), the 5-year overall survival (OS) and leukemia-free survival (LFS) estimated from androgen treatment were 65.4% and 79.6%, respectively. Achievement of HI was associated with longer OS (hazard ratio [HR], 0.412; 95% CI, 0.209–0.815; P=.011) and LFS (HR, 0.512; 95% CI, 0.269–0.975; P=.042) in multivariate analysis. There were no significant differences in HI and OS rates between danazol and oxymetholone, however, danazol showed a trend for longer LFS compared to oxymetholone (P=.086).

Conclusions: Our data suggest that androgen can be a reasonable treatment option for lower-risk MDS patients with significant cytopenias and the response seems to be related to longer OS and LFS. Prospective studies are warranted to investigate the efficacy of androgen therapy in lower-risk MDS.

Keyword: Myelodysplastic Syndrome, Lower-Risk, Androgen, Danazol

OP01-6

Lenalidomide as a second-Line therapy after failure of hypomethylating agents in patients with myelodysplastic syndrome (VIOLTET study)

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Background: There is no standard therapy after the failure of hypomethylating agents (HMAs) in myelodysplastic syndrome (MDS)

without only providing supportive cares including transfusion or cytokine therapies when the patient is not eligible for allogeneic hematopoietic cell transplantation. Lenalidomide is the treatment of choice in case of MDS with 5q deletion. A study of lenalidomide for non-5q deletion MDS patients showed that transfusion independency rate was 26% which was relatively acceptable and suggested that lenalidomide could be used for non-5q deletion MDS patients.

Methods: We conducted the prospective phase II trial to evaluate the efficacy of lenalidomide for patients who failed to HMA (ClinicalTrials.gov Identifier: NCT01673308). Patients took lenalidomide 10mg daily for 3 weeks and rested for a week. New cycle began every 4 weeks. The primary objective was the objective response rate (ORR; CR+PR+marrow CR+HI). Unknown or not evaluable response were regarded as failure. The planed sample size was 29 (P0: 10%, P1: 30%, α-error:0.5, β-error:0.2) patients. The major inclusion criteria were adult MDS by WHO classification and they should be treatment failure after HMAs (azacitidine or decitabine) which were defined as either intolerant to HMAs or progressive disease after HMA.

Result: Total 38 patients were included in this analysis. Among them, 1 patient didn't receive study drug at all. Male was 25 (65.8%) patients. Median age was 67 (range 40-82) years. Reasons for stopping HMA were no response in 10, progression in 14, adverse events in 3 and other causes in 4 patients. WHO classification was follows; RA in 4, RARS in 1, RCMD in 8, RAEB-1 in 4, RAEB-2 in 8, MDS with 5q deletion in 2 and not known in 4 patients. IPSS at study enrollment were low (n=4), INT-1 (n=12), INT-2 (n=9), high risk (n=3) and unknown (n=3) risk. Revised IPSS were very low (n=3), low (n=3), intermediate (n=5), poor (n=2), very poor (n=8) and unknown risk (n=3). Median cycles of lenalidomide was 3 (range 0-21). The responses after 4 cycles were CR in 4, SD in 14, failure/not evaluable in 20 patients. The maximal responses were CR in 7, mCR in 1, PR in 3, HI in 3, SD in 10, failure in 14 patients. Best ORR was 14/38 (36.8%) patients, with 24/38 receiving clinical benefit (63.2%, inclusive of SD). The toxicity profile was tolerable except for hematological toxicities including neutropenia and thrombocytopenia. Among 3 patients with 5q deletion, 1 patient achieved CR but 2 patients failed. Median overall survival was 15.4 (95% CI 5.9-24.9; Figure 3) months. Two patients received alloHCT after progression or failure to lenalidomide.

Conclusions: Lenalidomide showed reasonable response and excellent overall survival after failure of HMA in adult MDS with tolerable toxicities. Therefore, lenalidomide can be a promising option after failure of HMA even in non-5q deletion MDS.

Keyword: Myelodysplastic Syndrome, Lenalidomide, Hypomethylating Agent Failure

OP02-1

A pragmatic, non-interventional study to evaluate effectiveness and safety of clofarabine in Korean pediatric patients with refractory or relapsed acute lymphoblastic leukemia

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Background: Clofarabine, a second-generation purine nucleoside analogue, is used in advanced leukemia patients. Based on previous studies, clofarabine was approved by the US Food and Drug Administration in 2004 for patients with refractory or relapsed pediatric acute lymphoblastic leukemia (ALL) who had previously received at least two chemotherapy regimens. This study was designed to produce data to assess the efficacy of clofarabine in Korean pediatric ALL patients, in order to carry out coverage with evidence development.

Methods: This multi-center prospective study enrolled patients with ALL who failed to respond or relapsed after two or more chemotherapy regimens and for whom the physician has decided to give clofarabine. The primary endpoint was overall remission rate (OR) of all patients. Secondary endpoints were overall response rate (ORR), time to remission, the proportion of patients receiving hematopoietic stem cell transplantation (HSCT) and overall survival rate (OS) at 6 month. In addition, safety was evaluated.

Result: A total of 60 patients were enrolled between June 2014 and July 2018. The median age at enrollment was 12.0 years (range 2.0-26.0 years). Disease status at enrollment was as follows: refractory disease in 21, first relapse in 13, and second relapse in 26 patients. According to the immunophenotype, B-cell, T-cell, and mixed phenotype accounted for 39 (65.0%), 14 (23.3%), and 5 (8.3%) of the 60 patients, respectively. The immunophenotype of the remaining two patients was not available. Most patients (97.7%) were treated with clofarabine in combination with cyclophosphamide and etoposide. Eleven (18.3%), sixteen (26.7%), and one (1.7%) of the 60 patients achieved complete remission (CR), CR except for platelet count recovery and partial remission, respectively. The OR and ORR was 45.0% and 46.7%, respectively. The median time to response was 10.3 weeks. Sixteen patients (26.7%) had a successful HSCT. The OS at 6 months was 47%. The median survival of patients who received and did not receive HSCT were 22.2 months (95% confidence interval [CI], 6.3-30.8 months) and 3.9 months (95% CI, 3.0-5.1 months). The adverse drug reactions (ADRs) reported in more than 10% were febrile neutropenia (63.3%), vomiting (55.0%), nausea (53.3%), diarrhea (38.3%), stomatitis (18.3%), pyrexia (18.3%) and alanine aminotransferase elevation (18.3%). The ADRs leading to fatal event were sepsis in 5, febrile neutropenia in 2, lung infection in 1, pneumonia in 1, and septic shock in 1 patient, respectively.

Conclusions: Clofarabine showed promising results and is expected to broaden treatment strategies available to refractory or relapsed Korean pediatric ALL patients. Long-term follow up are needed in this population.

Acknowledgments: This study was funded by Sanofi.

Keyword: Clofarabine, Korean, Pediatrics, Acute Lymphoblastic Leukemia

OP02-2

The genotype distribution and pharmacogenetic effect on mercaptopurine dose of NUDT15 and TPMT in Korean children with acute lymphoblastic leukemia

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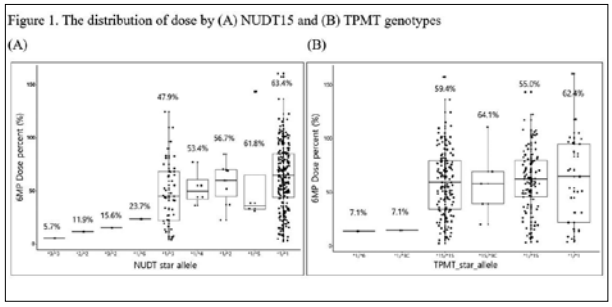
Background: To improve treatment outcomes of childhood acute lymphoblastic leukemia (ALL), constant mercaptopurine (MP) dose titration is essential to maintain steady drug exposure, while minimizing myelosuppression. Since June 2016, 3 institutions (Asan medical center, Seoul National University Children's hospital, Samsung medical center) have conducted multicenter pharmacogenetic study, and collected blood sample of pediatric ALL patients. Through this analysis, we intended to explore variant allele frequencies of NUDT15 and TPMT in Korean pediatric ALL patients, and evaluate the pharmacogenetic effect of the variants.

Methods: Whole exome sequencing was carried out with genomic DNA from 272 ALL patients registered at the multicenter pharmacogenetic study. Because the dose of MP is being adjusted during maintenance phase in response to toxicity, the dose at the last maintenance cycle would be the maximal tolerable dose (MTD) to most of the patients. As the MTD of MP will be inversely proportional to the toxicity of MP, MP dose of the last cycle was analyzed as an indicator of toxicity. The dose percent was the percentage of the actual dose divided by the planned per protocol. Laboratory results and medication records were extracted from electrical medical records.

Result: The allele frequencies were 88.4% for NUDT15 *1, and 1.8, 8.0, 0.7, 0.7, and 0.2% for *2, *3, *4, *5, and *6, respectively. The NUDT15 phenotypes based on diplotypes included normal activity (n=212), intermediate activity (n=57), and low activity (n=3), occurring in 77.9, 21.0 and 1.1% of the patients, respectively. The allele frequencies of TPMT *1, and TPMT *1S were 28.9% and 69.9%, respectively. There were only 2 variant alleles of TPMT, and the frequencies were 1.1, and 0.2% for *3C and *6. The average dose percent of MP was 63.4%, 57% and 3% in patients with normal NUDT15 activity, intermediate activity, and low activity, respectively (Figure 1). Patients with homozygous variant alleles of NUDT15 were significantly associated with a lower tolerated dose of MP ($P<0.001$). Among the heterozygous variants, the dose percent of *1/*3 group was 47.9%, while that of *1/*6 group was only 23.7%. For TPMT, no patient showed homozygous variant alleles, and only 7.1% of the scheduled dose was given in the patient population that showed heterozygous variant allele.

Conclusions: This study was the first multicenter pharmacogenetics study in Korean pediatric ALL, and the result showed that the tolerable dose of MP depends on the variants of NUDT15 or TPMT. Therefore, if the pharmacogenetic surveillance of each patient is conducted in advance, and the individualized starting dose of MP is recommended, the dosage changes and disruption period of MP due to toxicity will be reduced. We are planning a prospective study on this, and we expect to provide appropriate dosage guidelines for Korean ALL patients in the future.

Keyword: Acute Lymphoblastic Leukemia, Mercaptopurine, Pharmacogenetics, Korea



OP02-3

Mutational profiling through exome sequencing along with MYD88 L265P analysis could facilitate the diagnosis of vitreoretinal lymphoma

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Background: Vitreoretinal lymphoma (VRL), previously known as intraocular lymphoma, is a rare form of malignancy. Although the disease is highly aggressive with elevated mortality rate, there are no standard of differential diagnosis from posterior uveitis when the amount of vitreous is so limited. MYD88 L265P mutation is reported to be identified in the vitreous of approximately 70% of patients with VRL. In view of the need of establishing new procedures to support the diagnosis of VRL, we explored the exome of lymphoma cells and the prevalence of MYD88 L265P mutation in Korean VRL patients.

Methods: We performed the exome sequencing of vitreous of 8 patients with matched germline blood or buccal swab samples. The patients suspicious of VRL and underwent standard vitrectomy between July 2016 and September 2018 were enrolled. Sequencing data were analyzed and compared with those of CNS lymphoma. We established real-time PCR system for MYD88 L265P mutations. Vitreous of eight patients and an additional patient were subjected to the test.

Result: Approximately 150 somatic mutations were identified through whole exome sequencing. Previously reported frequently mutated genes such as PIM1, CD79B, KMT2D, MYC and MYD88 were found to be mutated. Mutational profile of VRL showed similarity to that of DLBCL. A patient has possible germline predisposition mutation in ERCC6 gene. Most VRL showed complex karyotype. The detection limit of MYD88 L265P real-time PCR was approximately 2%, and 5 out of 9 patients had MYD88 L265P mutation.

Conclusions: MYD88 L265P real-time PCR could be a good diagnostic tool for the patients with VRL harboring MYD88 L265P mutation. We concluded that exome or gene panel testing of VRL and confirmation of the presence of a number of somatic mutation and mutation profile may facilitate the diagnosis of VRL in a subset of patients.

Keyword: Vitreoretinal Lymphoma, Exome Sequencing, MYD88 L265P

OP02-4

Utility of MLPA as a cost effective diagnostic and prognostic method in hematological malignancies: Experience of A tertiary care centre from India

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Background: Despite the advances in paediatric cancer therapy worldwide, personalized therapy decisions for patients in low and middle income countries (LMICs) are primarily dependent upon diagnostic information derived from cost effective but sensitive and rapid test results. Multiplex ligation dependent probe amplification (MLPA) assay is a validated and robust method of detecting

different types of genetic variations including copy number abnormalities (CNAs), small deletions-insertions, fusion genes etc. We evaluated the routine usage of MLPA in different paediatric hematological malignancies for its robustness and cost effectiveness.

Methods: A total of 125 pediatric patients suffering from different cancers [B cell acute lymphoblastic leukemia, n=105; T cell acute lymphoblastic leukemia, n=15; and Le fraumeni syndrome (n=5)] were analyzed by MLPA assay using MRC-Holland kits P335, P383, P327 and P056-C1. A total of 20 controls were run for analysis and normalization of samples in different batches. DNA was extracted from peripheral blood mononuclear cells and processed for MLPA reaction as per protocol. After MLPA-PCR, fragments were resolved by capillary electrophoresis on ABI 3130 Genetic Analyzer (Applied Biosystems) and the peak intensities were analyzed using Coffalyser.net software (MRC-Holland)

Result: CNAs in IKZF1, PAX5, EBF1, BTG1, RB1, CDKN2A/B and genes from PAR1 region viz., CSF2RA, IL3RA, P2RY8, SHOX region and CRLF2 were successfully analyzed in pediatric B-ALL patients and were detected in 70% of cases, with predominantly deletions found in CDKN2A/B (36%), PAX5 (18%) and IKZF1 (16%). T-ALL patients were analyzed for CNAs in RB1 and CDKN2A/B genes and were found to be present in 13% and 100% of cases, respectively. lamp 21 amplification was noted in only two of the 105 cases (2%) screened. For Le Fraumeni syndrome, none of the cases showed mutation in MLPA assay, however when confirmed through Sanger's sequencing, 2 of the samples showed previously reported deletions in Tp53 gene. MLPA reaction did not fail in any of the samples analyzed. All control reference samples and the control probes within each target probemix had a very low SD of <2%

Conclusions: The cost for performing MLPA on patient's samples was around 1500 INR or approximately 22 USD. With such low cost MLPA was found to be highly reliable for analysing and reporting genetic variation in haematological malignancies using kit P335, P383 and P327. However, the probemix for Le Fraumeni syndrome was found to be inefficient in detecting deletions in Tp53 gene and therefore modification is suggested in the probemix P056-C1 for diagnosis of Le Fraumeni syndrome patients. Despite above limitations, MLPA can be utilized as an effective and rapid screening test to make timely therapeutic and prognostication decisions especially in ALL cases.

Keyword: MLPA, Copy Number Abnormalities, Acute Leukemia, Probes

OP02-5

Genetic characteristics and long-term outcomes of Korean adult patients with Ph-Like ALL versus non-Ph-Like ALL

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Background: Recently, a high-risk subgroup of B-cell precursor acute lymphoblastic leukemia (BCP-ALL) called Philadelphia chromosome (Ph)-like ALL was identified in adolescents and young adults. However, there are conflicting data regarding the incidence and prognosis of Ph-like ALL in adult patients. We tried to identify the prevalence and genetic characteristics of Ph-like ALL in adult patients with newly diagnosed BCP-ALL. Furthermore, we analyzed the clinical characteristics, long-term outcomes, and prognostic impact of Ph-like ALL compared with non-Ph-like ALL (Ph-positive ALL or B-other ALL).

Methods: Between 2009 and 2015, 406 adult patients with newly diagnosed BCP-ALL who received modified hyper-CVAD chemotherapy were included in this analysis (median age, 43 years [range, 15-65 years]). Our post-remission therapy was based on allogeneic-HCT if a donor is available. Ph-like ALL was determined by next generation sequencing using the Archer® FusionPlex® ALL Kit (ArcherDX Inc., CO) which can detect fusions, point mutations, and expression levels in 81 genes associated with ALL, and additional confirmative FISH, RT-PCR, and direct sequencing analyses were done.

Result: Overall, 64 (15.8%) of the 406 patients were Ph-like ALL, and the cohort was divided into patients with ABL-class rearrangements (n=10), CRLF2 rearrangements (n=15), JAK2 rearrangements (n=9), other JAK-STAT sequence mutations (n=12), and RAS mutations (n=18). The remaining 280 patients were divided into Ph-positive ALL (n=197) and B-other ALL (n=83; including 21 patients with KMT2A [MLL] rearrangements). Ph-positive ALL were older (median 47 vs. 40 [B-other] vs. 35 years [Ph-like ALL]; $p < 0.001$) and had higher leukocyte counts (median, 33.1 vs 12.4 [B-other] vs. 11.8?10^9/L [Ph-like ALL]; $p < 0.001$) compared to other subgroups. There were less high-risk patients in Ph-like ALL

subgroup (50.0% vs. 75.9% [B-other] and 85.3% of [Ph-positive ALL]; p < 0.001). Although patients with Ph-like ALL were more likely to achieve delayed complete remission (CR), the overall CR rate was similar between the 3 subgroups (Ph-like ALL, 95.3%; Ph-positive ALL, 95.9%; B-other ALL, 90.3%; p=0.166). A higher proportion of patients with Ph-like ALL actually received allogeneic HCT in CR1 similar to Ph-positive ALL (Ph-like ALL, 85.9%; Ph-positive ALL, 84.2%; B-other ALL, 73.5%; p=0.067). With a median follow-up of 62.8 months (range; 6.0-129.9), outcomes of patients with Ph-like ALL were not inferior compared with outcomes of patients with non-Ph-like ALL. Disease-free survival rates at 5 years were 53.2% for Ph-like ALL, 41.1% for Ph-positive ALL, and 40.9% for B-other ALL (p=0.205). However, the 5-year cumulative incidence of relapse was significantly lower (23.7%) in Ph-like ALL compared to 40.2% of Ph-positive ALL, and 44.9% of B-other ALL (p=0.037). These findings were similarly maintained when patients receiving HCT were analyzed. Within the Ph-like ALL subgroup, patients with ABL1-class and CRLF2-rearrangements had worse 5-year OS (30.0% and 46.7%) than patients with JAK2 rearrangements, JAK-STAT sequence mutations and RAS mutations (77.8%, 75.0% and 66.3%; p=0.031).

Conclusions: Our data showed a different frequency of subtypes (lower incidence of CRLF2 rearrangements, higher RAS mutations) and treatment outcomes (non-inferiority) of Ph-like ALL compared with other Western reports. Our Ph-like ALL cohort showed a low incidence of high-risk feature, thus, the patients were younger with low WBC count. In addition, our intensified chemotherapy or allogeneic-HCT based strategy might overcome the poor prognosis.

Keyword: Acute Lymphoblastic Leukemia, Philadelphia Chromosome, Philadelphia-Like, Next Generation Sequencing, Hematopoietic Cell Transplantation

OP02-6

Outcomes after second allogeneic hematopoietic cell transplantation in relapsed acute lymphoblastic leukemia: A single-center experience

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Background: Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative option for adult patients with acute lymphoplastic leukemia (ALL). However, no standard therapy is elucidated for patients relapsed after allo-HCT, but one potential curative option is second allo-HCT after second remission. We analyzed patients treated with second allo-HCT and tried to find out risk factors for survival outcomes.

Methods: We retrospectively analyzed 35 adult ALL patients (median 35 years old, range 16-66) treated with second allo-HCT in second remission consecutively from 2010 to 2017, all of them relapsed after previous allo-HCT (median 12.8 months, range 2.9-99.4). After second remission, most patients were recommended urgent second allo-HCT from available donor within 6 months, but some patients with Ph-positive ALL responding to salvage tyrosine kinase inhibitors or with isolated EMR were delayed for second allo-HCT.

Result: Of 35 patients, 3 patients were T-cell ALL, 16 were Philadelphia chromosome (Ph)-negative B-cell ALL, and 16 were Ph-positive ALL. Extramedullary relapse (EMR) were observed in 11 patients, and 5 of them were isolated EMR without hematological relapse. At the time of second allo-HCT, 17 were in complete remission (CR) and 18 were in CR without full hematological recovery. Among 16 Ph-positive ALL patients, 9 were in complete molecular response, 2 were in major molecular response, and 5 were in poor molecular response. After median follow-up of 38.2 months (range 7.5-86.3), 3-year overall survival (OS) and disease-free survival (DFS) was 31.9% and 26.0%, respectively. Cumulative inicidence of non-relapse mortality (NRM) and relapse at 3 years was 29.1% and 45.4%. Acute GVHD was observed in 17 (12 with grade I-II, 4 with grade III, 1 with grade IV) and chronic GVHD was observed in 14 (mild 7, moderate 4, severe 3) out of 31 patients who were alive at least 100 days after HCT. We identified late relapse > 6 months and early allo-HCT within 6 months (48.1% vs. 12.5% ; HR=0.27, 95%CI 0.1-0.7, p=0.014) and chronic GVHD (49.0% vs. 27.8% ; HR=0.28, 95%CI 0.1-0.8, p=0.021) showed favorable 3-year OS in the entire cohort. Among patients with Ph-positive subgroup, post-HCT complete molecular response was related with superior OS (66.7% vs. 0.0% ; HR=0.09, 95%CI 0.01-0.69, p=0.021).

Conclusions: Our data suggested that second allo-HCT might be a feasible choice for some patients relapsed after previous allo-HCT as a curative treatment option when urgent allo-HCT is planned especially in late relapse. Safe salvage therapy and additional post-HCT pre-emptive therapy should be considered for better transplant outcomes.

Keyword: Acute Lymphoblastic Leukemia, Allogeneic Hematopoietic Cell Transplantation, Relapse

Table 1. Patient characteristics

	Value (% or range)
Median Age, years old	35 (16-66)
Gender, Male	22 (63)
Subtype of ALL	
B-cell	32 (92)
T-cell	3 (8)
Cytogenetic-risk (NCCN) at diagnosis	
Standard-risk	16 (46)
Poor-risk	19 (54)
Ph-chromosome	16 (46)
Complex karyotype	3 (8)
Cytogenetic-risk (NCCN) at relapse	
Standard-risk	10 (28)
Poor-risk	25 (71)
Ph alone	6 (17)
Ph with clonal evolution	10 (29)
Others without clonal evolution	3 (8)
Others with clonal evolution	6 (17)
Status at 1st relapse	
WBC (x 10^9/L), median	8.21 (2.32-180.23)
Hemoglobin (g/dL), median	11.7 (5-16.3)
Platelet (x 10^9/L), median	86 (17-263)
PB blast (%), median	25 (0-92)
BM blast (%), median	89 (1-100)
CR duration after prior HCT, median	12.8 (2.9-99.4)
≤ 6 months	9 (26)
> 6 months	26 (74)
Type of relapse	
BMR alone	24 (69)
EMR alone	5 (14)
BMR+EMR	6 (17)
Time from relapse to second HCT, median	5.1 (2.8-39.0)
≤ 6 months	25 (71)
> 6 months	10 (29)
Status at second HCT	
CR	17 (49)
CR with incomplete recovery	18 (51)
Comorbidity (HCT-CI)	
Low-risk (score < 3)	19 (54)
High-risk (score ≥ 3)	16 (46)
Donor	
Matched sibling donor	2 (6)
Matched unrelated donor	18 (51)
Mismatched unrelated donor	9 (26)
Haploidentical donor	2 (6)
Cord blood	4 (11)
Conditioning intensity	
Myeloablative	6 (17)
Reduced toxicity	17 (49)
Reduced intensity	12 (34)

Abbreviation:

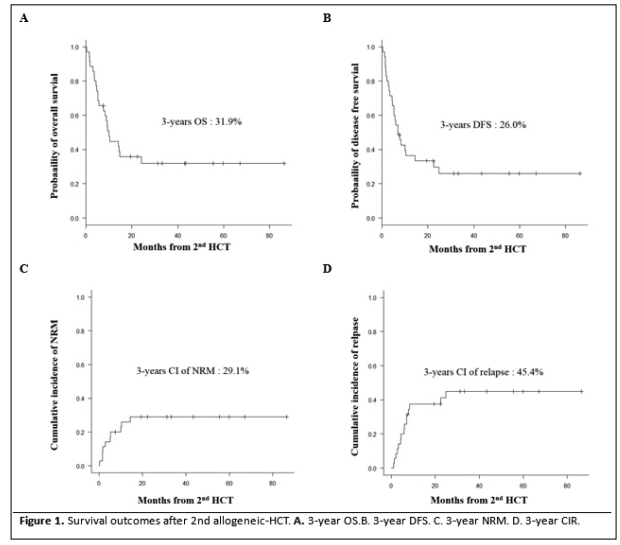
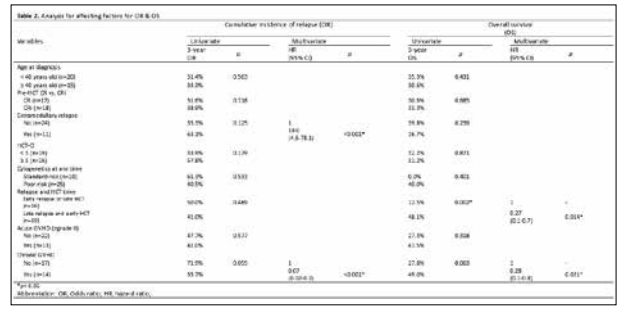


Figure 1. Survival outcomes after 2nd allogeneic-HCT. **A.** 3-year OS.B. 3-year DFS. C. 3-year NRM. D. 3-year CIR.



OP03-1

Diffuse large B-cell lymphomas carrying chromosomal abnormalities showed a poor prognosis despite aggressive treatment

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL); 27% of cases involve the bone marrow which is assessed by bone marrow (BM) biopsy performed at the time of diagnosis. A large, retrospective cohort study recently presented that the histologic evidence of DL-

BCL involvement obtained via staging BM biopsy showed adverse outcomes in overall survival (OS) and event-free survival (EFS) after R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) treatment. This result affects poor survival outcomes independently of the IPI score, emphasizing the necessity of accurate pretreatment assessment of bone marrow pathology. Furthermore, the complex karyotype abnormalities noted in the BM from DLBCL patients indicate a much poorer survival outcome and aggressive treatment such as frontline allogeneic hematopoietic stem cell transplantation (HSCT) should be considered.

Methods: We reviewed 597 newly diagnosed DLBCL patients from Seoul St' Mary's Hematology hospital between August 2009 and December 2016. The median age of the patients was 59 (range, 17 to 88) years old and males accounted for 58.4% of all patients. 301 patients (49.9%) showed high-risk IPI (≥ 3) scores and BM biopsy confirmed DLBCL BM involvement in 92 patients (15.3%) via BM biopsy. Among those 92 BM involved patients, 32 patients (34.8%) presented with a complex karyotype possessing 3 or more chromosomal abnormalities. We decided the appropriate candidates for frontline autologous HSCT after three cycles of R-CHOP, are generally patients diagnosed as high-risk DLBCL in which stem cell mobilization continued following the end of the last R-CHOP cycle.

Result: After a median follow-up duration of 45 (range 0 to 118) months, estimated 4-year OS and EFS was 80.9% and 61.5%, respectively. The 92 patients with pathologic confirmed bone marrow involvement showed significant poor survival outcomes (OS 86.6% vs. 55.1%, p<0.001 and EFS 70.6% vs. 25.2%, p<0.001), and 46.7% (n=43) of them carried chromosomal abnormalities. The chromosomal abnormalities were also significantly correlated with poor survival outcomes (OS 85.0% vs. 38.2%, p=0.001 and EFS 65.7% vs. 18.5%, p=0.001), especially in patients carrying complex karyotype abnormalities (n=32, OS 24.6% and EFS 5.2%). After six cycles of R-CHOP treatment, 15 out of 43 patients showed chromosomal normalization without further relapse, but the remaining 17 and 11 patients showed no response in chromosome abnormalities and relapse of chromosome abnormalities after normalization with poor survival outcomes (OS 71.1%, 19.6%, and 19.5%, p=0.0132), respectively.

Conclusions: This study demonstrated that not only the BM involvement of DLBCL patients but also the chromosomal abnormalities revealed in the involved BM have a significant correlation with poor survival outcomes, especially in those who possessed complex karyotype abnormalities. Additionally, the primary chromosomal abnormalities in DLBCL patients, including complex karyotypes, at the time of diagnosis, should be considered high-risk features due to the inadequate response to either frontline or salvage autologous HSCT combined with further rescue chemotherapies. In conclusion, although further research is required using a well-designed prospective study with a larger number of patients, DLBCL patients with proven chromosomal abnormalities should consider aggressive risk-adapted treatment such as frontline allogeneic HSCT to achieve a better survival outcome.

Keyword: DLBCL, Complex Karyotype, Autologous HSCT, Bone Marrow Involvement

OP03-2

Telomere length and its correlation with gene mutations in chronic lymphocytic leukemia in a Korean population

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Background: Telomere length (TL) is a prognostic indicator in Caucasian chronic lymphocytic leukemia (CLL), but its significance in Asian CLL remains unknown. To investigate the prognostic significance of TL and its correlation with cytogenetic aberrations and somatic mutations, we analyzed TL measurements at the cellular level by interphase fluorescence in situ hybridization in patients with CLL in Korea.

Methods: The present study enrolled 110 patients (41 females and 69 males) diagnosed with CLL according to the World Health Organization criteria (2001-2017). TLs of bone marrow nucleated cells at the single-cell level were measured by quantitative fluorescence in situ hybridization (Q-FISH) for 71 patients. The correlations of TL with clinical characteristics, cytogenetic aberrations, genetic mutations, and overall survival were assessed.

Result: The mean TL in CLL (T/C ratio 8.34 (± 3.68)) was significantly shorter than that in the normal control (T/C ratio 17.29 (± 4.42)). Patients with complex karyotypes, del(11q22), TP53 deletion and/or TP53 mutation, ATM deletion and/or ATM mutation, and SH2B3 mutation showed significantly shorter TLs. Shorter TL was correlated with lower hemoglobin levels and adverse survival (mean TL < 9.35). When the proportion of cells with extremely short TL (< 7.61) was over 90%, patients showed adverse survival in CLL. Complex karyotype, TP53 mutation, and number of mutated genes were determined to be significant adverse variables by multivariable Cox analysis.

Conclusions: TL was attrited in CLL, and attrited telomeres were correlated with adverse survival and other well-known adverse prognostic factors. We infer that TL is an independent adverse prognostic predictor in Koran CLL.

Keyword: Chronic Lymphocytic Leukemia, Telomere Length, Quantitative Fluorescence In Situ Hybridization

OP03-3

International prognostic index improves prognostic value of interim PET-CT scans in diffuse large B-cell lymphoma

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Background: Interim 18F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) scan may predict outcomes in patients with diffuse large B-cell lymphoma (DLBCL). However, overall accuracy in predicting treatment outcomes on adopting 5-point Deauville score (DS) was considerably low in DLBCL because of mainly low positive predictive value of interim PET-CT scans. This suggested that additional tool might be needed to more accurately predict treatment outcomes. International prognostic index (IPI) was greatly associated with outcomes for DLBCL and considered to reflect biologic aggressiveness of DLBCL. Thus, we hypothesized that combined assessments using DS on interim PET-CT scan and baseline IPI might improve the prediction of treatment outcomes in DLBCL patients. In this study, we aimed to establish the risk predicting model integrating DS on interim PET-CT as an estimate of early metabolic response and baseline IPI as a predictor of biologic aggressiveness in patients with newly diagnosed DLBCL.

Methods: In this retrospective cohort study, we consecutively enrolled patients with newly diagnosed DLBCL. Patients were eligible if they were histologically confirmed with DLBCL from Jan 2007 to June 2016, received R-CHOP, and had PET-CT scan data at baseline and at interim after 3 cycles of R-CHOP. Primary CNS or transformed DLBCLs were excluded. Interim PET-CT was assessed using 5-point DS and four point or higher was regarded as positive. All PET-CT scans were assessed by 2 experienced nuclear medicine physicians, who were masked to treatment outcomes of the patients.

Result: A total of 316 patients were screened for eligibility. Ninety-six patients were excluded from the analysis due to following reasons: unavailable baseline (n=9) or interim PET-CT scans (n=48), early death before interim PET-CT (n=16), Primary CNS or transformed DLBCLs (n=15), and insufficient medical records (n=8). Thus, 220 patients were analyzed. Median age was 64 years (range, 19-87) and 132 (60%) were male. Based on the IPI risk, patients were classified as the low or low-intermediate (LI; N=126, 57%), and high-intermediate (HI) or high (N=94, 43%) groups. Interim DS was determined as 1 (n=67, 30.5%), 2 (n=65, 29.5%), 3 (n=39, 17.7%), 4 (n=36, 16.4%), and 5 (n=13, 5.9%). With a median follow-up of 56.6 months (IQR 36.0-71.8), 5-year progression-free survival (PFS) rate was 65.2% (95% CI, 58.1-72.3) and overall survival (OS) rate was 69.9% (95% CI, 63.2-76.6). Interim DS (1-3 vs 4-5) and the IPI (low-LI vs HI-high) were independently associated with PFS (for interim DS of 4-5, hazard ratio [HR], 2.96 [95% CI, 1.83–4.78], P < 0.001; for HI-high IPI, HR, 4.84 [2.84–8.24], P < 0.001) and OS (for interim DS of 4-5, HR, 2.98 [1.79-4.98], P < 0.001; for HI-high IPI, HR, 5.75 [3.14-10.51], P < 0.001) in the multivariate analysis. We stratified patients into 3 groups based on the risk of progression: Low (low-LI IPI and interim DS 1-3), Intermediate (low-LI IPI with interim DS 4-5, or HI-high IPI with interim DS 1-3), and High (HI-high IPI and interim DS 4-5) risk groups. The risk stratification model showed a significant association with PFS (for low risk vs intermediate risk, HR 3.98 [95% CI, 2.10-7.54], P<0.001; for low risk vs high risk, HR 13.97 [7.02-27.83], P<0.001) and OS (for low risk vs intermediate risk, HR 4.14 [2.01-8.54], P<0.001; for low risk vs high risk, HR 16.05 [7.59-33.94], P<0.001).

Conclusions: Combining interim DS with baseline IPI can improve risk stratification in patients with newly diagnosed DLBCL.

Keyword: Diffuse Large B-cell Lymphoma, Positron Emission Tomography, International Prognostic Index, Prognosis, Deauville Score

OP03-4

Screening for monoclonal B-Lymphocytes expansions in a hospital-based Chinese population with lymphocytosis

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Background: Monoclonal B-cell lymphocytosis (MBL), characterized by detectable monoclonal B-cells in peripheral blood with an absolute B-cell lesser than 5×10 cells/L, is a precursor condition of B-cell lymphoproliferative disorders (B-LPD). The prevalence and spectrum of MBL in Chinese population has not been well-defined.

Methods: We conducted a hospital population-based lymphocytosis screening project in our institute. In Zhongshan Hospital, complete blood count (CBC) is performed on more than 2,000 patients daily and more than 98% of whom are patients visiting non-hematological department. Hence, by screening lymphocytosis with CBC, we could observe the prevalence of MBL in large-scale hospital population and to identify patients with early-staged B-LPD. We screened all CBC results performed on all visiting individuals in 10 continuous working days in July of 2018. Peripheral blood sample with lymphocytosis were collected and further studied by flow cytometry to determine B cell clonality and disease classification.

Result: A total of 22952 patients who received CBC were reviewed, and 264 patients (1.15%, 264/22952) were lymphocytosis. Circulating monoclonal B-lymphocytes population in PB were detected in a total of 14 out of 264 patients by immunophenotyping, indicating a prevalence of 5.3%. The median age of these patients was 68.5 years (43–85 years). Among the 14 patients, 4 were diagnosed with CLL and 10 with MBL. The prevalence increased with age (Figure 2), from 1.2 % in patients younger than 59 years to 12.9 % for patients over 60 years. The prevalence of CLL in the cohort is 17.4/100,000. MBL was confirmed by flow cytometry immunophenotyping in 10 out of the 264 patients presented with lymphocytosis, yielding the overall prevalence of 3.8% (95% CI, 1.5% to 6.1%) that increased with age. In elderly over 60 years, the prevalence of MBL is 8.7 (95% CI, 2.8% – 14.6%). MBL with non-CLL phenotype (Figure 3C) was the most prevalent subtype (8, 80%) among the 10 MBL cases, followed by CLL-like phenotype (1, 10%) (Figure 3A) and atypical CLL phenotype (1, 10%) (Figure 3B) MBL subtypes. The absolute clonal B-cell count ranged from 0.2-1.5×10^9/L (median 0.65×10^9/L) among all 10 MBL cases, including 6 cases whose counts were above 0.5×109/L (defined as high count MBL). Concomitants MBL and monoclonal gammopathy of unknown significance (MGUS) were found in two patients, both of whom had CD5 negative non-CLL phenotype MBL. Both patients with MGUS presented with IgM subtype, without overt evidence of lymphoma at the time of diagnosis. We evaluated the diagnostic performance of ALC for the detection of B-LPD and MBL in elderly over 60 years. ROC curve analysis revealed an AUC of 0.76 for the discrimination of B-LPD and an AUC of 0.61 for the discrimination of MBL (Fig. 3). When adjusting ALC of 4.7×10^9/L as cut-off, the sensitivity and specificity was 0.80 and 0.60, respectively.

Conclusions: By screening for lymphocytosis in a large cohort of Chinese hospital population, we detected a relatively high proportion of patients presented with monoclonal B-lymphocytes expansions in PB. The prevalence of MBL was 3.8% and increased with age, with prevalence of 8.7% in elderly patients. Unlike western countries, non-CLL type MBL was the most common MBL subtype. ROC curve analysis suggested screening lymphocytosis in elderly might be effective for detection of B-LPD.

Keyword: Monoclonal B-cell Lymphocytosis (MBL), B-cell Lymphoproliferative Disorders (B-LPD), Chinese, Prevalence

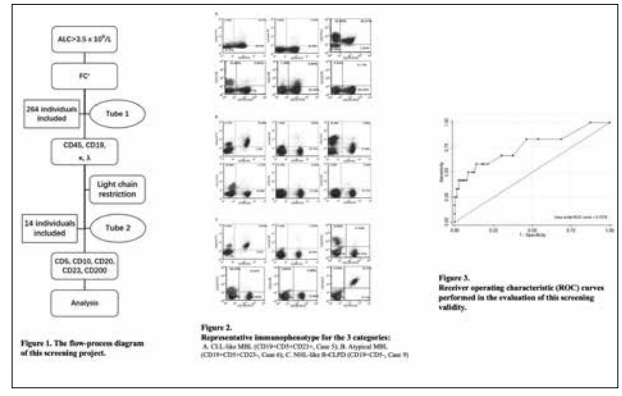

Figure 1. The flow-process diagram of this screening project.

Figure 2. Representative immunophenotype for the 3 categories: A. CLL-like MBL (CD19+CD5+CD23+, Case 5). B. Atypical MBL (CD19+CD5+CD23-, Case 6). C. NHL-like B-CLPD (CD19+CD5+, Case 9)

Figure 3. Receiver operating characteristic (ROC) curves performed in the evaluation of this screening validity.

OP03-5

Peripheral T cell lymphoma - Demographic profile and outcomes : 17 years experience from tertiary cancer centre, India

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Background: Peripheral T Cell Lymphoma (PTCL) is a rare heterogeneous group of lymphomas with aggressive behavior. It is associated with inferior outcomes compared to B cell lymphomas. We present our institute experience of treating PTCL over a period of 17 years

Methods: Patients aged between 2 and 74 years diagnosed with PTCL from 2000-2017 were analyzed retrospectively to look at baseline features, pathological subtypes, prognostic factors. Event free survival (EFS) and Overall survival (OS) were calculated using Kaplan-Meier method and the factors were compared using log-rank test.

Result: During the study period 144 patients diagnosed with PTCL were analysed, of which 101 (70%) were males and 43 (30%) were females.Mean age at diagnosis was 46 years (2-74 years). Of the 144 patients, 42 (29.2%) had limited stage (stage I/II) disease and 102 (70.8%) had advanced stage (III/IV). The most common histological diagnosis was PTCL NOS (not otherwise specified) observed in 60 patients. Anaplastic large cell lymphoma (ALCL) was seen in 65 patients. Of these, 38 were ALK positive, 8 were ALK negative and ALK status was not known in 19. The other subtypes observed were Natural Killer T Cell (NK T cell) lymphoma in 9 patients, Angioimmunoblastic T Cell Lymphoma (AITL) in 5 patients, HepatoSplenic T-cell lymphoma (HSTCL) in 2 patients, Adult T Cell Lymphoma(ATCL) in 2 patients and subcutaneous panniculitis T cell lymphoma in one patient. Patients were treated with various standard chemotherapeutic regimens including LMB 89/ BFM90/ CHOP/CHOPE/EPOCH/MACOP-B/crizotinib/Oral Metronomic chemotherapy and other salvage regimens.Stem cell transplantation(SCT) was done in 13 patients of which 5 had ASCT in first Complete Remission (CR1) and 8 had at relapse after salvage therapy.Of these 13 patients, 9 are in remission post transplantation and 4 had relapse. The median duration of follow-up was 21 months (range:1 month- 215 months), Patients with limited stage disease had an 2-year EFS and OS of 64% and 71% respectively and patients with advanced stage disease had 2-year EFS and OS of 38 % and 57% respectively. (P value for EFS is 0.006 and OS is 0.03). Patients with PTCL had a 2 year EFS and OS of 25% and 44 % respectively, ALCL had 64 % and 79% respectively (P value for EFS-0.003 and OS is 0.000). Factors (Gender, B symptoms, number of extranodal sites involvement, LDH, performance status) were analyzed in predicting EFS and OS but were statistically found to be insignificant. Early stage disease was significantly associated with better EFS and OS .

Conclusions: Majority of patients with PTCL present with advanced stage disease. Outcomes of patients with ALCL are better than those with having other histologies. Hematopoietic stem cell transplantation should be offered to high risk patients achieving good response to chemotherapy.Novel therapies are necessary to improve the outcomes.

Keyword: Peripheral T Cell Lymphoma, Demographics, Response Rates, Salvage therapies, Transplantation, Survival

Baseline clinical and Laboratory Characteristics

Parameter	Categories	PTCL+ AITCL	ALK+ ALCL	ALK- & UNKNOWN ALCL	OTHERS	ALL
Age						
	<50	30	35	19	9	93
	>/=50	35	3	8	5	51
Sex						
	male	47	28	17	9	101
	female	18	10	10	5	43
Performance status (ECOG)						
	0,1	43	19	19	11	92
	2-4	22	19	8	3	52
Stage						
	1,2	14	12	8	8	42
	3,4	51	26	19	6	102
Bulky disease						
	Yes	17	24	11	3	55
	no	48	14	16	11	89
LDH (mean;IU/L)[a]						
	Normal	9	3	8	1	21
	Elevated	50	28	16	10	104
aaIPI score[b]						
Low risk	0,1	11	7	8	3	29
Intermediate risk	2,3	32	23	15	6	76
High risk	4,5	16	1	1	2	20
B symptoms						
	Yes	25	16	14	4	59
	No	40	22	13	10	85
Ki 67[c]						
	>75%	10	11	3	3	27
	<75%	22	13	2	4	41
platelets						
	>1.5 lakh	54	32	24	11	121
	<1.5 lakh	11	6	3	3	23

a. Data available for 125 patients. b. Data available for 122 patients.

b. c.Data available for 68 patients.

OP03-6

A multicenter retrospective analysis of clinicopathologic features of monomorphic epitheliotropic intestinal T-cell lymphoma

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Background: Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) is a provisional entity in the 2017 WHO classifications of the lymphoid neoplasms, as it was found that features of MEITL differed from those of enteropathy-associated T-cell lymphoma. It is now considered that MEITL is more prevalent in Asia, and almost all cases of intestinal T-cell lymphoma in Asians might be MEITL. To further elucidate the clinicopathologic features of this new disease entity, we carried out a multicenter, retrospective analysis from 12 tertiary institutes in Korea.

Methods: A total of 42 patients who were diagnosed with MEITL between 2002 and 2017 were included in the analysis. Medical records including age, sex, stage, presenting symptoms, laboratory findings, primary sites, and treatment outcomes were collected. The histopathologic diagnoses were centrally-reviewed by experienced lymphoma histopathologists. The primary end-point of the analysis was overall survival (OS).

Result: The median age of the patients was 59 (range, 20 – 84) and 27 patients (64%) were male. None of the patients had prior history of Celiac disease. Thirty two patients (76%) were stage I-II by the Ann-Arbor classifications, and 28 patients (67%) were stage I-II1&2 by the Lugano classifications. The most frequent site of involvement was jejunum (N = 21) followed by ileum (N = 19), and 15 patients had multiple site involvement. In line with the previous reports, most cases expressed CD8 (79%) and CD56 (95%), and did not express CD30 (5%), and EBER (0%). T-cell intracellular antigen was positive in 14 out of 17 cases (82%). The median progression-free survival was 6.9 months (95% CI 4.3 – 9.6), and the median OS was 14.8 months (2.4 – 27.2). Thirty two patients (76%) received surgery, and 37 patients (88%) received chemotherapy. CHOP (N = 30) was the most frequently used regimen followed by CHOEP (N = 3), and ICE, IMVP-16, ESHAP and EPOCH (N = 1 each). Complete response (CR) rate was 38%, and there was a trend for a higher CR rate who had received etoposide-containing combinations vs. CHOP (71% vs. 37%, p = .095). Sixteen patients had undergone autologous stem cell transplantation (ASCT). Relapse or progression was documented in 24 cases, and the most frequent site was the primary site (N = 23). Of note, relapse at central nervous system was found in 4 cases. Older age (≥ 55 years), poor performance scale (2~4), advanced Lugano stage (IIE~IV), not achieving CR, and not receiving ASCT were associated with inferior OS.

Conclusions: Although most patients had limited-staged disease, the clinical outcomes of MEITL patients were dismal. While the optimal management of MEITL remains undetermined, achieving CR and consolidative ASCT seem to be essential. As CHOP might be insufficient for achieving CR, more efficient combinations should be investigated. In addition, considering the frequent local failure, as well as the CNS relapse, novel therapeutic approaches are required to improve survival.

Keyword: MEITL, Peripheral T-cell lymphoma, Prognosis

Characteristics	N (%)	Median OS (95% CI)	P
Age			0.009
< 55 years	15 (36)	25.7 (2.6 – 48.8)	
≥ 55 years	27 (64)	8.8 (0.0 – 18.0)	
ECOG PS			0.002
0~1	23 (55)	22.1 (0.2 – 44.0)	
2~4	19 (45)	6.5 (1.9 – 11.1)	
Ann-Arbor stage			0.211
I–II	32 (76)	14.8 (4.5 – 25.1)	
III–IV	10 (24)	8.7 (3.9 – 13.5)	
Lugano stage			0.010
$I–II_{1&2}$	27 (64)	18.8 (9.6 – 28.0)	
$II_E–IV$	15 (36)	4.9 (0.0 – 12.7)	
Serum Lactate dehydrogenase (N = 38)			0.779
Normal	27 (71)	14.8 (1.5 – 28.1)	
Elevated	11 (29)	13.2 (1.52 – 24.9)	
Bulky disease (> 5 cm)			0.470
No	30 (71)	18.5 (0.3 – 36.7)	
Yes	12 (29)	13.2 (0.0 – 26.8)	
Chemotherapy			> 0.001
Not received	5 (12)	1.2 (1.0 – 1.4)	
Received	37 (88)	18.5 (8.9 – 28.1)	
Response to 1st-line chemo (N = 37)			0.001
CR	16 (43)	39.1 (15.5 – 62.7)	
Non-CR	21 (57)	8.7 (4.8 – 12.6)	
ASCT (N = 37)			0.001
Not received	21 (57)	6.8 (4.0 – 9.6)	
Received	16 (43)	31.3 (17.2 – 45.4)	
First-line regimen (N = 37)			0.280
CHOP	30 (81)	14.8 (5.9 – 23.7)	
Other than CHOP	7 (19)	31.3 (3.1 – 59.5)	
Timing of ASCT (N = 16)			0.133
CR followed by up-front ASCT	4	39.1 (NE)	
PR followed by up-front ASCT	5	Not reached	
CR → PD followed by salvage ASCT	1	21.4 (NE)	
PR → salvage chemotherapy followed by salvage ASCT	4	18.8 (18.3 – 19.3)	
SD → salvage chemotherapy followed by salvage ASCT	2	12.2 (NE)	

OP04-1

Autophagy and unfolded protein response as the regulatory mechanism for the sensitivity of leukemia stem cells to G9a Inhibitor

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Background: Histone methyltransferase (HMTase) G9a has recently been emerged for the novel therapeutic target for acute myeloid leukemia (AML). However, resistance mechanism to HMTase associated cell death in leukemia cell is still elusive.

Methods: We investigated the levels of apoptosis and ER stress by G9a inhibitor BIX-01294 in leukemia cell lines. U937, cytarabine-resistant U937 (U937/AR) and KG1 were used. U937/AR cell line was established in our laboratory by exposing parental U937 cells to stepwise increasing concentrations of cytarabine.

Result: We initially examined the expression of G9a in leukemia cell lines and the primary AML cells obtained from a patient at the different time point. In U937/AR cells and primary AML cells obtained at relapse, G9a expression was increased compare to that in U937 cells and primary AML cells obtained at diagnosis, respectively. G9a expression was also increased in KG1 cells. In both of U937 and U937/AR, apoptotic cell death was induced by BIX-01294 in a dose-dependent manner. In contrast, apoptotic cell death was minimal in KG1 cells which are enriched in cells expressing a leukemia stem cell phenotype (CD34+CD38–). To address the activation of ER stress response by BIX-01294 in leukemia cells, we examined the effect of BIX-01294 treatment on PERK and eIF2α protein expression and phosphorylation levels. We found that treatment of U937, U937/AR, KG1 cells with 3μM of BIX-01294 for 24h caused an upregulation of phosphorylated PERK and eIF2α. The upregulation of PERK phosphorylation was associated with a decrease in PERK protein levels after treatment. To further address the role of the PERK phosphorylation in BIX-01294 sensitivity, we examined whether PERK inhibition using small interfering RNA (siRNA) or specific inhibitor could sensitize cells to BIX-01294–mediated death. The siRNA against PERK effectively inhibited BIX-01294–mediated phosphorylation of PERK in U937 and U937/AR cells. The addition of PERK siRNA led to a significant increase in the extent of BIX-01294–induced apoptotic cell death in U937 ($P = 0.0003$) and U937/AR ($P < 0.0001$) as compared with that of BIX-01294 treatment alone. PERK inhibitor GSK260641 significantly increased BIX-01294–induced apoptotic cell death in U937 ($P < 0.0001$) and U937/AR ($P = 0.006$) cells. To our surprise, addition of PERK siRNA or GSK260641 increased the sensitivity of KG1 cells to BIX-01294–mediated death in a dose-dependent manner ($P = 0.0003$ for siRNA, $P = 0.0053$ for GSK260641). In KG1 cells, BIX-01294 led to upregulation of beclin-1, increased LC3-II lipidation and formation of autophagosomes. Inhibition of autophagy enhanced BIX-01294-induced apoptosis in both of U937 and KG1 cells, indicating that prosurvival autophagy occurred in these cells. When PERK pathway was inhibited in KG1 cells, BIX-01294 still induced autophagy and dual inhibition of PERK pathway and autophagy significantly enhanced the apoptotic response to BIX-01294 in KG1 cells.

Conclusions: These data demonstrated that PERK activation and autophagy may have a pro-survival function to G9a inhibitor in leukemia cells including leukemia stem cells. The PERK phosphorylation arm and autophagy may represent the suitable targets for combating resistance to G9a inhibitor in AML. The mechanisms underlying the increased sensitivity of AML cells with PERK inhibition to G9a inhibitor are unclear at present and are needed to define in further studies.

Keyword: G9a, PERK, Leukemia Stem Cell, Autophagy

OP04-2

3-Methyladenine potentiates bortezomib-induced apoptosis of myeloma cell via increasing mitochondrial ROS through autophagy inhibition

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Background: Autophagy is considered a pro-survival mechanism, and cooperates with the ubiquitin proteasome system in maintaining the homeostasis of myeloma cells by degrading excessive and misfolded proteins for energy recycling. Therefore, the inhibition of autophagy could effectively induce death in myeloma cells, and synergize with proteasome inhibitors. The aim of this study is to investigate the mechanism of myeloma cell death induced by bortezomib (BTZ) and its crosstalk with autophagy, mitochondrial reactive oxygen species (ROS) and redox enzymes.

Methods: The change of autophagy, apoptosis, mitochondrial ROS and cellular level of redox enzymes, especially peroxiredoxin (Prx), thioredoxin (Trx), thioredoxin reductase (Trx-R) were studied using human myeloma cell lines, MM.1S and MM.1R with BTZ treatment. To evaluate the status of oxidation for redox enzyme, sulfinic acid (SO2) or multimeric form of Prx, Trx and Trx-R using western blot using non-reducing or reducing gel were studied.

Result: Mitochondrial over cytosolic ROS of MM cells was elevated significantly after 24 hour of BTZ (2.5 nM). Apoptosis of MM cell after BTZ treatment was increased in concordance with mitochondrial ROS increment of MM cells. N-acetylcystein (NAC) reversed BTZ-induced mitochondrial ROS elevation and apoptosis of MM cells as well. Increased expressions of cleaved caspase-9 and cleaved caspase-3 were also observed during BTZ-induced MM cell apoptosis. LC3-II expression was elevated along with increment of mitochondrial ROS and apoptosis of MM cells after BTZ treatment. Oxidation of PRX4 and TRX2 was observed during BTZ-induced apoptosis of MM cells. After treatment of NAC, LC3-II and PRX4/TRX2 expression was reversed. Inhibition of autophagy with 3-Methyladenine (3-MA) resulted in a further increase in BTZ-induced apoptosis and mitochondrial ROS in MM cells. When auranofin, a TRX-R2 inhibitor, was administered to MM cells, the oxidation of TRX-R2 and PRX4 by multimerization was observed simultaneously with the increase of autophagy and apoptosis, similar to that of bortezomib.

Conclusions: Our experiment showed crosstalk between autophagy and mitochondrial ROS and its redox enzymes during BTZ-induced MM cell apoptosis. Autophagy is induced during BTZ-induced MM cell apoptosis. Inhibition of autophagy with 3-MA potentiates BTZ-induced apoptosis of MM cells through increasing mitochondrial ROS. Our results provide new perspective on the cellular mechanism of action of BTZ and support the synergism of BTZ together with autophagy inhibitor in multiple myeloma cells.

Keyword: ROS, Autophage, Myeloma, PRX

OP04-3

Adoptive transfer of type 1-Regulatory T cell ameliorates GVHD by partial differentiation into Foxp3+CD4+T cell with CTLA-4 and ICOS dependent manner

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Background: Regulatory T cells are a component of the immune system involved in modulating immune reactions and in inducing tolerance. Among the various CD4+ regulatory T-cell subsets, CD4+CD25+Foxp3+ regulatory T (Foxp3+ Treg) cells and interleukin (IL)-10-producing type 1 regulatory T (Tr1) cells have been the subject of in vivo and in vitro studies. Among the several roles of Foxp3+ Treg cells, when there is enough Foxp3 cells functionally, they play an essential role in suppressing with effector T cells proliferation, cytokine production, and immune response to alloantigens in models of autoimmunity and organ transplantation. These results support a basic concept that Treg cells could be used for a therapeutic purpose to manage GVHD. Compared with Foxp3+ Treg cells, Tr1 cells do not constitutively express CD25 or Foxp3. Tr1 cells are distinct from Foxp3+ Treg cells because of their unique cytokine expression profile. Interleukin (IL)-10-producing type 1 regulatory T (Tr1) cells, which are Foxp3– memory T lymphocytes, play important roles in peripheral immune tolerance. Therefore, we hypothesize that adoptive transfer of Tr1 cells also will exert immunoregulatory effects in an animal model of GVHD after allogeneic HSCT.

Methods: We investigated whether Tr1 cells exert immunoregulatory effects in a mouse model of acute graft-versus-host disease (GVHD). Mouse CD4+T cells were induced to differentiate in vitro into Tr1 cells using vitamin D3 and dexamethasone, and these donor-derived Tr1 cells were infused on the day of bone marrow transplantation.

Result: More than 45% portion showed a co-expression of LAG-3 and CD49b in CD4+ cells and high expression of IL-10. Based on these results, our generated cells had fulfilled the characteristics of general Tr1 cells. Although the absence of specific surface markers that uniquely identify Tr1 cell, Gagliani et al. showed a highly representative method for Tr1 cell counts by using the coexpression

of LAG3 and CD49b. Tr1 cells, which were more than 45% of the purity and highly expressed IL-10, were consequently used for this study. The Tr1 cell-transferred group showed less weight-loss and a twofold higher survival rate than the GVHD group, together with markedly decreased histopathologic grades. It was associated with the expansion of CD4+IL-4+ type 2 T-helper (Th2) cells and CD4+CD25+Foxp3+ regulatory T (Treg) cells. Furthermore, Tr1 cells decreased the numbers of CD4+interferon (IFN)-γ+ Th1 and CD4+IL-17+ Th17 cells. Recipient mice harboured some Foxp3+ Tregs due to adoptive transfer of Tr1 cells, together with the up-regulated expression of costimulatory molecules, including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and inducible T-cell co-stimulator (ICOS); however, the Treg cells did not show plasticity. Therefore, adoptive Tr1 cell therapy may be effective against manifestations of GVHD, exert immunomodulatory effects in a manner dependent on CTLA-4 and ICOS, and induce differentiation of the transferred Tr1 cells into Foxp3+ Treg cells.

Conclusions: Adoptive transfer of Tr1 cells improved the survival outcomes and clinical manifestations of acute GVHD after allo-BMT. Tr1 cell-based therapy resulted in downregulation of Th1/Th17 responses and upregulation of Th2/Th1 responses in a manner dependent on CTLA-4 and ICOS; moreover, some of the transferred Tr1 cells differentiated into Foxp3+ Treg cells. In addition, the transferred Tr1 cells were stable, non-plastic, and enhanced immune tolerance. These findings may facilitate the development of novel therapeutic interventions for GVHD after allo-BMT.

Keyword: Tr1 cell, Graft-Versus-Host disease, Foxp3+Treg

OP04-4

Understanding thrombocytopenia: Role of microRNA in neonatal and adult megakaryopoiesis

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Background: Neonatal cord blood (CB) cells are promising alternatives to adult bone marrow (PB) in cellular therapies. CB cells have potential to develop into specialized cells, such as erythrocytes or megakaryocytes (MK). MKs are responsible for production of platelets and thrombocytopenia is a condition caused by a low platelet count (<150 x 109/L), which is common among sick infants. We hypothesize that developmental differences between CB and PB-MKs contribute to the vulnerability of neonates to develop severe thrombocytopenia. Non-coding microRNAs (miRNAs) may play a critical role in the regulation of the development of megakaryocytopoiesis. miRNAs have been shown to be involved in regulation of stem-cell differentiation in normal as well as malignant hematopoiesis, but their role in regulation of biological differences between adult and neonatal megakaryopoiesis is unknown.

Methods: Human cord blood (CB) and peripheral blood (PB) derived CD34+ cells were cultured in the presence of thrombopoietin for 14 days. Cultures expressing >90% CD41+ by flow cytometry were collected and 88 miRNAs involved in stem cell development and differentiation were examined. miRNA validation studies were performed in cell line models.

Result: The largest developmental difference was observed with miR-9, which was expressed 22-fold higher in neonatal MKs compared to adult. Furthermore, RUNX1 has emerged as a putative target of miR-9 by several bioinformatic databases, such as TargetScan, miRbase, and RNAhybrid. RUNX1 sequence, which miR-9 binds to, is conserved among vertebrates, showing the functional significance of the miR-9/RUNX1 axis during evolution. We compared hsa-miR-9 expression levels at different time points during MK development in neonates versus adults and found a constitutively increased pattern of hsa-miR-9 expression through all stages of neonatal MK development compared to adult. Whereas, RUNX1 expression was significantly lower through all the stages of neonatal MK development compared to adult. miR-9/RUNX1 axis was confirmed by a miR-9 mimic transfection study in a megakaryocytic leukemia cell line (Meg01). Interestingly, reduced expression of RUNX1 and increased rate of cell proliferation was observed in miR-9 mimic transfected cells as compared to control.

Conclusions: The present study shows functional significance of hsa-miR-9 in regulation of cell proliferation by targeting RUNX1 in human MKs development. Higher expression of miR-9 may contribute to the developmentally different and disease susceptible phenotype of neonatal MKs via regulation of RUNX1 expression. Therefore, it could be a potential target in neonatal thrombocytopenia and other platelet disorders.

Keyword: Megakaryocyte, Thrombocytopenia, MiRNA, RUNX1, Platelets

OP04-5

The expression level of prohibitin 2 as mitochondrial autophage receptor matches the prognostic chromosomal aberrations of hematological malignancies

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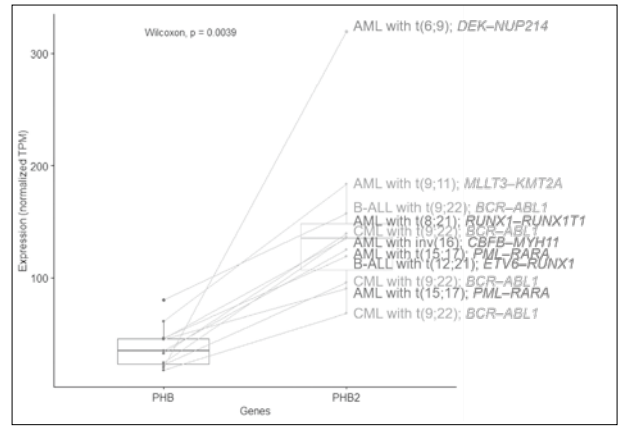
Background: Prohibitin (PHB) is a highly conserved class of proteins first discovered as inhibitors of cellular proliferation. Since then PHBs have been found to have a significant role in transcription, nuclear signaling, mitochondrial structural integrity, cell division, and cellular membrane metabolism, placing these proteins among the key regulators of pathologies such as cancer, neuromuscular degeneration, and other metabolic diseases. Recently, prohibitin 2 (PHB2) has been known to be involved in mitochondrial autophage (mitophage) as an inner mitochondrial membrane receptor. This study investigated how the severity of mitochondrial membrane damage, represented by the level of PHB2 gene expression, correlates with the diagnosis and prognostic cytogenetic abnormalities of hematological malignancy.

Methods: Messenger RNA sequencing (mRNA-Seq) was performed to measure the expression level of PHB in 11 patients who were diagnosed as hematological malignancies with recurrent genetic abnormalities (4 AMLs, 2 APLs, 2 B-ALLs, and 3 CMLs). Libraries were prepared with 1 ug of total RNA from bone marrow aspirates at initial diagnosis. Indexed libraries were then sequenced in the HiSeq2500 platform (Illumina, SanDiego, CA). The sequencing data was mapped to human reference transcripts (GRCh37 assembly in Ensembl) using HiSAT2 aligner (v2.1.0). Gene expression levels was measured as TPM unit using StringTie (v1.3.4) and normalized to 5 housekeeping genes. Statistical analysis and graphics were performed using R (v3.5.1).

Result: Expression level of PHB2 gene showed the strong prognostic predictor of hematologic malignancies. In AML, when listed in descending order of PHB2 expression level, it coincided with AML prognosis exactly: 319.8 as normalized TPM in AML with t(6;9) (poor-risk); 183.3 in AML with t(9;11) (intermediate risk); 138.9 in AML with t(8;21), 134.8 in in AML with inv(16), 125.0 and 90.1 in AML with t(15;17) (favorable risk) (Figure 1). Also, the expression level of PHB2 in ALL represented disease risk: 157.2 in B-ALL with t(9;22) (poor risk); 118.6 in B-ALL with t(12;21) (good risk). In 3 CML cases, the expression levels of PHB2 were relatively suppressed as 136.2, 95.5, and 68.1 than those of acute leukemia.

Conclusions: In this study, the severity of mitochondrial membrane damage, represented by the level of PHB2 expression, could exactly correlate and stratify the disease diagnosis and prognosis in 11 cases of leukemia. These preliminary results might highlight on the impact of mitophage on the key mechanism of molecular pathology and oncogenesis of leukemia as well as new diagnostic marker and therapeutic target.

Keyword: Prohibitin 2, Mitochondria, Hematological Malignancy, Prognosis, Risk Assessment, Biomarkers



OP04-6

Epigallocatechin gallate suppresses interleukin-1β Secretion by inhibition of NLRP3 inflammasome

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Background: Epigallocatechin gallate (EGCG) is a polyphenol

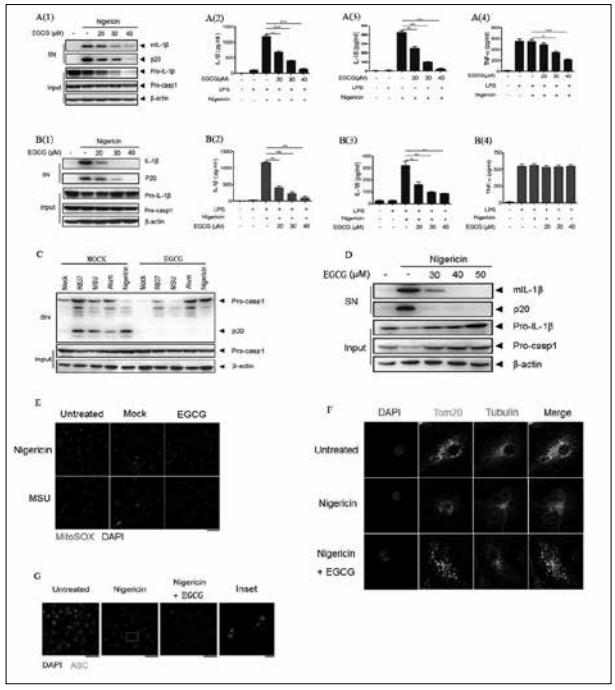
isolated from tea leaves compound with antibacterial, antiviral, antioxidant, anti-inflammatory and antitumor properties. In spite of this, the study of its biological mechanisms is far from thorough. Therefore, by using mouse bone marrow-derived macrophages (BMDMs) experiments, we hope to elucidate the inhibitory effect of EGCG on NLRP3 inflammasome and to investigate the mechanism by which EGCG inhibits the activation of NLRP3 inflammasome.

Methods: 1. Cell culture and stimulation: LPS-primed BMDMs were stimulated with MSU (150 μg/mL), Alum (300 μg/mL), and R837 (15 μg/mL) for 6 h or with nigericin (10μM) for 40 min to activate NLRP3 inflammasome. 2. Enzyme-Linked Immunosorbent Assay (ELISA) assays were used to detect IL-1β, IL-18, TNF-α in cultural supernatant. 3. Western blot was used to analyze p20, IL-1β, ASC dimer, NLRP3, actin expressionin cultural supernatant or macrophage lysates. 4. Assay the activity of enzyme in culture supernatant using LDH release in an attempt to analyze the effect of EGCG on cytotoxicity and pyroptosis induced by NLRP3-caspase-1 pathway activation. 5. To analyze cell fluorescent protein expression, Confocal laser scanning microscopy was used: MitoSOX for labeling ROS, Mito-tracker Deep Red for labeling mitochondria, mitochondrial for labeling protein TOM20, tubulin for labeling cell microtubules, ASC primary antibody and fluorescent secondary antibody for labeling ASCspeckles. 6. To analyze relative concentrations of NAD+ levels in different groups of cells, intracellular NAD+ levels were detected by using NAD/NADH quantification kit.

Result: 1. In mouse BMDMs experiments, EGCG was given before LPS primed BMDMs, and WB results showed that EGCG inhibited pro-IL-1β expression, caspase-1 activation and IL-1β secretion at 20-40 μM in a dose-dependent manner (Figure A); ELISA results showed the reduced secretion of IL-1β, IL-18, TNF-α ($P < 0.01$). 2. After LPS primed BMDMs, EGCG was administered and NLRP3 inflammasome was activated with nigericin. WB results showed that EGCG inhibited caspase-1 activation and IL-1β secretion at 20-40 μM in a dose-dependent manner(Figure B). 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 stimulus were used to activate NLRP3 inflammasome. WB found that EGCG down-regulated the activation of caspase-1(Figure C). 4. WB results showed that EGCG 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(Figure D). 5. Increased mitochondrial damage was found in the process of EGCG inhibition of NLRP3 inflammasomes activation induced by nigericin or MSU, including the detection of indicators such as ROS, ΔΨm, NAD+ (Figure E). 6. Imaging showed that EGCG prevented nigericin-induced translocation of impaired mitochondria to perinuclear area, and this microtubule-driven mitochondrial spatial localization process does not depend on microtubule acetylation level(Figure F). 7. Imaging indicated marked reduction of ASC speckles(Figure G).

Conclusions: 1. EGCG specifically inhibites the priming, assembly and activation of NLRP3 inflammasome; 2. EGCG inhibites the activation of NLRP3 inflammasome by blocking spatial localization of damaged mitochondria and the formation of ASC dimers and ASC speckles.

Keyword: EGCG, NLRP3, IL-1β, Inflammation



OP05-1

HLA-G-ILT2 interaction contribute to suppression of marrow B-cell growth in acquired aplastic anemia

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Background: Human leukocyte antigen-G (HLA-G) is a kind of non-classic I major histocompatibility complex antigen characterized by low polymorphism, restricted tissue distribution and spliced transcripts which encode four membrane-bound isoforms(mHLA-G, G1-G4) and three soluble protein(sHLA-G, G5-G7). HLA-G interacts withmultiple cell subsets such as T cells and B cells, and exerts pow-

erful immune suppression by binding with its receptors, immunoglobulin-like transcript (ILTs). As a paradigm of bone marrow failure syndrome, acquired aplastic anemia(AA) was thought to be a specific autoimmune disease for the aberrant T-cell immune homeostasis. And there was no data referred to the role of HLA-G on AA.

Methods: Human bone marrow mononuclear cells (BMMCs) and plasma were obtained from 31severe AA (SAA) patients, 15 non-severe AA(NSAA) patients and 28 healthy individuals. The concentration of sHLA-G in bone marrow plasma was determined by enzyme-linked immunosorbent assay. The relative expression level of HLA-G, ILT2 and ILT4 in BMMCs were quantified by real time polymerase chain reaction. Besides, the percentage of mHLA-G+, ILT2+ and ILT4+ cells in CD4+, CD8+, CD14+ and CD19+ BMMCs were respectively analyzed by flow cytometry (FCM).ILT2 level in different stage of marrow B cells was analyzed by FCM, in which mAbs targeted surface IgD (sIgD), sIgM, ILT2 and CD19 were used to stain BMMCs.Brdu incorporation rate of CD19+ marrow cells was compared using recombinant human HLA-G protein, AA bone marrow supernatant, anti-HLA-G and anti-ILT2 monoclonal antibodies.

Result: The concentration of sHLA-G in marrow plasma of AA patients was much higher than that in controls but no difference was found between SAA group and NSAA group.At transcriptional level, the ILT2 mRNA expression in AA group was elevated compared with control group while the HLA-G and ILT4 mRNA level was similar in the two groups. In addition, the percentage of CD19+ lymphocytes were downregulated in AA group, and the ratio of ILT2+ lymphocytes on CD19+BMMC in AA patients was significantly higher than in controls. The proportion of mature B cells among CD19+ B lymphocytes in BM from AA patients was significantly higher than from healthy subjects, while percentage of pro-B plus pre-B cells was much lower. ILT2-expressing cells in immature B cells and pro-B plus pre-B cells from AA patients was much more than from controls, in mature B cells ILT2 expression was similar between the two groups.The marrow B cells from healthy individuals co-cultured with HLA-G protein and AA patients' supernatant showed obviously decreased Brdu incorporation rate compared with control group. Anti-HLA-G mAb and anti-ILT2 mAb could reverse the effect and increase the Brdu incorporation rate.

Conclusions: Together, our results showed HLA-G/ILT2 was aberrantly expressed in AA patients' marrow cells, especially in the CD19+lymphocytes which indicated HLA-G/ILT2 tooka possible role in the abnormal humoral immunity in AA and blockade of HLA-G/ILT2 might be a reasonable therapeutic strategy for AA .

Keyword: Aplastic Anemia, HLA-G, ILT2

OP05-2

A phase 3, multicenter, noninferiority study of ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors

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Background: Ravulizumab (ALXN1210), a new complement C5 inhibitor with high C5 affinity and half-life 3-4 times longer than eculizumab, provides immediate, complete, and sustained C5 inhibition with extended dosing intervals. This phase 3, open-label study assessed the noninferiority of ravulizumab to eculizumab in complement inhibitor–naive adults with paroxysmal nocturnal hemoglobinuria (PNH).

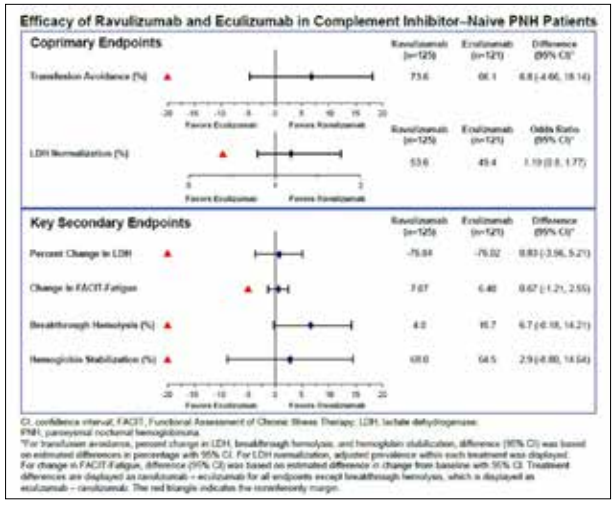
Methods: Patients with lactate dehydrogenase (LDH) ≥1.5 times the upper limit of normal and at least one PNH symptom were randomized 1:1 to receive ravulizumab or eculizumab for 183 days (N=246). Coprimary efficacy endpoints were proportion of patients remaining transfusion-free and LDH normalization. Secondary endpoints were percent change from baseline in LDH, change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score, proportion of patients with breakthrough hemolysis, stabilized hemoglobin, and change in serum free C5.

Result: Of 285 pts screened, 246 from countries across the Asia-Pacific region, Europe, and North and South America were randomized. All 125 ravulizumab pts and 119/121 eculizumab pts completed 26 wks of treatment. Ravulizumab was noninferior to eculizumab for both coprimary and all key secondary endpoints (Pinf < .0001): transfusion avoidance (73.6% versus 66.1%; difference of 6.8% [95% confidence interval (CI), -4.66, 18.14]), LDH normalization (53.6% versus 49.4%, odds ratio [1.19 (0.80, 1.77)]),

percent reduction in LDH (-76.8% versus -76.0%; difference [95% CI], -0.83% [-5.21, 3.56]), change in FACIT-Fatigue score (7.07 versus 6.40; difference [95% CI], 0.67 [-1.21, 2.55]), breakthrough hemolysis (4.0% versus 10.7%; difference [95% CI], -6.7% [-14.21, 0.18]), and stabilized hemoglobin (68.0% versus 64.5%; difference [95% CI], 2.9 [-8.80, 14.64]). Immediate, complete, and sustained inhibition of C5 (mean free C5 <0.5 µg/mL) was observed by end of first infusion of ravulizumab. Most frequently reported treatment-emergent adverse event (AE) was headache (36.0%/33.1% in pts receiving ravulizumab/eculizumab). Serious AEs were experienced by 8.8%/7.4% in the ravulizumab/eculizumab groups. There were no meningococcal infections.

Conclusions: Ravulizumab given every 8 weeks achieved noninferiority compared with eculizumab given every 2 weeks for all efficacy endpoints, with a similar safety profile. This trial was registered at ClinicalTrials.gov #NCT02946463.

Keyword: PNH, Ravulizumab, Eculizumab, Breakthrough Hemolysis



OP05-3

Prediction of thrombosis risk in patients with paroxysmal nocturnal hemoglobinuria

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematopoietic stem cell disease with high thrombosis rate which can be lethal for PNH patients. Because of the high mortality rate of thrombosis, it is very necessary to distinguish PNH patients with high risk of thrombosis in the early stage of the disease and to take targeted anticoagulant interventions early to reduce the bad prognosis of thrombosis.

Methods: By retrospectively analyzing the current known clinical and genetic indicators that may be associated with thrombosis in PNH patients, we tried to set up a system to predict the thrombosis risk with reference to the Framingham coronary heart disease risk model. Each patient with thrombosis was scored according to the model and validated based on actual thrombosis situation.

Result: There were 99 patients with PNH enrolled in the study, consisting of 55 males and 44 females, with a median age of 40 at the time of diagnosis, 17 patients had at least one thrombosis event at a median time of 48 (23-91) months of follow-up. Factors like PNH clone size, presence of thrombosis genes (rs495828), platelet count, and hemoglobin level at the time of diagnosis may be associated with thrombotic risk by univariate analysis and was calculated later in the prediction system. According to the model, patients with thrombosis had higher scores (score 23) than those without (score 12, P<0.001). Patients classified as low-risk (score less than 15), middle-risk (score 16-22) and high-risk (score over 23) had thrombosis rates of 6.90%, 13.60% and 62.50%, respectively (P<0.001). Compared with non-high-risk (middle-risk combing with low-risk) group, high-risk group showed higher cumulative incidence of thrombosis in 5 years (P<0.001). The median time of developing thrombosis after the diagnosis was 8.5m (1-36m) and 18m (5-67m), respectively in high-risk and non-high-risk group (P=0.043).

Conclusions: We established a thrombi risk prediction model for PNH. In this model, patients with thrombosis scored higher than those without. Patients identified as high-risk had higher incidence and cumulative incidence of thrombosis than other patients, and developed thrombosis earlier as well.

Keyword: Paroxysmal Nocturnal Hemoglobinuria (PNH), Thrombosis, Risk score, Prediction Model

OP05-4

High prevalence of anemia in elderly in South Korea: Urgent health-care problem before post-aged society-base on data from the KNHANES

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Background: South Korea is heading to post-aged society rapidly. Anemia in elderly populations have been reported to be wide spread compared to younger populations, and known to be related to great risk and mortality. However, national data of prevalence and characteristics of anemia in aged groups are not available yet in Korea. Purpose of this study is to evaluate the prevalence and characteristics of anemia in elderly populations, and analyze its associated risk factors by analyzing the data of National Health and Nutrition Examination Survey (KNHANES).

Methods: Data from the Korean National Health Nutrition Examination Survey (KNHANES) conducted from 2007 and 2016 were merged and analyzed. Analysis of the etiologies of anemia were conducted with the data of 2010 to 2012

Result: Prevalence of anemia in populations with age over 65 year was 14.0% (CI 95%, 13.3~14.7) in total, whereas the prevalence of anemia in populations with age under 65 year was 6.4% (CI 95%, 6.2~6.6). Prevalence of anemia in populations with age over 80 year was much higher (24.0% (CI 95%, 22~26)). Difference of prevalence of anemia according to the sex was predominant (12 % (CI 95%, 11~13) vs 16% (CI 95%, 15~17), P<0.001). Prevalence of anemia in population age over 65 years were analyzed according to the year of survey conducted, which were shown constantly from 9.0% to 12.7%. IDA was consist of 4.9% (CI 95%, 3.1~7.5) of elderly anemia, and chronic renal failure and liver cirrhosis were 0.8% (CI 95%, 0.3~1.8) and 84.6% (CI 95%, 37.8~98.0), respectively. Exact percentage of anemia associated to cancer and cerebro-cardiac vascular disease were not analyzed due to too many missing values. However, in risk analysis, underweight (BMI < 18.5) (OR 2.446 (CI 95%, 1.901~3.147), P<0.001), being beneficiary of social allowance (OR 1.649 (CI 95%, 1.259~2.159), P<0.001), had been suffered from cerebro- or cardiac vascular disease (OR 1.530 (CI 95%, 1.237~1.891), having cancer (OR 1.615 (CI 95%, 1.082~2.411), P=0.019), having chronic renal failure (OR 27.442 (CI 95%, 3.136~240.151), P=0.003) were strongly associated to risk of anemia. Insecurity in food supply, having other chronic disease (diabetes mellitus, hypertension, dyslipidemia, pulmonary tuberculosis, and liver cirrhosis) didn't showed statistically significant relation to risk of anemia.

Conclusions: South Korea is expected to become post-aged society soon. Prevalence of anemia in elderly population in South Korea was shown higher than the other data of previous studies. Further attentions and studies on etiologies and risk factors in elderly population are desperately needed.

Keyword: Aged, Anemia, South Korea, Prevalence

OP05-5

Vitamin-D and biochemical status in young children with beta-thalassemia major

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Background: Patients with Thalassemia major (TM) require lifelong blood transfusions for survival. However, iron toxication due to long-term blood transfusion in TM patients is the leading cause of devastating outcomes including endocrinopathies, osteoporosis, skeletal deformities, and solid organ failures. Young TM children with regular blood transfusion often have limited signs of severe complications. Therefore, close monitoring of the biomedical status in young children with TM is important to discover subclinical symptoms for early diagnosis and to predict prognosis.

Methods: Thirty-two children diagnosed with homozygous beta-Thalassemia major attended our department for regular blood transfusion to maintain a hemoglobin level of 90-105mg/L between January to June 2018. Clinical data of these patients were reviewed retrospectively and assessed for their demographic characteristics and serum biomedical status. Statistic analysis was performed by Prism GraphPad software. A p value less than 0.05 was considered statistically significant. This project was approved by the Ethics Committee at Shenzhen Children's Hospital.

Result: The age of the patients range from 1 to 12 years old (mean ± SD, 5±3 years old). The mean age at diagnosis was 14±15 months (mean ± SD) after birth. Nearly all patients (29/31) started their first blood transfusion at the age of diagnosis. The patients included 19 boys and 14 girls. Most patients (28/32) were on regular chelating therapy with at least one of the common chelating agents including DFM, DEF, and DFO. The mean age at the start of chelating therapy was 3±2 years old (mean ±SD). Half of the patients (16/32) had daily oral Vitamin D or calcium supplementations while nearly 16% (5/32) of them took Vitamin D or calcium tablets occasionally. Around one third (11/32) of the patients never had any oral supplementations. The biomedical status of the patients was assessed. Each patient had a moderate to severely elevated serum ferritin level compared to the normal range. Furthermore, patients were distributed into two groups based on the median age (<5 years old vs. ≥5 years old) for comparisons. Serum ferritin was significantly higher in children ≥5 years old than children <5 years old (*p<0.05, 1512±192.6 vs. 2337±299.8ng/ml, unpaired Student's t test). 25-hydroxyvitamin D (25(OH)D3) level was significantly lower in the

older children group (**p<0.01, 34.25±11.06 vs. 23.05±9.95ng/ml, unpaired Student's t test). No differences were observed in serum calcium, phosphorus, and alkaline phosphatase level between the two age groups of children. Liver functions were evaluated by testing serum ALT, AST, GGT, TBIL, and ALB levels. ALT was significantly increased in children ≥5 years of age (*p<0.05, 19.17±2.44 vs. 43.45±9.82IU/ml, unpaired Student's t test). The serum concentrations of AST, GGT, TBIL, and ALB showed no significant differences between the two age groups of children. In addition, no significant differences were discovered in the kidney and thyroid functions in both groups of patients.

Conclusions: Our results suggest that iron accumulation in older children may contribute to lower serum 25(OH)D3 and higher serum ALT level. Low level of serum 25(OH)D3 is a sign of vitamin D deficiency which could lead to osteopenia and skeletal disorders when grow older. ALT is a sensitive sign of liver malfunction due to iron overload in hepatic tissues. These findings provide critical guidance for clinicians of when to intervene to prevent severe complications in young TM children.

Keyword: Thalassemia Major, Vitamin D Deficiency, Blood Transfusion, Iron Overload, Pediatric

OP05-6

Application of rapamycin up-regulating treg cell ratio in children with chronic refractory immune cytopenia - A single-center case series

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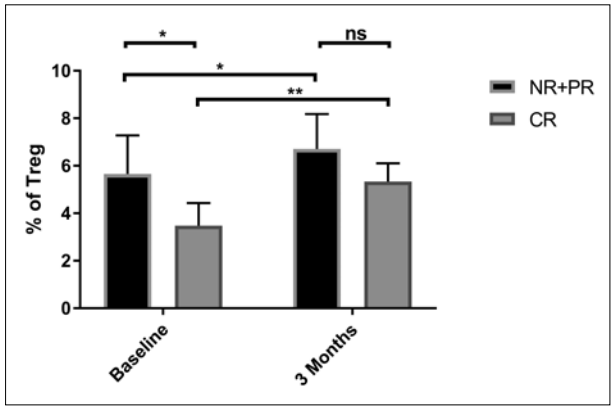
Background: Patients with autoimmune cytopenias are often refractory to standard therapies requiring chronic immunosuppression with medications with limited efficacy and high toxicity. Inhibiting the mTOR signaling pathway increased CD4 + CD25 + Foxp3 regulatory T cells (Treg cells) ratio is expected to control the progress.

Methods: This study was a single-center continuous case observational study. Recording items included baseline data, flow cytometry to detect lymphocyte subsets, treatment options, safety and efficacy. Rapamycin treatment: daily oral administration of rapamycin at 1.5 mg/m2, and weekly blood test concentration to adjust the dose to 5-15 ng/ml, two consecutive The blood concentration and liver function were monitored monthly after the blood concentration was stabilized. For the detection of Treg CD4+CD25+Foxp3+ cells, the cell surface and intracellular antigens were determined on the fresh cells at the time of the sample submission by cell staining. Two hundred microliters of cell suspensions were added to 5μl of appropriate solution of anti-CD25 and anti-CD4. Next, the mixture of cells and antibodies were incubated for 30min at 4℃ in the dark, fixed with fixation buffer, and washed twice by adding 1ml of cold 1X permeabiliztion buffer. The next step was incubation with anti-Foxp3.

Result: We present data on 11 patients using sirolimus as monotherapy. The overall effective rate (partial response and complete remission) at three months was 72.7% (8/11): 1 AIHA and 2 ES patients achieved complete remission. The others (ITP) was 62.5% (5/8 cases). Treg cells in 7 patients (7/11 patients, 63.6%) before treatment were lower than the normal range (5%-10%): 3.6% (2.0%-4.2%). After 3 months of treatment with RAPA, Treg in peripheral blood The cells were significantly elevated (P = 0.001) to 6.0% (4.3%-7.0%), and all of the 7 patients achieved partial remission (2 cases) or complete remission (5 cases). Four patients with Treg cells at least 5% of Treg cells had no significant increase in Treg cells after rapamycin treatment (P>0.05), 2 (50%) were partially relieved, and 2 (50%) were ineffective. The children were statistically analyzed according to the complete effective (CR) group and the non-completely effective group (PR+NR): the proportion of Treg cells before and after administration in the CR group (%) were 3.48±0.95 and 5.34±0.76, respectively. The proportion of Treg cells (%) was 5.65 ± 1.63 and 6.71 ± 1.46, respectively. The results suggest that: (1) The proportion of Treg cells before and after taking the drug was significantly increased in the CR group (P=0.007) and the PR+NR group (P=0.029).(2) In the CR group, The proportion of Treg cells before administration was significantly lower than PR+NR group (P=0.028); (3) There was no significant difference in the proportion of Treg cells between CR group and PR+NR group (P=0.09)

Conclusions: Treg increased significantly after three months of rapamycin treatment. Children were divided into complete effective (CR) group and non-fully effective group (PR+NR) according to the curative effect. The proportion of Treg cells in CR group was significantly lower than that in PR + NR group before rapamycin. The results suggest that regulation of Treg cells is expected to control childhood chronic refractory immune-related cytopenia.

Keyword: Chronic Refractory Immune Cytopenia, Treg, Rapamycin



OP06-1

Predictive role of circulating immune cell subtypes early after allogeneic hematopoietic stem cell transplantation in patients with acute leukemia

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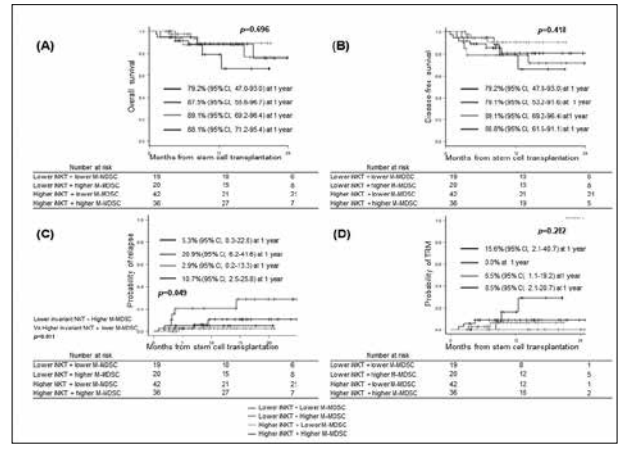
Background: Cells of innate immunity normally recover in the first weeks to months after allogenenic hematopoietic stem cell transplantation (allo-HSCT). Their relevance in terms of graft-versus-host disease (GVHD) and graft-versus-leukemia (GVL) effect is largely unknown. The predictive role of early recovery in the immune cells on acute GVHD and GVL effect after allo-HSCT was investigated in patients with acute leukemia who achieved the first complete remission.

Methods: Peripheral blood samples were taken at the median of 14 days (range, 12_29 days) after allo-HSCT. A cohort including 119 samples and characteristics of patients were analyzed. Immune cell populations were identified by flow cytometry.

Result: The median age was 49.0 years (range, 21_69) at transplantation. Univariate analysis showed that age less than 40 years old, lower frequencies of CD8+ T cells, invariant natural killer T (iNKT) cells, monocytic myeloid derived suppressor cells (M-MDSCs) and higher frequency of immature MDSCs were associated with occurrence of grade III-IV acute GVHD. Multivariate analyses showed that iNKT cells (hazard ratio (HR), 0.453, 95% CI, 0.091_0.844, p=0.024) and M-MDSCs (HR, 0.271, 95% CI, 0.078_0.937, p=0.039) were independent factors. Combination of higher frequencies of both cell subsets was associated with lower incidence of grade III-IV acute GVHD, whereas patients with lower frequency of iNKT cells and higher frequency of M-MDSCs showed significant higher probability of relapse.

Conclusions: iNKT cells and M-MDSCs could be relevant cell biomarkers for predicting acute GVHD and/or relapse in acute leukemia patients treated with allo-HSCT.

Keyword: Invariant NKT Cells, Myeloid-Derived Suppressor Cells, Acute Leukemia, Graft-Versus-Host Disease, Graft-Versus-Leukemia Effect, Allogeneic Hematopoietic Stem Cell Transplantation



OP06-3

The outcome of hematopoietic stem cell transplantation (HSCT) in pediatric patients with hemophagocytic lymphohistiocytosis (HLH) in Korea

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; On Behalf of Korean Histiocytosis Working Party

Background: HSCT is an established treatment modality for familial HLH (FHL), recurrent or refractory HLH despite chemoimmunotherapy, and CNS disease.

Methods: The Korea Histiocytosis Working Party retrospectively collected nation-wide data from the patients diagnosed with HLH and underwent allogeneic HSCT between 2009 and 2017. The clinical characteristics and treatment outcomes of the patients were analyzed.

Result: A total of 44 patients were enrolled. There were 31 patients with FHL (4 FHL2, 26 FHL3, and 1 FHL4), 7 infection associated HLH, and 6 secondary HLH of unknown cause. All the patients were treated with HLH-2004 protocol, and 30 patients achieved complete response (CR) after treatment for 8 weeks, while 14 did not. The main reasons for receiving transplantation were FHL in 26, reactivation in 17, and refractory disease in 1. The conditioning regimens were busulfan-based in 16 patients, fludarabine-based in 4, treosulfan-based in 7, and busulfan/fludarabine-based in 17. Stem cell sources used for HSCT were from peripheral blood in 36 patient, cord blood in 7, and bone marrow in 1. The donor types of HSCT were unrelated donor in 33 patients and related in 11 (7 matched sibling donor, 4 haploidentical donor, 1 partially matched donor). The causes of death of 7 patients were disease reactivation/progression in 3, acute GVHD with/without VOD in 3, and graft failure in 1. Five year overall survival rates were 82.4%, respectively. The disease status at the time of HSCT was CR in 37 patients, and non-CR in 7. The 5-year survival rate of patients who received HSCT in CR was 87% and 63% for patients transplanted while in non-CR status (p=0.046). Patients who received HSCT using peripheral blood stem cells had a better 5-year survival rate of 86% compared to 75% of patients who received cord blood stem cells, significantly. The presence of neurologic symptoms, disease status after intial 8 week therapy, conditioning regimen, and CD 34 positive cell count did not have statistically significant impact on survival.

Conclusions: HSCT improved the survival of patients who had familial, or relapsed, or refractory HLH in the Korean nation-wide HLH registry. These results are similar to other reports in the literature. The disease status at the time of HSCT and the stem cell source of the transplant were the important prognostic factors that affected the survivals of the HLH patients who underwent HSCT.

Keyword: Hemophagocytic Lymphohistiocytosis, Hematopoietic Stem Cell Transplantation, Familial HLH, Pediatric, Genetic Diagnosis, Korea

OP06-4

HLA-haploidentical transplantation for thalassemia major using NF-08-TM haploid regimen

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Background: Thalassaemia is one of the most common monogenic diseases worldwide. Thalassaemia major(TM) is the severe form of this inherited disorder. Allogeneic hematopoietic stem cell transplant (HSCT) is the only way to cure this disease and free patients from transfusion. Lack of HLA-matched related or unrelated donor is a major obstacle limiting the use of allogeneic HSCT. On the other hand, almost every patient has haploid identical donor. Haploid HSCT refers to that an identical full-length DNA is shared by the recipient and the donor. The possibility of a haploid compatibility is 100% between parents and children, while 75% between siblings.

Methods: This is a retrospective study reviewing the results of TM patients who received haploid HSCT Using NF-08-TM haploid Regimen in Hematology department of Shenzhen Children's Hospital from September 2016 to November 2018. We used a novel NF-08-

TM haploid protocol to treat 44 patients with TM, including 30 of which were parents being the donor and 14 sibling haploid donors.

Result: The median age at transplantation was 7 years (range, 3.5-12.5years), and the ratio of male-to-female patients was 28:16. The median follow-up time was one year (range, 6-27months). The estimated 1-year overall survival and TM free survival were 97.8% and 97.8%. The cumulative incidence of graft rejection and grades III–IV acute GVHD is 0% and 0%. Among the 44 patients, one patient died because of intracranial hemorrhage. The mortality was 2.27%.

Conclusions: Haploid HSCT provides an alternative way of treatment for Thalassemia major patients without HLA matched donor. Our results showed that NF-08-TM haploid protocol is a promising treatment strategy.

Keyword: HSCT, Haploidentical Transplantation, Thalassemia Major

OP06-5

Comparison of haploidentical and umbilical cord blood transplantation using targeted busulfan in children and adolescent with hematologic malignancies

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Background: Haploidentical related (Haplo) donors and umbilical cord blood (UCB) stem cell sources represent common alternative donor strategies used when a matched sibling donor or matched unrelated donor is not available for hematopoietic stem cell transplantation (HSCT). The aim of this study was to compare the results of graft source on outcome of children and adolescents with hematologic malignancies after Haplo and UCB HSCT in the setting of targeted busulfan-based myeloablative conditioning using intensive pharmacokinetic (PK) monitoring.

Methods: We retrospectively analyzed outcomes in 140 patients with high risk hematologic malignancies who received allogeneic HSCT from Haplo donors (n=36), UCB (n=24), and unrelated donors (n=80) in Seoul National University Children's Hospital from JAN 2009 to FEB 2018. Because UCB HSCT had been conducted until 2016 while Haplo HSCT using posttransplantation cyclophosphamide (PTCy) was started from 2014 in our institution, differences over time of HSCT must be considered to compare them. Therefore, unrelated group was divided into Unrelated A (n=51) who received HSCT from 2009 to 2013 and Unrelated B (n=29) from 2014, which were compared each other first with the purpose of using them as a control to compare Haplo with UCB groups. Patients who received the first allogenic HSCT using an intensive PK monitoring, targeted busulfan-based myeloablative conditioning were included. The total target area under the curve of busulfan was set at 74,000 to 76,000 μg × h/L. The majority of UCB and unrelated groups received busulfan, fludarabine ± etoposide regimen with antithymocyte globulin. Busulfan, fludarabine and cyclophosphamide with PTCy were used in Haplo group.

Result: First of all, Unrelated A group was compared to Unrelated B group. The median follow-up years were 5.7 (0.2-9.5) and 1.8 (0.3-4.5), respectively. The event-free survival (EFS) rates at 2 years (78.1±5.8% versus 72.3±9.1%, P=0.917) and overall survival (OS) rates at 2 years (83.7±5.3% versus 77.8±9.1%, P=0.874) in Unrelated A and B groups were similar. Under the assumption that there was no significant survival difference over time of HSCT from 2009 to 2013 and that from 2014 in our institution, the outcomes of Haplo and UCB groups were compared subsequently. The median follow-up years were 4.8 (0.1-9.3) and 1.8 (0.3-4.5), respectively. The median time to neutrophil and platelet recovery were 15 days (13-21) versus 14 days (12-40) (P=0.059), and 27 days (13-71) versus 46 days (21-77) (P<0.001) in Haplo and UCB groups. The cumulative incidence (CI) rates of acute GVHD grade II-IV, grade III-IV, and extensive chronic GVHD in Haplo and UCB groups were 38.9% versus 54.2% (P=0.479), 2.8% versus 29.2% (P=0.004), and 11.7% versus 12.5% (P=0.906), respectively. The CI rates of nonrelapse mortality were significantly lower in Haplo group (0% versus 33.6%, P<0.001), while the relapse incidences were not different (18.3% versus 8.6%, P=0.272). The EFS rates at 2 years (79.3±7.0% versus 54.2±10.2% %, P=0.034) and OS rates at 2 years (85.8±6.7% versus 65.7±9.9%, P=0.029) in Haplo and UCB groups were significantly different.

Conclusions: In this study, the CI rates of nonrelapse mortality and acute GVHD III-IV was lower in Haplo group than in UCB transplants, which translates into a better EFS and OS rate in Haplo group. Our results suggest that haploidentical HSCT with PTCy using intensive PK monitoring, targeted busulfan-based myeloab-

lative conditioning regimen is a safe and promising alternative option for patients with hematological diseases who lack an HLA-matched donor.

Keyword: Haploidentical, Cord Blood, Posttransplantation cyclophosphamide, Children, Hematologic malignancies, Stem Cell Sources

OP06-6

Different circulating T cells are associated with early relapse after autologous HSCT in patients with multiple myeloma and classical hodgkin lymphoma

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Background: The development of lymphoid neoplasms is associated with still insufficiently studied interactions between tumor cells, bone marrow stromal microenvironment and immunocompetent cells. At the same time, the specific mechanisms for the development of distinct diseases vary greatly. Multiple myeloma (MM) is a hematologic malignancy characterized by an uncontrolled proliferation of a B cell precursor clone that retains the ability to differentiate to plasma cells in the bone marrow. Unlike MM and other malignancies, tumor cells in Hodgkin lymphoma (HL) constitute ≤ 1% of the mass of the entire tumor tissue, while the main substrate consists of non-tumorous immune and stromal cells. Both MM and primary resistant/relapsed HL are indications for high-dose chemotherapy (HDC) with autologous hematopoietic stem cell transplantation (AHSCT). Previous chemotherapy courses, irradiation and conditioning lead to a significant damage to the tumor cells and their microenvironment, as well as inhibit hematopoiesis and temporarily restrict the recruitment of de novo derived immune cells to the tumor affected tissues. We investigated dynamics of circulating CD3+, CD4+, CD8+, CD16+/CD56+, CD19+, CD4+FOXP3+ lymphocyte recovery following HDC auto-HSCT in MM and classical HL patients and assessed relationship between the restoration of these populations and the development of early relapse.

Methods: Patients with HDC and AHSCT between September 2009 and November 2017 were enrolled in the study. Circulating CD3+, CD4+, CD8+, CD16+/CD56+, CD19+, CD4+FOXP3+ cells of 79 MM and 79 HL patients were evaluated using flow cytometry before HDC with AHSCT, at the day of engraftment, and following 6 and 12 months.

Result: CD8+ T cells, CD16+/CD56+ NK cells and CD4+FOXP3+ Tregs recovered intensively. CD4+ T cell and CD19+ B cell restoration was delayed. Studied populations were not statistically significant between HL patients with high or standard/intermediate risk of relapse. CD4+FOXP3+ T cells at the time of engraftment were increased in MM patients with the relapse or progression during 12 months following AHSCT (n=10) compared to non-relapsed patients (n=50): 6.7 % (5.3—8.9 %) vs 4.9 % (2.8—6.6 %); PU = 0.026. Area under the curve was 0.72 (95% CI: 0.570—0.878; p=0.026). CD4+FOXP3+ T cell relative count > 5.84 % allowed to predict early relapse (70.0 % sensitivity, 68.0 % specificity, with 2.19 likelihood ratio). Circulating CD4+FOXP3+ T cell count was not associated with the percentage of myeloma plasma cells in a bone marrow but depended on its amount in autografts (logit-regression, odds ratio: 13.50, P = 0.0014). CD3+ T cells at the time of engraftment were increased in HL patients with the early relapse (n=15) compared to non-relapsed patients (n=51): 960 / µL (613—1460 /µL) vs 461 /µL (273—714 /µL); PU = 0.0028. Area under the curve was 0.76 (95 % CI: 0.63—0.89; p=0.0037). CD3+ T cells > 717 /µL allowed to predict early relapse (69.2 % sensitivity, 75.0 % specificity, with 2.77 likelihood ratio).

Conclusions: These findings elucidate several interactions between early systemic recovery of T cell subsets and tumor progression following HDC with AHSCT. A higher relative count of CD4+FOXP3+ T cells itself, under the lymphopenic conditions, can lead to a restriction of effector T cell expansion. The subsequent lack and/or decreased function of T cells can promote the progression of MM. Large numbers of CD3+ T cells in PB of HL patients at the engraftment might be advantageous for tumor cells. Simultaneously, it might be a marker of an anti-tumor immune response, although not effective enough.

Keyword: Lymphocyte Recovery, Autologous hematopoietic Stem Cell Transplantation, Multiple Myeloma, Hodgkin Lymphoma, Early Relapse

OP07-1

Molecular abnormalities and their correlation with the prognosis of younger Indian patients with de novo myelodysplastic syndromes: AIIMS study

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Background: Myelodysplastic Syndromes (MDS) in the developed countries are mainly found in the elderly population but is being increasingly reported in young adults in Asia. Limited studies on the molecular biology of young MDS patients have been reported from the Asian countries and the results are contradictory. 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.

Methods: Karyotyping was done.Mutation screening of JAK2, IDH2, RAS and FLT3 genes, hTERT gene expression was done by PCR and RT-PCR. PCR-ELISA TRAP assay was performed to assess the telomerase activity. Methylation specific PCR was done to access the methylation status of tumor suppressor genes in a series of 100 MDS patients and results were correlated with disease severity, progression and survival.

Result: Of the 100 patients 67 were males and 33 were females (median age: 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%). Progression was observed in 21 patients. Patients with age <60 years had significantly low IPSS scores (p< 0.001), more transfusion dependent (p< 0.02), and shorter Median overall survival(OS) (p= 0.007). Abnormal karyotype was found in 25/51 (49%) patients. Median OS 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. 6 patients (50%) aged< 60 years and had RAS mutations progressed to acute leukemia. FLT3 mutations were absent in all patients. JAK2 and IDH2 mutations were present in 26% and 6% of patients respectively. Telomerase activity was increased in 17% cases and 7 patients progressed. hTERT mutation was present in 17% cases and 5 patients progressed. p15 INK4b methylation was present in 40% patients. Progression was observed significantly more frequent in patients with methylated p15INK4b gene (p<0.02). Significant difference observed between the progression free survival (PFS) 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 progression (p=0.006). The median OS 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 patients with age ≥60 years. The median OS was significantly shorter in patients with methylated calcitonin gene (p=0.005).FHIT gene was methylated in 43% of patients. Significant difference observed between PFS of patients with methylated and unmethylated FHIT gene (p=0.002). The median OS 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 in MDS patients (HR 5.15, 95% CI, 1.64-16.1 P=0.005).

Conclusions: 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 patients from India as well as rest of the world with large sample size is needed.

Keyword: Myelodysplastic Syndromes, Molecular, India, Methylation

OP07-2

Immunogenic cell death in acute myeloid leukemia: Synergy with venetoclax

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Background: We investigate the effect of pharmacologically active compounds act as immunoadjuvants able to trigger a cancer stress response and release of damage-associated molecular patterns (DAMPs) in myeloid leukemia [1]. These reactions occur through an increase in the immunogenicity of cancer cells that undergo stress followed by immunogenic cell death (ICD). These processes result in a chemotherapeutic response with a potent immune-mediating reaction. Compounds that induce ICD may function as an interesting approach in converting cancer into its own vaccine. However, several parameters determine whether a compound can act as an ICD inducer including the nature of the

inducer, the premortem stress pathways, the cell death pathways, the intrinsic antigenicity of the cell, and the potency and availability of an immune cell response [2].

Methods: To assess the capacity of pharmacological compounds, we use a multifactor approach:

- detecting ER stress markers;
- investigating and quantifying caspase-dependent or independent cell death;
- measuring the release of danger associated molecular patterns;
- quantifying phagocytosis of compound
- treated cells by both murine and human monocyte-derived macrophages;
- perform colony formation assays and in vivo zebrafish xenografts;
- and perform vaccination assays with immunocompetent mice.

Result: We identified ICD-inducing capacities of old (coumarinics) and novel (stemphol, cardiac glycoside UNBS1450) inducers of immunogenic cell death together with Venetoclax and experimental BH3 mimetics. We detected their capacity to trigger synergistic cell death in myeloid leukemia in an attempt to overcome apoptosis-resistant myeloid leukemia alone or in combination with other chemotherapeutic compounds.

Conclusions: Thus, the identification of hallmarks of ICD is important in determining the prognostic biomarkers for new therapeutic approaches and combination treatments [3]. In myeloid leukemia, combination treatments of ICD-inducing pharmacological agents [4] with Venetoclax showed positive synergistic effects [5] allowing to confer immunogenicity to otherwise cytotoxic non-immunogenic treatments.

References:

1. Radogna, F.; Diederich, M., Biochem. Pharmacol. 2018, 153, 12-23. 2. Mazumder, A.; Lee, J. Y.; Talhi, O.; Cerella, C.; Chateauvieux, S.; Gaigneaux, A.; Hong, C. R.; Kang, H. J.; Lee, Y.; Kim, K. W.; Kim, D. W.; Shin, H. Y.; Dicato, M.; Bachari, K.; Silva, A. M. S.; Orlikova-Boyer, B.; Diederich, M., Cancer Lett. 2018, 438, 197-218. 3. Ji, S.; Lee, J. Y.; Schror, J.; Mazumder, A.; Jang, D. M.; Chateauvieux, S.; Schnekenburger, M.; Hong, C. R.; Christov, C.; Kang, H. J.; Lee, Y.; Han, B. W.; Kim, K. W.; Shin, H. Y.; Dicato, M.; Cerella, C.; Konig, G. M.; Orlikova, B.; Diederich, M., Cancer Lett. 2018, 416, 109-123. 4. Diederich, M.; Muller, F.; Cerella, C., Cardiac glycosides: From molecular targets to immunogenic cell death. Biochem. Pharmacol. 2017, 125, 1-11. 5. Cerella, C.; Gaigneaux, A.; Mazumder, A.; Lee, J. Y.; Saland, E.; Radogna, F.; Farge, T.; Vergez, F.; Recher, C.; Sarry, J. E.; Kim, K. W.; Shin, H. Y.; Dicato, M.; Diederich, M., Leukemia 2017, 31, (3), 755-759.

Keyword: Immunogenicity, Cell Death, AML, Targeted Treatments, Synergy, Personnalized Treatments

OP07-3

Prediction of clinical outcomes with assessment of sarcopenia and adipopenia by computed tomography in adult patients with acute myeloid leukemia

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Background: Sarcopenia and adipopenia have been suggested to implicate prognostic significance in cancer patients including acute myeloid leukemia (AML). Single section of computerized tomography (CT) at the third lumbar vertebra (L3) has been widely used, although abdominal CT is not routinely assessed in many patients with AML. Therefore, we evaluated the value of CT scan at the first lumbar vertebra (L1) to predict clinical outcomes.

Methods: This retrospective study enrolled 104 patients who were diagnosed with AML in National Cancer Center, Korea, between 2012 and 2017. CT scan at diagnosis was available in 96 cases. With the measurements of skeletal muscle, visceral and subcutaneous adipose tissue which were corrected by the square of height, sex-specific cutoffs were designated to maximize the log-rank values of survival outcome. Those results appointed 36 patients (37.5%) to sarcopenia, 29 (30.2%) to visceral adipopenia and 49 (51.0%) to subcutaneous adipopenia. We compared clinical outcomes such as overall survival (OS), progression-free survival (PFS) and treatment-related mortality (TRM).

Result: Median age at diagnosis was 58 and 50 patients were male. Patients' baseline characteristics such as age distribution, performance status, disease subtypes and risk stratification were not significantly different. Standard induction chemotherapy was done for 67 patients (69.8%), while 23 (24.0%) received hypomethylating agents. With a median follow-up of 21.5 months, the sarcopenic group revealed significantly worse OS (median 17.8 months vs. not reached, p=0.021) and TRM (54.7 vs. 8.5%, p=0.001). Visceral adipopenia was also significantly associated with inferior OS (12.7 vs. 31.7 months, p=0.006), PFS (3.7 vs. 31.7 months, p=0.003) and TRM (46.2 vs. 15.2%, p=0.003). The analysis of subcutaneous adipopenia showed similar results with poor OS (17.9 months vs. not

reached, p=0.001), PFS (6.2 months vs. not reached, p=0.005) and TRM (35.5 vs. 10.8%, p=0.001). Multivariable analyses presented sarcopenia, visceral adipopenia and subcutaneous adipopenia were significant poor prognostic factor for OS (HR 2.57, 95% CI 1.34-4.95, p=0.005; HR 2.01, 95% CI 1.05-3.85, p=0.036; HR 2.56, 95% CI 1.30-5.01, p=0.006; respectively) with adjustment for age (>60), Eastern Cooperative Oncology Group performance status (>1) and risk stratification (high risk vs. others). In subgroup analysis for patients who received standard induction therapy, sarcopenia, visceral adipopenia and subcutaneous adipopenia were still significant to predict worse TRM (29.0 vs. 7.3%, p=0.035; 37.0 vs. 6.4%, p=0.006; 27.0 vs. 3.4%, p=0.010; respectively).

Conclusions: In conclusion, sarcopenia and adipopenia assessed by single section of CT at L1 level would be useful to predict clinical outcomes including TRM in patients with AML. Validation in the future is warranted.

Keyword: AML, Sarcopenia, Adipopenia, TRM, Prognosis

OP07-4

Hyperleukocytosis at initial diagnosis of AML: Cytogenetic and molecular feature and prognostic implication in patients undergoing allogeneic-HSCT

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Background: Hyperleukocytosis (HL) in acute myeloid leukemia (AML) has traditionally regarded as clinical risk factor for poor prognosis. Recently, increasing evidence suggests the association of HL and distinct molecular feature. However, there is debate about the prognostic importance of HL in transplanted AML patients, with inconsistent results from previous studies.

Methods: A total of 806 patients who were diagnosed AML at Seoul Saint Mary's hospital between Mar 2012 and Oct 2018 were included, and were analyzed for association of HL and cytogenetic and molecular abnormalities. To determine the prognostic relevance of HL, data from 648 patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) between Nov 2008 and Apr 2018 was used for the analysis. In this study, HL was defined as a total white blood cell counts greater than 100 x 109/L, and patients with acute promyelocytic leukemia (APL) was not included.

Result: At initial diagnosis, 151 out of 806 (18.7%) showed HL, and 32 patients (4.0%) further experienced HL during the treatment course or at relapse. Patients with initial HL had higher incidences of normal karyotype (NK), intermediate risk karyotype other than NK, and more frequently allocated into ELN adverse risk group. Although core binding factor (CBF)-AML as a whole, was less common in patients with initial HL, within CBF-AML group only, inv(16) comprised majority cases of initial HL. In addition, patients with initial HL were more likely to be FLT3-ITD and NPM mutated, and showed significantly lower BAALC expression level. These cytogenetic and molecular features were similarly observed in patients with HL during the treatment course or at relapse. Among 648 patients who underwent all-HSCT, ELN risk group and disease status at allo-HSCT were significant prognostic factor for overall survival (OS) and leukemia free survival (LFS). It was not significantly different between patients with initial HL and without initial HL (hazard ratio [HR] of 1.003, 95% confidence interval [CI], 0.662-1.520, p=0.988 for OS, and hazard HR of 1.075, 95% CI, 0.725-1.594, p=0.718). When the analysis was performed in each ELN risk group only, we cannot observe significant difference of OS and LFS according to initial HL.

Conclusions: AML with HL can be understood as having distinct cytogenetic and molecular characteristics. When analyzing transplanted patients only, HL per se did not show prognostic relevance for OS and LFS.

Keyword: AML, Hyperleukocytosis, FLT3, NPM1, Transplantation, Outcome

OP07-5

Germline predisposition gene mutations in pediatric acute myeloid leukemia

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Background: Acute myeloid leukemia (AML) with germline predisposition gene mutations is caused by a combination of germline and additional somatic mutations. Unlike adult AML, background of pediatric AML is mainly based on the genetic predisposition. Since AML with germline predisposition gene mutations requires different clinical management such as donor selection for bone marrow stem cell transplantation or appropriate genetic counseling, detection of germline predisposition gene mutations is becoming important. In the present study, we investigated the prevalence of germline predisposition gene mutations in Korean pediatric AML.

Methods: Seventeen bone marrow samples at initial diagnosis of pediatric AML and 16 paired specimen of complete remission and 1 saliva sample were collected. Targeted multi-gene sequencing was performed using 359 or 506 gene panel which is composed of WHO 2016 genetic predisposition genes and known leukemia-related genes.

Result: Eleven out of 17 patients (64.7%) harbored germline predisposition gene mutations. A total of 24 germline predisposition gene mutations were found: seven mutations of 6 Fanconi anemia genes (FANCA, FANCD2, FANCI, FANCJ, FANCN and FANCP), 4 mutations of 3 genes related to telomere biology disorder (CTC1, RTEL1, and WRAP53), 2 germline myeloid neoplasm-associated genes (DDX41 and RUNX1), 2 mutations of 1 gene of severe congenital neutropenia (VPS13B) and 9 other cancer-related genes (ATM, BRCA1, CHEK2, MET, MLH1, MSH6, PARP1, SETBP1 and ZNF208). On the other hand, twelve out of 17 patients (70.6%) carried more than one coexisting somatic mutations (FLT3, ULK4, KRAS, BCR, KIT, ALPK2, ATR, BRD4, CREBBP, DDX54, GATA1, MAP3K1, MUC16, NCOA3, RAD21, SF1, TNFSF9, TRA2B, WRAP53, ZNF93, and ZNF676). Mean number of mutated genes per one patient was 1.8. Somatic mutations detected in pediatric AML were overlapped with those of adult AML in 32.3% (4 FLT3, 3 KRAS, 2 KIT and 1 RAD21 mutations), while 17 genes (ULK4, BCR, ALPK2, ATR, BRD4, CREBBP, DDX54, GATA1, MAP3K1, MUC16, NCOA3, SF1, TNFSF9, TRA2B, WRAP53, ZNF93, and ZNF676) were detected only in pediatric AML.

Conclusions: Germline predisposition gene mutations were present in 64.7% of pediatric AML patients, which is remarkedly high compared to adult AML. The present study revealed high prevalence of underlying genetic background in pediatric AML, suggesting that an identification of a germline mutation is pivotal in routine work-up of pediatric AML.

Keyword: Germline Predisposition, Pediatric Acute Myeloid Leukemia, Targeted Multi-Gene Sequencing

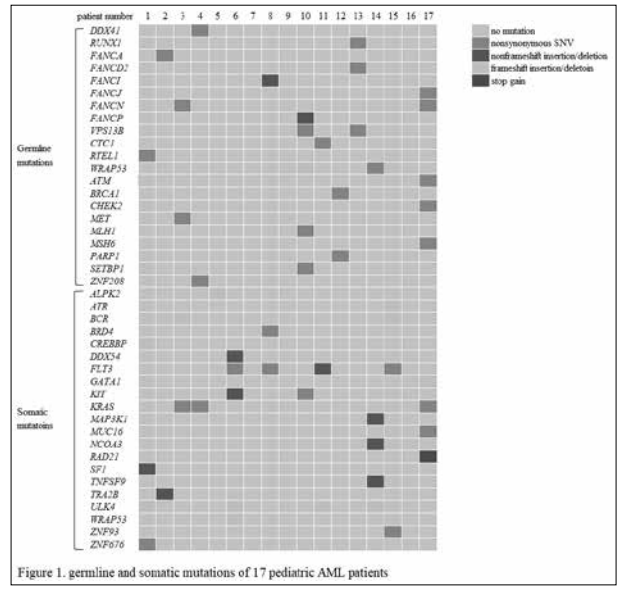

Figure 1. germline and somatic mutations of 17 pediatric AML patients

OP07-6

HSCT is an effective method to Improve the prognosis of AML in children with c-Kit mutation-analysis of 131 cases

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Background: Acute myeloid leukemia (AML) is one of the common malignant hematological diseases in children, and the prognosis of different biological subtypes varies greatly. c-KIT is an important receptor tyrosine kinase that regulates myeloid hematopoiesis. In AML, c-kit mutations mainly occur in exon 8 and exon 17, and these mutations cause c-KIT to have tyrosine kinase activity at all times. There is already a lot of evidence that c-kit mutation is associated with poor prognosis. How to improve the long-term

survival rate of children with c-kit mutation has been a hot topic. Hematopoietic Stem Cell Transplantation (HSCT) is first aimed at supporting treatment, and the current therapeutic effect of HSCT on leukemia has far exceeded the scope of supportive care. So, we aim to investigate the effect of hematopoietic stem cell transplantation on the survival of AML children with c-kit mutation.

Methods: The clinical features, overall survival (OS), relapse-free survival (RFS), and event-free survival (EFS) were analyzed of children with/without c-kit mutations, which were identified by first-generation sequencing. There were 33/131 AML patients with c-kit (exon 8 and exon 17) mutations. We also analyzed the effects of hematopoietic stem cell transplantation on OS, RFS, and EFS in AML children with c-kit mutation.

Result: Of the 131 patients who had detected exon mutations in c-kit gene (exon 8 and exon 17), 33 were positive for c-kit gene exon mutation (c-kit+), and the mutation rate was 25.19%. Among the children with newly diagnosed bone marrow blast cells rate <50%, the proportion of c-kit mutation was significantly higher than that of newly diagnosed bone marrow blast cells rate ≥50% (P=0.0028). The c-kit mutation group was mainly distributed in M1/M2 in the cell morphology classification (P=0.0054). There was no significant difference in the age, sex, white blood cell (WBC), platelet (PLT), and hemoglobin (HGB) ratio between the c-kit mutation group and the wild-type group. (P>0.05). The 5-year overall survival rate of these 131 patients was 73.2±4%, and the 5-year event-free survival rate was 70.2±4.2%. Among them, 59 patients underwent hematopoietic stem cell transplantation and 72 patients did not receive hematopoietic stem cell transplantation. Although there was no significant difference (P>0.05) in RFS and EFS between the transplanted and non-transplanted groups, the OS of the transplant group was significantly higher than that of the non-transplant group (P=0.0140), and the improvement in OS was mainly due to the significant increase in survival rate of c-kit+ AML patients with transplantation (P=0.0487). However, transplantation had no significant effect on the survival rate of children without c-kit mutation (P>0.05). The results of COX multivariate regression analysis in the prognostic factors of patients, showed that transplantation can significantly improve the OS (95% CI, 1.692-8.251; P=0.001) and EFS (95% CI, 1.184-4.812; P=0.015) in AML patients.

Conclusions: The c-kit mutation is common in children with AML, especially in children with M1/M2 subtype. The proportion of bone marrow blast cells in patients with c-kit mutation is significantly lower than that in patients without c-kit mutation; hematopoietic stem cell transplantation can effectively prolong the survival of AML children with c-kit mutation.

Keyword: C-Kit Mutation, Hematopoietic Stem Cell Transplantation, AML, Prognosis, Children

c-kit Mutation and Clinical Features of AML Patients at Diagnosis

Characteristics	c-kit⁻ (wildtype)	c-kit⁺(mutation)	Chi-square	*P* value
Case (n)	98	33		
Gender			1.693	0.1931
Male	63	17		
Female	35	16		
Age (Month)			0.008167	0.928
< 10 years	75	25		
≥ 10 years	23	8		
BM Blast at diagnosis (%)			8.936	0.0028
< 50	23	17		
≥ 50	74	16		
Blood cells				
Initial WBC (×10⁹/L)			0.7339	0.3916
< 50	73	27		
≥ 50	25	6		
HGB (g/L)			0.06447	0.7996
< 90	69	24		
≥ 90	29	9		
Initial PLT (×10⁹/L)			1.583	0.2083
< 50	50	21		
≥ 50	48	12		
FAB subtype			10.43	0.0054
M1/M2	40	24		
M4/M5	45	8		
Others	13	1		

OP08-1

Next-generation sequencing study of V(D)J rearrangements on non-CR patients showing MRD negativity by next-generation flow

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Background: International Myeloma Working Group (IMWG) evaluates treatment response based on plasma cell percentage in bone marrow, amount of light chain, concentration of monoclonal protein assessed by immunofixation and/or protein electrophoresis. In 2016, IMWG newly adopted next-generation flow (NGF) as an additional assessment tool for the detection of MRD, but next-generation sequencing (NGS) for IgH rearrangement was not included. In the present study, we conducted NGS of V(D)J rearrangements on multiple myeloma (MM) patients who did not achieve CR, yet showed NGF MRD negativity, to investigate the discrepant results.

Methods: A total of 35 myeloma patients under treatment was enrolled. We performed NGF with 8-color antibody panel using

Navios flow cytometer (Beckman Coulter, USA) and Infinicyt software (Cytognos SL, Spain). IgH rearrangement NGS was performed using 'survey' level ImmunoSEQ assay (Adaptive Biotechnologies, USA) on each sample. Paired specimens at initial diagnosis BM and follow-up BM were subjected to NGS study. The results of sequencing data were processed by the ImmunoSEQ Analyser web-based relational database for analysis.

Result: Out of 11 patients who achieved CR or sCR, seven patients showed NGF MRD negativity (63.6%). Among 24 patients who failed to achieve CR, four patients (1 VGPR, 1 PR, 1 MR, and 1 SD) showed MRD negativity by NGF. In those four patients with discrepancy between IMWG treatment response and NGF results, we compared the results of IgH NGS on BM specimens at initial diagnosis with those after treatment. Of the four non-CR patients with NGF MRD negativity, all of the patients showed IgH rearrangement by NGS. NGS revealed a persistence of residual clone in one patient, an acquisition of new clones in two patients, and heterogenous clones in one patient. Patient with PR had same dominant clone both initial diagnosis BM (87.13%; proportion of clone) and follow-up BM (19.38%). Two patients (one with MR, the other SD) acquired new clones after treatment. Patients with MR had a newly appeared clone (1.49%) carrying DJ rearrangement which was non-productive, whereas dominant clones found in the three other patients were productive VDJ rearrangement. Patient with SD had newly appeared clones in follow-up BM (5.24%, 4.72%, 3.11%, 2.09%) which were absent in initial BM. The last patient, with VGPR, showed heterogeneous clones without a dominant clone at follow-up BM by NGS. Results including laboratory tests are summarized in Table 1.

Conclusions: IgH rearrangement NGS revealed malignant clones in 100% of patients who did not achieve CR, but showed NGF MRD negativity. These results suggest that IgH rearrangement NGS can detect malignant clones which may not be identified by NGF. Immunophenotype switching may contribute to this escape of neoplastic plasma cells from NGF monitoring in non-CR patients. Complementary NGS test is needed to detect such drifting clones for monitoring of MRD in MM.

Keyword: Multiple myeloma, IMWG Criteria, MRD, Next Generation flow, IgH Rearrangement, IgH-Next Generation Sequencing

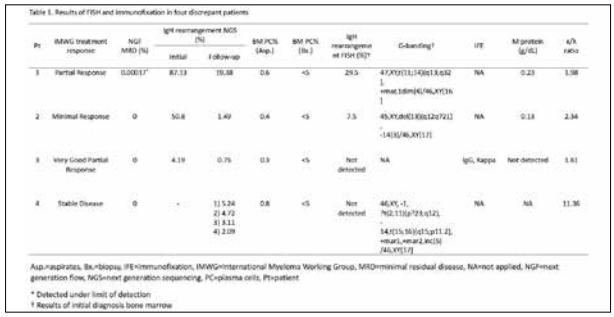

Table 1. Results of FISH and immunofixation in four discrepant patients

Pt	IMWG treatment response	NGF MRD (%)	IgH rearrangement NGS (%)		BM PC% (Asp.)	BM PC% (Bx.)	IgH rearrangement FISH (%)*	G-banding†	IFE	M-protein (g/dL)	κ/λ ratio
			Initial	Follow-up							
1	Partial Response	0.00013*	87.13	19.38	0.6	<5	29.5	47,XY,t(11;14)(q13;q32)[ ],+mar,1dim[4]/46,XY[16]	NA	0.23	1.98
2	Minimal Response	0	50.8	1.49	0.4	<5	7.5	45,XY,del(13)(q12q21)[ ],-14[3]/46,XY[17]	NA	0.18	2.34
3	Very Good Partial Response	0	4.19	0.76	0.3	<5	Not detected	NA	IgG, Kappa	Not detected	1.61
4	Stable Disease	0	-	1) 5.24 2) 4.72 3) 3.11 4) 2.09	0.8	<5	Not detected	46,XY,-1,-7q[2.11](p??3;q12),-14,t(15;16)(q15;p11.2),+mar1,+mar2,inc[5]/46,XY[17]	NA	NA	11.36

Asp.=aspirates, Bx.=biopsy, IFE=immunofixation, IMWG=International Myeloma Working Group, MRD=minimal residual disease, NA=not applied, NGF=next generation flow, NGS=next generation sequencing, PC=plasma cells, Pt=patient

* Detected under limit of detection

† Results of initial diagnosis bone marrow

OP08-2

Bone marrow tracer uptake pattern of PET/CT in multiple myeloma: Image interpretation criteria and prognostic value

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Background: The value of bone marrow (BM) imaging pattern assessed by 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in multiple myeloma (MM) remains unclear. And no unified standardized interpretation criteria have been established to define different BM imaging pattern.

Methods: In an effort to assess the value of BM imaging pattern assessed by 18F-FDG PET/CT in MM and to find out the appropriate image interpretation criteria to define different BM metabolic pattern, we retrospectively studied PET/CT imaging data of 52 healthy individuals and 172 newly diagnosed MM patients.

Result: In our healthy cohort, BM FDG uptake (represented by the average SUVmean of L1 and L2 vertebral body) were higher than that of liver (SUVmean), spleen (SUVmean) and mediastinal blood pool (SUVmax) in 1 (1.9%), 11 (21.2%) and 4 (7.7%) patients, respectively, in physiological status. Hence, we defined pathological abnormal increase in BM background tracer uptake as BM FDG uptake > liver SUVmean. With this criteria, we categorized four BM FDG uptake pattern in MM: focal (focal lesion in BM with FDG uptake > liver), diffuse (diffuse homogenous BM FDG uptake > liver), mixed pattern and normal BM uptake pattern. Sixty (34.9%) patients had focal (Figure 1A), 6 (3.5%) had diffuse (Figure 1B), 66 (38.4%) had mixed pattern (Figure 1C) and 40 (23.3%) had normal BM uptake. In all patients with MM, plasma cell infiltration rate differed in different uptake pattern: patients with diffuse/mixed bone marrow FDG uptake pattern had the highest mean bone marrow plasma cell infiltration rate, followed by those with focal pattern (Kruskal-Wallis test, $P < 0.0001$). Furthermore, BM tracer uptake pattern demonstrated correlations with prognostically relevant baseline parameters: diffuse/mixed pattern was correlated with higher BM plasma cell infiltration rate, more advance ISS stage, lower hemoglobin level, higher level of β2-microglobulin and serum creatinine. Diffuse/mixed BM tracer uptake pattern (Figure 2A-B), more than ten FDG-avid focal lesions (PET-FL) at baseline (Figure 2C-D), presence of extramedullary disease (EMD, Figure 2I-J), and a standardized uptake value (SUV-FL) > 5.3 (Figure 2E-F) adversely affected estimated 3-year progression free survival (3-yr PFS; diffuse/mixed pattern: 26.8%; PET-FL > 10: 26.0%; EMD: 0.0%; SUV-FL > 5.3: 32.5%) and overall survival (3-yr OS; diffuse/mixed pattern: 50.6%; PET-FL > 10: 44.8%; EMD: 0.0%; SUV-FL > 5.3:

51.0%). Presence of paramedullary soft tissue lesion adjacent to bone marrow shortened PFS with borderline adverse influence on OS (Figure 2K-L). Clinical outcomes were not significantly influenced by the number of osteolytic lesion on CT images (Figure 2G-H). In multivariate analysis, diffuse/mixed BM FDG uptake pattern was confirmed to be an independent predictor associated with inferior OS (HR 7.10; 95% CI 1.33-37.95) and PFS (HR 5.98; 95% CI 1.30-27.54).

Conclusions: In conclusion, we propose an FDG uptake higher than that of liver is a proper positivity cut-off to discriminate physiological and pathological uptake in bone marrow for patients with multiple myeloma. With these interpretation criteria, the bone marrow PET/CT pattern can be defined as four types: normal, focal, diffuse and mixed. A diffuse/mixed BM FDG uptake pattern is a reliable predictor of inferior outcome in multiple myeloma.

Keyword: Myeloma, PET/CT, Bone Marrow

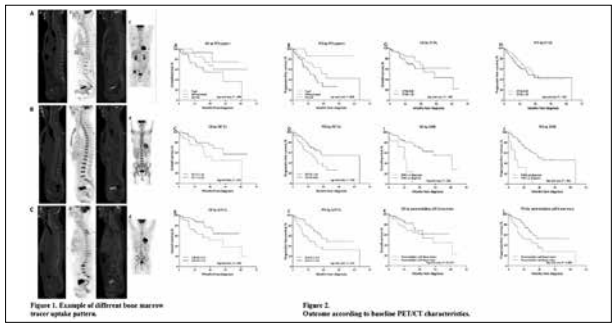

Figure 1. Example of different bone marrow tracer uptake pattern.

Figure 2. Outcome according to baseline PET/CT characteristics.

OP08-3

Real world experience of carfilzomib, and dexamethasone versus pomalidomide-based combination chemotherapy after a 2nd-Line therapy in RRMM

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Background: Carfilzomib, and dexamethasone (Kd) and pomalidomide and dexamethasone with or without cyclophosphamide (Pd or PCd) are options for treatment of relapsed and/or refractory multiple myeloma (RRMM). Since its approval by Health Insurance Review & Assessment Service in South Korea in February, 2018 and January, 2017, respectively, the experiences of these novel drug combinations are accumulating.

Methods: One-hundred and sixteen patients from 16 hospitals participating in the Korean multiple myeloma working party (KMMWP) were retrospectively analyzed by review of medical records. Multiple myeloma patients who relapsed or were refractory to 2 or more lines of chemotherapy regimens and who had been treated with Kd (Kd group, N=21) or pomalidomide-based chemotherapy (Pom group, N=95) were included. Patients who had been administered with both carfilzomib and pomalidomide-combination chemo-therapies sequentially, the drug used in advance was analyzed. The pomalidomide group included patients who had undergone Pd (N=26), PCd (N=46), and cyclophosphamide add-on Pd (N=23).

Result: Median age at the time of administration of Kd or Pomalidomide-based regimen were 57 years (range, 43-75 years) and 66 years (range, 36-82 years), respectively. There were no significant differences in international staging system (ISS) and revised ISS between the two groups. The median lines of previous chemotherapy were 3 (2-7) and 3 (2-8) in Kd and Pom group, respectively. Drugs previously exposed were bortezomib, lenalidomide, thalidomide, daratumumab, which were included in 21 (100%), 20 (95.2%), 11 (52.4%), and 1 (4.8%) in the Kd cohort, respectively;

and 94 (98.9%), 93 (97.9%), 51 (53.7%) and 2 (2.1%) in the Pom cohort, respectively. Median cycles of Kd and Pomalidomide-based chemotherapy were 3 (1-11) and 4 (1-22), respectively. Overall response (partial response or better) rate in the Kd and Pom group were 33.3% (including 15.0% of very good partial response, VGPR or better) and 44.2% (including 13.7% of VGPR or better), respectively (P=0.336). Mean time to best response after starting of each chemotherapeutic regimens were 140 days (95% CI, 43.89-236.10 days) and 229 days (95% CI, 122.07-335.93 days) in the Kd and Pom cohort, respectively (P=0.391). In the Kd and Pom group, median progression-free survival (PFS) were 8.97 months (95% CI, 3.49-14.44 months) and 9.33 months (95% CI, 6.60-12.07 months), respectively (P=0.053) and overall survival (OS) were 16.67 months and 12.30 months (95% CI, 2.22-22.38 months), respectively (P=0.324).The most common adverse events were hematologic toxicities in Kd and Pom cohort; anemia (all grades, 85.7% versus 90.5%, P=0.453), thrombocytopenia (all grades, 81.0% versus 695%, P=0.424), and neutropenia (all grades, 57.1% versus 84.2%, P=0.014). The most common non-hematologic toxicity was fatigue (all grades, 0% versus 25.3%, P=0.006). Heart failure occurred in 4.8% versus 2.1% (P=0.454) in Kd and Pom group, respectively.

Conclusions: In patients who relapsed or were refractory to 2 or more regimens, the use of carfilzomib or pomalidomide primarily did not show significant differences in terms of overall response, PFS or OS. The adverse event profile was different in both groups. The updated result from the data of KMMWP will be presented in the meeting.

Keyword: Multiple Myeloma, Relapsed/Refractory, Carfilzomib, Pomalidomide

OP08-4

PD-1 blockade reinvigorates bone marrow CD8+ T cells from multiple myeloma patients in the presence of TGF-B inhibition

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Background: Immunosuppressive milieu of multiple myeloma (MM) is associated with various cellular and non-cellular factors that foster immune escape leading to tumor progression. While immune checkpoint inhibitors have achieved significant clinical success in many types of solid tumors, recent clinical trials of immune checkpoint blockade performed in patients with MM failed to demonstrate significant anti-tumor efficacy. To enhance the clinical efficacy of immune checkpoint blockade in MM, elaborate characterization of tumor antigen-specific T cells is an essential prerequisite. Herein, we investigated the immunophenotypic and functional characteristics of tumor antigen-specific T cells in patients with MM. In addition, using direct ex vivo experimental techniques, we tried to examine how to manipulate the immunosuppressive microenvironment to maximize anti-myeloma responses of the tumor-specific T cells.

Methods: Bone marrow (BM) aspirates and paired peripheral blood (PB) samples were collected from 52 newly diagnosed MM patients at Chungnam National University Hospital. Immunophenotypes of CD8+ T cells from BM and PB of newly diagnosed multiple myeloma patients were analyzed by multicolor flow cytometry. Using MHC multimer technique, myeloma antigen-specific CD8+ T cells were defined in selected patients. Also, antigen-specific proliferation and cytokine production of CD8+ T cells were studied direct ex vivo.

Result: Using MHC multimer technique, we could successfully define CD8+ T cell population specifically recognizing the HLA-A*0201-restricted epitopes (either "SLLMWITQC" or "LLLGIGILV"), included in myeloma tumor antigens NY-ESO-1 and HM1.24. The vast majority of myeloma-antigen specific CD8+ T cells expressed high level of PD-1 and also co-expressed other types T cell inhibitory receptors. More strikingly, PD-1+ myeloma-specific CD8+ T cells had a distinct pattern of transcriptional factor expression, high level of Eomes and low level of T-bet, indicating that they were profoundly exhausted functionally. Consistently, BM CD8+ T cells from MM patients exhibited reduced proliferation and cytokine (INF-γ and TNF-α) production upon the stimulation of T-cell receptor signals compared to those from patients with other asymptomatic plasma-cell neoplasms and other B-cell lymphomas. Anti-PD-1 did not increase the proliferation of BM CD8+ T cells from MM patients, but it increased the proliferation of those cells from other B-cell lymphomas, indicating that the T-cell exhaustion in MM is hardly reversed by PD-1 blockade alone. Next, we investigated whether blocking TGF-β signaling in combination with PD-1/PD-L1 axis blockade could restore the function of BM CD8+ T cells of MM patients, we found that combination of TGF-β signaling blockade (either anti-TGF-β1 or Galunisertib, a small molecule inhibitor of TGF-β receptor I) with anti-PD-1 significantly

increased the frequencies of cytokine-producing CD8+ T cells in response to ex vivo TCR stimulation, compared to a single PD-1 or a single TGF-β blockade. Likewise, myeloma antigen-specific proliferation of CD8+ T cells was significantly enhanced with addition of TGF-β signaling blockade.

Conclusions: Although PD-1/PD-L1 axis acts as a major component of immunosuppressive milieu in multiple myeloma, the efficacy of PD-1 blockades in multiple myeloma might be hampered by complicated microenvironment consisting of T cell-intrinsic and -extrinsic factors. Our results provide an ex vivo evidence of incorporating TGF-β signaling blockade to immune checkpoint inhibition to enhance anti-tumor T cell responses in multiple myeloma.

Keyword: Multiple Myeloma, T Cell, PD-1, TGF-B

OP08-5

A multicenter, phase II study of response-adapted lenalidomide-based therapy for elderly patients with newly diagnosed multiple myeloma in Korea

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Background: Lenalidomide and low dose dexamethasone is one of the standard treatments for older adults with multiple myeloma (MM). Lenalidomide monotherapy has not been evaluated newly diagnosed MM patients, and it might be valuable for vulnerable patient population to decrease toxicity from therapy. We conducted a phase II trial evaluating a response-adapted strategy for elderly patients with newly diagnosed MM without high-risk features.

Methods: Patients had symptomatic MM with standard-risk (B2-microglobulin?5.5, absence of t(4;14), t(14;16), 17p deletion, aneuploidy or 13q by metaphase cytogenetics) and were ineligible for high-dose therapy and stem cell transplantation. Patients received lenalidomide daily for the first 21 days of two 28-days cycles (without dexamethasone). If patients had a minimal response (MR) or better after 2 cycles, the continued lenalidomide monotherapy until progression. If patients had stable disease (SD) after 2 cycles, 100mg of prednisolone was added on days 1-5 of each cycle. In the event of progressive disease (PD) on lenalidomide monotherapy or lenalidomide plus prednisolone, patients received lenalidomide and dexamethasone (40mg weekly). This study used the uniform response assessment of the International Myeloma Working Group (IMWG) with the addition of MR.

Result: From July 2010 to August 2012, 34 eligible patients were enrolled at 13 centers in Korea, and 28 patients were used for efficacy analysis. The median age was 70 (range, 48-81) and 53.6% were females. Ten patients (35.7%) were ISS stage I, and 18 patients (64.3%) were ISS stage II. Major of patients (78.6%) were ECOG performance status 1. Of 28 patients, the overall response rate (ORR, ≥PR) to lenalidomide monotherapy or lenalidomide plus prednisolone was 64.3% (18/28). Only 10 patients received additional dexamethasone after disease progression, and the ORR of lenalidomide plus dexamethasone was 70% (7/10). Totally, 21 patients (75%) experienced a partial response or better to this response-adapted therapy. After median follow-up of 55 months, the median progression-free survival (PFS) was 16.1 months (95% CI, 7.1-25.1), and the median overall survival (OS) was 51.8 months (95% CI, 37.4-66.2). The most common hematologic adverse event was neutropenia (46.7%), and 36.7% of patients experienced grade ≥3 neutropenia. And 56.7% of patients experienced infection including pneumonia, and 17 patients (26.7%) had grade ≥3 infection.

Conclusions: The response-adapted lenalidomide-based therapy is feasible in newly diagnosed MM patients who were not eligible to high-dose therapy, showing compatible response rates and survivals. Further investigation with large-scale, prospective studies are warranted.

Keyword: Myeloma, Lenalidomide, Older Adults, Response-Adapted Therapy

OP08-6

Preclinical and clinical results of combination immunotherapy; Cancer vaccine with immune modulator, checkpoint inhibitors and epigenetic regulator

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Background: Antigen-specific cancer vaccines elicit tumor-suppressive responses by targeting various tumor-associated antigens (TAA) expressed on cancer cells. The discovery of novel immunogenic peptides from selected TAA offers new immunotherapeutic options, either as a vaccine or cell-based immunotherapy. A large number of clinical trials have demonstrated the immunogenicity of cancer vaccines with minimal toxicities and low side effects in cancer patients. We have identified and developed a multipeptide-based cancer vaccine targeting various TAA including XBP1, CD138 (Syndecan-1) and CS1 (SLAMF7) antigens, which have been implicated in pathogenesis and overexpression in various types of cancer including hematologic malignancies and solid tumors. With encouraging preclinical data, we recently performed clinical trials and completed Phase 1 (cancer vaccine alone) and Phase 2a (combination immunotherapy with cancer vaccine) studies using a cocktail of XBP1, CD138 and CS1 peptides specific to HLA-A2, which is the most dominant MHC Class I molecule in North America and second most dominant in Asia, in smoldering multiple myeloma (SMM) patients. Vaccination in SMM patients induced XBP1, CD138 and CS1-specific memory CD8+ cytotoxic T lymphocytes (CTL) and Th1-type of immune responses, which were further enhanced in combination with Lenalidomide, as evidenced by increased Tetramer+ CTL and functional immune responses. At current, three additional clinical studies are on-going as multi-center trials in the U.S. to examine the efficacy of cancer vaccine in the patients with hematologic malignancy or triple-negative breast cancer in combination with immune modulator, different types of checkpoint inhibitors and/or epigenetic regulator.

Methods: To expand therapeutic opportunities beyond HLA-A2 specificity, we have recently identified novel immunogenic peptides specific to HLA-A24 molecule, which is the most frequent MHC Class I molecule in Asia and the second most dominant MHC Class I molecule in North America.

Result: Individual HLA-A24 peptides, XBP1 UN [185-193; I S P W I L A V L], XBP1 SP [223-231; V Y P E G P S S L], CD138 [265-273; I F A V C L V G F] and CS1 [240-248, L F V L G L F L W], induced antigens-specific CD8+ CTL with anti-tumor immune responses against both multiple myeloma and various solid tumors (breast cancer, colon cancer, pancreatic cancer) in an HLA-A24 restricted manner. Phenotypic characterization of peptides-specific CTL revealed upregulation of immune costimulatory (41BB, CD40L, OX40, GITR) and checkpoint antigens (PD1, CTLA, LAG3, TIM3), especially in antigen-specific memory CTL subsets. These antigens-specific memory CD8+ CTL displayed increased anti-tumor functional activities and proliferation in combination with clinical grade of checkpoint inhibitors (anti-PD1, anti-LAG3, anti-PD-L1), immune agonists (anti-OX40, anti-GITR) or epigenetic regulator (HDAC inhibitor; ACY241).

Conclusions: These results highlight the potential therapeutic application of HLA-A24-specific XBP1/CD138/CS1 targeting cancer vaccine, especially with a wide application in Asia, to evoke the antigen-specific CD8+ CTL immune responses against a broad spectrum of cancers including various types of hematologic malignancies and solid tumors. Moreover, we provide the rationale for combination immunotherapies of the HLA-A24 multi-peptide vaccine with immune mondulator, checkpoint inhibitors, immune agonists and/or HDAC inhibitor to boost tumor-specific memory CTL activities. Clinical trials to treat patients in Asia with myeloma or solid tumors expressing these antigens are planned.

Keyword: Cancer Vaccine Application in Asia, HLA-A24-Specific Multipeptide Vaccine, Target Hematological Malignancy and Solid Tumors, Combination Immunotherapy, Clinical Development, Multicenter Clinical Trials

OP09-1

Clinical features and treatment outcomes of hodgkin lymphoma: A Retrospective review in A Malaysian tertiary centre

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Background: Hodgkin lymphoma (HL) is a clinicopathologically unique, aggressive B-cell lymphoma, which is one of the most curable of all haematological malignancies. This study aimed to assess the characteristics, clinical course, and treatment outcome for HL in a Malaysian tertiary centre.

Methods: A retrospective review was conducted to include patients with the diagnosis of HL from 2013 till 2017. Demographic data, clinical characteristic, treatment regimens, and outcome were collected from the medical record and analysed.

Result: 70 patients were recruited with the median age of 26.5 (IQR+11) years old. Majority of the patients were male (60%) and 70% of them were Malay. Nodular sclerosis was the most common histology (75.4%), followed by mixed cellularity (10.1%), and others (14.5%). The median follow-up time was 26.7 (IQR+16.6) months. All of the patients received chemotherapy but only 7% of them received radiotherapy as consolidation. ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) was the most commonly used chemotherapeutic regimen (82.9%) followed by escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone)(17.1%). Following treatment, 71.4% of the patients achieved complete remission. 4 patients relapsed after first remission and 3 of them achieved second remission after induction therapy with autologous stem cell transplantation. The 2-year and 5-year overall survival (OS) of the entire cohort were 96.6% and 88.5% respectively. The progression free survival (PFS) for 2-year and 5-year were 91.6% and 75.1%. The 2-year OS and PFS in advanced stage disease were 93.8% and 88.8%, compared to 100% and 95% in early stage disease (p=0.376; p=0.322).

Conclusions: The treatment outcomes from our centre are comparable to the published data. Longer study duration will be necessary to identify the OS and PFS benefits from different chemotherapeutic regimen.

Keyword: Hodgkin Lymphoma, Malaysia, Treatment Outcome

OP09-2

Primary central nervous system lymphoma : An institutional experience from India with uniform chemotherapy protocol

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Background: Primary central nervous system lymphoma (PCNSL) is a rare lymphoma. The management of PCNSL poses a unique challenge in low income and resource-limited settings. The information regarding PCNSL in India is scarce

Methods: All the pathologically confirmed PCNSL cases between January 2006 and June 2016, at our center, were analyzed retrospectively. The influence of potential prognostic parameters on event free survival (EFS) and overall survival (OS) was investigated by log-rank test and Cox regression analysis

Result: A total of 87 patients were included in this study. Only a single patient was found positive for HIV-serology. The median age was 50 years with a male: female ratio 2:1. Motor symptoms (60.61%) were most common. Multiple lesions in brain imaging were found in 81.82%. CSF cytology was positive in 15.85 %. Poor performance status (>2) was seen in 58.58%. Diffuse large B cell lymphoma (DLBCL) was most common histology (97.7%). Approximately ~20% patients were not eligible for treatment predominantly due to poor general condition.All patients were treated with high-dose methotrexate (HDMTX)-based combination chemotherapy (DeAngelis protocol) with or without rituximab and whole-brain radiotherapy (WBRT). The response rate was 80.5% (complete response = 41%, and with rituximab based protocol= 56%, p=0.001). At a median follow-up duration of 34 months, the median EFS and OS were 20.4 months and 31.7 months respectively. Treatment-related late neurotoxicity was seen in eight patients (10%). In the multivariate analysis infratentorial involvement (with/without supratentorial involvement), low serum albumin (<3.5gm/dL) and without rituximab based therapy were found to be independent predictors of poor EFS .Low serum albumin (<3.5gm/dL) and infratentorial involvement were found to be independent predictors of OS.

Conclusions: In the present study, younger patients who were mostly immunocompetent (~99%) presented with high-burden disease at baseline (multiple lesions, poor PS) with ~20% patients been unsuitable for treatment. Rituximab based protocol has impact on CR rate and event free survival.

Keyword: Primary CNS Lymphoma, Outcome, India, Rituximab, Resource-Limited Settings.

OP09-3

Busulfan, etoposide, cytarabine and melphalan (BuEAM) as a conditioning regimen for autologous stem cell transplantation in patients with non-Hodgkin

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Background: High-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) is the treatment of choice for the patients with relapsed or high risk NHL. Although the high-dose conditioning regimens commonly used in patients with non-Hodgkin lymphoma (NHL) are BEAM (BCNU, etoposide, cytarabine, and melphalan), BEAC (BCNU, etoposide, cytarabine, and cyclophosphamide), survival of patients with NHL received above high-dose chemotherapy followed by ASCT was still unsatisfactory.

Methods: We prospectively evaluated the efficacy and toxicity of busulfan, etoposide, cytarabine and melphalan (BuEAM) including iv busulfan instead of BCNU of standard BEAM as a conditioning for ASCT in patients with NHL. The high-dose chemotherapy consisted of Bu (3.2 mg/kg i.v. q.d. from day -6 to day -5), E (200 mg/m2 i.v. b.i.d. on day -4 and day -3) A (1 g/m2 i.v. q.d. on day -4 and day -3) and M (140 mg/m2 i.v. q.d. on day -2) at 7 centers in Korea.

Result: Two hundred five patients were enrolled onto the study. Main subgroup was diffuse large B cell lymphoma (n=104, 50.7%), T cell lymphomas (n=59, 29.8%), and NK/T cell lymphoma (n=22, 10.7%). Upfront ASCT was performed in 160 patients (78.0%), and salvage ASCT in 45 patients (22.0%). The disease status of the patients before HDT/ASCT consisted of 133 patients (64.8%) with complete response and 72 patients (35.2%) with partial response. Treatment related toxicities included nausea in 149 patients (72.7%), diarrhea in 127 patients (62.0%), anorexia in 107 patients (52.2%) and stomatitis in 97 patients (47.3%), which were grade I or II in the majority of cases. The common grade III toxicities were stomatitis (6.9%), diarrhea (5.9%), and anorexia (5.4%). There were no VOD, and transplant-related mortality occurred in 4 patients (1.95 %), due to infection. One hundred fifty three patients (74.6%) achieved a complete response and 13 patients (6.3%) after ASCT, while 28 patients (13.7%) showed progressive disease. At a median follow-up duration of 38.6 months, the estimated 3-year overall survival and progression free survival for all patients was 74.5% and 56.6%, respectively.

Conclusions: The conditioning regimen of BuEAM for ASCT was well tolerated and seemed to be effective in patients with relapsed or high risk NHL.

Keyword: Non-Hodgkin Lymphoma, Transplantation, Conditioning

OP09-4

Predictive parameters for neutropenia after R-CHOP chemotherapy with prophylactic peg G-CSF in patients with diffuse large B-cell lymphoma

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Background: Neutropenia is a major cause of morbidity following rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy for DLBCL. It occurs mainly in the first cycle of chemotherapy and results in an increased early mortality rate. To manage this problem, prophylactic administration of

G-CSF after chemotherapy was introduced, and recently, pegylated G-CSF has been widely administered. Even with peg G-CSF, neutropenia occurs, and predicting its occurrence is challenging.

Methods: We retrospectively reviewed the medical records of 115 patients with newly diagnosed DLBCL between 2014 and 2017 at Pusan National University Hospital. All patients received R-CHOP chemotherapy followed by prophylactic peg G-CSF. Patient records of diagnosis and treatment outcomes were collected. Neutropenia (ANC<1.0x109/L) after chemotherapy was determined from CBC on the 7th day of chemotherapy.

Result: Seventy-five men (65.2%) and 40 women (34.8%) underwent R-CHOP chemotherapy and received prophylactic peg G-CSF. The median age at diagnosis was 61 years. Fifty-six patients (48.7%) had Ann Arbor stage IV cancer, and 30 patients (26.1%) exhibited B symptoms. Eighteen patients (15.7%) had bone marrow involvement, and the median bone marrow cellularity was 40%. Abnormal chromosomes were detected in 23 patients' genes (20%), and lactate dehydrogenase was elevated in 79 patients (68.7%). Thirty-nine patients (33.9%) had IPI scores 0–1, 51 patients (44.3%) had IPI scores 2–3, and 25 patients (21.7%) had IPI scores 4–5. Of the patients from whom samples underwent immunohistochemical staining for MYC and BCL-2 or 6, 57.6% had double- or triple-expressor DLBCL, and 30.6% patients had GCB subtype disease according to Hans' algorithm. Forty-eight patients (41.7%) received reduced doses of R-CHOP considering their older age. Among patients, neutropenia occurred in 32 patients (27.8%), and febrile neutropenia was detected in 17 patients (14.8%). On univariate analysis, Ann Arbor stage ≥4 (p<0.01), B symptoms (p=0.03), higher IPI scores (p<0.01), extranodal involved site ≥2 (p=0.01), and bone marrow involvement (p=0.02) were statistically significant predictors of neutropenia events. On multivariate logistic regression, Ann Arbor stage ≥4 (HR, 6.43 [95% CI, 2.37–17.55], p<0.01) was the only factor predictive of neutropenia. (Table 1) Patients with neutropenia showed worse overall survival (24.7 months vs. NR, p<0.01) than that in patients without neutropenia and there was trend toward having worse disease-free survival in patients with neutropenia (17.0 vs. 27.8 months, p=0.07).

Conclusions: In our study, 27.8% of patients with newly diagnosed DLBCL experienced neutropenia after their 1st cycle of R-CHOP chemotherapy, although peg G-CSF was administered prophylactically. The occurrence of neutropenia was also related to survival. Neutropenia was associated with parameters such as Ann Arbor stage≥4, B symptoms, high IPI scores, extranodal involvement, and bone marrow involvement, which were associated with the progression of the disease. The Ann Arbor stage was also statistically significant in multivariate analysis. Therefore, physicians should consider these parameters prior to administering chemotherapy and pay greater attention to patients at high risk of developing neutropenia.

Keyword: DLBCL, R-CHOP, Neutropenia, Peg G-CSF

Table 1. Univariate and multivariate analyses of factors affecting the occurrence of neutropenia

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value*	HR (95% CI)	P-value*
Age (≥60 years)	0.49 (0.21-1.11)	0.088	NA	
Gender	2.01 (0.87-4.65)	0.102	NA	
Ann Arbor Stage≥4	5.88 (2.27-15.19)	0.000	6.43 (2.37-17.55)	0.000
B symptoms	2.62 (1.08-6.34)	0.033	1.71 (0.61-4.81)	0.311
ECOG≥2	2.15 (0.78-5.98)	0.142	NA	
IPI≥3	4.67 (1.91-11.42)	0.001	1.63 (0.53-5.03)	0.398
Bulky mass	0.76 (0.25-2.29)	0.631	NA	
Extranodal involved site≥2	3.83 (1.34-10.94)	0.012	0.94 (0.15-5.8)	0.946
BM involve	3.43 (1.21-9.74)	0.021	1.34 (0.42-4.34)	0.623
Chromosome	1.74 (0.65-4.7)	0.274	NA	
Elevated LDH	1.56 (0.62-3.91)	0.347	NA	
Double or Triple expressor	1.5 (0.34-6.58)	0.591	NA	
Non-GCB type	1.47 (0.55-3.95)	0.447	NA	
CTx. Dose (mini R-CHOP)	0.55 (0.23-1.31)	0.179	NA	

*P-values were derived via Logistic regression analysis.
HR, hazard ratio; CI, confidence interval; NA, not applicable.

OP09-5

Clinical characteristics of childhood hemophagocytic syndrome and analysis of underlying genetic deficiency

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Background: To investigate the clinical manifestations, the laboratory findings, treatments protocol, overall survival rate of children with hemophagocytic lymphohistiocytosis (HLH). To explore the genetic etiology in HLH patients, provide the theoretical basis for pathogenesis and improve the further treatment.

Methods: In order to analysis retrospectively of clinical data in pediatric patients who were hospitalized in Shenzhen Children's Hospital meeting with the "HLH-2004" diagnostic criteria from January 2010 to June 2017, we summarized the clinical manifestations and laboratory data, treatment and outcomes of these patients. We developed a custom panel to capture the exons of 9 genes associated with HLH to detect single nucleotide variants (SNVs) by next generation sequencing (NGS).

Result: The data of 144 HLH cases were analyzed. The ratio of male and female is 1.22:1. The median age was 1.67 years old. pHLH accounted for 14.3% (6/42), sHLH accounted for 87.5% and reasons of unknown resources accounted for 8.3%(12/144) respectively. Secondary HLH divided into infection-associated HLH, autoimmune-associated HLH and malignancy-associated HLH. They were accounted for 79.9% (115/144), 3.5% (5/144) and 4.2% (6/144), respectively. EBV-associated HLH was prominent in infection-associated HLH, accounting for 45.1% (65/144). HLH 2004 basing stratification treatment was performed in all patients. The mortality was 18.1% (26/144) and overall survival was 81.9% (118/144). The mortality differed from different causes such as infection-associated HLH, autoimmune-associated HLH and malignancy-associated HLH, accounting for 11.4% (13/114), 20% (1/5) and 83.3% (5/6). The clinical manifestations were common for fever (100%), liver enlargement (82.0%), spleen enlargement (40.3%), pulmonary infiltration (72.9%), serious effusion including thoracic cavity, enterocoelia and pericardium (43.1%) and jaundice (30.6%). Laboratory findings were common for two or three lineages decrease of peripheral blood cells (97.9%), hemophagocytes in bone marrow (97.2%), hypertriglyceridemia (64.6%), elevated lactate dehydrogenase (78.5%), hypofibrinogenemia (53.5%), prolonged activated partial thromboplastin time (28.5%), elevated serum ferritin (95.1%) and alanine aminotransferase (82.6%). Univariate analysis showed that prolonged APTT, jaundice and elevated BUN were indicated unfavorable prognosis. Multivariate analysis indicated that jaundice and elevated BUN increased the risk for poor prognosis by 6.83 and 6.30 times. Forty-two cases were analyses by genetic method. Six cases had suspected and known mutations, while 15 cases were genes carrier. Twenty-one cases were negative. Genetic evaluation revealed two novel mutations in the LYST gene in a five-year-old Chediak-Higashi Syndrome (CHS) boy. He received treatment with HLH-2004 protocol. We performed sibling HLA-matched hematopoietic stem cell transplantation (HSCT). He had full-donor chimerism with complete reconstitution of the all hematopoietic stem cells at 19 months of follow-up after transplantation.

Conclusions: Our study indicated that EBV was the main cause for HLH. Jaundice and elevated BUN were indicated unfavorable prognosis. Stratified treatment had good treatment response and reached an overall survival of 81.9%. Whole genome low-coverage sequencing technique was a good way to diagnosis pHLH. It was a good opportunity to perform hematopoietic stem cell transplantation in the stable phase of CHS patient. It indicated that HSCT will improve the prognosis in pHLH patients.

Keyword: hemophagocytic Lymphohistocytosis, Next Generation Sequencing, Prognostic Analysis, Chediak-Higashi Syndrome, Molecular Analysis, Hematopoietic Stem Cell Transplantation

OP09-6

Identification of genetic mutation in pediatric patients with HLH : The study of Korean clinical research network for histiocytosis

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory clinical syndrome of uncontrolled immune response. HLH can be classified into genetic (primary) and acquired (secondary) forms according to the underlying defect. The primary HLH can be categorized into 2 subgroups, one including 5 subtypes of familial HLH (FHLH; PRF1, UNC13D, STX11, and STXBP2), and the other expanding subgroup of separate primary immune deficiencies. As HLH is a group of diseases that show genetic heterogeneity, this analysis was conducted to discover genetic causes of HLH by conducting NGS-based genetic panel tests on Korean HLH patients who did not have typical FHL mutations.

Methods: From 2013 to present, 18 institutions have participated to establish prospective registry and collect bio-samples of histiocytosis. A total of 117 Korean pediatric patients with HLH were registered in this registry, and 44 pediatric patients without definite mutations in FHL causative genes were analyzed using a targeted 14-gene panel test (AP3B1, BLOC1S6, CD27, ITK, LYST, MAGT1, PRF1, RAB27A, SH2D1A, SLC7A7, STX11, STXBP2, UNC13D, and XIAP). Identified variants were filtered and analyzed in silico and the allele frequencies were compared to those in population database.

Result: Targeted gene panel tests revealed 6 patients (13.6%) having at least 1 HLH-associated mutation (Table 1; 1 AP3B1, 1 ITK, 1 RAB27A, 1 SH2D1A, 1 STX11, 1 STXBP2). All patients had no family history, and 4 out of 6 six patients had high blood Epstein Barr virus (EBV) titers at the time of diagnosis. All patients received HLH-2004 chemotherapy for the initial treatment. Three patients showed reactivation, and 2 patients with reactivation received stem cell transplantation and currently alive without disease. Patient No 1. was initially presented with EBV associated HLH. However, pan-

cytopenia continued and hepatomagaly was worsened despite of 8 weeks of chemotherapy. Repeated bone marrow biopsy was performed and diagnosed as systemic EBV T-cell lymphoma of childhood. The gene panel analysis confirmed that this patient had a mutation in the AP3B1 gene. AP3 deficiency leads to a defect in cytotoxicity of NK cells and cytotoxic T cells, thus this patient might have the impaired ability against EBV, causing HLH and malignancy. Patients No 4. had typical HLH presentation with multiple lymphadenopathy. No pathologic mutation of the PFR or UNC13D gene was found. HLH activity was repressed during the first 2 weeks of therapy, however, reactivated again with central nervous system (CNS) involvement. The patients died of persistent HLH. As a result of this analysis, this patient had exon 2-4 deletion in the SH2D1A gene, which made the diagnosis as XLP1 syndrome. This might be the reason of the aggressive course of this patient. Four patients (No. 1,2,4,5) were initially classified as secondary HLH due to the association of EBV, however it was found that there was a genetic abnormality at the base that was related to HLH.

Conclusions: The unknown genetic mutations in Korean patients with HLH beyond the typical FHL mutations were identified using a targeted gene panel analysis. This result revealed complex genetic heterogeneity lying in Korean patients with HLH, therefore a comprehensive genetic testing at the time of diagnosis is crucial for the proper treatment of HLH in the future.

Keyword: Hemophagocytic Lymphohistiocytosis, Primary HLH, Gene Panel, Korea

Table 1. Variants predicted to be significant identified by HLH-associated 14-gene panel test

No.	Sex	Age at diagnosis	HLH-associated variant	Family History	EBV association	Reactivation (RFS, mon)	HSCT	Survival	Others
1	M	10.3	AP3B1:c.942G>A	No	Yes	No	Not done	Alive with lymphoma	Systemic EBV T-cell lymphoma of childhood was diagnosed 2 months after HLH presentation
2	M	6.7	ITK:c.1741C>T	No	Yes	No	Not done	Alive in CR	
3	F	1.4	RAB27A:c.569A>T	No	No	No	Not done	Alive in CR	
4	M	9.4	SH2D1A:exon2-4 deletion	No	Yes	Yes (0.9)	Not done	Died of persistent HLH	Diagnosed with XLP1 syndrome
5	M	16.5	STX11:c.246C>T	No	Yes	Yes (2.1)	Done	Alive in CR	
6	M	3.4	STXBP2:c.429+5G>A	No	No	Yes (21.8)	Done	Alive in CR	

HLH, hemophagocytic lymphohistiocytosis; EBV, Epstein Barr virus; RFS, reactivation free survival; mon, months; HSCT, hematopoietic stem cell transplantation; CR, complete remission

OP10-1

An epidemiologic study for disease transformation and second cancers in Korean patients with myeloproliferative neoplasms

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Background: Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (pMF) are three major components of myeloproliferative neoplasms (MPNs). They may be transformed to either secondary MF (sMF) or secondary acute myeloid leukemia (sAML). In addition, they can have second cancers during follow up (FU). It is important to understand the incidence rates and patterns of the transformation and second cancers because by the information we can understand clinical courses of MPNs holistically and figure out the actual socio-economic impact of MPNs on patients and communities.

Methods: South Korea has a compulsory National Health Insurance System (NHIS), covering near the entire population. Claims data from health care providers to NHIS are submitted to the Health Insurance Review and Assessment Service (HIRA) for reimbursement for a service provided to patients, make a nationwide epidemiologic studies feasible. By analyzing the HIRA database, we conducted an epidemiologic study to elucidate clinical course of MPNs patients focusing on disease transformation and second cancers. Cumulative incidence (CI) of transformation or second cancer were calculated considering death as a competing risk.

Result: A total of 7,471 patients (median age 60 years, range 11-106) who were diagnosed as one of the three kinds of MPNs from Jan. 2008 to Dec. 2016 and with appropriate F/U data for the analysis were included (4,405 for ET, 2,470 for PV, and 596 patients for pMF). Among ET patients (median F/U duration 46.7 months), 223 patients (5.06%) underwent any transformation during study period; ET→PV (i.e., initially diagnosed ET but changed to PV later; N = 80), ET→PV→sMF (N = 2), ET→PV→sAML (N = 1), ET→sMF

(N = 68), ET→sMF→sAML (N = 6), and ET→sAML (N = 66), respectively. Among PV patients (median F/U duration 47.4 months), 33 patients (1.36%) underwent transformation to either sMF (N = 13) or sAML (N = 20), respectively. Among pMF patients (median F/U duration 31.9 months), 81 patients (13.59%) underwent transformation to sAML. Patients whose diagnosis was changed from ET to PV during F/U showed higher transformation rate to sMF (2.41% vs. 0.53%; p = 0.0273) and a tendency of higher sAML (1.20% vs. 0.81% to sAML; p = 0.6950) compared to primary PV patients. Five-year CI of transformation to sMF and sAML were 1.4% and 1.91% in ET patients, 0.69% and 0.97% in PV patients, and N/A and 16.54% in pMF patients, respectively (Table 1). Five-year CI of second lymphoid malignancies and solid cancers were 0.66% and 10.68% in ET, 0.17% and 6.67% in PV, and 1.30% and 12.09% in pMF patients, respectively.

Conclusions: Although this study has relatively short F/U duration and lacks information regarding mutational status, it clearly shows that 1) transformations are common in MPNs patients in the order of pMF, ET, followed by PV, 2) Patients whose diagnosis had changed from ET to PV during F/U had a tendency of higher transformation rate, and 3) MPNs Patients had a significantly high risk for second solid cancers. Longer F/U of those population and future studies by subgroup analyses of PV (primary PV vs. transformed or masked PV) and ET (ET vs. pre-fibrotic MF according to 2016 WHO criteria) would further clarify the characteristics of transformation and second cancer in MPNs patients.

Keyword: Myeloproliferative Neoplasms, Second Malignancy, Secondary Acute Myeloid Leukemia, Myelofibrosis

OP10-2

The temporal sequence and the differences of somatic mutation acquisition determines clinical behaviors of JAK2 positive myeloproliferative neoplasms

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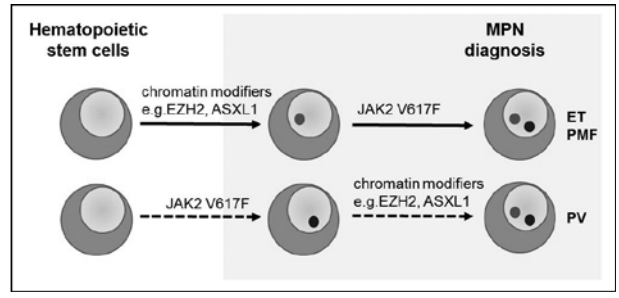
Background: Despite the better understanding of the pathogenesis of myeloproliferative neoplasms (MPN), we are yet to understand why JAK2 positive MPN patients manifest different phenotypes despite harboring JAK2 mutation as a common denominator and what drives secondary transformations. To this end, we have carried out this study to provide better understanding of genetic backgrounds of JAK2 positive MPN in selected patients.

Methods: Using target sequencing, we analyzed mutational status of 17 polycythemia vera (PV), 16 essential thrombocythemia (ET), 8 primary myelofibrosis (PMF) who tested positive for JAK by polymerase chain reaction.

Result: We found that the sequence somatic mutations in relation to JAK2 influences the clinical behavior of the disease. More specifically, focusing on ASXL1, EZH2 and JAK2, we found that ASXL1 or EZH2 mutation acquisition after JAK2 leads to PV, while ASXL1 mutation acquisition before JAK2 leads to ET or PMF. We also found that that mutations in TP53, ASXL1, and splicing genes are associated prognosis of MPN. Lastly, PMF was more frequently associated with splicing mutations, while PV was more closely related to mutations in chromatin modifiers. The presence of these mutations influenced hemogram findings at MPN diagnosis.

Conclusions: Our findings provide better understanding of mutational landscape of MPN in their chronic state and secondary transformed state.

Keyword: Myeloproliferative Neoplasms, JAK2, NGS



OP10-3

Retrospective screening for myeloproliferative neoplasms in patients with cerebral infarctions as revealed using the revised 2016 WHO criteria

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Background: Arterial and venous thromboses are major clinical events in patients with Philadelphia-negative myeloproliferative neoplasms (MPNs) including essential thrombocythemia (ET) and polycythemia vera (PV). Cerebral infarction (CI) is a thrombosis; sometimes, MPN is evident in individuals newly diagnosed with CI. The World Health Organization revised the MPN diagnostic criteria in 2016, but these were not widely used to evaluate patients with cerebral infarctions until recently. We retrospectively evaluated the likelihood of MPNs in CI patients, using the revised criteria.

Methods: The medical records of CI patients admitted to the Chungnam National University Hospital from January 2016 to December 2017 were retrospectively reviewed. Patients with erythrocytosis or thrombocytosis were divided into those with reactive, possible, probable, or proven MPN.

Result: A total of 1,729 CI patients (1,003 males; 726 females) of median age 73 years (range, 19–96 years) were reviewed. Thrombocytosis (platelets ≥450,000/μL) was evident in 69 (4.0%) patients either at diagnosis or during follow-up. Reactive thrombocytosis was the most common form of thrombocytosis (N=62, 3.6%); three (0.2%) patients were considered to exhibit possible ET; and four (0.2%) proven ET. The causes of reactive thrombocytosis (N=62 patients) included infection (N=59, 95.2%), bleeding (N=1, 1.6%), and iron-deficiency (N=1, 1.6%). Erythrocytosis was evident in 79 (4.6%) patients either at diagnosis or during follow-up. Reactive erythrocytosis was the most common form of erythrocytosis (N=50, 2.9%), followed by possible PV (N=21, 1.2%), probable PV (N=6, 0.3%), and proven PV (N=2, 0.1%). None of the 27 patients with possible or probable PV underwent further investigations; in particular, JAK2 mutational status was not explored. Reactive erythrocytosis (N=50) was detected during diagnosis in 28 (56.0%) patients and during follow-up in 22 (44.0%); all cases were attributable to hemoconcentration. Of the four patients with proven ET, two lacked any other predisposing factor for thrombosis. All patients with proven ET and PV exhibited multifocal cerebral infractions and previously undetected infarctions on CI diagnosis.

Conclusions: Many CI patients with erythrocytosis did not undergo further evaluation in terms of PV diagnosis. JAK2 mutational status should be evaluated in such patients.

Keyword: Myeloproliferabtive Neoplasm, Essential Thrombocythemia, Polycythemia Vera, Cerebral Infarction, JAK2 Mutation

OP10-4

Clinical characteristics and risk groups of chronic myeloid leukemia in children

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Background: Chronic myeloid leukemia (CML) is relatively rare in children Both pediatric and adult patients CML have fusion gene BCR-ABL1. In 2012, Krumbholz et al have shown that breakpoint distribution in BCR is different in pediatric CML compared with adult CML. These differences in the genomic landscape may contribute to the more aggressive clinical characteristics in pediatric CML compared with adult CML. In 2011, we had a research to evaluate clinical - hematological characteristic and treatment outcome this disease with small sample size in 37 pediatric CML This is the reason that we would like to do this research again with a larger sample size in Viet Nam to evaluate of clinical, hematological characteristics and risk group of pediatric chronic myeloid leukemia (CML).

Methods: The routine cytogenetics and molecular test were performed by standard methods and all clinical characteristics and risk group of pediatric CML were reviewed by using clinical records

Result: A total 85 patients were included in the study (median age: 12 years). 25% patients were referred or hospitalized because of physconia and fever. Splenomegaly was the most popular symptom (95.6%). There were only 4,7% of patients do not have clinical manifestations at the time of diagnosis. About hematological characteristics: Hemoglobin (< 8 g/dl) accounted 36.5%; white blood cells rose above 100 x 109/L in 80% and platelets increased over 450 x 109/L in 60% of patients. Low and intermediate risk groups were similar according Sokal score; ELTS score of the low-risk group was significantly higher than that of 82.4% of the patients; low risk group in Eutos score accounted for nearly two-thirds.

Conclusions: Compare to previous reports regarding adult CML patients, the clinical characteristics are worse in our pediatric CML cohort. And it may be justified to use more potent TKIs such as dasatinib, nilotinib and radotinib in pediatric CML.

Keyword: Pediatric Chronic Myeloid Leukemia, Risk Groups, Clinical and Hematological Characteristics

OP10-5

Expression and clinical significance of PTEN gene in chronic myeloid leukemia (CML) patient in Indian population

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Background: Chronic myeloid leukemia (CML) starts in certain blood-forming cells of the bone marrow and it constitute about 30% to 60% of all adult leukemia in India. CML is a clonal myeloproliferative disorder characterized by the presence of a balanced genetic translocation of chromosomes 22 and 9, chromosome (Philadelphia chromosome). The resulting breakpoint cluster region-Abelson murine leukemia (BCR-ABL) fusion oncogene is translated into the BCR-ABL oncoprotein that activates number of signal-transduction pathways which affect the growth and survival of hematopoietic cells. PTEN tumor suppressor gene is down regulated by BCR-ABL in CML stem cells and its deletion is associated with acceleration of disease. However, it is unknown whether PTEN functions as a tumor suppressor in human Philadelphia chromosome–positive leukemia that includes chronic myeloid leukemia and is induced by the BCR-ABL oncogene in human. Little is known about the association of PTEN gene in blood cancer. Our study may help in identifying factors which may play a role in increasing susceptibility to CML and possible outcome.

Methods: A total one hundred and nine (109) cases of CML were analyzed for detection of mutation, mRNA and protein expression and promoter methylation of the PTEN gene. Polymerase chain reaction, single-strand conformational polymorphism (SSCP) followed by DNA sequencing were applied for mutations detection across all the nine exons, while mRNA and protein expression was evaluated by qPCR and western blot respectively. The methylation status was performed by methylation specific PCR (MS-PCR). Reverse Transcriptase PCR (RT-PCR) was performed to detect BCR-ABL fusion transcript. Finally we correlate above finding with clinicopathologic characteristics of the patient.

Result: The novel PTEN mutations were observed in 8.3% (9/109) including two silent mutations. High percentage (61%) cases were shown positive hypermethylation, while (72%) cases shown loss of protein expression than control samples. Interestingly, all mutated cases shown loss of PTEN expression, while 7/9 cases shown positive promoter methylation. In addition, out of total methylated positive samples, 79% shown loss of PTEN expression and it was significantly correlated (p=0.06). PTEN Promoter methylation was observed in 36% cases in Chronic Phase and 40% cases in Accelerated Phase. Among the all methylation positive cases, 42% were found to be positive for BCR-ABL fusion transcripts while, 33% cases were negative for BCR-ABL fusion transcript.

Conclusions: We found that epigenetic inactivation of PTEN is significantly correlated with the presence of high level of loss of PTEN expression (61% vs 72 % respectively), are quite novel. This shows the possibility of involvement of PTEN hypermethylation in CML development. Our data suggested that PTEN expression may be plays an important role in the susceptibility of the disease progression and also provide valuable prognostic information to aid treatment strategies.

Keyword: PTEN, BCR-ABL, Chronic Myeloid Leukemia, Hypermethylation, Real Time PCR, Single-Strand Conformation Polymorphism

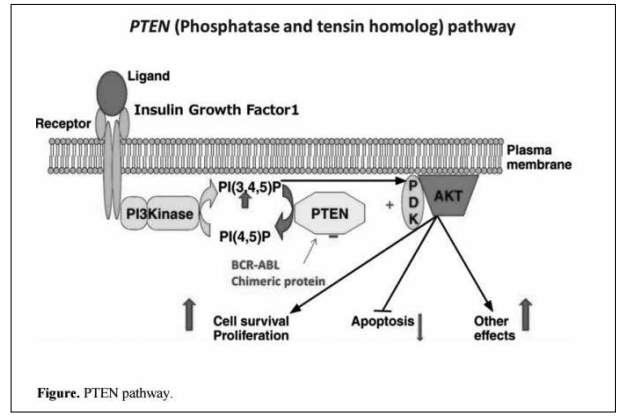

Figure. PTEN pathway.

OP10-6

Pilot prospective phase II study of Nilotinib combined by chemotherapy for myeloid blastic phase of chronic myeloid leukemia or bcr-Abl positive acute

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Background: Various chemotherapies were tried and found that there were no highly effective chemotherapies for chronic myeloid leukemia myeloid blastic phase (CML-MBP). Imatinib in patients with these advanced CML is also disappointing because of low response rates as well as short response duration, and sudden transformation to BC is found even in initial CML-CP patients. Some studies showed that nilotinib or dasatinib was better than imatinib in terms of rapid response and higher molecular response in newly diagnosed CML patients. We tried 2nd generation TKI, nilotinib and high-dose daunorubicin induction chemotherapy combination to find out the combination therapy could improve response rate and survival in patients with CML-MBP or acute myeloid leukemia with BCR/ABL1 (AML-BCR/ABL1).

Methods: The primary end point of the study was complete remission (CR) rate after induction chemotherapies (IC). Patients received cytarabine 200 mg/m2/day by continuous IV infusion over 24 hours daily for 7 days (D 1-7) along with daunorubicin 90 mg/m2/day iv daily for 3 days (D 1-3). Nilotinib 400mg bid PO was added continuously without interruption from D8 of induction chemotherapy until allogeneic hematopoietic cell transplantation (alloHCT) or during 2 years. Re-induction chemotherapy was given as cytarabine 200 mg/m2/day by continuous iv infusion over 24 hours daily for 5 days (D 1-5) plus daunorubicin 45 mg/m2/day iv daily for 2 days (D 1-2) when D14 bone marrow blasts exceeded 5%. Four courses of high-dose cytarabine (Cytarabine 3 g/m2) was administered in 3-hour IV infusion every 12 hours on days 1, 3, and 5 (a total of six doses per course). This prospective phase II study was terminated early due to slow enrollment.

Result: Total 10 (6 male & 4 female) patients were enrolled. Six patients were diagnosed as CML-MBP and 4 patients as AML-BCR/ABL1. Median age at diagnosis of CML-MBP was 50.9 (22.5-63.0) years. Five patients had received prior therapies (low-dose cytarabine in 1, imatinib in 2 and dasatinib in 2 patients). Median time from CML-MBP to induction chemotherapy was 3.12 (0-3.12) months. All patients received IC. Nilotinib was suspended temporarily during IC in 5 patients (hyperbilirubinemia in 2, cytopenia in 1, rash in 1 and poor general condition in 1 patient). Nine patients showed bone marrow (BM) blast<5% in early evaluation. CR was achieved in all (CR in 9 patients and CRi in 1) patients. One patient who had achieved CRi died of pneumonia without full hematological recovery during IC. Molecular response (MRIS) at the time of CR was not-evaluable in 1, MR1.0 in 3, MR2.0 in 2, MR3.0 in 2 and MR4.5 in 2 patients. Eight patients received 1 or 2 cycles of consolidation and 1 patient died during consolidation therapy. Five patients proceeded to alloHCT after consolidation. Two more (1 by relapse after alloHCT and 1 by graft-versus-host disease) patients died after alloHCT. Two patients died after alloHCT (1 by relapse and 1 after stopping nilotinib by toxicities). Median overall survival was 4.961 (95% CI, 1.522-8.400; Fig 1) months. Four patients are still alive (3 patients after alloHCT and 1 patient without alloHCT; 6.41+, 12.16+, 29.37+ and 43.63+ months).

Conclusions: In conclusion, nilotinib combined with IC is feasible and a good bridging therapy for these extremely rare CML-MBP or AML-BCR/ABL1 if they are IC-eligible.

Keyword: Chronic Myeloid Leukemia, Blastic Phase, Nilotinib, Acute Myeloid Leukemia with BCR/ABL1

OP11-1

Single-center clinical data analysis of hereditary thrombocytopenia in children with chronic thrombocytopenia

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Background: Hereditary thrombocytopenia (HT) is clinically hard to differentiate from immune thrombocytopenia (ITP) in children and thus ultimately interferes with treatment. Our study aimed to know the detection rate of HT in children chronic thrombocytopenia and its clinical and laboratory characteristics for an early clinical identification and diagnosis of HT in future.

Methods: Retrospectively collected data from children thrombocytopenia who had been treated in Beijing Children's Hospital from April 2016 to May 2018 whose present history lasted for more than 1 year and had poor response to immunotherapy. We screened HT in these patients by Next Generation Sequencing (NGS). Finally, clinical and laboratory characteristics were summarized and analyzed in these children HT.

Result: A total of 161 children chronic thrombocytopenia were included. 43 cases (26.7%) were found to have gene mutations. We analyzed the genetic rules of the mutant gene, the family ver-

ification and the clinical manifestations of the proband and some related laboratory tests and found 24 cases (14.9%) who can be diagnosed as HT. Among the HT patients, the proportion of males and females was 15:9, and the median onset age was 0.58 years, which was significantly lower than that of non-HT cases (median onset age was 4.36 years), P value <0.001; proportion of mucosal hemorrhage and visceral hemorrhage (31.8%/13.7) %) of HT was significantly higher than non-HT cases (15.3%/0.6%) with a P value <0.001. 12/24 cases of HT with positive family history; considering the average platelet volume and platelet morphology in peripheral blood smear, HT could be divided into small platelet HT, positive platelet HT and large platelet HT. Some cases had well response to immunotherapy but seemed easy to relapse during the withdrawal period, while the others responded poorly to therapy. Different clinical manifestations of HT suggest different pathogenesis, which can be divided into megakaryocyte differentiation defect, megakaryocyte maturation defect, platelet release defect and platelet survival time shortening.

Conclusions: In this study, the detection rate of HT in children chronic thrombocytopenia was 14.9%. The pathogenesis and clinical phenotype of HT was different. Some of them were effective for immunotherapy, which were easily confused with ITP. It is clinically necessary to perform NGS in children thrombocytopenia with early onset, abnormal platelet morphology, prolonged disease course and severe mucosal/visceral hemorrhage, in order to differentiate HT from children ITP in time to avoid misdiagnosis.

Keyword: Children, Hereditary Thrombocytopenia, Next Generation Sequencing

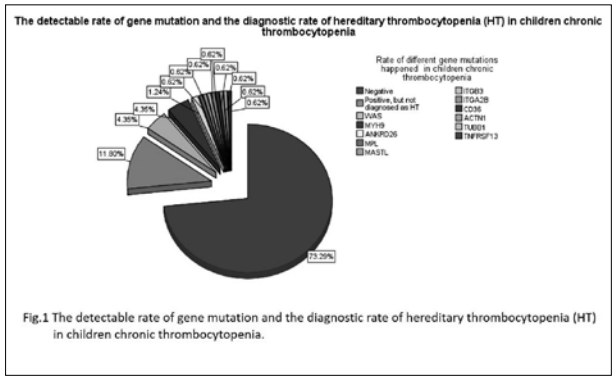

Fig.1 The detectable rate of gene mutation and the diagnostic rate of hereditary thrombocytopenia (HT) in children chronic thrombocytopenia.

OP11-2

Developing a diagnostic predictive model for immune thrombocytopenic purpura based on immature platelet fraction

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Background: Immune thrombocytopenic purpura (ITP) is known as an acquired, immune-mediated disease characterized by isolated thrombocytopenia. ITP can be diagnosed on the basis of clinical manifestations and many studies have asserted that a routine bone marrow examination is not necessary. The immature platelet fraction (IPF) has been incorporated into the differential diagnosis of thrombocytopenia. In this study, we assessed usefulness of IPF as a diagnostic marker and developed a diagnostic predictive model for ITP.

Methods: We retrospectively analyzed 568 patients with thrombocytopenia who presented to Korea University Guro hospital between April 2013 and December 2017. We classified patients into 2 groups: those diagnosed with ITP and those without ITP. ITP was diagnosed according to IWG diagnostic criteria. Non-ITP group included thrombocytopenia due to bone marrow disease, infection, drug, liver disease, etc. We used an automated hematologic analyzer (Sysmex XE-2100) to quantify the IPF and estimated other laboratory variables. All data were statistically analyzed using SPSS version 20. Logistic regression analysis was performed with the laboratory variables to access their diagnostic contribution. We used receiver-operating characteristic (ROC) and the point with the highest sum of sensitivity and specificity on the ROC curve was determined as the cut-off value of each variables.

Result: A total of 206 and 362 patients were diagnosed as ITP and non-ITP. The median IPF is significantly higher in the ITP group, with a value of 8.7% vs. 5.1% in the non-ITP group, and cut-off value for differentiation of ITP was 7.0% with a sensitivity of 61% and a specificity of 70%. Since ITP remains a diagnosis of exclusion, some patients who did not undergo a bone marrow examination might have been misclassified into the ITP group. To exclude the possibility of misclassification, we conducted a subgroup analysis

of only patients who had undergone a bone marrow examination (BM group). Total of 200 patients performed bone marrow examination, 77 and 123 were classified into the ITP and non-ITP group. The median IPF was significantly higher in ITP group, with a value of 12.5% vs. 4.7% for the non-ITP group. The cut-off value was 7.8%, with a sensitivity of 75% and a specificity of 76.7%. The median IPF was higher in this subgroup and the sensitivity and specificity of the cut-off value were also higher than the former group. We confirmed that IPF could be a useful parameter for diagnosing ITP, but since IPF alone is not enough to diagnose ITP, we also evaluated other laboratory variables by the logistic regression analysis. Hb, LDH, ferritin showed statistical significance. Our model gave point to each of variables; 1 to high hemoglobin(>12g/dl), low ferritin(≤177ng/ml), low LDH(≤420IU/L) and IPF ≥7 and <10, 2 to IPF ≥10. The final score was obtained by summing the points. We applied this scoring system to a group of patients diagnosed by bone marrow examination. We demonstrated that ITP could be highly predicted in patients with more than 3 points. Accuracy, precision and recall were 87%, 82% and 86%, respectively.

Conclusions: The results showed that IPF could be a good diagnostic marker for ITP. We suggested the diagnostic predictive model for ITP using IPF, hemoglobin, LDH and ferritin. This model could predict ITP with high probability and avoid a bone marrow examination.

Keyword: Immune Thrombocytopenic Purpura, Immature Platelet Fraction

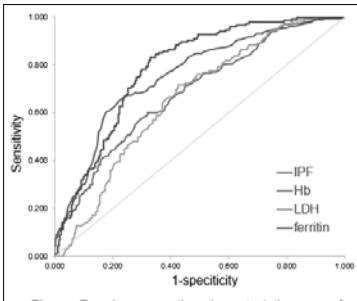

Figure. Receiver-operating characteristic curve of IPF, Hemoglobin, LDH and ferritin

Variables	Cut-off	P-value
IPF (%)	7	<0.001
Hb (g/dL)	12	<0.001
LDH (IU/L)	420	0.047
Ferritin (ng/mL)	177	0.001

Table. Variables included in the diagnostic predictive model

OP11-3

Insufficient receptor editing leads to B cell central intolerance and subsequent autoantibodies accumulation in primary immune thrombocytopenia

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Background: The antibody-mediated platelet destruction is the most important pathogenic mechanism in primary immune thrombocytopenia (ITP). The antibody is detectable in approximately 50-60% patients with ITP. However, it is not clear how these anti-platelet antibodies are generated in ITP patients. Receptor editing is a process to change the specificity of immature B cell receptors (BCR) by a secondary recombination of immunoglobulin genes, which are the main part of central tolerance of B cells. The aim of this study is to investigate how the anti-platelet antibodies are generated and overcome the central B cell tolerance in patients with ITP.

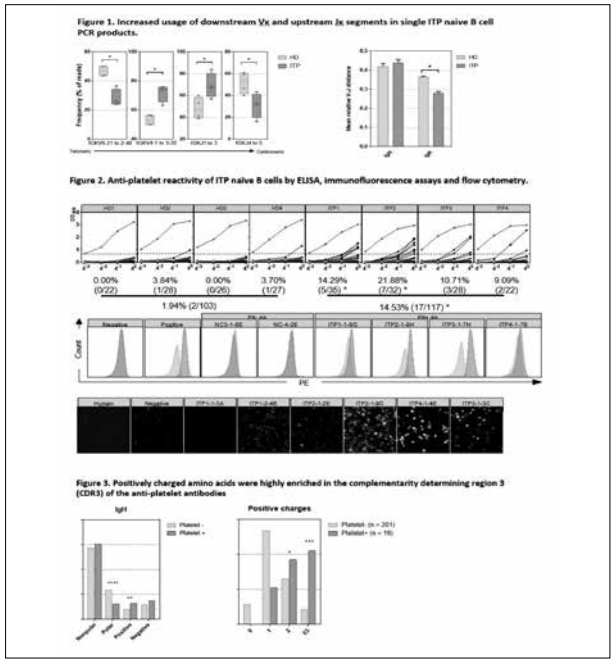
Methods: We first performed next-generation sequencing on peripheral B cells of ITP patients and found a distinct immunoglobulin gene κ chain (Igκ) repertoire from the healthy control. We then performed single cell RT-PCR on naïve B cells to clone both Ig heavy chain (IgH) and Ig light chain (IgL) genes from the same cells. The paired IgH and IgL were co-transfected and the recombinant monoclonal antibodies were expressed and purified. The reactivity of these antibodies against platelet antigens was determined by ELISA, immunofluorescence assays, and flow cytometry with human platelets. Cross-reactivity of these antibodies was tested by ELISA coated with double strand DNA, insulin and lipopolysaccharides. Ig gene sequence features were analyzed by programs including IMGT, IgBLAST, and VHRFA-1.

Result: The deep sequencing revealed that the ITP-derived Igκ preferentially used the downstream Vκ (Vκ1-20) (44.65% vs. 42.20%, p = 0.0210) and upstream Jκ (Jκ1-2) (27.82% vs. 23.38%, p = 0.0210) segments compared with those derived from healthy controls, which indicated a defective receptor editing of B cells in ITP patients. The PCR products confirmed the Vk (71.92% vs. 53.13%, p = 0.00155) and Jk (69.02083% vs. 48.34321%, p = 0.0337) usage bias in the naive B cell compartment of ITP patients. Utilizing single cell RT-PCR, 220 recombinant antibodies were cloned and expressed derived from naïve B cells in 4 ITP patients and 4 healthy controls. Low numbers of somatic mutations validated that the antibodies were derived from naive B cells. ELISA assay

showed that 14.53% (17/117) of the ITP-derived naïve B cells were platelet- reactive, in contrast to the 1.94% (2/103) in healthy donor-derived naïve B cells, suggesting a defective B cell tolerance in the early developing stage. The anti-platelet reactivity was also confirmed by immunofluorescence assays and flow cytometry. Cross-reactivity test revealed that the anti-platelet antibodies were polyreactive to multiple antigens. Sequence analysis revealed that positively charged amino acids were highly enriched in the complementarity determining region 3 (CDR3) of the anti-platelet antibodies, which possibly generates the potential to interact with the negatively charged glycoproteins.

Conclusions: In summary, this study provides evidence of defective early B cell tolerance and accumulation of anti-platelet naïve B cells in patients with ITP. This defect might be a result of insufficient receptor editing in IgL.

Keyword: ITP, Anti-Platelet Antibodies, Receptor Editing, Central B Cell Tolerance



OP11-4

ROTEM parameters as predicting factors for bleeding in immune thrombocytopenic purpura

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Background: Immune thrombocytopenic purpura (ITP) is one of the most common benign hematologic disorders. ITP patients present with a severe reduction in platelet counts and suffer from an increased risk of bleeding. However, several studies have shown that platelet counts do not accurately predict the risk of bleeding in these patients. As such, there remains the needs to identify a predictor or set of parameters that can accurately assess the risk of hemorrhage in patients with ITP. Assessment of rotation thromboelastometry (ROTEM) parameters is used primarily to assess the risk of bleeding in surgery and trauma cases. Although there are a few reports on using ROTEM parameters to evaluate the risk of bleeding in ITP patients, a direct comparison of their predictive value for hemorrhage risk with platelet counts is needed. In the present study, we compare the ability to predict hemorrhage in ITP patients between platelet counts and multiple ROTEM parameters, such as MCF EXTEM, platelet MCE, A10 EXTEM, and AUC EXTEM.

Methods: We performed a case series prospective study on patients diagnosed with acute, persistent, and chronic ITP who received treatment at the Department of Hematology, Cho Ray Hospital from December 2017 to July 2018. The inclusion criteria were platelet counts of <30 G/L and no clinically significant bleeding (grade ≥2 according to WHO Bleeding Scale) at the beginning of the study. A p-value of 0.05 was considered statistical significance.

Result: Forty-five patients met the sampling criteria. After 24 hours of following up, 14 patients (31.1%) experienced clinically significant bleeding. The mean platelet counts of patients with and without clinically significant bleeding were 6.21 ± 5.79 G/L and 9.81 ± 6.69 G/L, respectively. There was no statistically significant difference in platelet count between the two groups ($p = 0.09$). The mean MCF EXTEM values of the two groups were 23.29 ± 6.81 mm and 35.03 ± 9.46 mm, respectively, with a statistically significant p-value of 0.000. Similarly, the differences in platelet MCE values ($p = 0.001$), A10 EXTEM ($p = 0.000$), and AUC EXTEM ($p = 0.000$) were also statistically significant between the two groups (Table 1). Further, MCF EXTEM had an AUC value of 0.844 (95% CI: 0.721-0.968), a sensitivity of 92.9%, a specificity of 80.6% in predicting clinically significant bleeding in ITP patients, with a cut-off

value of 29.5 mm. The AUC value for platelet MCE was 0.811 (95% CI: 0.676-0.946), with a sensitivity of 78.6%, a specificity of 80.6%, and a cut-off value of 19.95. A10 EXTEM had an AUC of 0.841 (95% CI: 0.727-0.955), a sensitivity of 85.7%, a specificity of 74.2% with a cut-off value of 21.5 mm. Finally, AUC EXTEM had an AUC value of 0.848 (95% CI: 0.726-0.969), a sensitivity of 92.9%, a specificity of 80.6%, with a cut-off value of 2940.

Conclusions: The results obtained from this preliminary study demonstrate that ROTEM parameters might be used as predicting factors for hemorrhage in ITP patients. Future studies with a larger sample size is warranted to confirm our findings, which will allow better and timelier bleeding management in ITP patients.

Keyword: ROTEM, Thrombocytopenia, Bleeding Risk, ITP

Parameters	Clinically Significant Bleeding (n = 14)	No Clinically Significant Bleeding (n = 31)	P-Values
Platelet Counts	6.21 ± 5.79 G/L	9.81 ± 6.69 G/L	0.09
MCF EXTEM	23.29 ± 6.81 mm	35.03 ± 9.46 mm	0.000
Platelet MCE	12.41 ± 14.87	36.92 ± 22.22	0.001
A10 EXTEM	16.86 ± 4.74 mm	25.45 ± 4.27 mm	0.000
AUC EXTEM	2331.64 ± 670.87	3478.29 ± 935.98	0.000

Table 1: Summary of parameters in patients with and without clinical significant bleeding

OP11-5

Increased pathogenic Th17 cells in primary immune thrombocytopenia

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Background: Th17 cells play a critical role in the pathogenesis of many inflammatory and autoimmune diseases, including rheumatoid arthritis, multiple sclerosis and so on. However, not all Th17 cells are pathogenic. TGF-β1 plus IL-6 can induce non-pathogenic Th17 cells, while TGF-β3, IL-6, and IL-23 were crucial for driving pathogenic phenotype. Primary immune thrombocytopenia (ITP) is an autoimmune disease with aberrant change of immune cytokines, including increased expression of IL-6 and IL-23. However, the function of pathogenic Th17 cells in the pathogenesis of ITP has not been well defined. More importantly, dexamethasone (DXM), as the first-line treatment for ITP, may restore the aberrant level of pathogenic Th17 cells in ITP, thus providing new insights into the mechanism of DXM treatment.

Methods: Peripheral blood was obtained from 45 active ITP patients and 48 healthy controls. We detected the level of pathogenic Th17 cells (CD3+CD8-IL-17+IFN-γ+IL-10-) and non-pathogenic Th17 cells (CD3+CD8-IL-17+IFN-γ-IL-10+) by flow cytometry. CD4+ cells were isolated from peripheral blood mononuclear cells (PBMCs) by MACS. The mRNA expression level of cytokines/chemokines (Cxcl3, Ccl4, Ccl5, Il3, Il22 and Casp1), transcription factors (Tbx21 and Stat4), effector molecules (Gzmb, Lag3 and Lglas3) and immune regulation molecules (Il-10, Ahr and Ikzf3) in CD4+ T cells was determined by RT-PCR. To evaluate the effect of DXM treatment, PBMCs from ITP patients were treated with DXM(10μM) or not and then the level of pathogenic Th17 cells and mRNA expression of molecules mentioned above were detected. Data were analyzed using SPSS 21.0 software.

Result: We identified increased pathogenic Th17 cells in peripheral blood from active ITP patients in comparison to healthy controls (p=0.028; Fig 1a). Interestingly, significant difference was also observed in non-pathogenic Th17 cells between patients and controls (p=0.0001; Fig 1b). Compared with healthy controls, mRNA expression of Cxcl3, Il-22, Tbx-21 and Il-23r was significantly increased in ITP patients (p=0.007, 0.028, 0.04 and 0.02, respectively; Fig 1c-f), whereas that of Il-10 and Ahr was significantly decreased (p=0.0001 and 0.0001, respectively; Fig 1g and h). Besides, clinical analysis showed that the percentage of pathogenic Th17 cells in severe patients was higher than that in non-severe patients. In vitro, pathogenic Th17 cells treated with DXM significantly decreased compared with untreated group (p=0.008; Fig2 a, b). Furthermore, after treated with DXM, the mRNA expression in CD4+ cells decreased significantly among the following regulated molecules related to pathogenic Th17 cells, such as Cxcl3, Ccl4, Ccl5, Il-23r and Tbx-21(p=0.023, 0.008, 0.008, 0.008 and 0.023, respectively; Fig 3a-e), while some molecules increased significantly, such as Ahr and Il-10 (p=0.008, 0.016, respectively; Fig 3f, g).

Conclusions: In summary, our results indicated that patients with ITP exhibited increased level of pathogenic Th17 cells. DMX treatment restored the level of pathogenic Th17 cells and the expression of pathogenic Th17-related molecules. Aberrant pathogenic Th17 cells may contribute to the pathogenesis of ITP and represent a novel therapeutic target.

Keyword: Primary Immune Thrombocytopenia, Pathogenic Th17, Dexamethasone

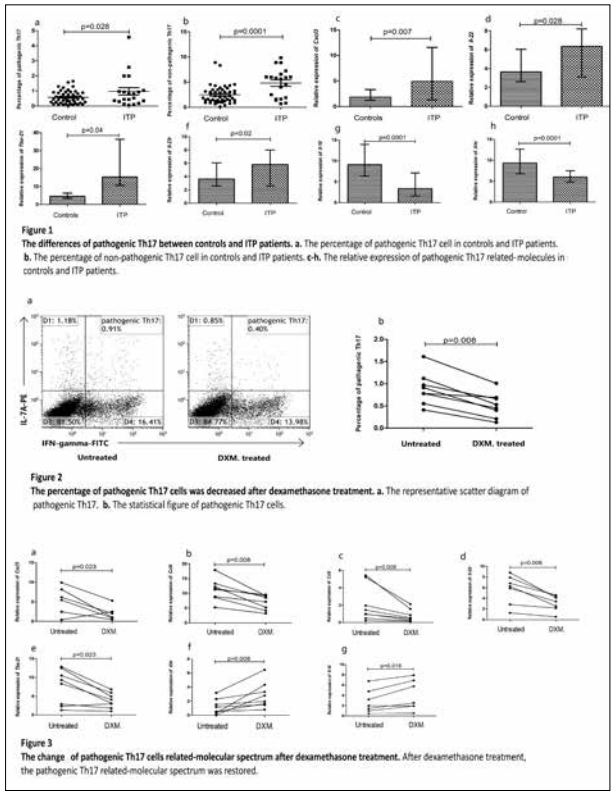

Figure 1
The differences of pathogenic Th17 between controls and ITP patients. a. The percentage of pathogenic Th17 cell in controls and ITP patients. **b.** The percentage of non-pathogenic Th17 cell in controls and ITP patients. **c-h.** The relative expression of pathogenic Th17 related-molecules in controls and ITP patients.

Figure 2
The percentage of pathogenic Th17 cells was decreased after dexamethasone treatment. a. The representative scatter diagram of pathogenic Th17. **b.** The statistical figure of pathogenic Th17 cells.

Figure 3
The change of pathogenic Th17 cells related-molecular spectrum after dexamethasone treatment. After dexamethasone treatment, the pathogenic Th17 related-molecular spectrum was restored.

OP11-6

Prediction value of risk assessment model deep vein thrombosis with padua prediction score

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Background: Deep venous thrombosis (DVT) is the third most common cardiovascular pathology, after coronary artery disease and stroke. Hospitalization is a major risk factor for DVT, and many events that occur among hospitalized patients with DVT can be prevented. Padua Prediction Score is a model for assessing the risk of DVT events in hospitalized patients. This study aims to assess the sensitivity, specificity, accuracy and predictability of the risk assessment model of Padua Prediction Score for the diagnosis of DVT in Dr. Sardjito Hospital, Yogyakarta, Indonesia

Methods: This research was a diagnostic test of the Padua Prediction Score to assess the risk of DVT patients in Dr. Sardjito Hospital Yogyakarta, Indonesia conducted from October 2015 until September 2017. This observational cohort study used an independent and blinded assessment. The subjects of this study were patients aged more than18 years treated in inpatient installation of Dr. Sardjito Hospital, Yogyakarta, Indonesia for more than 3 days with risk factors for DVT during hospitalization (1) cancer in patients with local or extensive metastasis and/or in patients undergoing chemotherapy or radiotherapy that has been running for 6 months, (2) history of venous thromboembolism, (3) decreased mobility in bed rest patients over 3 days, (4) the presence of thrombophilic conditions ie defects in antithrombin; protein C or S; factor V Leiden; G20210A prothrombin mutation; syndrome antiphospholipid, (5) trauma or surgery less than 1 month (6) Age more than 70 years old (7) failed breath or heart failure, (8) ischemic stroke or acute myocardial infarction (9) acute infection or rheumatology disorder (10) obesity with body mass index more than 30 kg/m2 and (11) received hormonal therapy and agreed to participate in the study by signing an informed concent sheet. Subjects will be assessed Padua prediction score which will be classified into high risk and low risk then will do first doppler ultrasound to know whether there is DVT or none. Subjects with DVT on first doppler ultrasound will be excluded. Subjects were monitored for 90 days. The subjects will examine doppler ultrasound again at the end 90 days or complaint sign and/or symptoms of DVT prior 90 days monitoring. Diagnostic tests aim to determine the value of sensitivity, specificity, accuracy, positive predictive value, negative predictive value.

Result: During the 2-year study there were 230 subjects consisting of 146 subjects (63.5%) with high risk DVT and 84 subjects (36.5%) with low risk DVT. At the end, there were 133 subjects (57.8%) who completed the research, with 75 subjects (56.4%) in high risk and 58 (43.6%) subjects in low risk. The results showed 90% sensitivity value, specificity 46.34%, accuracy 49.62%, positive predictive value 12%, negative predictive value 98.28%, positive likelihood ratio of 1.677 and negative likelihood ratio of 0.216. There was a correlation between the Padua score with acceleration of DVT events (r: -0.345). Subjects with high risk DVT will have 7 times higher risk of developing DVT than those with low risk.

Conclusions: The Padua prediction score has good predictive value in estimating DVT incidence so it can be used as one of the modality screenings to assess DVT risk in hospitalized patients

Keyword: Deep Vein Thrombosis, Diagnostic Test, Risk Assessment Model, Padua Prediction Score

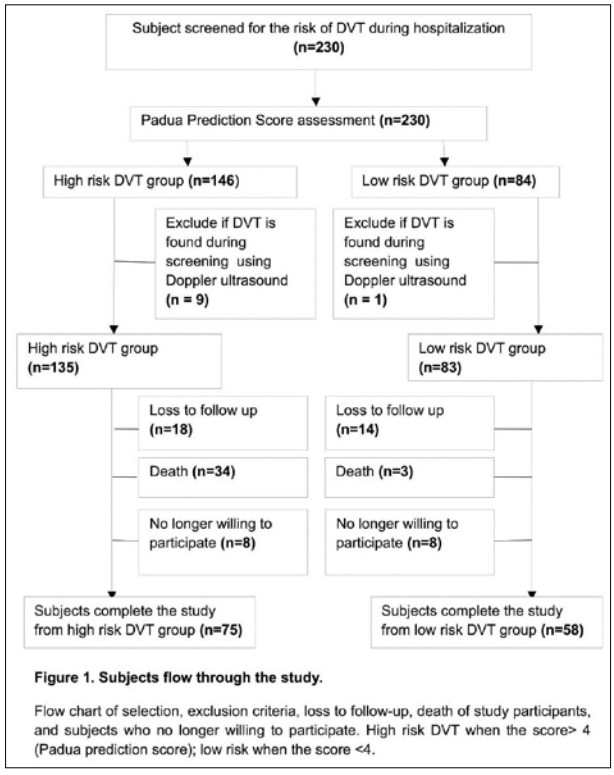

Figure 1. Subjects flow through the study.

Flow chart of selection, exclusion criteria, loss to follow-up, death of study participants, and subjects who no longer willing to participate. High risk DVT when the score> 4 (Padua prediction score); low risk when the score <4.

OP12-1

Cytoprotective autophagy in bone marrow endothelial cells enhance hematopoietic stem cells in poor graft function patients after allo-transplant

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Background: Poor graft function (PGF) remains a serious complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Our previous work reported that abnormal bone marrow (BM) endothelial cells (ECs) were involved in the pathogenesis of PGF patients after allo-HSCT (BBMT 2013; BMT 2016; Blood 2016), but the explicit mechanism requires further clarification. Autophagy is a self-degradative process responsible for the elimination of cytosolic components including proteins and damaged organelles. Recent findings demonstrated that stimulation of autophagy could reduce oxidative status and angiogenic potential in ECs after high-glucose exposure, from diabetic patients. However, little is known regarding the autophagy of BM ECs in PGF patients. Therefore, the current study was performed to evaluate whether autophagy in BM ECs play a role in the pathogenesis of PGF. Moreover, to investigate the effects of autophagic regulation on ECs and thereby regulating hematopoietic stem cell (HSCs).

Methods: In the prospective case-control study, the autophagy levels were compared in BM ECs from PGF patients, and their matched good graft function (GGF) patients. The expression levels of autophagy-related markers (LC3, Beclin1, and P62), and intracellular autophagosomes were detected by immunohistochemical staining, flow cytometry, western blot and transmission electron microscopy. The autophagic vacuoles were detected by Monodansylcadaverine (MDC) staining assay. Subsequently, rapamycin (the autophagy activators) or hydroxychloroquine (HCQ, the autophagy inhibitor) were administrated to the 7-day cultivated BM ECs. The BM ECs were evaluated by cell counting, DiI-Ac-LDL and FITC-lectin-UEA-1 double staining, migration, cell proliferation, and levels of reactive oxygen species (ROS). To explore whether autophagy would affect the ability of BM ECs to support HSCs in vitro, BM CD34+ cells from healthy donors were co-cultured with cultivated BM ECs. Colony-forming unit (CFU) and the apoptosis of co-cultured HSCs were analyzed.

Result: The defective autophagy in BM ECs, characterized by decreased intracellular autophagosomes and autophagic vacuoles, decreased expression of LC3-II and Beclin1, and high level of P62, were observed in PGF patients compared with GGF patients. Moreover, the co-culture of BM CD34+ cells with BM ECs showed significant deficient CFU plating efficiency, and increased apoptosis of CD34+ cells in PGF patients. In vitro upregulation of autophagy by rapamycin quantitatively and functionally improved BM ECs, which manifested as more DiI-Ac-LDL and FITC-lectin-UEA-1 double stained cells, increased capacities of migration, lower levels of ROS and apoptosis via regulating Beclin1 pathway, whereas inhibition of autophagy by HCQ aggravated the BM ECs from PGF patients. Furthermore, in vitro upregulation of autophagy by rapamycin significant improved CFU plating efficiency, and decreased apoptosis in BM HSCs co-cultured with BM ECs from PGF patients.

Conclusions: These findings suggest that defective autophagy in BM ECs may be involved in the pathogenesis of PGF. The effect of rapamycin in PGF patients is potentially mediated by improving the dysfunctional BM ECs to support HSCs. Therefore, it would be of value to investigate whether upregulating of cytoprotective autophagy of BM ECs may ameliorate PGF, thereby providing a novel clinical intervention for PGF in the future.

Keyword: Poor Graft Function, Allo-Transplant, Endothelia Cells, Hematopoietic Stem Cells, Autophagy, Rapamycin

OP12-2

Aberrant bone marrow M1/M2 Macrophage polarization may contribute to prolonged isolated thrombocytopenia after allotransplantation

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Background: Prolonged isolated thrombocytopenia (PT), defined as the engraftment of all peripheral blood cells other than platelets, remains a challenging complication following allogeneic hematopoietic stem cell transplantation (allo-HSCT), and the underlying mechanisms have not yet been elucidated thoroughly. Megakaryocytopoiesis is a consecutive process regulated by multiple signals in the bone marrow (BM) microenvironment. Macrophage (MΦ), commonly exist in two distinct subsets: classically activated inflammatory MΦ (M1) and alternatively activated anti-inflammatory MΦ (M2), is one of the important components of BM immune microenvironment. Specific BM and spleen MΦ depletion was found to provoke megakaryocytopoiesis in a mouse model of immune thrombocytopenia. Recently, we demonstrated that an unbalanced M1/M2 ratio and dysfunctional BM MΦs contribute to poor graft function after allo-HSCT (BJH 2018). However, little is known about the quantity and functional roles of BM M1/M2 and the impact of these cells on megakaryocyte and platelet development in PT patients following allo-HSCT.

Methods: This prospective case-control study enrolled 16 patients with PT, 32 matched patients with good graft function (GGF), defined as persistent successful engraftment after allotransplant, and 12 healthy donors (HD). Standard monocyte subsets, defined by cluster of differentiation CD14 and CD16, were quantified by flow cytometry. In addition, based on the phenotype of polarized macrophages in vitro, M1(CD68+CCR2+) and M2 (CX3CR1+CD163+) from BM samples were analyzed by flow cytometry. BM CD14+ monocytes were isolated from BM mononuclear cell and were cultured with recombinant human M-CSF to obtain MΦs. The functions of BM derived MΦs were evaluated by migration and phagocytosis assay. CD34+ cells from HD were co-cultured with BM derived MΦs from PT and GGF patients for megakaryocyte differentiation, and the quantification of the MKs, MK apoptosis, MK polyploidy distribution, platelet production and colony-forming unit megakaryocytes (CFU-MKs) were analyzed.

Result: Alterations in standard monocyte subsets (classical, intermediate and non-classical) were found when comparing patients among PT, GGF and HD. In particular, elevated intermediate and non-classical monocyte subsets were observed in PT patients when compared with those in GGF patients. Moreover, PT patients displayed an unbalanced M1/M2 ratio compared with the GGF and HD, attributable to a reduction in M2 and an increase in M1. Migration and phagocytosis function of PT-MΦs did not significantly differ with GGF and HD MΦs. The percentages of megakaryocytes and mature megakaryocytes were significantly lower in CD34+ cells cocultured on PT-MΦs compared to those observed on GGF-MΦs. The platelet release values and megakaryocyte apoptosis in the GGF-MΦs group were higher than in the PT-MΦs group. Meanwhile, lower CFU-MKs efficiency were markedly showed in CD34+ BM cells which were co-cultured with PT-MΦs compared those co-cultured with GGF-MΦs.

Conclusions: In summary, the current study demonstrated the abnormal BM M1/M2 MΦs polarlarition with normal funtion, which have a negative impact on megakaryocyte maturation and platelet production in PT patients. Therefore, it would be of value to understand the underlying molecular mechanisms of M1/M2 that regulates megakaryocytopoiesis, and investigate the appropriate approach to balance the M1/M2, which may be a promising therapeutic approach for PT patients.

Keyword: Allogeneic Hematopoietic Stem Cell Transplantation, Prolonged Isolated Thrombocytopenia, Bone Marrow Microenvironment, Macrophages, M1/M2

OP12-3

G-CSF-induced macrophage polarization may prevent acute graft-versus-host disease after allogeneic hematopoietic stem cell transplant

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Background: Macrophage (MΦ) was defined into two broad subsets, M1 (classical MΦs), which produce pro-inflammatory cytokines, or M2 (alternative MΦs), which produce anti-inflammatory cytokines. An imbalance MΦ polarization has been shown to play a critical role in many diseases. Therefore, repolarization of MΦs may be a novel therapeutic option. The impact of granulocyte colony-stimulating factor (G-CSF) on MΦs in humans is unclear. Moreover, little is known about the association between MΦ subgroups in allografts and the occurrence of acute graft-versus-host disease (aGVHD) in patients who undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT). To determine whether the different MΦ subsets could be mobilized into the bone marrow (BM) and peripheral blood (PB) through G-CSF administration and whether MΦ polarization in BM allografts was associated with the occurrence of aGVHD, which may help clarify the potential roles of MΦs in G-CSF-induced immune tolerance in allo-HSCT.

Methods: In the current study, 89 patients who underwent allo-HSCT at Peking University People's Hospital and their own donors were enrolled between April 1 2017 and October 31 2017 and were followed up to September 1 2018. Subsequently, we investigated the effects of G-CSF on the percentages of M1 (CD68+CCR2+), M2 (CX3CR1+CD163+) MΦs both in BM and PB of healthy donors by flow cytometry. Moreover, the effects of G-CSF on MΦs function, including DiI-Ac-LDL uptake, DAPI binding assay, migration assay and mixed-lymphocyte reaction were investigated in vitro. Subsequently, we evaluated the association of M1/M2 MΦs ratio with the occurrence of aGVHD in patients who underwent allo-HSCT.

Result: The current study demonstrated that G-CSF mobilized MΦs polarization in both PB and BM, characterized by a decrease in pro-inflammatory M1 MΦs were found in the G-CSF mobilized-BM (G-BM, 4 days after G-CSF) and G-CSF mobilized-PB (G-PB, 5 days after G-CSF) compared to the stable-BM (S-BM) and stable-PB (S-PB) pre-G-CSF administration. Moreover, a decrease in anti-inflammatory M2 MΦs were observed in the G-PB, whereas a reciprocal increase in anti-inflammatory M2 MΦs in the G-BM. As a result, the M1/M2 MΦs ratio was markedly decreased in G-PB and G-BM of healthy donors, which may alter the Th1/Th2 response. Moreover, the current study demonstrated dysfunctional BM MΦs after G-CSF-induced mobilization, characterized by decreased migration capacity and increased phagocytic activity. After coculture with G-BM MΦs, BM T cells favoring a type 2 response, characterized by reduced Th1 and Tc1 percentages, increased Th2, Tc2 and Treg lineage percentages. In addition, our clinical data indicate that patients who received an infusion with a higher M1/M2 ratio exhibited a higher incidence of grade 2-4 aGVHD.

Conclusions: In summary, the results presented here indicate that G-CSF-mediated MΦ polarization, characterized by a decreased M1/M2 ratio in both PB and BM samples from healthy donors, may influence the Th1/Th2 response. In addition, our clinical data indicate that patients who received a higher BM M1/M2 ratio infusion exhibited a higher incidence of grade 2-4 aGVHD. Therefore, we speculate that the M1/M2 ratio may predict the occurrence of grade 2-4 aGVHD.

Keyword: Macrophages, Allogeneic Hematopoietic Stem Cell Transplantation, Acute Graft-Versus-Host Disease, Granulocyte Colony-Stimulating Factor

OP12-4

Early transplantation-related mortality within 50 days after allogeneic hematopoietic stem cell transplantation in patients with acute leukemia

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Background: Transplantation-related mortality (TRM) is a major obstacle to allogeneic hematopoietic stem cell transplantation (HSCT). Patient age, donor type, disease state, and regimen intensity are known to be associated factors of TRM. Within 50 days after transplantation, there is a high incidence of infection prior to engraftment and a high incidence of organ toxicity associated with the conditioning regimen. Patients without special complications will also be discharged within 50 days of transplantation. However, there is no study of early TRM within 50 days. Based on big data from National Health Insurance Service, we conducted a study to identify the incidence and risk factors associated with early TRM within 50 days in allogeneic HSCT.

Methods: Patients were enrolled from 2003 to 2015 with the diagnostic codes of acute leukemia and the infusion codes of allogeneic HSCT in South Korea. Based on the medical charge and drug codes, we compared the clinical characteristics of early TRM and non-TRM group.

Result: The total number of patients was 5,395, the median age was 38 years and the male was 55.1%. Acute myeloid leukemia was 3,490 (64.7%), and acute lymphoblastic leukemia was 1,905 (35.3%). The 3,453 (64.0%) patients were received myeloablative conditioning regimen and 1,942 (36.0%) patients received reduced intensity of conditioning. The number of transplants increased from 671 in 2003-2006, 1,287 in 2007-2009, 1,578 in 2010-2012, and 1,859 in 2013-2015. The 151 patients (2.8%) died within 50 days. The median age of non-TRM and early TRM group was 38 and 41 years, respectively (p=0.014). The proportion of women was higher in the early TRM group (54.3%, p=0.018). The duration from diagnosis to transplantation was significantly longer in the early TRM group (6.2 versus 5.1 months, p<0.001). The 331 patients (6.1%) had previously received at least one HSCT and early mortality was higher in these patients (9.4%, p<0.001). Also, the interval from the previous transplantation was significantly shorter in early TRM (11.1 versus 15.0 months, p=0.014). Early TRM was higher in patients who received more than 13 platelet transfusions (p=0.017) and 8 more red blood cell transfusions (p=0.001). The 793 patients (14.7%) had iron chelation prior to transplantation and their early TRM rate was as low as 0.3% (p<0.001). There was no increase in TRM in patients with more than 3 underlying diseases. Early TRM rates in peripheral blood, bone marrow, and cord blood HSCT were 2.9%, 1.7%, and 6.1%, respectively (p<0.001), cord blood transplant was significantly higher. There was no difference in early TRM according to year, conditioning regimen, and regimen intensity.

Conclusions: In this study, the incidence of early TRM within 50 days was 2.8%. Early TRM was associated with age, gender, previous transplantation, previous transfusion, iron chelation, and stem cell source.

Keyword: Transplantation Related Mortality, Allogenic Stem Cell Transplantation, Risk Factors, Acute Leukemia

OP12-5

Incidence of anicteric veno-occlusive disease/sinusoidal obstruction syndrome and defibrotide efficacy following hematopoietic stem cell transplant

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Background: Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a progressive, potentially life-threatening complication of hematopoietic stem cell transplant (HSCT) or nontransplant chemotherapy. Of traditional diagnostic criteria for VOD/SOS, only Baltimore criteria requires bilirubin >2 mg/dL. Hyperbilirubinemia is not required by modified Seattle criteria, and it may be a late finding in the progression of VOD/SOS. Defibrotide (DF) is approved to treat severe hepatic VOD/SOS post-HSCT in patients aged >1 month in the European Union and to treat hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT in the US and Canada. Literature suggests that VOD/SOS with bilirubin <2 mg/dL before Day +21 is uncommon in adults. This post hoc analysis examines the incidence of VOD/SOS without elevated bilirubin, before and after Day +21 post-HSCT, and survival in DF-treated patients in the expanded-access (T-IND) program (2007–2016).

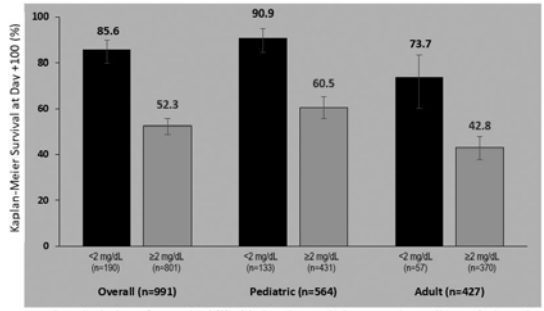
Methods: The original T-IND protocol required post-HSCT diagnosis of VOD/SOS per Baltimore criteria or biopsy; the protocol was amended in 2012 to include patients diagnosed using the modified Seattle criteria. Patients received DF 25 mg/kg/day; recommended treatment duration was ≥21 days.

Result: Of 991 post-HSCT patients in the T-IND with recorded bilirubin level at diagnosis, 190 (19%) had bilirubin <2 mg/dL (135 [71%] diagnosed with VOD/SOS by Day 21 post-HSCT; 55 [29%] diagnosed after Day 21). Of these, 133 were pediatric patients aged ≤16 years (24% of the 564 post-HSCT pediatric patients; 107 [80%] diagnosed by Day 21; 26 [20%] diagnosed after Day 21), and 57 were adults aged >16 years (13% of the 427 post-HSCT adults; 28 [49%] diagnosed by Day 21; 29 [51%] diagnosed after Day 21). Across all 1000 post-HSCT patients in the T-IND (including 9 without baseline bilirubin data), Kaplan-Meier estimated Day +100 survival was 58.9% (95% CI, 55.7%–61.9%); Figure 1 shows survival by bilirubin level and age group. In the overall population of patients with bilirubin <2 mg/dL, 61.1% of patients had ≥1 treatment-emergent adverse event (TEAE), 18.4% had ≥1 treatment-related adverse event (TRAE), and 21.1% had ≥1 hemorrhage event. For patients with bilirubin ≥2 mg/dL: 73.8% had ≥1 TEAE, 21.7% had ≥1 TRAE, and 31.1% had ≥1 hemorrhage event.

Conclusions: In the T-IND, 19% of post-HSCT patients with VOD/SOS had bilirubin <2 mg/dL at diagnosis (24% of children; 13% of adults). Accordingly, 190 patients would not have been diagnosed if hyperbilirubinemia was a required criterion. Of patients with bilirubin <2 mg/dL, 80% of pediatric patients and 49% of adults were diagnosed with VOD/SOS ≤21 days post-HSCT, showing that anicteric VOD/SOS can develop within 21 days post-HSCT in a considerable number of pediatric and adult patients. These results confirm that pediatric patients may not have hyperbilirubinemia, and further clearly show that anicteric VOD/SOS is also present in some adults prior to Day 21. DF treatment was associated with higher survival in patients with bilirubin <2 mg/dL compared with those with levels ≥2 mg/dL. These results compare favorably with the overall study findings, suggesting that treatment before the onset of hyperbilirubinemia may lead to better outcomes. The safety profile of the T-IND was similar to that of previous studies of DF for the treatment of VOD/SOS. Support: Jazz Pharmaceuticals.

Keyword: Veno-Occlusive Disease, Sinusoidal Obstruction Syndrome, Defibrotide, Bilirubin, Hematopoietic Stem Cell Transplantation, Efficacy

Figure 1. Higher Kaplan-Meier Estimated Day +100 Survival for Post-HSCT VOD/SOS Patients with Bilirubin at Diagnosis <2 mg/dL Compared with ≥2 mg/dL Overall and by Age Group



Numbers include patients with bilirubin level recorded at VOD/SOS diagnosis (9 patients were excluded overall, with 6 pediatric patients aged ≤16 years and 3 adults aged >16 years).
Error bars indicate 95% confidence intervals.
HSCT, hematopoietic stem cell transplantation; T-IND, expanded-access program; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

OP12-6

Phase I trial of repeated infusions of bone-marrow derived mesenchymal stem cells in steroid-refractory chronic graft-versus-host disease patients

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Background: Chronic graft-versus-host disease (cGHVD) is the most common long-term complication of allogenic hematopoietic stem cell transplantation which is associated with poor quality of life and increased risk of morbidity and mortality. Currently, there is no standardized treatment available for patients who do not respond to steroids. As an alternative to immunosuppressive drugs, mesenchymal stem cells (MSCs) have been used to treat and prevent steroid-refractory acute GVHD patients. These studies and reports have also provided a basis for using MSCs in steroid refractory cGVHD patients.

Methods: To evaluate the safety and efficacy of repeated infusions of MSCs, we enrolled ten severe steroid-refractory cGVHDs patients. Steroid refractory was defined as either no response to steroids lasting at least 4 weeks or progression of disease during treatment or tapering lasting at least 2 weeks. Patients were intravenously administered with MSCs produced from third-party bone marrow donors at a 2-week interval for a total of four doses. Each dose contained 1x106 cells per kg body weight and all four doses consisted of MSCs from the same donor and same passage.

Result: We enrolled ten patients (3 female/ 7 male, with a median age of 41.5(range 17-68). Median of cGVHD affected organs was 3 (range 2-4) including the skin (n=4), eyes (n=8), oral cavity (n=9), lung (n=1), liver (n=2) and joints (n=6). All ten patients received their planned four doses of MSCs, administering a total of 40 infusions. Median time from initial cGVHD diagnosis to first MSC treatment was 709 days (range 222-4413). MSC infusions were well tolerated with no immediate or delayed toxicities. After 8 weeks of the first MSC infusion, all ten patients showed partial response showing alleviation in clinical symptoms and increased quality of life. Organ responses were seen in skin (n=2), eyes (n=5), oral cavity (n=8), liver (n=1), and joint(n=5). However, one patient died of progressive GVHD and one patient relapsed from primary disease.

Conclusions: Repeated infusions of MSCs was feasible and safe and may be an effective salvage therapy in patients with steroid-refractory cGVHD. Further large-scale clinical studies with long-term follow up is needed in the future to determine the role of MSCs in cGVHD.

Keyword: Chronic Graft-Versus-Host Disease, Mesenchymal Stem Cells, Cell Therapy, Phase I Clinical Trial

POSTERS

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PP-001

Inhibition of Unc-51-Like kinase 1 (ULK1) preferentially induces apoptosis and autophagy in FLT3-ITD- mutated acute myeloid leukemia cells

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Background: In normal karyotype acute myeloid leukemia (AML), FLT3-ITD mutation is associated with dismal prognosis with early relapse even after allogeneic stem cell transplantation. Unfortunately, to date small-molecule inhibitors of FLT3 have resulted in only partial and transient clinical responses with residual leukemic blasts acquiring resistance to FLT3 inhibitors. Therefore, elucidation of novel molecular targets should be necessary for effective eradication of FLT3-ITD AML cells. Evidences are accumulating on the functional roles of autophagy in the initiation and maintenance of AML as well as the development of drug resistance. Unc-51-like kinase 1 (ULK1) is a conserved serine-threonine kinase that plays a central role in the initiation of autophagy.

Methods: We investigated the effect of MRT68921, a potent inhibitor of both ULK1 and ULK2 in AML cell lines. MOLM-13, MV4;11 and U937/FLT3-ITD cell lines were used. U937/FLT3-ITD cell line was established in our laboratory by transducing of FLT3-ITD in parental U937 cell using retroviral infection in order to clarify whether FLT3-ITD is involved in the drug resistance in AML.

Result: Our group demonstrated that ULK1 is potentially involved in the development of resistance of AML leukemia stem cells to BET inhibitor, JQ1. The fact that ULK1 is the only conserved serine/threonine kinase in the autophagy cascade makes it a very attractive target for therapeutic development. However, the role of Ulk1 in FLT3-ITD AML remains unclear. In this study, we observed that MRT68921, a potent inhibitor of both ULK1 and ULK2, induced apoptotic cell death in FLT3-ITD-mutated AML cell lines (MV4-11, Molm13, U937/FLT3-ITD-muated) in a dose-dependent manner. However, apoptosis-inducing effect of MRT68921 was significantly lower in FLT3-WT AML (HL-60, U937). Cell death was accompanied with cleavage of caspases and PARP, which were partially blocked with caspase inhibitor z-VAD-fmk, indicating the caspase-dependent mechanism exists. MRT68921 treatment led to a notable decrease in the levels of phosphorylated (p) ATG13 (Ser 318) as well as total ULK1 and p-ULK1 (Ser 555). Interestingly, MRT68921 induced LC3-II lipidation, autophagosome, and GFP/LC3 punta formation, indicating autophagy was paradoxically activated in FLT3-ITD-mutated AML cells. AMPKα phosphorylation (T712) was increased in MTR68921-responsive cells. In contrast, autophagy induction was negligible to modest in FLT3-WT AML cells. Treatment of FLT3-ITD cells with autophagy inhibitors, 3-MA, bafilomycin A1, and hydroxychloroquine, markedly enhanced the MRT68921-induced apoptosis, strongly suggesting that prosurvival autophagy activation occurred with MRT68921 in FLT3-ITD cells. Reduction in the levels of total FLT3 and p-FLT3 protein were observed concurrently with downregulation of p-STAT5 in FLT3-ITD cells. Endoplasmic reticulum stress-associated proteins, p-PERK and p-eIF2α were also downregulated with MRT68921 in FLT3-ITD cells.

Conclusions: Taken together, targeting the ULK1 pathway could be an effective therapeutic strategy for combating FLT3-ITD AML. Inhibition of prosurvival autophagy pathway could enhance the anti-leukemia effects of MRT68921.

Keyword: ULK1, FLT3-ITD AML, Autphagy

PP-002

RNA CRISPR-Cas9 efficiently down regulates pCrKL signalling in K562 BCR-ABL cell line: Insights from in-vitro experiments with gene editing

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Background: Tyrosine kinase inhibitors (TKI's) have revolutionized the treatment of CML over past two decades. In addition, advances in transplant for high risk disease have brought about good outcomes in most cases. However, toxicities and emergence of resistant clones have compelled scientists to look forward to gene editing tools as alternate effective and viable treatment options. Hence, in current study we planned to investigative in vitro efficiency of CRISPR-Cas9 mediated BCR—ABL gene silencing in K562 cell line and study its downstream effects.

Methods: BCR-ABL1 specific primers were used to amplify and sequence the region of K562 cell line using automated Sanger sequencing platform. sgRNA (single guide RNA) and Homology directed repair template targeting the chimeric region was designed and off-target analysis was conducted using DESKGEN Genetics online server. Restriction site overhangs for BpiI were added to the top and bottom

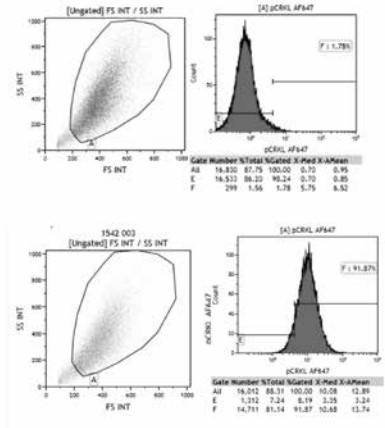
strands of the sgRNA sequence. CRISPR-Cas9 cloning backbone plasmid pCAG-eCas9-GFP-U6-gRNA was procured from Addgene and the SgRNA was inserted into plasmid along with HRD template using digestion-cloning method and insertion verified with sanger sequencing. The plasmid was then transfected using lipofectamine into both control (HEK293T) and K562 cell lines. The GFP labeled and transfected cells were flow sorted and exome sequencing performed to rule out off target insertion. The cells were then subjected to BCR-ABL mRNA and downstream pCrKL signalling analysis

Result: The SgRNA was successfully inserted into the CRISPR-Cas9 plasmid following over digestion. The K562 cell line transfection efficiency following Lipofectamine use was around 20%. Flow sorting revealed all 100% GFP labelled transfected cells. WES did not reveal any non-specific or off target effects. RT-PCR from the transfected cells showed >90% reduction in Homology-directed-detectable transcript as compared to untransfected K562 cells. Downstream analysis of pCrKL however revealed a significant but suboptimal drop in signalling to the tune of 2.6 times the unstransfected unstained K562 cells (MFI 5.11 Vs. 13.16; p=<0.05).

Conclusions: The in vitro experiments show successful silencing of BCR-ABL transcript however with a relatively low efficiency of 20%. This could be due to the lipofectamine method used per se and can be improved with use of neon transfection system. Another reason could be different intronic breakpoints within the chimeric fusion gene of BCR-ABl within the K562 cell line which would require tailor-made target SgRNA for silencing. This could also be the reason for sub-optimal reduction in pCrKL signalling to the tune of 2.6 times only. Imatinib on other hand results in at least 5 times reduction in pCrKL signalling. The experiments suggest that better results may be obtainable if RNA-CRISPR-CAS 13 plasmid is utilised since it would do direct silencing of mRNA transcript irrespective of intronic regions in BCR-ABL gene breakpoint and fusion

Keyword: CRISPR-CAS9, SgRNA, Silencing, CML

Figure 1: Upper plot shows unstained CRISPR+K562 cells (MFI-5.75) while lower plot shows pCrKL stained CRISPR+K562 cells (MFI-10.68)



PP-003

HTLV-1 bZIP factor modulates p53 pathway by stabilizing PICT1 complex

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Background: Human T-cell leukemia virus type-1 (HTLV-1) is known to cause a type of cancer, referred to as adult T-cell leukemia/lymphoma (ATLL), and a demyelinating disease called HTLV-1 associated myelopathy/Tropical spastic paraparesis (HAM/TSP). HTLV-1-infected T cells have been hypothesized to contribute to the development of these disorders, although the precise mechanisms are not well understood. The HTLV-1 provirus possesses structural and enzymatic proteins typical of all retroviruses (i.e., gag, pol, env) and LTR on both ends. HBZ (HTLV-1 bZIP factor) gene was identified as a gene transcript from the 3'-LTR in a pX region. Notably, HBZ is consistently expressed in all ATLL cells, suggesting that HBZ appear to promote the development of ATLL. 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.

Methods: We conducted a yeast two-hybrid screen using full-length HBZ as bait and newly identified PICT1. Association of HBZ with PICT1 was investigated in mammalian cells and binding domains both of HBZ and PICT1 were detected. Subcellular distribution, when coproduction of HBZ together with PICT1 in cells were examined confocal microscopic.

Result: Interaction between HBZ and PICT1 were confirmed in mammalian cells by co-immunoprecipitation (Co-IP) assay. C-terninal domain of PICT1 bound to the central domain of HBZ. The molecular interaction of HBZ with PICT1 might alter the mutual subcellular localization. Thus, we examined the cellular localization of HBZ and PICT1 in transiently transfected HEK-293T 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 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. Our current study is focused on understanding the molecular significance by which the interaction between HBZ and PICT1 regulates the p53 pathway.

Conclusions: Our results suggested that HBZ may be affected the function of PICT1 and help us to understand the pathogenesis of HTLV-1.

Keyword: HTLV, HBZ, P53, Ubiquitin, ATL

PP-004

Prognostic impact of interim and post-treatment positron emission tomography status in mantle cell lymphoma patients treated with frontline R-CHOP

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Background: Although 18F-Fluorodexoyglucose positron emission tomography (18F-FDG-PET) is widely used for initial staging and therapeutic response evaluation in aggressive lymphoma, the prognostic impact is currently controversial for evaluation process in mantle cell lymphoma (MCL). Therefore, to better determine the role of PET in the management of MCL, we retrospectively analyzed the prognostic value of interim PET(iPET) and end-oft-treatment PET (associated) image as well as other biologic risk factors in a uniform MCL cohort undergoing standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen with the long-term follow-up duration.

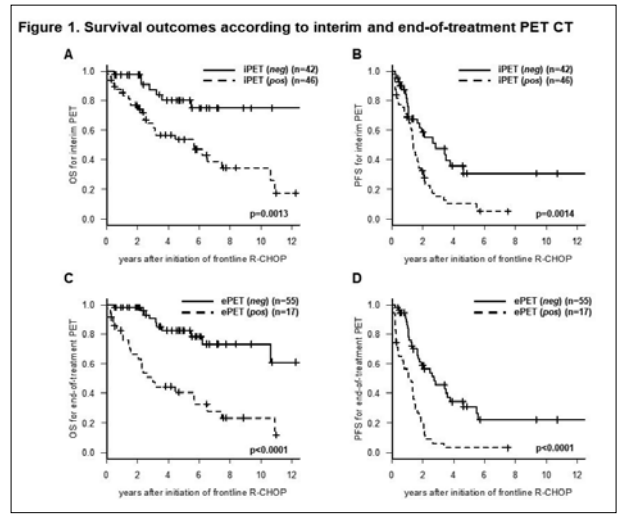
Methods: Adult patients who diagnosed with consecutive MCL from January 2007 to January 2018 at our single center were screened, and all patients had histopathologically confirmed CD20-positive, cyclin D1-positive and non-blastoid subtype B-cell. In consecutive 90 MCL patients who were treated with uniformed frontline R-CHOP, and survival outcomes and other biologic markers during interim or end-of-treatment PET were retrospectively evaluated using Deaville 5-point scale method.

Result: With a median follow-up duration of 42 months (range, 9-144 months), 3-year overall survival (OS) and progression-free survival (PFS) were 73% and 43%, respectively. iPET-positive was associated with poor OS (80% and 53% of 5-year OS, p=0.0013) and poor PFS (31% and 10% of 5-year PFS, p=0.0014), and ePET-positive had poor OS (82% and 41% of 5-year OS, p<0.0001) or poor PFS (32% and 7% of 5-year PFS, p<0.0001) (Figure 1). The subgroup analysis by autologous hematopoietic stem cell transplantation was shown similar results. The low FDG-avidity group (iPET-negative → ePET-negative, n=38) showed the best favorable PFS and the high FDG-avidity group (iPET-positive → ePET-positive, n=16) was poor PFS outcome. Also, the fluctuating group (iPET-positive → ePET-negative, n=17 or iPET-negative → ePET-positive, n=1) had tended to show an intermediate PFS rate (p=0.062). When other subset analysis was performed according to a period of achieving metabolic response, early metabolic response (defined as constantly ePET-negative status from iPET-negative), it showed the more positive PFS outcome than a group of delayed metabolic response (defined as ePET-negative conversion from iPET-positive) or no metabolic response (defined as non-converted ePET-positive from iPET-positive) with statistical significance (p=0.0387).

Conclusions: The role of PET CT is important to be able to evaluate a tumor metabolic burden in real time as it is non-invasive imaging biomarkers. Taken together, interim and end-of-treatment PET CT may predict OS and PFS in patients with frontline R-CHOP treated-MCL, and risk-adapted therapeutic approach including of auto-HSCT determined by interim or post-treatment PET CT should be investigated in future clinical practice.

Keyword: Ibrutinib, Interim PET CT Scan, Mantle Cell Lymphoma, Prognosis

Figure 1. Survival outcomes according to interim and end-of-treatment PET CT



PP-005

Genetic alterations and their clinical implications in langerhans cell histiocytosis

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Background: MAPK pathway activation is known to be associated with oncogenesis of Langerhans cell histiocytosis (LCH). The purpose of this study was to investigate the frequency of genetic mutations and their correlation with clinical features and prognosis in Korean patients with LCH.

Methods: Genomic DNA was extracted from formaldehyde-fixed and paraffin-embedded samples from patients who were pathologically confirmed with LCH and treated at Asan Medical Center. Profiling of somatic mutations for 41 critical genes related to tumor development was performed using OncoMap version 4.4-Core under the MassARRAY technology platform (Sequenom, San Diego, CA).

Result: A total of 51 LCH cases were evaluated. A median age at diagnosis was 4.3 years (range, 0.1-55.8 years), and male-to-female ratio was 0.8:1. Forty-two patients had single system disease (23 with unifocal bone disease, 15 multifocal bone disease, 4 with skin disease), and 9 had multisystem disease (6 without risk organ involvement, and 6 with risk organ involvement. OncoMap assay revealed that 24 patients (47.1%) harbored BRAF mutation, and 16 (31.4%) MAP2K1 mutation. One patient had both BRAF and MAP2K1 mutations. Other recurrent mutations included CHEK2 (n = 7), ARID1B (n = 6), and NTRK1 (n = 2) mutations. The age at diagnosis and the presence of multisystem involvement did not differ according to genetic mutations. Patients with BRAF or MAP2K1 mutations seemed to have more unifocal bone disease than patients without those mutations (P = 0.075). The 5-year overall survival and relapse-free survival (RFS) rates of all patients were 100% and 65.8%, respectively. RFS was not different according to genetic mutations.

Conclusions: Our study showed that BRAF and MAP2K1 mutations can be frequently demonstrated in Korean patients with LCH. Our results suggest that mutation profiles were associated with organ involvement but did not predict the severity of the disease.

Keyword: Langerhans Cell Histiocytosis, MAPK Pathway, BRAF, MAP2K1

PP-006

Predictive role of circulating microRNA-29c-3p expression for autologous stem cell transplantation in patients with newly diagnosed multiple myeloma

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Background: Autologous stem cell transplantation (ASCT) following induction chemotheraphy has emerged as a standard option for transplant-eligible patients with newly diagnosed multiple myeloma (MM). Although circulating microRNA has been suggested as a predictive biomarker in MM, its relevance in ASCT setting have not been well studied. Based on our previous report which observed down-regulation of six micro RNA (miR-26a-5p, miR-29c-3p, miR-30c-5p, miR-193a-5p, and miR-331-3p) was associated with poor outcomes in cohort with relapsed MM (Haematologica, 2017), we explored predictive role of these marker on survival outcome following ASCT in MM.

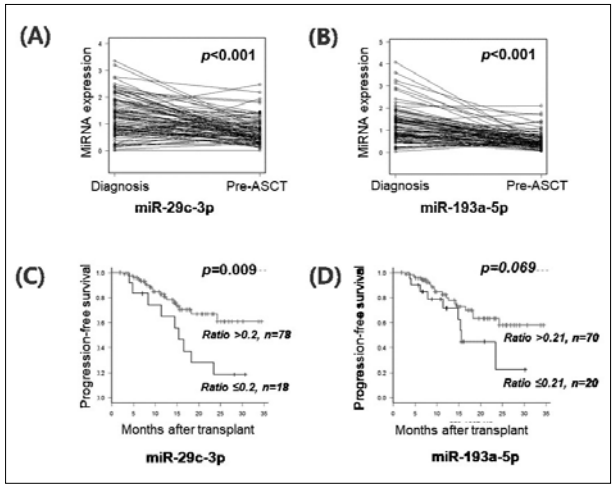
Methods: Paired peripheral blood samples were taken at two points: the diagnosis and before ASCT. A cohort including 90 samples and characteristics of patients were analyzed. MicroRNAs were identified by quantitative reverse transcription PCR (unit, delta Ct value). To determine the significant cut-off level of each ratio of microRNAs' expression (at pre-ASCT/at diagnosis) for predicting profession-free survival (PFS) prediction, receiver operating characteristics curves were generated.

Result: For dynamics of microRNA, mean expressions of miR-29c-3p and miR-193a-5p showed significant decrement after induction chemotherapy (miR-29c-3p, 1.286±0.757 at diagnosis and 0.732±0.483 at pre-ASCT, p<0.001; miR-193A-5p, 1.232±0.774 at diagnosis and 0.527±0.384 at pre-ASCT, p<0.001), whereas other four microRNA did not present evident change of expression through sampling points. In univariate analysis, lower ratio of miR-29c-3p (≤0.2) and miR-29c-3p (≤0.21), higher ratio of 26a-5p

(>3.125) and 331-3p (>4), and clinical factor of international staging system (ISS) III were potential factors associated with adverse PFS. Multivariate analyses showed that ISS III (hazard ratio, 3.42, 95% CI, 1.602-7.302, p=0.001) and lower ratio of miR-29c-3p (hazard ratio, 3.015, 95% CI, 1.345-6.757, p=0.007) were independent factors for poor PFS. Based on these two factors, two risk groups (3-years PFS: 75.0% in low risk and 32.6% in high risk, p<0.001) were identified.

Conclusions: Despite significant decrement expression of miR-29c-3p at pre-ASCT, the ratio of expressed miR-29c-3p in pre-ASCT to that in diagnosis can be a relevant tool to predict prognosis after ASCT in MM patients.

Keyword: MicroRNA, Myeloma, Autologous, Transplantation, Progonosis



PP-007

Incidence, prevalence, mortality, and causes of death associated with Waldenström macroglobulinemia in Korea: A nationwide, population-based study

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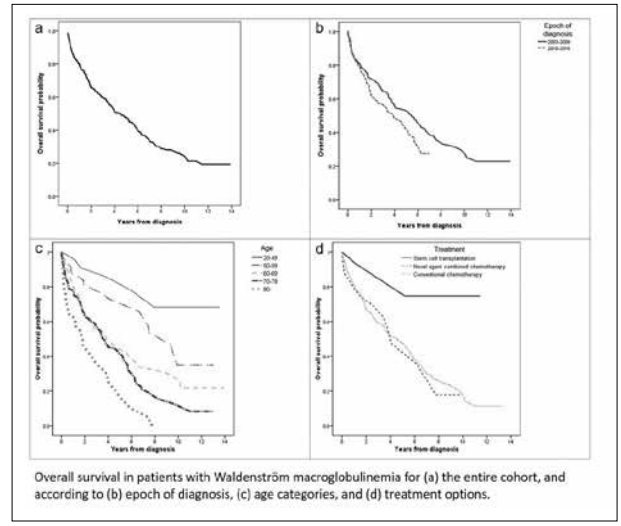
Background: The epidemiological features of Waldenström macroglobulinemia (WM), including the incidence, prevalence, mortality, survival with competing risks, and causes of death, have seldom been investigated at a national level, particularly in East Asia.

Methods: We used a national population-based database, maintained by the Health Insurance Review and Assessment Service of the Korean government, which includes information on all WM patients diagnosed according to uniform criteria, between 2003 and 2016.

Result: The total number of patients newly diagnosed with WM during the study period was 427, with a male-to-female ratio of 3:2. The incidence increased from 0.03 to 0.10 per 105 between 2003 and 2016, and the prevalence was 0.42 per 105 in 2016. A total of 217 patients with WM died during the study period (standardized mortality ratio = 7.57), and the overall survival (OS) of WM patients was 47.5%. On multivariate analysis, older age was found to be a significant factor associated with worse OS. Stem cell transplantation, however, offered better outcomes (hazard ratio = 0.163; P = 0.0109). WM was the most common cause of death (n = 102, 48.6%), followed by other malignant neoplasms (n = 82, 39.0%).

Conclusions: The national incidence of WM in Korea, a racially homogeneous country in Asia, was lower than that in previous reports from other countries, reflecting ethnic disparities. However, during the period studied, the incidence increased, and mortality was the highest ever reported. The main causes of death were directly attributable to WM; stem cell transplantation was considerably effective. This study reflects the need for greater awareness of WM, particularly in Asian countries.

Keyword: Waldenström Macroglobulinemia, Epidemiology, Incidence, Mortality, Survival



Overall survival in patients with Waldenström macroglobulinemia for (a) the entire cohort, and according to (b) epoch of diagnosis, (c) age categories, and (d) treatment options.

PP-008

Nationwide epidemiologic study for disease transformation and secondary cancers in Korean children and young adults with myeloproliferative neoplasms

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Background: Myeloproliferative neoplasms (MPNs) are a rare, heterogeneous group of clonal hematopoietic stem cell disorders, characterized by aberrant proliferation of one or more myeloid lineages leading to an overproduction of both mature and immature cells. Three major components of classical BCR-ABL-negative MPNs are polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (pMF). They may be transformed to either secondary MF (sMF) or secondary acute myeloid leukemia (sAML). In addition, they can have second cancers during follow up (FU). These classical MPNs primarily occur in middle and advanced age adults, and are exceptionally rare in pediatric age.

Methods: We conducted an epidemiologic study to elucidate clinical course of MPNs in children and young adults under 30 years of age focusing on disease transformation and second cancers by analyzing the Health Insurance Review and Assessment Service (HIRA) database which includes almost all hospital-based patients' information in Korea.

Result: A total of 352 patients who were diagnosed as one of the three kinds of MPNs from Jan. 2008 to Dec. 2016 (242 patients for ET, 104 for PV, and 6 for pMF) were included. Six pMF patients were excluded from further analysis. Among 242 ET patients, the male-female ratio was 119 to 123, and median age at diagnosis was 22 years (range 13-29). Four ET patients (1.65%) underwent any transformation during the study period (median FU duration 49.5 months); ET→PV (i.e., initially diagnosed ET but changed to PV later; N = 2), and ET→sMF (N = 2). Among 104 PV patients, the male-female ratio was 96 to 8, and median age at diagnosis was 24 years (range 11-29). No PV patients were transformed into sMF during the FU period (median 45.9 months). sAML did not develop in both ET and PV patients. Solid cancers occurred in 5 ET patients and 3 PV patients. Five-year overall survival and transformation-free survival (to PV, sMF and cancer) were 98% and 96.12% in ET, 100% and 97.29% in PV, respectively.

Conclusions: This is the first population-based study in Korean children and young adults with MPNs. ET is more common than PV, whereas pMF is very rare. Transformations of ET to PV or sMF occurred in a small number of patients. Considering long latency to transformation in MPNs, continuous observation is needed. In addition, second solid tumors should also be carefully observed. Further research is necessary in this patient group, including studies involving other complications such as thromboembolism and bleeding.

Keyword: Myeloproliferative Neoplasms, Essential Thrombocythemia, Polycythemia Vera, Transformation, Children, Young Adults

PP-009

Distribution chemotherapy response modulating genetic polymorphisms in Armenian population

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Background: Primary chemotherapy drug resistance is a one of the major issues of medical hematology-oncology affecting about 20% of all patients. In Armenia, clinical data suggest that the rate of primary resistance depends on the disease and treatment type and varies in the range of 10-30%. One of the mechanisms of resistance is a drug inactivation mediated by metabolizing enzymes and it has been known that the variability of those genes contributes to the response to drugs and treatment efficacy. In Armenia a number of drugs are used for treatment acute and chronic hematology-oncological diseases, such as Doxorubicin and Vincristine (lymphoma), Rituximab (lymphoma), Cladribine (hairy cell leukemia), interferon alfa-2a (chronic myeloid leukemia) and asparaginase (acute lymphoblastic leukemia). However, the distribution of genetic polymorphisms that modulate response to the above mentioned drugs in unknown in Armenians. In this study we were aimed at performing pilot characterization of distribution of single nucleotide polymorphisms affecting chemotherapy treatment response in Armenian population.

Methods: We used genome wide genotyping data of 168 healthy Armenians from three freely available datasets used in population genetics studies. 112 single nucleotide polymorphisms (SNPs) interfering the mentioned treatment agents were obtained from

Pharmgkb database. The distribution of allele frequencies in Armenians were compared to the allelic rates in European population available in 1000 Genomes and HapMap project (retrieved using LDLink software).

Result: Minor allele frequency (MAF) associated with altered response to drugs (table 1) was varying in the range of M±SD (min-max): 0.25±0.14 (0.00-0.49). The minor allele frequency of 18 SNPs was significantly higher in Armenians compared with European population. Another 18 SNPs were significantly underrepresented in Armenians. Six SNPs (MAF min-max: 0.22-0.48) were associated with the altered response to 5 and more drugs.

Conclusions: Our results demonstrate the overall enrichment of genetic factors connected to the risk of failure and toxicity of chemotherapy in Armenian population and necessitate the further research on cumulative impact on the on the chemotherapy response in patients with blood cancers.

Keyword: Genetic Polymorphisms, Chemotherapy

Table 1. Number of chemotherapy response associated SNPs and their MAF distribution

Drug/Treatment	N, SNPs	MAF min-max
Doxorubicin and Vincristine	28	0.05-0.49
Rituximab	14	0.05-0.44
Cladribine	2	0.10-0.28
Interferon alfa-2a	13	0.28-0.46
Asparaginase	2	0.24-0.46

PP-010

Twenty years' experiences of exchange transfusion in Korea

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Background: Exchange transfusion (ET) is an efficacious and reliable modality to replace patient's blood with donor blood or products for severe neonatal hyperbilirubinemia, hemolytic disease of the newborn, and neonatal sepsis. It can also prevent kernicterus or bilirubin-related mortality. This study assessed the indications and clinical outcomes of ETs in one tertiary hospital in Korea.

Methods: Between March 1999 and March 2018, we conducted 65 sessions of ETs in 23 neonates. ET was performed based on the estimated blood volume using fresh red blood cells and fresh frozen plasma. We collected patient clinical information, including demographic data and indications for ET, and laboratory data, and compared pre- and post-ET laboratory data. The clinical outcomes of the patients were also assessed.

Result: The median age of neonates was 3 days at the first ET. A median birth weight was 2,980 g and a median gestational age was 36±6 weeks. The male and female ratio was 13:10. Hyperbilirubinemia was the most common indication for ET, and blood group discrepancies was the prevalent cause of hyperbilirubinemia. The other indications of ETs were leukocytosis and hyperkalemia, and severe anemia in three preterm babies. Blood examination revealed decreased WBC counts, increased Hb levels, and decreased platelet counts (WBC, Hb, and platelet: P <0.05, median value change: 35.9%, 31.7%, and 16.7%), after ET. Bilirubin levels also decreased immediately after ET (P <0.05, median value change: 32.0%). However, electrolyte levels and C-reactive protein (CRP) levels did not change significantly. Adverse events occurred in eleven (47.8%) patients during and/or within 24 hours after ET. The most common adverse events were hypoxemia and hypotension. One infant with hyperkalemia experienced hypercalcemia leading to the cardiorespiratory arrest. However, no patient expired within 24 hours after ET. Despite receiving ET, eight infants progressed to kernicterus and died.

Conclusions: The indications for ET differed from those in previous studies in Korea. ET was an effective treatment modality for leukocytosis as well as hyperbilirubinemia. Although the mortality was low, adverse events were relatively common after ET.

Keyword: Exchange Transfusion, Hyperbilirubinemia, Indication, Adverse Event

Table 1. Indication of exchange transfusions (n = 23, 66 sessions of ET)

Indication	No. of exchange transfusions sessions		
	1	2	≥3
Blood group incompatibility (n=8)			
Other blood group incompatibility*	6	1	
Rh incompatibility		1	
Hereditary spherocytosis (n=2)		1	1¶
Hepatic failure with underlying disease† (n=2)	2		
TPN induced hyperbilirubinemia with underlying disease‡ (n=2)	1		1**
Hemochromatosis (n=1)	1		
Meconium peritonitis (n=1)			1††
Citrullinemia (n=1)			1‡‡
Extremely low birth weight§ (n=1)	1		
Chorioangioma (n=1)	1		
Hyperbilirubinemia, unspecified (n=1)	1		
Severe anemia with underlying disease‖ (n=1)	1		
Hyperkalemia (n=1)	1		
Leukocytosis (n=1)		1	
Total	15	4	4

anti-E (1), anti-E&c (4), anti-E&c and Jk (1); †Mesenchymal anomaly and congenital hepatomegaly; ‡VACTER (Vertebral defects, anal defects, cardiac defects, tracheo-esophageal fistula defects and renal defect) and ARDS (acute respiratory distress syndrome); §Gestational age 32+6 weeks, birth weight 870 g; ||Neuroblastoma; ¶ 11 sessions; ** 14 sessions; †† 6 sessions; ‡‡ 12 sessions.

PP-011

Antileukemic activity of Thiazole-Pyrazole conjugates against human leukemic cell via inhibition of epidermal growth factor receptor (EGFR)

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Background: Acute myeloid leukaemia (AML) accounts for 80% of all acute leukaemia cases in adult humans. Despite immense steps forward in studies on the pathogenesis, AML remains a dreadful disease difficult to cure because of remission. Thus, the discovery of novel targeted drugs is of immense importance to treat AML. The inhibitors of epidermal growth factor receptor (EGFR) have proved its efficacy because of selective targeting of cancerous cell and potent inhibitory activity. Thus, in the present study, a novel series of thiazole-pyrazole hybrids were developed as anti-leukemic agent and mechanistic evaluation.

Methods: The molecules were synthesized via cyclo-condensation reaction in excellent yield. The compounds were tested for determination of anticancer activity against leukemic cells (HL-60). The effect of compound on the cell cycle phase and apoptosis were also studied. The docking study was also carried out on the 3D crystal structure of EGFR-TK (PDB ID: 1M17) to enumerate key contacts for bioactivity.

Result: The compounds showed considerable inhibition against HL-60 with greatest potency in compound 4d with IC50 of 3.41 μm . Further mechanistic analysis showed that, compound 4d causes inhibition of HL-60 cells by inducing apoptosis and arresting the cell cycle at G2/M phase. The compound 4d causes induction of PARP, caspase-3 and caspase-9 to stimulate caspase-3 mediated apoptosis in a concentration dependent way. Compound 4d also showed to interact predominantly in the active site lined by Arg470, Glu-472 and Asn-473 of EGFR.

Conclusions: As a concluding remark, thiazole-pyrazole conjugates have shown promising anti-leukemic activity via induction of apoptosis and inhibition of EGFR-TK in leukemic cells.

Keyword: Leukemia, Synthesis, Apoptosis, EGFR, Cell Cycle

PP-012

2-Phenylpyrimidine coumarin induces apoptosis via activation of caspase and inhibition of PI3K/Akt/mTOR-Kinase in human leukemic cell

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Background: Acute myeloid leukemia (AML) is the most common form of acute leukemia. It was responsible for about 85% of adult cases and considered as a foremost cause of cancer related death in young adults. The existing clinical agents to treat AML are associated with a wide range of morbidities and the overall low survival rate due to drug resistance. The aberrant activation of phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) has been implicated as key signalling pathway for the progress AML. Thus, its inhibition offers selective advantage for the innovative therapy against AML.

Methods: The effect of 2-phenylpyrimidine coumarin (2-PC) was assessed on the cellular viability of against leukemic cells (HL-60) via MTT assay. The compounds were assayed using Annexin V and propidium iodide (PI), fluorescent microscopy, transwell migration, and cell-cycle analysis against HL-60 cell for the anticancer effect. Western blot analysis was also carried out to analyze the effect of 2-PC on the apoptosis related proteins.

Result: 2-PC reduces viability of HL-60 cells in concentration dependent manner. It also showed induction of apoptosis via enhancing the level of late and early apoptotic cells. In western blot analysis, 2-PC causes down-regulation of the anti-apoptotic proteins Bcl-XL and Bcl-2 and up-regulation of the pro-apoptotic proteins Bax, Bid, PARP and caspase-3. The phosphorylation of PI3K, Akt and mTOR was also enhanced by 2-PC in HL-60 cells.

Conclusions: The data of the present study demonstrated the utility of 2-PC against AML due to significant anticancer activity via induction of apoptosis in leukemic cell together with inhibition of PI3K/Akt/mTOR.

Keyword: Synthesis, Leukemia, Apoptosis, PI3K-AKT-MTOR, Kinase

PP-013

Impact of the immuno-microenvironmental changes in AML by blocking both CXCR4 and dual immune checkpoints

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Background: Inhibition of programmed death (PD)-1/PD-ligand (PD-L)1 axis in solid cancer is regarded as a key factor to actively revive the suppressed immune cells. However, the significance of PD-1/PD-L1 expression in acute myeloid leukemia (AML) is not yet established, thus, we investigated anti-leukemic effects of plerixafor, inhibitors of dual immune checkpoints combined with standard chemotherapy in an AML mouse model.

Methods: Leukemic model was generated by the transplantation of C1498 (murine AML cell line) cells into C57/Bl-6 mice. We treated with cytosine arabinoside (Ara-C) (100mg/kg, I.P.), plerixafor (2.5 mg/kg, S.C.), and anti-PD-1 (200 μg/mouse, I.P.), anti-PD-L1 (200 μg/mouse, I.P.) with additive manners. Flow cytometric analysis and histologic examination were performed to read the therapy-responsive changes of immune cell subsets and blasts reduction.

Result: Our data consistently indicated noticeable benefits of this triple or quadruple combinational treatment with plerixafor, anti-PD-L1/anti-PD-1, and Ara-C in removal of blasts in vivo. The modulation of immune status through the suppression of negative immune cell subsets including Tregs and/or MDSCs in AML could possibly lead to a more efficient leukemic blasts ablation. Interestingly, NK cells were increased in multiple combinational therapy groups in peripheral blood and spleen at D+21, but not in D+14.

Conclusions: We demonstrated the impact of a strategic multiple combinational therapy with Ara-C, plerixafor and anti-PD-1, anti-PD-L1 in an AML mouse model by showing immuno-microenvironmental changes. This approach should be a novel way to pursue some clues for changing paradigm of anti-leukemic therapy in real clinic.

Keyword: Acute Myeloid Leukemia, Leukemia Mouse Model, Plerixafor, PD-1/PD-L1, Immune Cells, Immuno-Microenvironment

PP-014

A case of jumping translocation of 1q42 in acute myeloid leukemia patient

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Background: Jumping translocation (JT) is a kind of unbalanced translocation that one donor chromosome segment fused to multiple recipient chromosomes. In hematologic malignancies, JT is related with acute myeloid leukemia (AML), myeloid dysplastic syndrome and multiple myeloma. Pericentromeric region of chromosome 1 (1q11, 1q12, 1q21) has been reported as donor chromosome. We report a case with JT occurred in telomeric 1q42 region in AML, which has not been reported yet. A 37-year-old female with a previous history of AML (diagnosed as AML M0 at 10 years ago, relapsed 5 years ago) showed abnormal result of peripheral blood smear with 3% blasts in routine follow up. Complete blood count revealed a leukocyte count of 2,300 /㎕; hemoglobin was 12.1 g/㎗ and platelets were 194,000 /㎕. Bone marrow aspirate showed 40.95 % of large leukemic blasts with M0 morphology. Cytochemistry was negative for PAS, MPO, SBB, DSE (<3 %). Bone marrow biopsy showed 30% of cellularity and increased blasts. Immunophenotyping was positive for CD45, CD34, HLA-DR. CD13 and CD117, negative for CD33, MPO, CD14, CD64, CD19, CD22, CD3 and TdT. No fusion transcript was detected in RT-PCR, but conventional chromosomal study showed new JT; 46, XX, der(1)t(1;?)(q42;?)[3]/46, XX, t(1;2)(q42;q21)[3]/46, XX [14] (other previous chromosomal studies were all 46, XX[20]). The patient was treated with cytarabine and daunorubicin after diagnosis. An 1q telomeric region as donor chromosome in JT with AML was not reported before, it would be a novel break point.

Keyword: Acute Myeloid Leukemia, Jumping Translocation

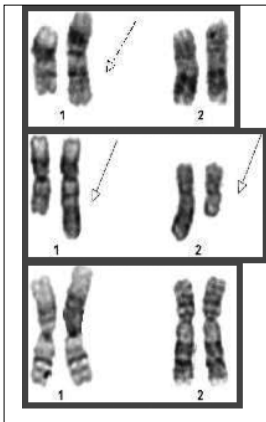

Image: Karyogram of 1 and 2 chromosome of patient

46,XX,der(1)t(1;?)(q42;?) [3] / 46,XX,t(1;2)(q42;q21) [3] / 46,XX [14]

PP-015

Flow cytometric characteristics of distinct population in acute basophilic leukemia

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Background: WHO definition of acute basophilic leukemia is acute myeloid leukemia showing primary differentiation is to basophils. It has little information about prognosis but the cases observed have been associated with a poor prognosis. We experienced two cases of acute basophilic leukemia showing characteristic distinct population by flow cytometry. The first case was 70-year-old female who visited to the hospital symptoms of general weakness. WBC 41,000/㎕, Hb 9.4g/㎗, PLT 110,000/㎕ were observed in CBC. Peripheral blood smear showed leukocytosis with 47% blasts and 27% basophils. Bone marrow aspiration revealed hypercellularity with 56% blasts and 19% basophils. Flow cytometry showed two distinct population, one group was positive to CD34 and other myeloid markers including CD13, CD33, CD117, and MPO, but the other group was positive to CD13 and CD22, negative to CD34, other myeloid and lymphoid markers. No fusion transcript was detected, but conventional chromosomal study showed 47, XX,+mar[20]. The patient was treated with cytarabine and daunorubicin after diagnosis. Follow up bone marrow study was done three weeks later from initial diagnosis, revealed hypocellularity with 2% blasts, 12% basophils, and 36% plasma cells including mature and immature forms. Serum electrophoresis showed an abnormal peak in the gamma globulin area, and immunofixation electrophoresis detected IgG-kappa monoclonal gammopathy. The second case was 89-year-old female who visited to the hospital symptoms of palpitation and general weakness. WBC 74,500/㎕, Hb 9.0g/㎗, PLT 36,000/㎕ were observed in CBC. Peripheral blood smear showed leukocytosis with 89% blasts and 2% basophils. Bone marrow aspiration revealed hypercellularity with 77% blasts and lesser than 1% basophils. This patient also showed two distinct population on flow cytometry, one group was positive to myeloid markers include CD13, CD33, CD117, and MPO, negative to CD34, but other group was positive to CD13, CD33 and CD22, negative to CD34, other myeloid and lymphoid markers. No fusion transcript was detected, but conventional chromosomal study showed 47, XX,+8[20]. Conservative treatment was done for the patient due to old age. Follow up CBC shows continuous decreasing of blast, but continuous increasing of basophil. The patient was expired one month later from initial diagnosis, showing 90% basophils in last CBC results. Two cases show similar characteristics on flow cytometry. It can be helpful for diagnosis of acute basophilic leukemia.

Keyword: Acute Basophilic Leukemia, Flow Cytometry

PP-016

PTEN/AKT signaling mediates chemo-resistance in refractory acute myeloid leukemia through enhanced glycolysis

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Background: Primary refractory acute myeloid leukemia (AML) and early recurrence of leukemic cells are among the most difficult hurdles in the treatment of AML. Moreover, uncertainties surrounding the molecular mechanism underlying refractory AML create challenges for the development of novel therapeutic drugs. However, growing evidence suggests a contribution of PTEN/AKT signaling to the development of refractory AML.

Methods: To assess PTEN/AKT signaling in AML, we evaluated two types of AML cell lines: control HL60 cells, and KG1α cells, a refractory AML cell line that shows idarubicin and AraC resistance.

Result: We first found that PTEN protein was depleted and AKT phosphorylation levels were elevated in KG1α cells compared with HL60 cells. These changes were associated with increased expression of glucose transporter 1 and hexokinase 2, and increased lactate production. AKT inhibition decreased proliferation of KG1α cells and decreased extracellular acidification without affecting HL60 cells. Notably, AKT inhibition increased responsiveness of KG1α cells to chemotherapy with idarubicin and AraC.

Conclusions: Taken together, our findings indicate that altered PTEN/AKT signaling is associated with refractory AML through a change in metabolic flow, effects that could be rescued by inhibition of AKT activity.

Keyword: Refractory Acute Myeloid Leukemia, PTEN/AKT, Glycolysis

PP-017

A genome-wide CRISPR screen identifies PTEN critical for NL101 sensitivity in acute myeloid leukemia

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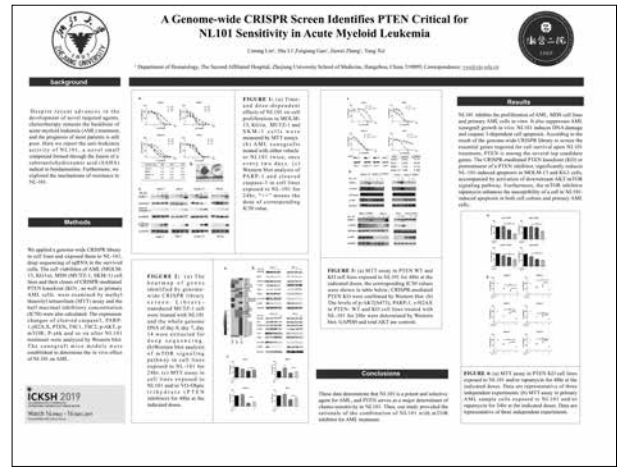
Background: Despite recent advances in the development of novel targeted agents, chemotherapy remains the backbone of acute myeloid leukemia (AML) treatment, and the prognosis of most patients is still poor. Here we report the anti-leukemia activity of NL101, a novel small compound formed through the fusion of a suberanilohydroxamic acid (SAHA) radical to bendamustine. Furthermore, we explored the mechanisms of resistance to NL101.

Methods: We applied a genome-wide CRISPR library to cell lines and exposed them to NL101, deep sequencing of sgRNA in the survived cells. The cell viabilities of AML (MOLM-13, KG1α), MDS (MUTZ-1, SKM-1) cell lines and their clones of CRISPR-meditated PTEN knockout (KO), as well as primary AML cells, were examined by methyl thiazolyl tetrazolium (MTT) assay and the half maximal inhibitory concentration (IC50) were also calculated. The expression changes of cleaved caspase3, PARP-1, γH2A.X, PTEN, TSC1, TSC2, p-AKT, p-mTOR, P-s6k and so on after NL101 treatment were analyzed by Western blot. The xenograft mice models were established to determine the in vivo effect of NL101 on AML.

Result: NL101 inhibits the proliferation of AML, MDS cell lines and primary AML cells in vitro. It also suppresses AML xenograft growth in vivo. NL101 induces DNA damage and caspase 3-dependent cell apoptosis. According to the result of the genome-wide CRISPR library to screen the essential genes required for cell survival upon NL101 treatment, PTEN is among the several top candidate genes. The CRISPR-meditated PTEN knockout (KO) or pretreatment of a PTEN inhibitor, significantly reduces NL-101-induced apoptosis in MOLM-13 and KG1α cells, accompanied by activation of downstream AKT/mTOR signaling pathway. Furthermore, the mTOR inhibitor rapamycin enhances the susceptibility of a cell to NL101-induced apoptosis in both cell culture and primary AML cells.

Conclusions: These data demonstrate that NL101 is a potent and selective agent for AML, and PTEN serves as a major determinant of chemo-sensitivity to NL101. Thus, our study provided the rationale of the combination of NL101 with mTOR inhibitor for AML treatment.

Keyword: CRISPR Library Screen, PTEN, Chemotherapy, Small-Molecule Inhibitor, AML



PP-018

Efficacy and safety of lenalidomide as monotherapy and multitherapy in the management of acute myeloid leukemia: A meta-analysis

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Background: Acute myeloid leukemia (AML) is a type of cancer that affects the blood-forming cells of the bone marrow. In the past few years several epidemiological studies published assessing the efficacy of lenalidomide in AML and presented variable findings on its efficacy. So, this meta-analysis is aimed to understand the pooled effect of lenalidomide as monotherapy and multitherapy in AML patients.

Methods: 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 5.3.

Result: A total of 11 studies qualified for the final inclusion in the meta-analysis after the screening of 424 articles. This meta-analysis is comprised of 407 patients of whom 42.77% were female. The pooled overall response for AML patients treated with monotherapy was 22% (95% CI: 15% to 31%), while the overall response was higher 36% (95% CI: 28% to 45%) and 31% (95% CI: 24% to 40%) 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 22% (95% CI: 15% to 31%) and 31% (95% CI: 19% to 46%) for combination therapy [(Lenalidomide + Azacitidine) and (Lenalidomide + Cytarabine)]. The overall survival was 2 to 8.2 months for lenalidomide monotherapy. Myelosuppression was the most common adverse event reported in patients receiving lenalidomide followed by thrombocytopenia.

Conclusions: Lenalidomide was found to be effective in AML patients but the combination therapy was more effective than monotherapy. Safety profile was also found to be satisfactory.

Keyword: Acute Myeloid Leukemia, Cancer, Epidemiology, Lenalidomide, Hematology, Meta-Analysis

PP-019

Decitabine efficacy and safety in the management of acute myeloid leukemia: A meta analysis of observational studies

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Background: Acute myeloid leukemia (AML) is the 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. So, this meta-analysis was designed to understand the overall efficacy and safety of decitabine by pooling all the studies.

Methods: This meta-analysis was conducted by adhering to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines. Databases like PubMed, Embase and Cochrane library were searched to identify the eligible studies till 31st November 2018 by two independent reviewers. Search was restricted to English language and human studies. Complete remission, overall response, and survival were categorized under the efficacy parameters. Safety outcomes comprised of adverse event and death rate. Subgroup analysis was also performed based on treatment duration. Depending upon the presence or absence of heterogeneity, random or fixed effect model was applied. Review Manager (RevMan) software was used for performing the statistical analysis.

Result: Finally, only ten articles were found to be eligible for inclusion in the meta-analysis. This meta-analysis was based on 798 patients with median age of 74 years and 56.8% were male. Significant heterogeneity (I2 >50%) was observed so, random effect model was applied instead of 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 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 5-days 4 weeks treatment regimen 6.40 months (95% CI: 4.24–8.56)]. The death rate was lie between 7% to 17%. Thrombocytopenia was the most common adverse events.

Conclusions: Decitabine was found to be effective drugs 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, Epidemiology, Sysytematic Review, Meta-Analysis

PP-020

Acute promyelocytic leukemia - retrospective analysis from a tertiary care oncology centre from South India

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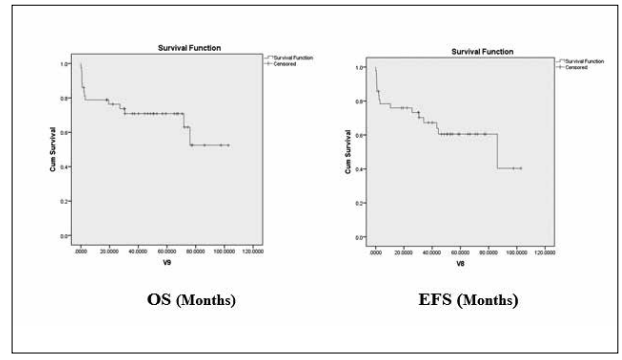
Background: Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia with distinct clinical behavior and prognosis. There is paucity of data in APL from India. The present study was conducted to look at the disease characteristics and outcome of the patient with APL treated at our centre.

Methods: The study included patients with APL treated at our centre between 2008 and 2016. Data was extracted retrospectively from the case records. Overall survival (OS) and event free survival (EFS) were calculated using the Kaplan-Meier methods and the factors were compared using the log-rank test

Result: The study included 43 patients among whom 28 (65%) were male and 15 (35%) were female patients. The median age was 25 years (2-58 years). Thirteen (30%) patients were less than 18 years. Fever was recorded in 37 (86%) patients and bleeding manifestations were present in 35 (81%) patients at diagnosis. Disseminated intravascular coagulation was present in 10 (23%) patients. Twenty-two patients (51%) had white blood count more than 10,000/cumm and 19 (44%) patients had platelets below 40,000/micL. The risk stratification showed, low-risk in 13 (30 %) patients, intermediate-risk in 8 (18%) and high-risk in 22 (52%). Febrile neutropenia was observed in 18 (42%) patients. All the patients received All-Trans Retinoic Acid (ATRA). Daunorubicin was given in 29 (67%) patients, cytarabine (ARAC) in 13 (30%) patients, arsenic trioxide (ATO) in 15 (35%) patients during induction and consolidation therapy. Chemotherapy free regimen consisting of ATRA and ATO was used in 13 (30%) patients and chemotherapy-based regimens was used in 30 (70%) patients. Maintenance therapy was completed in 15 (35%) patients. Complete remission post induction therapy was achieved in 32 (75%) patients and in the remaining 11 (25%) patients, 2 (4%) patients had early induction mortality (first seven days of induction), and 7 (16%) patients had late induction mortality (after seven days of initiating induction therapy). ATRA syndrome was observed in 23 (53%) patients and all the patients responded to steroids. Central Nervous system (CNS) relapse was detected in 1(2%) patient and bone marrow (BM) relapse was identified in 4 (9%) patients. Allogenic stem cell transplant was performed in one (2%) patient and 2 (4%) patients underwent autologous stem cell transplant. At last follow-up, 14 (32%) patients were dead, 9 (21%) deaths occurred during induction, 2 patients died during consolidation due to sepsis, and 3 died due to disease relapse. Treatment was abandoned in 8 (19%) patients. The median duration of follow up was 39 months (range 0.5 – 116 months). Median EFS was 86 months. Five-year OS for all patients was 70%, and for low-risk, intermediate-risk and high-risk was 78%, 68% and 70% respectively.

Conclusions: Majority of mortality in APML occurs during the induction phase, emphasizing the need of good supportive care. The outcomes in our study are comparable to real-world data from other centres.

Keyword: Acute Promyelocytic Leukemia, ATRA, ATO



PP-021

Impact of treatment and transplantation on survival in a phase 3 study of CPX-351 vs 7+3 in older adults with newly diagnosed, high-risk/secondary AML

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Background: CPX-351 (Vyxeos®) is a dual-drug liposomal encapsulation of cytarabine and daunorubicin at a synergistic 5:1 molar ratio. In a randomized, phase 3 study (NCT01696084) of CPX-351 vs 7+3 in patients (pts) aged 60-75 years with newly diagnosed, high-risk/sAML, CPX-351 significantly improved median overall survival (OS; 9.56 vs 5.95 mo; HR=0.69 [95% CI: 0.52-0.90]; 1-sided

P=0.003), event-free survival (EFS; 2.53 vs 1.31 mo; HR=0.74 [95% CI: 0.58-0.96]; 2-sided P=0.021), and rates of complete remission (CR; 37.3% vs 25.6%; 2-sided P=0.040) and CR or CR with incomplete platelet or neutrophil recovery (CR+CRi; 47.7% vs 33.3%; 2-sided P=0.016). The improved CR+CRi rate likely contributed to a higher rate of pts undergoing hematopoietic cell transplantation (HCT) with CPX-351 (34.0% vs 25.0%; 2-sided P=0.098). HCT is potentially curative, and the higher HCT rate with CPX-351 could have impacted long-term survival. Exploratory analyses evaluated survival in pts with HCT and used a time-dependent proportional hazards model to adjust the impact of CPX-351 vs 7+3 treatment on survival based on HCT status as a time-dependent covariate.

Methods: Pts were randomized 1:1 to receive up to 2 inductions with CPX-351 (100 units/m^2 [cytarabine 100 mg/m^2 + daunorubicin 44 mg/m^2] on Days 1, 3, and 5 [2nd induction: Days 1 and 3]) or 7+3 (cytarabine 100 mg/m^2/day continuously for 7 days [2nd induction: 5 days] + daunorubicin 60 mg/m^2 on Days 1-3 [2nd induction: Days 1-2]). Pts with CR/CRi could receive up to 2 consolidations with CPX-351 (65 units/m^2 [cytarabine 65 mg/m^2 + daunorubicin 29 mg/m^2] on Days 1 and 3) or 5+2 (as in 2nd induction). Pts could receive HCT at the discretion of their treating physician.

Result: A total of 309 pts were enrolled (CPX-351: n=153; 7+3: n=156); baseline characteristics were balanced between arms. A total of 52 (34.0%) pts in the CPX-351 arm and 39 (25.0%) in the 7+3 arm underwent HCT; most pts with HCT were aged 60-69 years (CPX-351: 69.2%; 7+3: 84.6%), had ECOG status ≤1 (CPX-351: 92.3%; 7+3: 94.9%), and were in CR (CPX-351: 57.7%; 7+3: 48.7%) or CRi (CPX-351: 19.2%; 7+3: 12.8%). Median time to HCT from first study dose was 114.5 days with CPX-351 and 113.0 days with 7+3. Median OS landmarked from the date of HCT was longer with CPX-351 vs 7+3 (not reached vs 10.25 mo; HR=0.46 [95% CI: 0.24-0.89]). When HCT was treated as a time-dependent covariate in an exploratory analysis, the HRs remained strongly in favor of CPX-351 vs 7+3 for OS (0.71) and EFS (0.74; Table), suggesting CPX-351 treatment may be associated with prolonged OS and EFS regardless of HCT status.

The CPX-351 adverse event profile was generally consistent with the known safety profile of 7+3. Grade 3-5 adverse events in ≥10% of pts in the CPX-351 or 7+3 arms included febrile neutropenia (68.0% vs 70.9%), pneumonia (19.6% vs 14.6%), and hypoxia (13.1% vs 15.2%). Early mortality rates with CPX-351 vs 7+3, respectively, were 5.9% vs 10.6% at Day 30 and 13.7% vs 21.2% at Day 60.

Conclusions: CPX-351 treatment was associated with significantly longer median OS and EFS and higher rates of CR+CRi and HCT vs 7+3 in older pts with newly diagnosed, high-risk/secondary AML. While it is expected that HCT had a positive impact on survival in this study, exploratory analyses that adjusted for HCT status over time suggest CPX-351 treatment has a positive impact on OS and EFS regardless of HCT status.

Keyword: Cytarabine, Daunorubicin, Event-Free Survival, Hematopoietic Cell Transplantation, Liposomal, Overall Survival

Table. Impact of HCT vs Treatment on OS and EFS

Factor level	n (%)[a]	HR (95% CI)[b]
OS		
Treatment arm		
CPX-351	153 (49.5)	0.71 (0.54-0.92)
7+3	156 (50.5)	
HCT status		
With HCT	91 (29.4)	0.51 (0.35-0.75)
Without HCT	218 (70.6)	
EFS		
Treatment arm		
CPX-351	153 (49.5)	0.74 (0.57-0.96)
7+3	156 (50.5)	
HCT status		
With HCT	91 (29.4)	0.82 (0.45-1.48)
Without HCT	218 (70.6)	

[a]Out of the total study population of 309 patients.
[b]The last factor level listed is the reference level for the associated HRs. The HRs are stratified by age category and AML sub-type.

PP-022

CPX-351 Vs 7+3 in older adults with newly diagnosed acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) enrolled in a phase 3 study

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Background: CPX-351 (Vyxeos®) is a dual-drug liposomal encapsulation of cytarabine and daunorubicin at a synergistic ratio. In a randomized, phase 3 study (NCT01696084) of CPX-351 vs conventional 7+3 cytarabine/daunorubicin in patients (pts) aged 60-75 years with newly diagnosed, high-risk/secondary AML, CPX-351 significantly improved overall survival (OS) and remission rates. The WHO 2016 AML-MRC designation applies to AML pts with: 1) history of myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm, 2) MDS-related cytogenetic abnormality, or 3) multilineage dysplasia in >50% of ≥2 cell lineages in the absence of NPM1 or biallelic CEBPA mutations. Pts with AML-MRC typically have poor outcomes to standard induction chemotherapy. An exploratory analysis of the phase 3 study compared outcomes for CPX-351 vs 7+3 in pts who met the WHO 2008 AML-MRC criteria.

Methods: Pts were randomized 1:1 to receive up to 2 inductions with CPX-351 (100 units/m^2 [cytarabine 100 mg/m^2 + daunorubicin 44 mg/m^2] on Days 1, 3, and 5 [2nd induction: Days 1 and 3]) or 7+3 (cytarabine 100 mg/m^2/day continuously for 7 days [2nd induction: 5 days] + daunorubicin 60 mg/m^2 on Days 1-3 [2nd induction: Days 1-2]). Pts achieving complete remission (CR) or CR with incomplete platelet or neutrophil recovery (CRi) could receive up to 2 consolidations with CPX-351 (65 units/m^2 [cytarabine 65 mg/m^2 + daunorubicin 29 mg/m^2] on Days 1 and 3) or 5+2 (as in 2nd induction). Pts could receive hematopoietic cell transplantation (HCT) at the discretion of their physician.

Result: Of 309 enrolled pts, 246 met the AML-MRC criteria (CPX-351: n=123; 7+3: n=123); 59.0% had antecedent MDS, 9.3% had antecedent CMML, and 31.7% had de novo AML with MDS karyotype. Baseline characteristics of AML-MRC pts were similar between treatment arms (median age 68 years; 64.6% male; 11.0% with ECOG status of 2). A 2nd induction cycle was received by 33.3% of AML-MRC pts in the CPX-351 arm and 37.8% of pts in the 7+3 arm.

Among AML-MRC pts, median OS was longer with CPX-351 vs 7+3 (9.07 vs 5.95 months; HR=0.70 [95% CI: 0.53-0.93]). Within the AML-MRC subgroup of pts, the CPX-351 arm had higher rates of CR+CRi (48.0% vs 32.5%; OR=1.83 [95% CI: 1.09-3.09]), CR (37.4% vs 24.4%; OR=1.80 [95% CI: 1.02-3.17]), and HCT (33.3% vs 24.4%; OR=1.53 [95% CI: 0.86-2.74]) vs 7+3. Among AML-MRC pts who underwent HCT, median OS landmarked from the date of HCT was longer with CPX-351 vs 7+3 (not reached vs 10.68 months; HR=0.48 [95% CI: 0.24-0.96]).

Early mortality rates with CPX-351 vs 7+3, respectively, were 4.9% vs 8.9% at Day 30 and 13.8% vs 20.3% at Day 60 in AML-MRC pts.

The treatment-emergent adverse event (TEAE) profile of CPX-351 in AML-MRC pts was consistent with the overall study population and generally comparable between treatment arms (Table). Three AML-MRC pts discontinued treatment due to a TEAE (cardiac failure [CPX-351], cardiomyopathy [CPX-351], and ejection fraction decreased [7+3]). Grade 5 TEAEs occurred in 8.9% vs 14.3% of AML-MRC pts treated with CPX-351 vs 7+3, respectively; those occurring in >1 pt in a treatment arm included sepsis (2.4% vs 0.8%), disease progression (1.6% vs 3.4%), multi-organ failure (0.8% vs 1.7%), and respiratory failure (0.8% vs 1.7%).

Conclusions: In this subgroup analysis, CPX-351 improved OS and remission rates vs 7+3 in older pts with AML-MRC, while maintaining a similar safety profile.

Keyword: Cytarabine, Daunorubicin, Hematopoietic Cell Transplantation, Liposomal, Overall Survival, Safety

Table. Summary of TEAEs

n (%)	CPX-351 (n = 123)	7+3 (n = 119)
TEAEs in ≥30% of pts		
Febrile neutropenia	86 (69.9)	84 (70.6)
Nausea	62 (50.4)	61 (51.3)
Constipation	58 (47.2)	54 (45.4)
Diarrhea	57 (46.3)	80 (67.2)
Peripheral edema	53 (43.1)	61 (51.3)
Fatigue	44 (35.8)	43 (36.1)
Epistaxis	44 (35.8)	21 (17.6)
Cough	43 (35.0)	25 (21.0)
Headache	40 (32.5)	28 (23.5)
Decreased appetite	38 (30.9)	49 (41.2)
Grade 3 TEAEs	110 (89.4)	107 (89.9)
Grade 4 TEAEs	26 (21.1)	29 (24.4)
Grade 5 TEAEs	11 (8.9)	17 (14.3)
During the treatment period	7 (5.7)	11 (9.2)
Serious TEAEs	53 (43.1)	46 (38.7)
Serious TEAEs in ≥2% of pts		
Sepsis	8 (6.5)	4 (3.4)
Ejection fraction decreased	6 (4.9)	5 (4.2)
Febrile neutropenia	5 (4.1)	8 (6.7)
Respiratory failure	5 (4.1)	5 (4.2)
Pneumonia	4 (3.3)	4 (3.4)
Acute respiratory failure	4 (3.3)	2 (1.7)
Bacteremia	3 (2.4)	0
Disease progression	2 (1.6)	4 (3.4)
Hypoxia	1 (0.8)	3 (2.5)
Discontinuation due to a TEAE	2 (1.6)	1 (0.8)

PP-023

Genetic mutation profiling of acute myeloid leukemia using targeted next generation sequencing

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Background: Genetic mutations in acute myeloid leukemia (AML) are important factor not only for diagnosis but for risk stratification and target therapy. And mutation detection using next generation sequencing (NGS) provides broader knowledge about it. So, we identify mutation profiling of AML cases by targeted next generation sequencing based on an experience of a tertiary hospital.

Methods: A total of 80 bone marrow aspirate or peripheral blood samples from AML patients were tested for genetic mutation profiling from February 2018 to November 2018. The patients included 39 of AML with recurrent genetic abnormalities, 31 of AML, not otherwise specified, 7 of AML with myelodysplasia-related changes, 2 of secondary AML and 1 of concurrent AML and multiple myeloma. Library preparation and target gene capture for NGS was performed by HEMEaccuTest (NGeneBio, Seoul, Korea) with 123 gene panel. The product was sequenced using MiSeqReagent Kit v3 (300cycles) and MiSeqDx sequencer (Illumina, San Diego, CA, USA).

Result: All of 80 AML cases were revealed to have mutation and total count of the mutation was 675. Top five mutations were observed in FLT3 (36.3%), TET2 (31.3%), DNMT3A (28.8%), RELN (25.0%) and CEBPA (22.5%) genes. The average of co-occurrence mutation per patient was 8.4 (range, 2-22). And variants of tier I (strong clinical significance), tier II (potential clinical significance) and tier III (unknown clinical significance) per patient were 1.1 (range, 0-3), 1.3 (range, 0-5) and 6.1 (range, 1-19), respectively, on average. Top three genes involved by tier I variants were FLT3 (25.0%), NPM1 (16.3%) and TP53 (15.0%) and that by tier II were TET2 (22.5%), DNMT3A (20.0%) and NRAS (15.0%). In the induction failure group of de novo AML (n=23), top five mutations were detected in TET2 (43.5%), TP53 (34.8%), DNMT3A (30.4%), FLT3 (30.4%) and NRAS (26.1%) genes.

Conclusions: We identified genetic mutations with high prevalence using NGS in the AML patients and observed some of the mutations are relatively more in the chemotherapy resistant group. Also, we found frequently occurred mutations which have clinically significant evidence. Therefore, detection of mutations using targeted NGS could provide more insight into the prognosis and therapeutic choice in the AML patients.

Keyword: Acute Myeloid Leukemia, Mutation Profiling, Next Generation Sequencing

PP-024

Beyond hypomethylating agent (HMA) failure in elderly acute myeloid leukemia (AML) patients

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Background: With increasing use of hypomethylating agent (HMA) as a first line treatment in elderly AML patients, we also encounter a frequent situation of HMA failure. But, data specifically addressing outcome after HMA failure in a homogeneous group of AML is remain limited.

Methods: A total of 95 AML patients who were treated with decitabine between Oct 2011 and Mar 2018 were retrospectively reviewed. Patients who had completed at least one cycle of decitabine for AML as a 1st line treatment, and stopped treatment were included in this analysis. Definition of HMA failure includes patients who failed HMA treatment due to no response (stable disease or progressive disease), patients who lost response, patients who failed treatment due to toxicity regardless of response.

Result: The median age was 73 years (range, 63-86). According to cytogenetics at the time of diagnosis (total, n=89), normal karyotype (NK) was most common accounting for 56.2% (n=50), and intermediate risk karyotype other than NK (n=21, 23.6%), poor risk

cytogenetics (n=14, 15.7%) and core-binding factor (CBF)-AML (n=4, 4.5%) were followed. Among the patients with available data for ELN risk stratification (total, n=80), favorable, intermediate and adverse risk groups were comprised 22.5% (n=18), 52.5% (n=40) and 25.0% (n=20), respectively. Before cessation of HMA treatment, the patients received median 5 cycles of decitabine (range, 1-36), and response rate among the patients with available information (n=62) were 45.2% (responder: CR [n=11, 17.7%], CRi [n=11, 17.7%], CRp [n=4, 6.5%], PR [n=2, 3.2%]; non-responder: SD [n=26, 41.9%], PD [n=8, 12.9%]). With regard to the reason for HMA cessation, intolerance was most common (n=39, 47.6%), and loss or response (n=25, 30.5%) and lack of response (n=18, 22.0%) came next. After completion of last HMA cycle, 36 patients (37.9%) were died, 15 patients (15.8%) were lost to follow up, 22 patients (23.2%) received best supportive care (BSC), and 22 patients (23.2%) received chemotherapy. The median overall survival (OS) after HMA failure was 2.8 months (95% confidence interval, 2.1-3.5 months), and it was not differed by response to HMA (responder vs non-responder, p=0.1181), reason for HMA cessation (loss or response vs lack of response, p=0.7318), and further treatment (chemotherapy vs BSC, p=0.1212). NPM1 mutated patients were more likely to survive longer than non-mutated patients after HMA failure (median 8.6 months vs 2.0 months, p=0.0253). Overall, 8-week mortality after HMA failure was estimated to 21.7% (18 out of 83 with available information).

Conclusions: The prognosis after HMA failure in AML patients was dismal. Efforts focus on the prevention of resistance to HMA and enhancing therapeutic efficacy of front-line HMA based therapy is necessarily needed.

Keyword: AML, HMA Failure, Outcome

PP-025

Dialkyl resorcinol stemphol disrupts calcium homeostasis triggering immunogenic necroptosis in acute myeloid leukemia

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Background: Stemphol (STP), a natural dialkyl resorcinol, is a phytotoxin extracted from Stemphylium globuliferum and was also described as a self-inhibitor in Pleospora herbarum. Despite its significant bioactivity, so far, the anti-tumor potential of STP was never investigated. Since the interplay between different cell death and cell stress modalities became an attractive pharmacological target, for this study, we investigated the cytotoxic effect of STP on Ca2+ homeostasis. We demonstrate for the first time in vivo and in vitro anticancer potential of STP. From a mechanistic point of view, we used a multi-parametric approach to document how a Ca2+ flux from ER to cytosol eventually culminating in mitochondrial Ca2+ overload triggers non-canonical cell death via mPTP opening.

Methods: To evaluate the anticancer potential of STP, we used U-937, HL-60, and THP-1 (AML cell lines), A549 (lung cancer cell line), and MCF-7 (breast cancer cells line). To analyze STP-induced calcium regulation, we used EGTA (extracellular calcium inhibitor), TSG (SERCA inhibitor), 2-APB (IP3R inhibitor) and dantrolene (RyR inhibitor) were used as specific calcium channel inhibitors. For the translational potential of STP in human leukemia patients, we assessed the effect of STP on 3D tumor formation by using zebrafish xenograft with AML patient cells.

Result: Stemphol inhibited viability, proliferation and colony formation capacity of three human AML cells (U-937, HL-60, and THP-1) and showed a similar range of IC50 for all four leukemia cells (K-562, Jurkat, RAJI, and U-937) at each time point. We demonstrated that STP significantly inhibited the tumor-forming ability of U-937 at 30 μM of STP by using a zebrafish xenograft approach thus validating in cellulo results. Moreover, we concluded that STP facilitated Ca2+ release from ER to cytosol essentially through IP3R in AML cells. We next showed that STP could undergo a direct interaction with SERCA triggering Ca2+ release. Based on docking simulation, STP was located at the same site as TSG on SERCA with the binding energy of -6.0 kcal/mol then we suggest that STP acts as a SERCA inhibitor comparable to thapsigargin (TSG). In addition to its effect on SERCA, we concluded here that STP induced a ROS-independent type of mPTP opening-dependent necrosis by facilitating Ca2+ transfer from ER and cytosol to mitochondria, essentially through IP3R and MCU. Moreover, considering the immunogenic potential of Ca2+ reduction in the endoplasmic reticulum, we also validated that STP can trigger HMGB1 release in 3 out of 4 patients tested so far, further increasing the translational potential of STP.

Conclusions: Stemphol (STP) is a novel phytotoxin triggering mixed apoptotic and non-apoptotic necrotic-like cell death in human acute myeloid leukemia (AML). Use of several chemical inhibitors highlighted that STP-induced non-canonical programmed cell death was Ca2+-dependent but independent of caspases, poly (ADP-ribose) polymerase-1, cathepsin, or calpains. Similar to

TSG, STP led to increased cytosolic Ca2+ levels, and computational docking confirmed binding of STP within the TSG binding pocket of the sarco/endoplasmic reticulum (ER) Ca2+-ATPase (SERCA). Finally, we observed that STP-induced necrosis is dependent on mitochondrial permeability transition pore (mPTP) opening. Importantly, the immunogenic translational potential of STP was validated by HMGB1 release of STP-treated AML patient cells. STP reduced colony and in vivo tumor-forming potential and impaired the development of AML patient-derived xenografts in zebrafish.

Keyword: Calcium, Caspase-Independent Apoptosis, Programmed Necrosis, Leukemia

PP-026

Evaluation of the ion torrent oncomineTM myeloid research assay for clinical applications in hematologic malignancy

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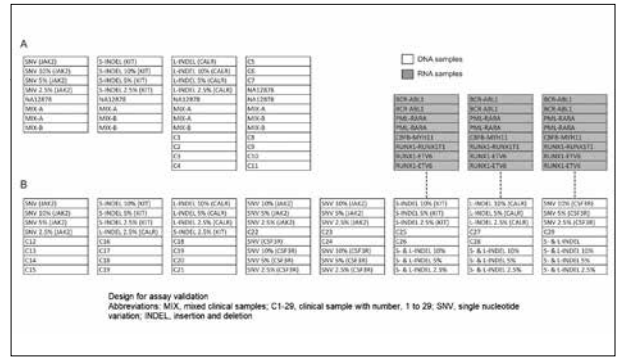
Background: Precision oncology using next generation sequencing (NGS) is essential in current diagnosis and treatment. In the clinical field in hematology, the usage of NGS tests is increasing greatly till now. As such, we evaluated the performance of the Ion Torrent OncomineTM Myeloid Research Assay (Thermo Fisher Scientific, Waltham, MA, USA) primarily in bone marrow and whole blood. Especially, we evaluated the sequencing performance of the platform using in house developed software.

Methods: A total of 104 tests was performed using the OncomineTM Myeloid Research Assay by collecting samples with somatic mutations, including single nucleotide variation (SNV), short insertion/deletion (INDEL, ≤20bp), and long INDEL (21bp – 61bp), which were confirmed by Sanger sequencing or other methods. The number of evaluated variants were 62. To evaluate clinical performance, the sensitivity, positive predictive value (PPV), precision of variant allele frequency and limit of detection (LOD) were analyzed. A probit analysis was performed for LOD. In addition, a rigorous coverage analysis by position for each exon was performed using in house developed software.

Result: The sensitivity and PPV for SNV, short INDEL, and long INDEL were 100% / 100% (N=36), 100% / 100% (N=18), and 100% / 100% (N=8), respectively. As for the precision of variant allele frequency, a reasonable performance within 15% of the coefficients of variation was showed, except in the long INDEL. LODs with 95% probability for SNVs, short INDELs, and long INDELs were 2.3%, 2.5%, and 1.1%, respectively. We found that the reason for good LOD values in INDEL detection is that the target region for INDELs were covered with very high coverage more than 3000X. In coverage analysis by in-house developed software, most exons were well-covered in base pair level, with minimal deterioration of coverage, except for three exons that seemed to be clinically non-significant.

Conclusions: OncomineTM Myeloid Research Assay showed good performance in detecting somatic mutations of clinical specimens. The platform also provided user friendly interface and pipeline in experiment and informatics.



PP-027

Role of allogeneic hematopoietic cell transplantation in acute myeloid leukemia patients with NPM1wt and FLT3-ITD negative group

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Background: One of the most potent prognostic factors affecting outcomes in AML is the presence of cytogenetic and molecular markers which can guide the selection of post-remission ther-

apies. Recently, favorable outcomes of NPM1wt/FLT3-ITDneg/non-CEBPAdm group after allogeneic hematopoietic cell transplantation (allo-HCT) have been reported, that is similar to those of favorable risk by the ELN risk classification. However, the role of allo-HCT compared to consolidation chemotherapy has not yet been elucidated.

Methods: The data of 88 patients who were diagnosed with AML and received intensive induction therapy from 2015 March to 2017 July were included in the current study. To address the time dependence of the allo-HCT, the Simon and Makuch method was used in the graphical representation and the Mantel-Byar test and Andersen and Gill methods for identifying risk factors for long-term survival.

Result: Median age of the patients were 53 years (range 21-69), and 49 patients (56%) were male. NPM1 mutation was detected in 14 patients (16%), and FLT3-ITD were none, low, and high ratio in 69 patients (78%), 9 (10%), and 10 (12%), respectively. The ELN risk classification divided the patients into favorable, intermediate, and adverse risk group in 31 patients (35%), 38 (43%), and 19 (22%), respectively. NPN1 and FLT3-ITD both negative group included 29 patients (33%). Allo-HCT was performed in 48 patients (55%). Overall, complete response (CR) after induction therapy achieved in 63 patients (72%), and 7 patients (8%) were primary refractory disease. CR rates did not differ between NPM1wt/FLT3-ITD negative group (n=17/29, 58.6%) and other intermediate risk group (n=6/9, 66.7%; p=0.967). With median follow-up duration of 12.9 months (range 1.3-39.0 months), one-year OS rate were 100%, 83.5±6.9%, 56.1±12.8% in favorable, intermediate, and adverse risk group ($p < 0.001$). Among intermediate risk group, OS rate of NPM1wt/FLT3-ITD negative group was similar to other intermediate risk (p=0.403). Allo-HCT was performed in 11 patients of NPM1wt/FLT3-ITD negative group. One-year OS rates did not differ between NPM1wt/FLT3-ITD negative and other intermediate risk (Mantel-Byar test p=0.622). In the multivariate analysis, ELN risk group was identified as the only risk factor for OS (HR 2.76, 95% CI 1.51-5.02, p<0.001). Allo-HCT was not an independent favorable factor for OS in NPM1wt/FLT3-ITD negative group (HR 0.47, 95% CI 0.09-2.47, p=0.372).

Conclusions: NPM1wt/FLT3-ITD negative group showed similar CR and OS rates compared to other ELN intermediate group. Allo-HCT did not improve the OS rate of this group. Therefore, the implication of allo-HCT to this group needs to be carefully considered considering other high risk factors.

Keyword: Acute Myeloid Leukemia, Allogeneic Hematopoietic Cell Transplantation, ELN Risk Group, NPM1 Mutation, FLT3-ITD Mutation

PP-028

Gene amplification and chromothripsis in acute myeloid leukemia with complex chromosomal abnormalities

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Background: AML patients with complex chromosomal abnormalities constitute 10-12% of all AML patients. Conventional cytogenetic analysis of these patients shows uncertainties such as additional material of unknown origin and marker chromosomes, which can be originated from gene amplification or chromothripsis, a catastrophic genomic event. We investigated the frequency and characteristics of gene amplification and chromothripsis in AML patients with complex chromosomal abnormalities using array comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) analysis.

Methods: We investigated a total of 17 patients who were diagnosed as AML with complex chromosomal abnormalities from Jan 2015 to June 2017 in Asan Medical Center. The abnormal clones with complex chromosomal abnormalities were more than 30% of the total analyzed cells. The conventional cytogenetic analysis was performed by G-banding technique after 24/48 hours culture of BM cells. The array CGH analysis was performed by SurePrint G3 Human CGH 180K microarray (Agilent Technologies, USA) with DNA samples extracted from BM cells at diagnosis. FISH was performed using bacterial artificial chromosome (BAC) clones located within amplified regions.

Result: The male proportion of the patients was 65% and the median age at diagnosis was 63 years (range 18-83 years). Complex chromosomal abnormalities of the patients showed a median of 8 (2-22) chromosomal abnormalities with median of 2 (0-4) marker chromosomes. 9 patients had hypodiploid clones, 3 patients had pseudodiploid clones, and 5 patients had hyperdiploid clones. From the array CGH analysis, the median number of copy number alterations was 9 (1-25). Copy number loss was frequently observed in 3p, 5q, 7q, 12p, 15q, 17p, and 18q regions and copy number gain in 1q and 21q regions. 65% of the total patients had

gene amplification and 53% had chromothripsis. All patients with chromothripsis also had gene amplification. Gene amplification was frequently observed in 21q regions. Chromothripsis was frequently observed in 3p, 3q and 21q regions. FISH analysis using BAC clone probes identified that the marker chromosomes had amplified oncogenes such as DAXX on 6p21.32, GPC5 on 13q31.3, UBE3A on 15q11.2, and ERG on 21q22.2. The patients with gene amplification and chromothripsis of 21q region showed tendency of shorter overall survival compared to the other patients (4.4±3.1 vs. 6.9±1.3 months, p=0.267).

Conclusions: Uncertainties of G-banding including marker chromosomes in AML with complex chromosomal abnormalities can be originated from the amplification or rearrangement of chromosomal segments with oncogenic potentials. Chromothripsis may contribute to the tumorigenesis from multiple rearrangements of chromosomal segments. Array CGH analysis is useful to investigate the origin of marker chromosomes and supplement the limitation of conventional cytogenetic analysis in patients with complex chromosomal abnormalities. Gene amplification and chromothripsis detected by array CGH can be applied to therapeutic target and prognostic investigation of AML with complex chromosomal abnormalities.

Keyword: Gene Amplification, Chromothripsis, Acute Myeloid Leukemia, Complex Chromosomal Abnormalities

PP-030

Clinical application of next-generation sequencing in diagnostic work-up of patients with acute myeloid leukemia and myelodysplastic syndrome

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Background: Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are characterized by varying biological and clinical heterogeneity. The ability of next-generation sequencing (NGS) to perform massively parallel sequencing has made high throughput and multiplexed sequencing of specific panels of gene. The aim of this study is to evaluate the diagnostic and clinical value of hematological malignancy panel as a diagnostic tool for patients with AML and MDS.

Methods: A total of 150 patients (99 AML and 51 MDS) having results of NGS between January 2018 and November 2018 were included in this study. We used hematologic malignancy panel (total 141 genes). Non-synonymous mutations and insertion and deletion mutations with variant allele frequencies (VAF) >5% and with Tier I to III were considered as oncogenic variants. FLT3 internal tandem duplication (ITD) was confirmed by fragment analysis followed by Sanger sequencing.

Result: In AML, there was an average 3.1 mutation per case. And 93 of 99 (93.9%) cases showed at least one mutation. The most common mutated genes was FLT3 (18.2% of AML cases) followed by TET2 (15.2%), NPM1 (14.1%) and DNMT3A (11.1%). The frequency of mutations was lowest in patients with AML with recurrent genetic abnormalities (RGA) (average n=2.8) compared to other WHO subtypes (MDS; 3.2, NOS; 3.8). In terms of the functional groups, mutations in activated signaling genes were most frequent (21.7% of all mutations), followed by myeloid transcription factor genes (16.5%) and DNA methylation-related genes (14.2%). Tier I mutations were occurred in 58.6% of AML cases, Tier II mutations were 51.5% and Tier III mutations were 62.6%. The subclonal mutations accounted for 23.6% of total mutations, among which NRAS and NPM1 mutation was most frequent and TP53 mutation had the lowest VAF value (average 6.1%). In AML with RGA, the subclonal mutations were frequently observed, accounting for 30.6% of cases for AML with RGA. In MDS, the average number of mutations per case was 2.6 and average VAF was 36.2%. The most frequently mutated genes in MDS were TET2 (25.5% of MDS cases) and DNMT3A, SRSF2 and TP53 (19.6%).

Conclusions: Hematologic malignancy targeted NGS is suitable for the routine diagnostic approach of AML and MDS allowing for an improved diagnosis, subclassification, prognosis and therapeutic implication. And this study will help establish guideline for NGS in hematologic malignancy.

Keyword: Next Generation Sequencing, Acute Myeloid Leukemia, Myelodysplastic Syndrome

PP-031

Reclassifying acute myeloid leukemia according to the revised 2016 WHO classification in a large patient group

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Background: The revised 2016 World Health Organization (WHO) classification of acute myeloid leukemia (AML) incorporates clinically relevant pathologic findings into the revised diagnostic criteria. The changes may lead to differences between the 2008 and 2016 classifications. In this study, we classify AML cases of our institution according to the 2008 and 2016 WHO systems, respectively, and analyze the characteristics of the discrepant cases.

Methods: The bone marrow (BM) archive of our institution was searched for AML patients between 2009 and 2018. We reviewed patient data for WHO classification systems such as karyotype, bone marrow morphology, prior history of myelodysplastic syndrome (MDS) or cytotoxic chemotherapy, and mutational status (NPM1, CEBPA and RUNX1). Of the 1,196 patients with AML, 10 patients were excluded due to the absence of a karyotype or failure to acquire metaphase cells. Thus, a total of 1,186 applicable cases were reviewed. We divided patients into six categories based on the WHO classification; recurrent genetic abnormalities (RGA), myelodysplasia-related changes (MRC), therapy-related AML (t-AML), not otherwise specified (NOS), AML associated with Down syndrome (DS), and not determined (ND).

Result: According to the 2008 system, the cases consisted of 583 (49.2%) RGAs, 305 (25.7%) MRCs, 219 (18.5%) NOSs, 25 (2.1%) t-AMLs, 4 (0.3%) DSs, and 50 (4.2%) NDs. According the 2016 system, they consisted of 586 (49.4%) RGAs, 275 (23.2%) MRCs, 108 (9.1%) NOSs, 24 (2.0%) t-AMLs, 4 (0.3%) DSs, 164 (13.8%) NDs, and 25 (2.1%) MDSs. The ND category was due to the incomplete mutation data, and the MDS category in 2016 system reflected the reclassification of erythroleukemia to MDS, where blast is less than 20% of total nucleated BM cells. The diagnostic concordance rate between the 2008 and 2016 systems was 83.2%. In the discrepant cases (n=199, 16.8%), apart from 115 ND cases that occurred because there was no RUNX1 mutation data, the NOS to RGA group (n=28) was the most common; AML with mutated RUNX1 (n=25) and de novo AML with BCR-ABL1 (n=3). The MRC to MDS was second most common group (n=21), followed by the RGA to NOS group resulted from AML with CEBPAsingle/NPM1wild-type/RUNX1wild-type (n=17) and the MRC to RGA group (n=9) resulted from AML with CEBPAbiallelic/isolated del(9q) (n=5), de novo AML with BCR-ABL1 (n=3), and AML with mutated NPM1/isolated del(9q) (n=1). The miscellaneous groups included the RGA to MRC (n=3), RGA to MDS (n=2), MRC to NOS (n=1), NOS to MDS (n=1), t-AML to t-MDS (n=1), and ND to RGA (n=1). According to the 2016 system, which provided more refined criteria for AML with gene mutations than 2008 system, AML harboring NPM1 mutation (n=157) were classified as 150 RGAs (95.5%), 5 MRCs (3.2%) and 2 MDSs (1.3%). AML harboring CEBPAbiallelic (n=52) were classified as 47 RGAs (90.4%) and 5 MRCs (9.6%). In addition, AML harboring RUNX1 mutation (n=38) were classified as 26 RGAs (68.4%), 9 MRCs (23.7%) and 3 NDs (7.9%).

Conclusions: Current study shows that about 17% of the AML classified according to the previous 2008 system is reclassified as the new category according to the revised 2016 system, and the classification discrepancy pattern reflects the removal of some characteristics as well as the addition of new subtype from 2008 to 2016 system. In addition, we identified AML with mutated NPM1 is more homogeneous than AML with CEBPAbiallelic and AML with mutated RUNX1 in the 2016 system.

Keyword: Acute Myeloid Leukemia, WHO 2008, WHO 2016, Reclassification

PP-032

Predictive role of geriatric assessment for early events in elderly AML fit for intensive chemotherapy; Interim data of a prospective cohort study

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Background: Geriatric assessment (GA) typically refers to a multidimensional assessment designed to evaluate an older person's

functional ability, physical health, cognition, psychological health, and social support. There is a significant heterogeneity in terms of their underlying health and resilience to the burden of disease and treatments in elderly AML (eAML). To date, a few have evaluated the predictive value of GA among newly diagnosed eAML.

Methods: This is a prospective cohort study to investigate the predictive roles of each domain of GA to discriminate vulnerable patients in eAML fit for intensive chemotherapy. Between November 2016 and October 2018, we enrolled newly diagnosed eAML patients aged ≥60 years considered fit for intensive chemotherapy, who had adequate performances (ECOG 0-2) and organ functions. All the enrolled patients were administered various questionnaires for an initial assessment and functional evaluation including social support (OARS), nutrition (MNA), psychological function (MMSE-KC, SGDS-K, PHQ-9, NCCN distress thermometer, Montgomery–Asberg Depression Rating Scale, and KNU-DESC), and physical function (SPPB, hand grip strength, professional ENT, and Ophthalmologic evaluation).

Result: Fifty-four patients were enrolled, in whom the mean age was 65 years (range: 60–74), 61% were males, and 9% and 22% of patients had on ECOG score of ≥2 and HCT-CT score of ≥3, respectively. Baseline GA evaluation conducted using MMSE-KC, an assessment tool that reflects the patient's cognition and psychological function, revealed impairment in 33% of patients. Impairments in physical performance status were detected in 30% via K-IADL scale and in 28% patients via SPPB scale.

All enrolled patients were treated with intensive chemotherapy, and 52% achieved first complete remission (CR1). Two patients experienced early death within 60 days (4%). During induction chemotherapy, the median recovery period for neutrophil and platelet counts was 27 (range, 24–29) and 31 (range, 28–36) days, respectively. No GA domains were associated with each response to chemotherapy and recovery of neutrophil and platelet counts. The median hospitalization days were 31.5 days (range, 21.0–104.0). Grade III-IV infection, hepatopathy, and acute kidney injury developed in 69%, 35%, and 19% of patients, respectively. Patients with impairments in cognitive and physical function detected by MMSE and SPPB scales, respectively, exhibited a higher tendency to occur grade 3–4 infection (MMSE, 61% vs. 83%; SPPB, 61% vs. 80%) and acute renal failure (MMSE, 14% vs. 28%; SPPB, 9% vs. 27%). Patients with impairments in physical function by K-IADL and PTA and cognitive function by MMSE were prone to have grade III-IV hepatotoxicity (K-IADL, 29% vs. 50%; PTA, 32% vs. 75%;, MMSE, 28% vs. 50%). Of various domains, MMSE (33%) was significantly associated with prolonged hospitalization period (32.9±1.3 vs. 44.9±5.1, p=0.033).

Conclusions: Our data demonstrate that significant proportion of eAML fit for intensive chemotherapy based on performance status and comorbidity had physical, nutritional, and cognitive impairments by initial GA assessments. These interim data focusing on early events suggest that impaired physical and/or cognitive functions may be associated with tolerance to intensive chemotherapy. This ongoing prospective study will enroll more eAML patients and further follow up currently enrolled patients, which will give us invaluable data about the association of each GA domain with early events related with tolerance to chemotherapy but also survival outcomes.

Keyword: Acute Myeloid Leukemia, Geriatric Assessment, Elderly

PP-033

Stable disease has survival benefit after hypomethylating agent in myelodysplastic syndrome

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Background: Hypomethylating agent (HMA) is the main drug for myelodysplastic syndrome (MDS) regardless of performing allogeneic hematopoietic cell transplantation (HCT). Current recommendation is continuing HMA as long as possible unless progressive disease. Evidence of clinical benefit of stable disease (SD) after HMA, however, is not clear. We retrospectively investigated the clinical role of SD after HMA in MDS.

Methods: Data were collected retrospectively. Diseases were classified according to WHO 2008 classification and chronic myelomonocytic leukemia was excluded in this analysis. Response was evaluated by IWG response criteria and categorized into 4 best response groups (CR/mCR/PR vs. HI vs. SD vs. PD/NE). Overall survival (OS) was calculated from start date of HMA. Survival benefit was evaluated using OS in various subgroups using log rank test and 5-year survival rate (5YSR) by Kaplan-Meier method.

Result: Total 699 MDS patients were collected retrospectively in 10 hospitals of Korea. Among them, 449 patients had received HMA for MDS by WHO 2006 classification. Finally, 449 patients were included in this analysis. Male was dominant (n=279, 62.1%). Median age was 65 (range, 15-83). Median Duration of HMA was 4.6 (range, 0-63.4) months. WHO 2008 subtype was RCUD in 75 (16.7%), RARS in 6 (1.3%), RCMD in 148 (33.0%), RAEB-1 in 93 (20.7%), RAEB-2 in 115 (25.6%), del(5q) in 3 (0.7%) and MDS-U in 9 (2.0%) patients. Best responses were CR/mCR/PR in 99 (22.0%), HI in 91 (20.3%), SD in 185 (41.2%) and PD/NE in 74 (16.5%) patients. HCT was performed 11/99 (16.7%) in CR/mCR/PR, 9/91 (13.6%) in HI, 37/185 (20.0%) in SD and 9/74 (12.2%) patients in PD/NE. The median survival after HMA were 24.7 (95% CI, 21.6-27.9) in CR/mCR/PR, 28.5 (95% CI, 21.0-36.0) in HI, 20.4 (13.8-27.0) in SD and 6.7 (95% CI, 4.0-9.4) months in PD/NE ($p<0.001$). The 5YSR of CR/mCR/PR, HI, SD and PD/NE were 13.7%, 23.7%, 34.9% and 2.9%, respectively. Median AML-free survival was 23.5 (95% CI, 18.5-28.6) in CR/mCR/PR, 26.6 (95% CI, 17.4-35.8) in HI, 20.1 (95% CI, 14.1-26.2) in SD and 4.1 (95% CI, 2.1-6.1) months in PD/NE ($p<0.001$). Median time to HCT or death was 23.5 (95% CI, 19.3-27.8) in CR/mCR/PR, 22.9 (95% CI, 16.6-29.1) in HI, 13.0 (9.8-16.3) in SD and 5.8 (95% CI, 3.7-8.0) months in PD/NE ($p<0.001$).

Conclusions: SD after HMA in MDS showed clear survival benefit over PD or NE through all clinical subgroups. This finding supports the continuous HMA therapy and consider HCT even if there is no clear response.

Keyword: Myelodysplastic Syndrome, Hypomethylating Agents, Stable Disease

PP-034

Red blood cell and platelet indices: Could it predict survival of patients with myelodysplastic syndrome?

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Background: Myelodysplastic syndrome (MDS) are a heterogeneous group characterized by dysplastic growth of hematopoietic progenitors, ineffective hematopoiesis, peripheral cytopenia and the risk of transformation to acute myeloid leukemia. The hypometylating agents (HMAs) such as azacitidine and decitabine, has been integrated into the standard of therapeutic option in MDS for last decade. Peripheral cytopenia is considered as an indicator of the severity of ineffective hematopoiesis. Automatic report of complete blood count (CBC) includes a variety of information on red blood cells (RBC) and platelet (PLT) including the mean volume of RBC and PLT and the range of RBC and PLT volume, whereas, While white blood cell (WBC) count mainly reports the proportions of different subsets of WBC. The purpose of this study was to evaluate dyserythropoiesis and dysmegakaryopoiesis in MDS by analysing RBC and PLT indices of CBC and correlate with survival outcomes.

Methods: We retrospectively reviewed 30 consecutive patients who received decitabine or azacitidine as the treatment of MDS between 2010 and 2018 at Hanyang University Seoul Hospital, Seoul, Korea. The Kaplan-Meier method was used for overall survival (OS). The Spearman's rho was used to assess the correlation between OS, RBC and PLT incides.

Result: Median age of at the diagnosis of MDS was 66 years (range, 25-82 years). Nineteen patients (57%) of 30 were male. Nineteen patients (57%) were treated with azacitidine, while 11 (37%) with decitabine. The IPSS risk group included 2 (7%) in Low, 21 (70%) in Intermediate-I, 4 (13%) in Intermediate-2, and 3 (10%) in High risk group. The IPSS-R categorized 8 (27%) into Low, 7 (23%) into Intermediate, 8 (27%) into High, and 7 (23%) patients into Very High risk group. OS of 30 patients was median 2.7 years (95% confidence interval (CI), 1.0-4.0 years). Twenty-four patients (80%) of 30 commenced HMA at the time of diagnosis of MDS, while 8 patients (20%) first put on watchful waiting strategy or received supportive care including transfusion and erythropoietin-stimulating agents until disease progression or worsening of cytopenia (median time to start HMA 17 months, range 4-108 months). Mean value of hemoglobin (Hb) was 7.5 g/dL(±2.0) and PLT count was 74 x 10^9/L(±55 x 10^9). The mean values of RBC and PLT indices were MCV (mean corpuscular volume) 98.6 fL (±19.6),

MCH (mean corpuscular hemoglobin) 33.5 pg (±4.1), MCHC (mean corpuscular hemoglobin concentration) 32.9g/dL (±1.6), RDW (RBC distribution width) 17.6% (±3.7), PCT (plateletcrit) 0.02% (±0.04), MPV (mean platelet volume) 10.9fL (±1.4), PDW (platelet distribution width) 13.4% (±4.1), and PLCR (platelet large cell ratio) 31.5% (±9.5). None of RBC or PLT indices was correlated with Hb concentration and PLT count. MCH showed the correlation with RBC and PLT indices, widely; strong correlation with MCV (ρ=0.754, P<0.0001), MPV (ρ=0.629, p=0.003), and PLCR (ρ=0.581, p=0.009); weak correlation with MCHC (ρ=0.440, p=0.015), RDW (ρ=-0.367, p=0.46), and PDW (ρ=0.502, p=0.24). PDW was strongly correlated with MPV (ρ=0.848, p<0.0001) and PLCR (ρ=0.893, p<0.0001). OS from the diagnosis of MDS showed weak correlation with MCV (ρ=0.364, p=0.048) and RDW (ρ=-0.365, p=0.047).

Conclusions: The RBC and PLT indices were not associated with the value of Hb and PLT count, of which severity has been the part of prognostic models such as IPSS and IPSS-R. However, it seems that MCV and RDW reflect dyserythropoiesis, although PLT indices failed to demonstrate the correlation with dysmegakaryopoiesis.

Keyword: Myelodysplasstic Syndrome, MCV, RDW

PP-035

Monocyte subset for the screening of chronic myelomonocytic leukemia

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Background: Monocytosis can be present in various conditions including malignancy, infection and inflammations. However, the morphology of monocytes cannot differentiate those from the hematologic malignancies or reactive conditions and no specific molecular changes are present in chronic myelomonocytic leukemia (CMML). Classical monocytes (CD14+/CD16–) have been suggested to be increased in the peripheral blood (PB) of CMML. Thus, we have evaluated whether monocyte subsets are useful in screening CMML in PB of patients with monocytosis.

Methods: Six color multiparametric flow cytometry including CD2, CD14, CD24, CD16, CD56, CD45 antibodies (BD Biosciences, San Jose, CA, USA) were performed. In total, 300,000 events were acquired and serial gating to exclude T cells, natural killer cells, granulocytes were performed. Monocytes were allocated into classical monocytes (MO1, CD14+CD16–), intermediate monocytes (MO2, CD14+/CD16+), or nonclassical monocytes (MO3, CD14low/CD16+) and the percentages in each monocyte subsets were assessed. The sensitivity and specificity were calculated with the cutoff value of MO1 suggested by Selimoglu-Buet et al. The cutoff value adjusted with highest area under the curve was recalculated.

Result: Monocyte subsets were performed in 30 samples including CMML (n = 4), other monocytosis (n = 11) and normal controls without monocytosis (n = 15). Sensitivity, specificity using the previously reported cutoff yielded, 100% and 73.1%, respectively. Adjusting the cutoff to 95.4% for MO1 yielded an increase of specificity to 76.9%. None of the normal controls showed MO1 >95.4%. However, few patients with monocytosis showed increase of MO1% and some of the patients had long history of monocytosis with other malignancy requiring further workup of CMML.

Conclusions: Monocyte subset analysis maybe useful in screening patients with monocytosis to differentiate CMML from other conditions. However, depending on the antibodies and the gating algorithms used, the cutoff value should be verified in each laboratory. Further evaluation including more CMML and other monocytosis patients are necessary.

Keyword: Chronic Myelomonocytic Leukemia, Monocyte Subset, Classical Monocytes, Flow Cytometry

PP-036

Polymorphism of TPMT and ITPA and their adverse effects of chemotherapy for acute lymphoblastic leukemia children in Bangladesh

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Background: The pharmacogenetics approach reduces the toxicity and increases safety of chemotherapy. 6-mercaptopurin (6-MP) metabolizing enzymes such as thiopurine S-methyltransferase (TPMT) and inosine triphosphate pyrophosphatase (ITPA) contribute to variables responses including adverse effects among patients treated with 6-MP for leukemia. But until now, there is no study among Bangladeshi population related to TPMT and ITPA polymorphism and their adverse effects on chemotherapy treatment. Therefore, this study was aimed to identify the distribution of TPMT and ITPA polymorphisms among Bangladeshi children and their association with the adverse effects of 6-MP which is used for maintenance therapy in acute lymphoblastic leukemia (ALL) patients.

Methods: This was a retrospective study conducted in two tertiary level hospitals in Dhaka city, central part of Bangladesh. We recruited 75 patients diagnosed with acute lymphoblastic leukemia (ALL) and 75 volunteers with minor illnesses. Genetic DNA was extracted from 0.2 ml peripheral blood of the patients on maintenance therapy and volunteers using the Genomic DNA Isolation Kit (QiAamp DNA Blood Mini Kit: Qiagen, Vealo, The Netherlands) following the instructions from the manufacturer. Polymorphisms of TPMT*3C (c.719A>G, rs1142345), TPMT*2 (c.238G>C, rs1800462), TPMT*3B (c.460G>A, rs1800460), and ITPAc.94C>A (rs1127354) were genotyped using the TaqMan Assay-on-Demand SNP Typing System (Applied Bio Systems, Foster City, CA, USA) following the manufacturer's instructions. PCR was performed on a 384-well format with 3ng of each DNA, and automatic allele calling was performed using ABI PRISM 7900HT data collection and analysis software, version 2.2.2 (Applied Biosystems).

Result: Age of the ALL patients and volunteers were 5 + 2.5 years (mean + SD) and 3.1 + 1.6 years (mean + SD) respectively. The frequency of TPMT*3B, TPMT*3C and ITPA polymorphisms among volunteers was 0.006, 0.020, and 0.093, respectively, and that of TPMT*3C and ITPA polymorphisms among ALL patients was 0.010 and 0.153, respectively. ALL patients with the TPMT*3C variant developed leucopenia (P=0.037), neutropenia (P=0.017), and thrombocytopenia (P=0.008). Those with the ITPA variant developed fever (OR=6.9, 95%CI=1-99-23-91), neutropenia (OR=7.68, 95%CI=2.21-26-61) liver toxicity (hyperbilirubinemia, OR=4.73, 95%CI=1.39-16.07), and raised serum ALT (OR=4.73, 95%CI=1.52-14.68).

Conclusions: Our study strongly suggests the importance of TPMT and ITPA genotyping in ALL patients to design more rational and cost effective treatment strategies.

Keywords: Polymorphism, TPMT, ITPA, Chemotherapy, Lymphoblastic Leukemia (ALL)

Table: Frequency of *TPMT and ITPA* alleles

Variations	rs number	Wild type	Heterozygous	Homozygous	Minor allele frequency
ALL patients					
*TPMT*2*	rs1800462	75	0	0	0.000
*TPMT*3B*	rs1800460	75	0	0	0.000
*TPMT*3C*	rs1142345	73	2	0	0.010
ITPAc.94C>A	rs1127345	55	17	3	0.153
Volunteers					
*TPMT*2*	rs1800462	75	0	0	0.000
*TPMT*3B*	rs1800460	74	1	0	0.006
*TPMT*3C*	rs1142345	72	3	0	0.020
ITPAc.94C>A	rs1127345	61	14	0	0.093

TPMT, thiopurine S-methyltransferase;*ITPA*, inosine triphosphate pyrophosphatase
Allele frequency was calculated by using Hardy-Weinberg principle.

PP-037

Customised superparamagnetic iron-oxide polymeric nanocarriers for targeted and controlled delivery of anti-tumor drug in acute lymphoblastic leukemia

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Background: Clinical application of most anti-cancer drugs in the treatment of leukemia is limited by their low solubility, decreased bioavailability and severe and toxic systemic side effects. Targeted and controlled delivery of these drugs can reduce their systemic toxic effects and enhance the therapeutic efficacy by increasing their bioavailability in the systemic circulation. Here we report the formulation and characterization of biocompatible superparamagnetic iron-oxide nanocarriers (SPIONs) composed of iron-oxide core and coated with three layers of highly biocompatible polymers namely aminocellulose, polyethylene glycol (PEG) and polyamidoamine (PAMAM). These nanocarriers were formulated to provide a biocompatible and effective platform for targeted and controlled anti-cancer drug delivery system for Acute Lymphoblastic Leukemia treatment.

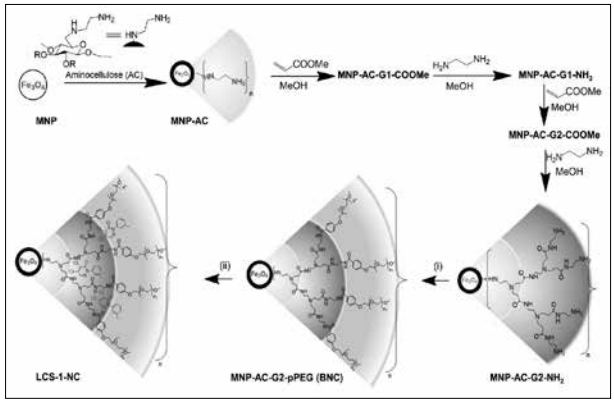
Methods: Nanocarriers were formulated by nanoprecipitation method, coated consecutively by a number of biocompatible polymeric layers and characterized for their size, shape, physicochemical characteristics & surface morphology by Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM), Field-Emission Electron Microscopy (F-SEM) & Atomic Force Microscopy (AFM). Drug loading capacity and drug encapsulation efficiency was done by UV-VISIBLE spectrophotometry and GC-MS analysis. The drug release study from the nanocarriers was studied in physiological phosphate buffer saline (PBS pH 7.4). Therapeutic efficacy and safety index was assessed by MTT assay. The apop-

tosis and DNA damage analysis was carried out by the immunofluorescent expression of apoptosis marker-cleaved caspase-3 and DNA damage markers γH2AX and 53BP1. Apoptosis was also assessed by Flow cytometry Annexin-FITC assay.

Result: The nanocarriers were of size range 50-100 nm, showed desired physicochemical and morphological characteristics in TEM, FE-SEM and AFM microscopies. Nanocarriers showed sustained release of drug in physiological medium at pH 7.4. These nanocarriers showed excellent biocompatibility profiles against HEK293 cells. The therapeutic efficacy of drug loaded nanocarriers was significantly enhanced statistically, as compared to drug alone. The results of confocal microscopy and FACS flow cytometry showed good cellular internalization of the nanocarriers inside the cells. The immunofluorescence expression of DNA damage markers γH2AX, 53BP1 and apoptosis marker cleaved caspase-3 in the cells treated with these nanocarriers established their excellent ability to induce DNA damage and apoptosis in cancer cells. The results of SDS-PAGE also showed the adsorption of some serum proteins over these nanocarriers leading to the formation of soft and hard protein corona over these. Protein corona coated nanocarriers were also quite biocompatible as seen in the results of MTT assay.

Conclusions: The synthesised nanocarriers showed the desired physicochemical and morphological characteristics, excellent biocompatibility and enhanced therapeutic drug efficacy. Their biocompatibility and increased surface area makes them a great candidate most suitable for biomedical applications in the treatment of many cancers including acute lymphoblastic leukemia. The sustained release profile and targeted delivery of these drug loaded nanocarriers will help in reducing the systemic toxicities and severe side effects associated with the applications of anti-cancer agents.

Keyword: Nanocarriers, Acute Lymphoblastic Leukemia, Drug Delivery, Biocompatible, Targeted Therapy, Cancer Nanomedicine



PP-038

Immuno phenotypes and the value of cluster of differentation in acute leukemia at National Children's Hospital, Vietnam

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Background: Immunophenotyping is an essential step of diagnostic workup of acute leukemia. It provides a lot of information for treatment decision and prognosis of effective treatment. In this study, we describe the immune phenotype of acute leukemia patients treated at the National Children's Hospital, Vietnam.

Methods: 520 acute leukemia pediatric patient (age of 1 month – 17 years) were done immunophenotyping from 4/2012 - 6/2018 by flowcytometry methods on Facs Canto II 6 colors.

Result: Acute B-cell Leukemia is 81.8%, Acute T-cell Leukemia is 10.5 %, Acute Myeloid Leukemia is 7.7%. Specific markers expression on leukemic B cells are: CD19 (98.8%), CD10 (97.4%), CD79a (99.1%), CD22 (77.9%), CD20 (29.2%), Kappa (1.7%), Lamda (1.7%). Leukemic T cells are: CD7 (100%), cCD3 (94,5%), CD5 (89.1%), CD3 (78.1%), CD4 (70.9%), CD8 (69.1%); Leukemic myeloid cells are: MPO (82.5%), CD33 (97.5%), CD117 (97.5%), CD13 (80.0%), CD14 (22.5%), CD41 (5%), GlyA (10%). Ectopic expression markers on leukemic cells: Leukemic B cells with expression of myeloid cell marker is 10.7% and of T cell is 2.8%; Leukemic T cell with expression of myeloid cell marker is 7.2%, and of B cell marker is 7.3%. Myeloid leukemic cells with expression of B cell is 7.5% and of T cell line is 7.5%. Bi-phenotype leukemia is 0.19%. The difference between morphology and immune phenotypes is 1.7%.

Conclusions: Immunophenotyping is effective methods in discrimination of Acute Leukemia type. It plays an important role in diagnosis and prognosis of acute leukemia.

Keyword: ALL, Acute Leukemia, Immunophenotyping, Flowcytometry, Facs Canto

PP-039

Temporal trends in nutritional status of children with acute lymphoblastic leukemia during intensive phase of treatment

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Background: Patients nutritional status has shown to impact the outcome in acute lymphoblastic leukemia (ALL). The present study was conducted to analyse the trends in change of nutritional status in children with ALL during the intensive phase of treatment.

Methods: The study included newly diagnosed patients with ALL less than 18 years of age treated with a uniform risk-stratified protocol between January 2014-December 2016. Patients height and weight were collected prospectively at diagnosis and at end of induction, consolidation, interim maintenance, and delayed intensification (before starting maintenance). The WHO weight for age (WA) and body mass index (BMI) reference standards were used to classify the nutritional status and values < -2 standard deviation (SD) and > 2 SD were considered undernourished and obese respectively.

Result: The study included 241 patients with a median age of 7 years and 59% patients were males. Undernutrition, normal nutrition, and obesity was observed in 29%, 69% and 2% of patients at diagnosis and 14%, 77% and 9% at the end of delayed intensification respectively (P<0.001). Significant weight change in patients was observed during the induction phase of treatment (P=0.02) and not between other phases of treatment. NCI high-risk category was the only parameter predictive of undernutrition at presentation. Patients whose BMI/WA was <-1SD or >1SD at diagnosis were not at risk of obesity or undernutrition later respectively. Maximum variation in nutritional status occurred in patients with WA/BMI between -1SD and 1SD. Changes in BMI/WA by 2SD during induction and 1SD between induction and start of maintenance was significantly associated with inferior event free survival (EFS) (P=0.049 and 0.013 respectively).

Conclusions: Weight changes during intensive phase of ALL treatment is associated with inferior EFS and predictor of future obesity. Strategies to optimise nutrition during treatment can help in improving outcomes in patients with ALL treated in developing countries.

Keyword: ALL, Nutrition, Pediatric Cancer

PP-040

Preliminary experience at a single centre in India with a collaborative multicentre risk stratified and response adapted protocol for treating pediatric ALL

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Background: The use of risk and response adapted protocol in developing countries has been hampered by lack of access to cytogenetic and minimal residual disease (MRD) testing. We share our experience with the first pan-India multi-centric indigenously developed risk and response adapted protocol for treating pediatric ALL.

Methods: The study included newly diagnosed patients with ALL between 1-18 years of age prospectively enrolled between January 2014-December 2016. Pre-B group patients were stratified as Standard Risk (SR), Intermediate Risk (IR) and High Risk (HR) and the T-cell group as SR and HR based on NCI criteria, disease bulk, cytogenetics, day 8 prednisolone response and post induction bone-marrow MRD. Event Free Survival (EFS) and Overall Survival (OS) were analysed using the Kaplan Meier method and log-rank test was used to compare variables.

Result: A total of 245 consecutive patients were eligible for analysis. The median age was 7 years and 60% patients were male. Pre-B cell phenotype was observed in 191/245 (78%) patients and T-cell in 55/245 (22%). The baseline and post-induction risk-stratification for the pre-B group was 22% SR, 63% IR, 15% HR and 12% SR, 28% IR and 59% HR respectively. Blast clearance on day 8 was observed in 179/245 (73%) patients. At a median follow-up of 22 months, the overall EFS and OS was 70% and 79% respectively. The EFS and OS for pre-B SR, IR and HR cohort was 77%, 84%, 67% (P=0.1) and 85%, 94% and 76% (P=0.05) respectively. The EFS and OS for T-cell 62% and 70% respectively. NCI risk stratification predicted EFS. Day 8 prednisolone response, immunophenotype, and MRD did not significantly predict EFS and OS

Conclusions: In contrast to data from developed countries the majority of patients with ALL in our cohort had high-risk disease. The survival outcome is comparable to similar results reported from other post-induction in India and better than our historical cohort.

Keyword: ALL, Survival, Pediatric Cancer

PP-041

Homozygous TCF3 mutation is associated with severe hypogammaglobulinemia and acute lymphoblastic leukemia

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Background: TCF3 (E2A) gene encodes E12 and E47 transcription factors which are essential in differentiation process of common lymphoid progenitors into B-lineage cells and are key regulators of B-cell development. Herein, we report the first homozygous TCF3 mutated patients. They presented reduced peripheral B cells, hypoagammaglobulinemia and acute lymphoblatic leukemia (ALL).

Methods: The study included two siblings born to tunisian first cousin parents. Immunological investigations included cellular phenotyping by flow cytometry and immunoglobulins measurement by nephelometry. Molecular studies included whole exome sequencing for identification of mutated gene and western blot to study protein expression.

Result: Patient P1 had recurrent pneumonia and meningitis since early childhood and mild facial dysmorphia. At age 7 years he presented pancytopenia and splenomegaly, the diagnosis of B-ALL was confirmed. At the age of 10 years, he died despite chemotherapy was resumed. Patient P2 suffered from recurrent pneumonia and failure to thrive. She also had facial dysmorphia. At age 14 years, she developed acute lymphoblastic leukemia. Immunological investigations revealed a very low number of peripheral CD19+B cells in patient P1 and ~3% CD19+B cells in patient P2. All immunoglobulin classes were absent in patient P1, while borderline low IgG and significantly decreased IgA and IgM serum immunoglobulin levels were observed in patient P2. Whole exome sequencing revealed a novel homozygous mutation within exon 9 of TCF3 (c.C807T) and resulted in a premature stop codon (p.Q270X). Both parents were heterozygous. The truncated protein, with no helix-loop-helix (HLH) functional domain, was absent as shown by a western Blot. In contrast to previous E47 deficient patients, patient P2 had normal expression of IgM but decreased levels of CD27+ memory B cells as well as of switched memory CD27+IgD– B cells. Detailed analysis of the T cell immunophenotype, revealed a significant increase in effectors memory CD8+ T cells and absent terminally differentiated effector T cells (TEMRA).

Conclusions: Considering the crucial role of TCF3 in the regulation of normal B cell development, it is not surprising that disruption of this transcription factor causes a profound B cell defect. Since TCF3 is also known to be affected (translocations and deletions) in B-ALL, this could explain the clinical phenotype herein observed. Indeed, a decrease in the level of PAX5 transcripts was observed in patient P1. This is consistent with data in mice showing that the loss of PAX5 in mature B cells leads to the development of aggressive progenitor B-cell lymphomas.

Keyword: Acute Lymphoblastic Leukemia, Hypogammaglobulinemia, TCF3 Homozygous Mutation, B cells, Consanguinity

PP-042

A comparative study of palmar and digital dermatoglyphic patterns among leukemic patients & non-leukemic Individuals: A meta-analysis

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Background: Dermatoglyphic patterns are the epidermal ridges seen on the surface of palm, sole & digits which plays a significant role in predicting the various human disorders. Recent association of the dermatoglyphic traits and specific chromosome aberrations has established a predicting tool as well as a diagnostic aid. Leukemia is a malignant disease with high prevalence in today's world occurred as a challenge and a serious threat to mankind. The early diagnosis of this fatal disorder can be important to undertake the preventive measures and hence reduce the morbidity and 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. The aim of this review was to systematically identify, review and appraise available literature that evaluated an association of different dermatoglyphic variables with hematological disorders.

Methods: An intense systematic literature search was conducted using keywords 'Dermatoglyphics', Leukemia, from PUBMED,

Google Scholar, EBSCO, HINARI etc. The review is performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Dermatoglyphics patterns like whorls, loops, arches and parameters like angles(atd, dat, adt), absolute finger ridge count (AFRC), total finger ridge count (TFRC), a-b ridge count, mainline index and pattern index line were studied.

Result: The mean ab-ridge count and the mean atd - angle was observed to be higher in leukemic subjects while the mean adt - angle was found to be lower in cases than controls. Studies on male leukemic patients revealed the higher frequency of digital whorls than control group whereas similar patients have more sydney palmar flexion creases than normal control subjects. The relationship between aberrant palmar creases and ALL in children who developed leukemia at a young age was investigated. Statistical analysis demonstrated significant differences in bilateral aberrant palmar creases between ALL children and relatives. The subjects without bilateral aberrant creases may show a preleukemic change in uterus prior to blood-brain barrier establishment. However, there were no significant differences in either bilateral or unilateral aberrant palmar creases between ALL children and their siblings. A study on children with ALL indicated increased whorls and decreased loops frequency. The quantitative parameters such as radial and double loops, central pocket loops and tented arches were proportionately less in the leukemic patients than controls. The mean pattern intensity indexes (PII) in the patients were higher than the controls which support the evidence of significant dermatoglyphic patterns in leukemia patients. A familial occurrence of the abnormal dermatoglyphic pattern has been found in leukemic patients.

Conclusions: Dermatoglyphics provide a simple, inexpensive, anatomical, and non-invasive means of determining the diseases which have a strong hereditary basis and can be employed as a method of screening the leukemia of the high-risk population on early detection, thus reducing the morbidity and mortality. Future studies can be done avoiding the limitations of earlier studies, reevaluating the existing data and hence ascertain the findings of dermatoglyphic research in medicine. Similar studies can be useful in rare forensic casework where the association of dermatoglyphic features with certain diseases is to be explored.

Keyword: Leukemia, Dermatoglyphics, Acute Lymphocytic Leukemia, Whorl

PP-043

The effect of GATA3 rs3824662 gene polymorphism on children with pre-B-cell acute lymphoblastic leukemia treated by CCLG-ALL 2008 protocol

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Background: GATA3 polymorphisms were reported to be significantly associated with susceptibility and poor outcome of pediatric B-cell acute lymphoblastic leukemia (B-ALL). The rs3824662 risk allele can directly influence GATA3 transcription, and show close relation with the early treatment response and the risk of relapse. However, the effect of GATA3 rs3824662 gene polymorphism on han nationality children with B-ALL pediatric patients has not been reported clearly. In this study we retrospectively analyzed the distribution of GATA3 rs3824662 polymorphism in han nationality children with pre-B-ALL and explored its impact on the treatment response and outcome of patients treated by CCLG-ALL 2008 protocol.

Methods: Samples came from 270 patients with newly diagnosed B-ALL treated by CCLG-2008 protocol and got complete remission (CR). All the patients analyzed have finished the whole treatment at least for 1 year, and the median time for follow-up was 56.78 months. The typing of GATA3 rs3824662 polymorphism was done using PCR and sanger sequencing. The statistical analysis of data was done using IBM SPSS statistics version 22 and GraphPad Prism 5. Fourteen patients were eliminated according to the deletion criteria. At last, the valid sample number was 256 cases.

Result: The genotype for CC, CA, and AA was 109 (42.6%),116 (45.3%), and 31 (12.1%) cases, respectively. A allele frequency accounted for 34.7% which was consistent with the frequency database reported for east Asian population. The percentage of AA genotype in high risk group was the highest among three risk groups (p=.027). However, AA genotype has no significant relation with such factors as gender, age, WBC, and fusion gene arrangement . As the treatment response was considered, we found that more patients with AA genotype showed resistant to prednisolone response than patients with CC and CA genotype (9/23 versus 22/202, p=.011). Furthermore, the percentage of AA genotype was higher in the group with M3 on day 15th than the other two groups (M1+ M2) (12/36 vs 19/189, p=.007). However, on day 33th and 12th week, the effect of AA genotype on the

treatment response got less. At last, the relapse patients distributed in AA genotype was 32.25% (10/31) and 22.22% (50/225) in CC+AC genotype which didn't reach significant difference (p=.453). The estimated 10 years overall survival (OS) in AA and AC+CC genotypes was 73.4(13.4)% and 87.7(2.2)%, respectively. The estimated 8 years event free survival (EFS) in AA and AC+CC was 64.2(9.7) % and 75.4(3.0) %, respectively. The estimated 8 years relapse-free survival (RFS) in AA and AC+CC genotypes was 64.2(9.7)% and 76.8(2.9)%, respectively. Patients with AA genotype in GATA3 rs3824662 had lower OS and EFS, and higher relapse rate, however, there was no significant difference (p=.439 for OS, p=.420 for EFS, and p=.305 for RFS).

Conclusions: In our retrospective study, we found that GATA3 rs3824662 risk allele is associated with high risk index such as poor prednisolone response and high blast cells on day 15th in han nationality pediatric B-ALL treated by CCLG-ALL 2008 protocol. Patients with AA genotype in GATA3 rs3824662 had lower OS and EFS, and higher relapse rate, however, these differences didn't reach statistic value. Our results suggest that intensive therapy by CCLG-2008 protocol may improve the outcome of these patients with AA genotype in GATA3 rs3824662.

Keyword: GATA3 rs3824662, SNP, B-ALL, China, Pediatric

PP-044

Comparision of parental perception on "Health Related Quality of Life (hrqol)" in children with acute lymphoblastic leukemia (on treatment) and normal

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Background: Acute lymphoblastic leukemia is the most common malignancy in pediatric population. Advancements in treatment have improved the prognosis of children with acute lymphoblastic leukemia (ALL). Treatment of ALL is of long duration as well as includes many complications of the treatment and the disease. Parents are always concerned about health related issues of their children but about the children having any disease especially any malignancy make them very emotional about them. Therefore, there is a need to explore health-related quality of life (HRQOL) in depth, specifically in local population, where the available data are minimal. This study was conducted to assess the varied items listed in the domains of HRQOL of Children with ALL during therapy from a parent's perspective and compared with healthy siblings.

Methods: Forty children on the therapy for ALL and 40 healthy siblings were enrolled, and the HRQOL was assessed for both by parents using PedsQL generic core 4.0 in local language (Urdu).

Result: Parents significantly overrated the HRQOL of ALL patients as compared to normal siblings in majority of domains. The general quality of life of children with ALL on therapy (70 ± 8.15) was significantly poorer than that of siblings (95 ± 9.5). Their abilities of self-care and, household work, and exercise were affected. They also have increased emotional problems (fear, anger, and sleeping problems) compared to healthy siblings. In the social health domain, children with ALL reported difficulty in maintaining friendships and competing. QOL of healthy siblings was good in physical and social health domains, but they had similar emotional problems such as anger and sadness. Our study validated that the QOL of children with ALL during therapy was significantly poorer than that of healthy siblings.

Conclusions: Our study identified various items in each domain of QOL that were affected in children with ALL. We suggest healthcare professionals to focus on these specific items so as to improve their overall QOL in children, not only with ALL but also for children with other chronic diseases.

Keyword: Acute Lymphoblastic Leukemia, Pediatric Population, Health-Related Quality of Life, HRQOL

PP-045

Detecting diplotype of NUDT15 variants and 6-Mercaptopurine sensitivity by target sequence cDNA of NUDT15

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Background: Two NUDT15 polymorphisms, c.36_37insGGAGTC and c.415C>T, located in exon 1 and exon 3, respectively, are critical to mercaptopurine metabolism in Asian children with acute lymphoblastic leukemia (ALL). The average mercaptopurine doses for treating Taiwanese ALL patients who are heterozygous or homozygous for NUDT15 polymorphisms were 19.4, and 4.4 mg/m2/d, respectively, much less than that for those carrying wild-type NUDT15 (35.8 mg/m2/d). Thus, screening for these NUDT15 variants should be performed for ALL patients in Asia to avoid 6MP intolerance. Sanger sequencing is cost-effective and simple; however, it cannot distinguish heterozygous patients with both variants in the same chromosome from the compound heterozygous with the two variants on different chromosomes. Patients with compound heterozagous NUDT15 variants is like homozygous and their 6MP tolerance is 4-5 times less than those heterozygous patients. Thereafter, a method to identify compound heterozygous NUDT15 variations is of clinical significance.

Methods: Fifty samples (39 with both c.36_37insGGAGTC and c.415C>T and 11 control samples) were examined. Germline genomic DNA and total RNA were extracted from PB or BM during disease remission. NUDT15 variants were genotyped by direct Sanger sequencing of genomic DNA. In order to determine the haplotypes of the two variants, we use next-generation sequencing for target sequencing. A single amplicon (562 bp), which covers all of the coding regions of NUDT15 was amplified from cDNA and analyzed by paired-end sequencing using Miseq reagent kit v3 (600 cycles).

Result: Of the 11 control samples, both Sanger sequence and cDNA target sequence are compatible. Of the 39 samples carrying the NUDT15 variations, 38 showed both c.36_37insGGAGTC and c.415C>T located on the same allele and one showed c.36_37insGGAGTC and c.415C>T located on different alleles. Moreover, of the 38 samples, two were complex homozygous, showing R34T on exon 1 in one allele, and both c.36_37insGGAGTC and c.415C>T in the other. For the two complex homozygous patients, their daily mercaptopurine doses were reduced to around 1-2% intensity of protocol design. This indicates that the phenotype and genotype of the two patients were compatible, and both of their NUDT15 variant alleles should be non-functional.

Conclusions: Target-sequencing of NUDT15 cDNA can determine whether patients with both c.36_37insGGAGTC and c.415C>T are compound heterozygous or mono-allelic variants. Also, we identified two patients with complex homozygous NUDT15 variants and they could only tolerate extremely low 6MP doses. Patients who are homozygous or compound heterozygous for the NUDT15 variants can only tolerate less than 5mg/m2/day intensity of mercaptopurine. Thus, pre-emptive screen for the NUDT15 genotypes is necessary before mercaptopurine administration.

Keyword: NUDT15, Mercaptopurine, Children, Leukemia, Diplotype, Target Sequencing

Diplotype of Nudix Hydrolase 15 (*NUDT15*) by Sanger sequence assay and cDNA target sequence

NUDT15	No.	Sanger sequence Assay		cDNA target sequencing		Comment
		Exon 1	Exon 3	Allele 1	Allele 2	
Experiment	1-37	WT/V17_18ins	WT/R139C	WT	V17_18ins…R139C	mono-allelic
	38	R34T/V17_18ins	WT/R139C	V17_18ins	R139C	Complex Homozygous
	39	R34T/V17_18ins	WT/R139C	R34T	V17_18ins…R139C	Complex Homozygous
Control	40	WT/V17_18ins	R139C /R139C	V17_18ins…R139C	WT	mono-allelic
	41	V17_18ins /V17_18ins	R139C /R139C	V17_18ins…R139C	V17_18ins…R139C	Homozygous
	42	V17_18ins /V17_18ins	R139C /R139C	V17_18ins…R139C	V17_18ins…R139C	Homozygous
	43	WT/ WT	WT/ WT	WT	WT	Wild type
	44	WT/ WT	WT/ WT	WT	WT	Wild type
	45	WT/ WT	WT/ WT	WT	WT	Wild type
	46	WT/ WT	WT/ WT	WT	WT	Wild type
	47	WT/ WT	WT/R139C	WT	R139C	mono-allelic
	48	WT/ WT	WT/R139C	WT	R139C	mono-allelic
	49	WT/V18I	WT/ WT	WT	V18I	mono-allelic
	50	WT/V17_18ins	WT/ WT	WT	V17_18ins	mono-allelic

WT: Wild type

PP-046

Sociodemographic, clinical and laboratory profile of acute leukemia patient in Sanglah General Hospital, Bali

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Background: Acute leukemia is the one of hematologic malignancy with rapid clinical progression and without any treatment the patient will die in few months. Lack of descriptive data about acute leukemia in Indonesia makes this study is important to be conducted. The aim of this study is to know the sociodemographic, clinical and laboratory profile of acute leukemia patients consisting of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) in Sanglah General Hospital, Bali.

Methods: This is an observational study with retrospective cross-sectional design conducted in Sanglah General Hospital, Bali from October-November 2018. The data was taken from medical records in the period of October 2017-September 2018. Sample was collected using total sampling method. The data was analyzed using statistical computer program.

Result: There are 52 patients suffering from acute leukemia with 51,92% of ALL and 48,07% of AML, the mean of age for ALL is 11,30±12,60 years and AML is 37,24±22,63 years. Acute lymphoblastic leukemia is dominantly found in female (59,26%) and AML in male (64,0%). The education level of patient with ALL is informal educated (59,25%) and AML is senior high school (16,0%). Based on the occupation, most of ALL patient are unemployed (55,55%) and AML patients are student (28,0%). The most common chief complain of ALL patient are weakness (25%) and fever (25%) meanwhile in AML is weakness (60%). Anemic condition is the most physical examination which found in both ALL (15,5%) and AML (41,7%). Based on hematological profile, ALL patient has high mean of WBC level 21,00±33,03 103/µL, lymphocyte (14,66±28,34 103/µL), monocyte (2,34±4,54 103/µL), eosinophil (0,15±0,33 103/µL), basophil (1,01±1,83 103/µL), and there is a low count of hemoglobin (9,67±2,53 103/µL), hematocrit (30,24±7,79 103/µL), and platelet (161,33±198,43 103/µL). Acute Myeloid Leukemia has high count of WBC (35,54±41,75 103/µL), lymphocyte (14,15±27,42103/µL), monocyte (10,91±16,54 103/µL), eosinophil (0,12±0,16 103/µL), and basophil (3,32±6,11 103/µL), low count of hemoglobin (9,12±2,09 gr/dL), hematocrit (28,12±6,59% 103/µL), and platelet (75,81±113,43 103/µL). Based on clinical chemical parameter, ALL has high count of AST (35,76±33,26 U/L), globulin (2,8±0,74), GGT (82,3±95,65 U/L), and LDH (1662,60±3126,44 U/L), low count of creatinine (0,48±0,61 mg/dL). Acute Myeloblastic Leukemia has high count of AST (53,75±88,48 U/L), ALT (36,96±35,81 U/L), LDH (5193,50±11158,94 U/L), GGT (76,14±94,36 U/L) and creatinine (0,99±0,79 mg/dL), but has low count of serum Na (135,77±4,68 mmol/L) and globulin (3,03±0,68). Mostly of the ALL patients treated with chemotherapy (63,0%), meanwhile in AML treated with chemotherapy and also blood transfusion (44%). The length of stay of each hospitalized episode of ALL patient is 12,78±8,00 days and AML patient 18,32±11,20 days. The most common subtype of ALL is L2 (69,2%) and AML is M2 (40%). After undergoing a treatment all patients of ALL and AML has recovered but discharged as outpatient.

Conclusions: In a year period, the proportion of ALL (51,92%) is greater than AML (48,07%) with their variation in sociodemographic, clinical and laboratory profile.

Keyword: Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Sociodemographic Characteristic, Clinical Profile, Laboratory Profile

PP-047

Two cases of burkitt leukemia with IGH-MYC rearrangement associated with precursor B-cell phenotype

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Background: Burkitt lymphoma is a highly aggressive lymphoma that often present in extranodal sites or as a leukemic phase. The molecular hallmark of Burkitt lymphoma is rearrangement of MYC, mostly involving the IGH locus as t(8;14)(q24;q32). Although the postulated normal counterpart of Burkitt lymphoma is a germinal center B cell, WHO classification notes that the immunophenotype of the blasts of Burkitt leukemia, a leukemic phase of Burkitt lymphoma, may have a phenotype of precursor B cells, in rare occasions. Here, we report two cases of patients at presentation had immunophenotype compatible with precursor B acute lymphoblastic leukemia (ALL), particularly pre-B acute lymphoblastic leukemia (pre-B ALL), and diagnosed with Burkitt leukemia based on IGH-MYC translocation.

Methods: For morphologic analysis, bone marrow aspiration and biopsy was performed. Immunohistochemistry and immunophenotyping was done for further identification of blasts cells. For cytogenetic study, karyotype in 20 metaphases were analyzed and IGH-MYC rearrangement was confirmed with fluorescence in situ hybridization (FISH) analysis with probe for IGH/MYC/CEP8.

Result: The first case, a 73-year-old male presented with dyspnea and anterior mediastinal mass revealed by imaging study. Laboratory results showed anemia with thrombocytopenia with blast cells in peripheral blood. Bone marrow aspirate was hypercellular with 87% of blast cells that were morphologically consistent with Burkitt lymphoma tumor cell morphology. An immunophenotype analysis showed blasts were positive for CD19, CD10, CD22, CD79a. Cytogenetic results showed complex chromosome with IGH-MYC rearrangement. The second case, a 7-year-old male presented with anemia, thrombocytopenia and blast cells in peripheral blood. The patient was previously treated with chemotherapy for osteosarcoma. Bone marrow aspirate was hypercellular with 95% of blasts expressing CD19, CD10, CD22. Morphologically, blasts resembled lymphoblasts. Cytogenetic analysis revealed

complex chromosome with IGH-MYC rearrangement. Both of the patients were initially diagnosed with precursor B ALL according to the immunophenotyping results and Burkitt leukemia when the cytogenetic results were available.

Conclusions: IGH-MYC rearrangement positive Burkitt leukemia displaying pre-B ALL phenotype has been rarely reported before. These two unusual cases demonstrate the importance of multidisciplinary evaluation of leukemic cells. In our case, two characteristics were apparent. First, the malignant cells were positive for CD10, CD19, but negative for TdT and CD34. There was no expression of light chains and CD20, compatible for pre-B ALL. Secondly, complex structural and numerical abnormalities including a reciprocal t(8;14) was noted. Further studies will be needed to elucidate the underlying pathogenesis and clinical characteristics of these rare cases.

Keyword: Burkitt Lymphoma/Leukemia, Precursor B Lymphoblastic Leukemia/Lymphoma

PP-048

Chymeric antigen receptor (CAR) T-cell immunotherapy : A new promising therapy for patients with relapsed B-cell acute lymphoblastic leukemia

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Background: Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children. Usually, ALL affect B cells, one of the cells In immune system. Relapsed B-cell acute lymphoblastic leukemia (B-ALL) remain significant causes of cancer-associated morbidity and mortality for children. The infusion of genetically engineered, autologous chimeric antigen receptor (CAR) T cells directed against CD19 expressed by normal and malignant B cells represents a novel approach to cancer therapy. This study aim to systematically review the current evidence of CAR T-cell therapies in relapsed B-ALL.

Methods: This literature review study uses online databases such as Science Direct, PubMed, and Google Scholar to find scientific articles related to immunotherapy for B-cell acute lymphoblastic leukemia in last seven years. The keywords are CAR T-cell immunotherapy and relapsed B-cell ALL. The data are reviewed systematically.

Result: Scientific articles about CAR T-cell immunotherapy in B-ALL were collected. CD19-directed CAR-T cells have recently been approved by the FDA for use in children and young adults with ALL and in adults with diffuse large B cell lymphoma (DLBCL) in the relapsed/refractory setting. CD22-directed CAR-T cells have shown efficacy against leukemia as well in a recent clinical trial, representing the first alternative CAR target to approach comparable efficacy to CD19 CAR-T cells. Some patients with life-threatening CD19 CAR T-cell induced sequelae have received anti-cytokine receptor antibody treatment to diminish CRS symptoms and/or corticosteroids to terminate CAR T-cell proliferation. Remarkably, 67-90% of children and adults with B-ALL treated with CD19 CAR T cells in these trials have achieved morphologic leukemia remission with many patients also in molecular remission.

Conclusions: The results demonstrated CAR-T cells are an effective, and rapidly evolving therapy for patients with relapsed B cell malignancies. More cases are needed to explore these beneficial effects.

Keyword: CAR T-cell, Immunotherapy, B Cell, Acute Lymphoblastic Leukemia

PP-049

Anti-leukemic effect of ajwain oil against DMBA induced leukemic rat model: Possible mechanism of action

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Background: Leukemia is a malignant blood disease induced by the over-generation of huge number of immature blood cells that enter the peripheral blood. Leukemia considered as the 9th most common cancer in men and 12th rank in women. Its etiologic factors such as environmental, genetic alteration, viruses, alcohol consumption, immune deficiency and chemicals. Available treatment for the disease are chemotherapy, allogeneic cell transplantation and radiation therapy with side effects. Due to side effect associated with the treatment, medicinal herbs treatment having the more attraction to treat the leukemia. The aim of the current study to scrutinize the antileukemic effect of ajwain oil against the 7, 12-dimethyl benza[a]anthracene (DMBA) induced leukemia in rats and explore the possible mechanism of action.

Methods: DMBA was used for the induction of leukemia in experimental 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.

Result: Ajwoin oil treated rats showed the increased body weight as compared to other groups. Moreover, ajwoin oil decreased the blasts (56%) in leukemic rats. Its also altered the hemotological parameters such as WBC (35%), lymphocytes (43%), neutrophils (41%), monocytes (38%), esnophills (46%), basophils (42%) and monocytes (54%), respectively. Ajwoin oil 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 of ajwoin oil treated group rats as compared to other groups.

Conclusions: The current study, showed the anti-carcinogenic effect of ajwain oil and highlights the possibility of its use in leukemia to minimize the side effect of the usual therapy.

Keyword: Leukemia, Hemotological, Cytotoxicity, DMBA, Sphingosine-1-Phosphate Receptor-1

PP-050

Chemo-protective effect of lemon oil against the benzene induced leukemia via regulation of growth factors and inflammatory mediators

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Background: The incidence of deadly diseases world widely is alarming and one of the deadliest disease currently killed to animal and human is cancer. Leukaemia has been characterized as a cancer of bone marrow or blood affecting haemopoietic stem cells, described by uncontrolled accumulation and proliferation of malignant leukocytes in peripheral blood and bone marrow usually results from mutation in DNA. The aim of the current investigation to explore the chemoprotective and antileukemic effect of lemon oil on benzene induced leukemia bearing rats.

Methods: Intravenous injection of benzene (0.2 ml) was used for the induction of leukemia. The rats were divided into different groups and received the different dose of lemon oil and cyclophosphamide. Body wright, hematological, antioxidant and pro-inflammatory parameters were estimated, respectively. Spleen and liver tissues were macroscopically and microscopically evaluated.

Result: Lemon oil significantly modulated the hematological parameters such as WBC (43%), lymphocytes (48%), neutrophils (40%), monocytes (35%), eosinophils (53%), basophils (36%) and monocytes (45%), respectively. Lemon oil also increased the level of GSH (43%), SOD (34%), CAT (47%) and reduced the MDA (65%) level. The inflammatory mediators like TNFα (34%), iNOS (54%), IL-1β (46%), IL-6 (54%), GM-CSF (44%) and VEGF (43%), respectively. Macroscopically, benzene induced group showed the enlargement of spleen and liver tissue and lemon oil treated group reduced the enlargement of spleen and liver tissue.

Conclusions: The current study suggested potential effect of lemon oil via reverse the leukaemic effect induced by benzene in the experimental rats via inflammatory mechanism.

Keyword: Chemoprotective, Lemon Oil, Leukemia, Inflammation, Hematological Parameter

PP-051

Detection of complex variant t(9;22) chromosome translocations in newly diagnosed cases of chronic myeloid leukaemia. A single institute experience

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Background: Chronic myeloid leukemia (CML) is a stem cell clonal disease characterized by the acquisition of a fusion protein, BCR-ABL1 oncogene, which leads to uncontrolled proliferation of myeloid elements in all stages of differentiation. The fusion gene is the result

of reciprocal translocation (9;22)(q34;q11) known as Philadelphia (Ph) chromosome. However, a small proportion of patients with CML have simple or complex variants of this translocation, involving various breakpoints in addition to 9q34 and 22q11.

Methods: This study was conducted for a time period of 05 years from 2012 to 2017 in the department of Oncology/ Hematology of Civil hospital, Karachi. Between April 2012 and April 2017, 88 CML patients were diagnosed in our Department. Informed consent was obtained from the patient in accordance with the Declaration of Helsinki. Diagnosis was done on the morphological basis and BCR-ABL mutation by PCR/FISH. Conventional cytogenetic analysis was performed on unstimulated 24-hour culture of a bone marrow (BM) specimen. The cells were cultured and processed by conventional methods, and the chromosomes were stained with trypsin-Giemsa banding (GTG-banding).

Result: A total of 88 patients were Philadelphia-positive CML, out of which 53(60.2%) were males & 35(39.7%) were females. Mean age was 48 yrs±11.43. Out of them, the group of 9 (10.2%) patients with complex cytogenetics were consisted of 5 females and 4 males, ranging in age at diagnosis from 32 to 66 yrs. All the patients were in chronic phase at presentation. Cytogenetic analysis by G-banding revealed the presence of 9 reciprocal three-way variant translocations of the classical t(9;22)(q34;q11). The chromosome breakpoints involved in these complex variant translocations were the following: 1p13, 1q21, 1p22, 2q31, 3q21, 3p21, 11q13, 15q24 and Xp11.2.

Conclusions: In our study 09 patients had complex variants of t(9;22). The presence of these complex variants at diagnosis and during the TKI treatment may announce treatment failure and/ or transformation to advanced stage (accelerated or blast). Early identification of these abnormalities may help in choosing therapy modalities.

Keyword: Chronic Myeloid Leukaemia, Complex Variant Translocations, Philadelphia Chromosome, BCR-ABL

PP-052

Optimal time points for BCR-ABL1 tyrosine kinase domain mutation analysis based on European LeukemiaNet recommendations in chronic myeloid leukemia

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Background: This study aimed to evaluate appropriate time points for mutation analysis by analyzing the mutation BCR-ABL1 via Sanger sequencing (SS) in 605 imatinib-treated patients with chronic-phase chronic myeloid leukemia.

Methods: Mutation frequencies were assessed upon achievement of 16 landmark responses of European LeukemiaNet and 2 additional responses including a complete hematologic response (CHR) at 3 months and a complete cytogenetic response (CCyR) at 12 months with the results of SS, using 961 peripheral blood samples.

Result: After 12 months of imatinib treatment, 28 (4.6%) patients had 33 mutations including 23 (69.7%) highly resistant T315I and P-loop mutations. Sequencing data from 650 samples were compared to cytogenetic responses. The mutation frequencies of optimal, warning, and failure groups were 0.5% (2/430), 1.8% (2/110), and 19.1% (21/110), respectively. The molecular response was assessed using 956 samples, and the mutation frequencies were 0.7% (3/425), 3.4% (12/358), and 7.6% (14/173) for the optimal, warning, and failure groups, respectively. For 2 additional responses, the mutation frequencies in patients with CHR at 3 months and with CCyR at 12 months were 0% (0/160) and 1.7% (4/242), respectively. Overall, via response-mutation matching analysis, frequent mutations were detected at 3 month-cytogenetic failure (25.0%), 12 month-cytogenetic failure (23.2%), and 6 month-cytogenetic failure (10.5%).

Conclusions: Irrespective of mutation frequency, failure of achievement of a cytogenetic response should be proceeded by appropriate mutation analysis.

Keyword: Chronic Myeloid Leukemia, Imatinib, Mutation, Sanger Sequencing, Resistance

PP-053

A retrospective study of paediatric chronic myeloid leukemia from a tertiary cancer centre, India

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Background: Chronic Myeloid Leukemia(CML) is rare in children and constitutes 2% of all leukemias. There is a paucity of data on pediatric CML from India. We present our institute experience of treating pediatric CML over a period of 16 years.

Methods: Patients aged between six months and eighteen years diagnosed with CML from 2000-2016 were analyzed retrospectively to look at the demographic features, treatment characteristics and the survival outcomes. Event free survival (EFS) and Overall survival (OS) were calculated using the Kaplan-Meier method and the factors were compared using the log-rank test.

Result: During the study period 72 patients were diagnosed with CML, of which 39 (55%) were males and 33 (45 %) were females. Median age at presentation was 13 years. Most common stage of presentation was the Chronic Phase (CP) with 62 (86%) patients followed by Accelerated phase (AP) and Blast Crisis (BC) with 7 (10%) and 3 (4%) patients respectively. Median follow-up duration was 70.4 months (4.8 months- 221 months). The 6-year EFS and OS were 52 % and 76% respectively. Complete hematological Response (CHR), Complete Cytogenetic Response (CCyR) and Major Molecular Response (MMR) was achieved in 60 (90%), 44 (66%) and 38 (57%) patients respectively. On comparing the patients who received chemotherapy (hydroxyurea/ Busulfan) to those who received Imatinib there was a significant improvement in EFS and OS, from 27% and 36 % to 57% and 83% respectively (P value = 0.04 and 0.000 respectively) in patients treated with Imatinib. Similarly, there was significant improvement in CHR, CCyR and MMR rates from 46%, 9% and 9% to 98%, 77% and 66% respectively. Primary Imatinib resistance was observed in 3 (4.4 %) patients. Toxicities of Imatinib observed were polyarthralgia in 12 (18%) patients, nausea/ vomiting/ diarrhea in 3 (4.5%), hematological toxicity in 6 (9%), skin rash in 4 (6%) and facial puffiness/ peripheral edema in 5 (6%) patients. Allogeneic Stem cell transplant (SCT) was done in one patient

Conclusions: Outcomes in Pediatric CML are comparable to that of Adults. Imatinib is well tolerated in children. Necessity of SCT has drastically decreased after the arrival of Tyrosine Kinase Inhibitors (TKI). More data is required to know the pharmacokinetics and the toxicity profile of the second line TKIs like Nilotinib and Dasatinib in children.

Keyword: Paediatric, Chronic, Myeloid, Leukemia, Demographics, Imatinib

Characteristics at diagnosis of CML patients evaluated at Baseline

Characteristics	Number of Patients	Percentage of Patients
Haemoglobin		
>10gm/dl	23	32
<10gm/dl	49	68
Total Leucocyte Count		
< 0.5 lakh	12	16.7
0.5- 1 lakh	7	9.7
1-2 lakh	32	44.4
>2 lakh	21	29.2
Platelet Count		
<0.5lakh	3	4.2
0.5-1lakh	1	1.4
1-3lakh	12	16.7
>3lakh	56	77.8
Spleen		
<10cm	29	40.3
>10cm	33	45.8
Sokal Score		
Low Risk	26	36
Intermediate Risk	28	39
High Risk	9	12.5
Missing Data	9	12.5
Lactate Dehydrogenase		
Normal	1	1.4
1-3times ULN	7	9.7
>3times ULN	29	40.3
Missing Data	35	48.6
Albumin		
<3.5 mg/dl	8	11.1
>3.5mg/dl	11	15.3
Missing Data	53	73.6

ULN-Upper Limit Of Normal

PP-054

Population pharmacokinetic and dose-response analyses of dasatinib to support dosage in Asian pediatric patients with chronic myeloid leukemia

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Background: Dasatinib is a second-generation tyrosine kinase inhibitor (TKI) approved for the treatment of pediatric patients with Ph+ chronic myeloid leukemia (CML) in chronic phase in the

US, EU, and Korea. Dasatinib has been evaluated in a phase 2 study (CA180-226/NCT00777036) in pediatric patients with CML chronic phase (CP), accelerated phase (AP), and blastic phase (BP) as a 60 mg/m^2 tablet once daily and 72 mg/m^2 powder for oral suspension (PFOS) once daily. Dasatinib was found to be safe and effective for the treatment of pediatric CML-CP. The objectives of current analyses were to characterize the pharmacokinetics (PK) of dasatinib with weight (WT)-tiered tablet and PFOS doses and to characterize dose-response (D-R) relationship between dasatinib treatment and efficacy, in Asian and non-Asian pediatric patients with CML.

Methods: A population PK (PPK) model was developed by adapting a previously developed pediatric PPK model to evaluate the effect of race on the PK of dasatinib using concentrations from 104 pediatric patients with leukemia and solid tumors across 3 clinical studies (NCT00306202, NCT00316953, and NCT00777036). The following covariate effects were evaluated in the PPK model: effect of WT on apparent clearance (CL/F) and apparent central volume of distribution (Vc/F), effect of formulation (PFOS versus tablet) on relative bioavailability (FR), and effect of Asian race on CL/F and Vc/F. The D-R analysis was performed with respect to an efficacy endpoint of time to achieve major molecular response (MMR), with the data available from 84 pediatric patients with CML-CP (NCT00777036). The D-R relationship was described using a Cox proportional hazard (CPH) model by including following covariates of interest: cohort (72 mg/m^2 PFOS versus 60 mg/m^2 tablet), age, WT, baseline BCR-ABL transcript level, and Asian race.

Result: A two-compartment model with first-order absorption and linear elimination well characterized dasatinib PK in pediatric patients. Dasatinib CL/F and Vc/F increased with increasing WT in pediatric patients. Asian race was not a significant covariate of CL/F and Vc/F, although Vc/F was modestly lower in Asian. FR of PFOS in pediatric patients was 30 to 40% lower relative to that of the tablet. Model-based simulation showed that proposed WT-tiered doses produced uniform exposures across the WT tiers. Steady-state exposures were similar between Asian and non-Asian with the proposed WT-tiered doses in the label. The D-R analysis showed that time to achieve MMR was longer in patients on PFOS versus tablet and shorter in Asian patients versus non-Asian patients, although the difference was not statistically significant.

Conclusions: The results from the PPK and D-R analyses suggest that no dose adjustment of dasatinib is required for Asian pediatric patients with CML-CP, and support the current dosing regimens approved in Korea.

Keyword: Pharmacometrics, CML, Pediatrics, Asian, Population Pharmacokinetics, Dose-Response

PP-055

A study of treatment-free remission evaluation in real-world chronic myeloid leukemia; Estimated cost-effectiveness analysis (ASTER-C)

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Background: Chronic myeloid leukemia (CML) needs taking life-long tyrosine kinase inhibitor (TKI) which arises serious toxicities such as peripheral occlusive disease and pulmonary hypertension as well as low-grade toxicities. Treatment-free remission (TFR) can make almost half CML patients achieving deep molecular response (DMR) free from TKIs. We investigated total costs of each TKI considering TFR in Korea.

Methods: Total numbers of annual newly-diagnosed CML patients were adopted from national cancer registration database. TFR was defined as achieving MR4.5 and lasting for 3 years. The proportion of MR4.5 was adopted from phase III studies of imatinib (IM), nilotinib (NIL) and dasatinib (DAS). TKI management followed life-long Markov model (Fig 1). Willingness to pay (WTP) was calculated for beneficial effects of patients who have achieved TFR and taking no TKIs as 2 times of gross domestic product per capita. Cost of progression was calculated based on the study by Jabbour et al. Patients older than 79y was not included in this study because TFR benefit is not considered in this age group. Duration of treatment and TFR was calculated separately according to age groups. We assumed that taking KTI lasted life-long until median life expectancy in Korea (80.87 years).

Result: Newly diagnosed annual CML patients were 443; 9 in age 0-14, 96 in age 15-34, 125 in age 35-49, 124 in age 50-64 and 89 in age 65-79. The theoretical number of patients who have sustainable TFR was 73 in IM, 93 in DAS and 119 in NIL. TFR as person-year in IM, DAS and NIL were 1940, 2521 and 3247, respectively. TFR (person-year) was very different according to age groups because of different incidence rates; 99.9 in age 0-14, 788.7 in age 15-34, 666.1 in age 35-49, 353.8 in age 50-64 and 33.7 in age 65-79 when IM was applied. TFR (person-year) were 128.2 in age 0-14, 1014.5 in age 15-34, 861.6 in age 35-49, 464.1 in age 50-64 and 52.8 in age 65-79 when DAS was applied. TFR (person-year) were 164.9 in age 0-14, 1305.6 in age 15-34, 1109.4 in age 35-49, 598.3 in age 50-64 and 69.0 in age 65-79 when NIL was applied. WTP according to

TFR was 121.3 in IM, 157.5 in DAS and 202.8 billion KW in NIL. Costs by progression were 32.8 in IM, 26.8 in DAS and 22.3 billion KW in NIL. Life-long maintenance costs for patients who did not achieved sustainable TFR without progression were 128.7 in IM, 294.2 in DAS and 327.1 billion KW in NIL. Net costs considering TFR and progression were 40.2 in IM, 163.5 in DAS and 146.6 billion KW in NIL.

Conclusions: Nilotinib was superior to other TKIs in terms of TFR benefit and progression cost according to our life-time Markov model. However, the net cost was lowest in IM. This analysis is limited by our assumption that MR4.5 is achieved by first 5 year and there is no further additional achievement of MR4.5 because of limitation of MR4.5 rates in each TKI trial.

Keyword: Chronic Myeloid Leukemia, Treatment-Free Remission, Cost-Effectiveness

PP-056

Highly sensitive detection of BCR-ABL in clinical samples by QXDx BCR-ABL %IS digital droplet PCR

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Background: The current therapeutic goal in chronic myeloid leukemia (CML) is treatment-free remission. To detect minimal residual disease (MRD), the demand for highly sensitive and accurate molecular monitoring techniques, such as droplet digital PCR (ddPCR), has increased consequently. The aim of this study is to determine the performance of standardized QXDx BCR-ABL %IS Kit (BioRad, Hercules, CA, USA), which uses ddPCR, for the detection of MRD in clinical samples in comparison with real-time PCR.

Methods: A total of 22 clinical samples were tested using the QXDx BCR-ABL %IS Kit (QXDx ddPCR Kit). All ddPCR tests were performed in duplicate according to the manufacturer's instructions. Calibration and quality control were performed for every batch. An Automated Droplet Generator, CFX96 thermal cycler, and QX200 Droplet Reader (BioRad) were used for ddPCR and interpretation. The results were compared with those obtained using the real-time PCR-based BCR-ABL Mbcr IS-MMR DX Kit (Ipsogen, Lyon, France).

Result: The QXDx ddPCR Kit was able to detect and quantify major BCR-ABL up to a molecular response of MR4.5 and real-time BCR-ABL Mbcr IS-MMR DX achieved MR3.5 in analyses of clinical samples. The assay ranges were MR1.0 to MR4.5 (10% to 0.0032% IS) for the QXDx ddPCR Kit and MR1.0 to MR3.5 (10% to 0.032% IS). Imprecision for the QXDx ddPCR Kit based on twelve repeat tests of a quality control material was 2.4% CV at the level of MR4.0. In a comparison study using patient samples showing MR1.0 to MR4.0 (10% to 0.01% IS), very strong correlation was obtained (r = 0.86).

Conclusions: This is the first implementation of the QXDx ddPCR Kit to clinical samples. The QXDx ddPCR Kit had better analytical sensitivity than that of real-time RT PCR assays, suggesting that it is a promising method MRD monitoring in patients with CML and for the informed selection of candidates for discontinuing tyrosine kinase inhibitors.

Keyword: BCR-ABL, Digital Droplet PCR, Chronic Myeloid Leukemia, Analytical Sensitivity, Minimal Residual Disease

PP-057

Survival outcomes with addition of methotrexate and cytarabine onto standard treatment for diffused large B-cell lymphoma (DLBCL): 3-year follow-up

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Background: Diffuse large B-cell lymphoma (DLBCL) is a heterogenous group of diseases with various outcomes depending on the clinical and biological features. Optimal induction therapy for high-risk diffuse large B-cell lymphoma (DLBCL) is still unclear, and clinical trials needed to evaluate alternative approaches. Objective: This study aimed to evaluate survival outcomes of induction therapy with addition of high dose methotrexate and cytarabine onto standard treatment RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) for 62 DLBCL patients.

Methods: Kaplan-Meier method for survival outcomes and log-rank test were used to analyze factors for univariate analysis.

Result: 38 patients received RCHOP/CHOP plus methotrexate or cytarabine or both (RCHOP/CHOP+MA/M/A) while 24 patients received only RCHOP/CHOP regimen. Mean age at diagnosis for enrolled patients was 50 ± 13.4 years (range, 18 – 77 years). Females seemed to have more treatment with RCHOP/CHOP+MA/M/A compared to males (48.5%). Significant difference found in overall survival (OS) comparing patients manifested with B symptoms and patients without B symptoms (p=0.035). With respect to initial response of frontline therapy, patients who achieved complete remission was associated with significantly improved OS (p= 0.0003). Median duration of follow-up was 37.5 months (range, 2-60 months). The 3-year OS was 71% with 3-year progression free survival (PFS) 67%. Overall survival and progression free survival rates of 38 patients received RCHOP/CHOP+MA/M/A showed significantly better compare to RCHOP/CHOP group (n=24) with p=0.04 and p=0.03, respectively. Interestingly, there is a trend seemingly better outcome in female cohort. Among 62 DLBCL patients who received ≥ 4 cycles chemotherapy, 2 (3.2%) experienced treatment-related mortality (TRM).

Conclusions: Addition of methotrexate and cytarabine onto RCHOP/CHOP regimen resulted in improved 3-year OS and PFS of DLBCL patients. TRM rate of RCHOP/CHOP+MA/M/A was comparable with standard treatment indicated that supportive management was adequate and appropriate.

Keyword: DLBCL, Survival Outcome, Methotrexate, Cytarabine, Standard Treatment, Induction Therapy

PP-058

High serum glucose during chemotherapy is associated with inferior survival outcome in patients with non-Hodgkin lymphoma

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Background: Hyperglycemia contributes to various health problems including infectious disease and cancer development. Lymphoma treatments involve high-doses of steroids and therefore include the risk of elevated blood glucose levels. This study was aimed to evaluate whether hyperglycemia during chemotherapy influences the prognosis of patients with non-Hodgkin lymphoma.

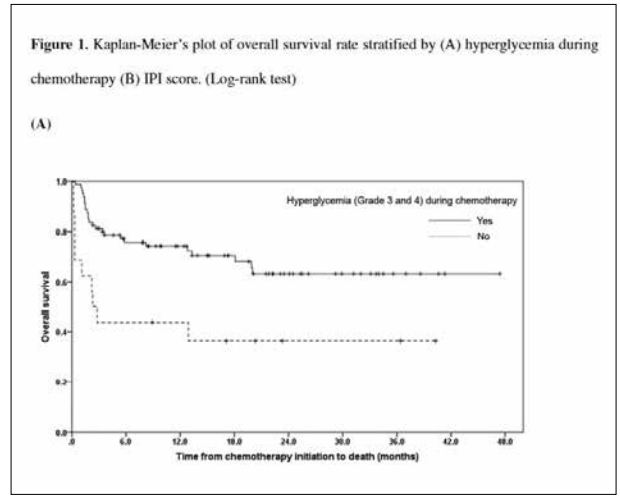
Methods: We retrospectively reviewed the medical records of all patients with non-Hodgkin lymphoma who were treated with a type of chemotherapy containing a corticosteroid at Chungbuk National University Hospital from January of 2014 to December of 2017. Severe hyperglycemia was defined as Clinical terminology criteria for adverse events categories greater than or equal to 3 (≥3; fasting glucose >250 mg/dL).

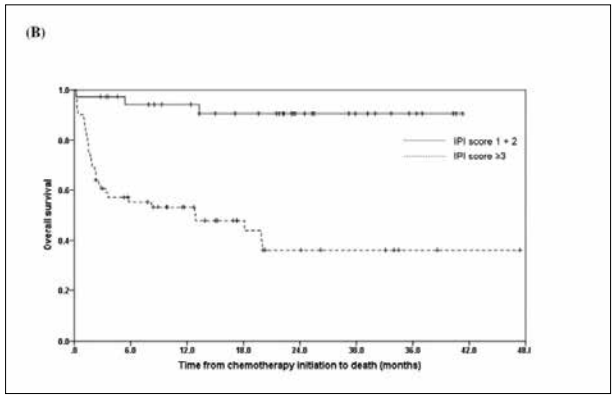
Result: A total of ninety-seven patients were reviewed. Median age was 65.7 years, and 74.2% were diagnosed with diffuse large-B cell lymphoma. Seventeen patients (17.5%) had type 2 diabetes mellitus (DM). During chemotherapy, 22 patients (22.6%) had grade 3 or higher hyperglycemia. The risk factors for hyperglycemia were obesity and underlying type 2 DM. There was no relationship between hyperglycemia and delayed treatment, reduced doses of chemotherapeutic agents, or the incidence of infectious complications. However, in a multivariate analysis of overall survival, hyperglycemia (hazard ratio 2.9, P = 0.004) was a significant risk factor for mortality, similar to high international prognostic index (IPI) score (hazard ratio 2.2, p = 0.019). On the other hand, DM itself was not directly related to overall survival. The one-year survival rate of patients with hyperglycemia tended to be lower than those without hyperglycemia. (37.5% vs 67.4%, P = 0.089)

Conclusions: The occurrence of hyperglycemia during chemotherapy is associated with low survival rates in lymphoma patients. In patients with diabetes, blood glucose levels should be carefully controlled during lymphoma treatment.

Keyword: Non-Hodgkin Lymphoma, Hyperglycemia, Steroid, Chemotherapy, Survival

Figure 1. Kaplan-Meier's plot of overall survival rate stratified by (A) hyperglycemia during chemotherapy (B) IPI score. (Log-rank test)





PP-059

Follicular lymphoma with leukemic presentation

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Background: Follicular lymphoma (FL) is a malignant B-cell lymphoma of follicular center B-cell origin, usually has at least a partially follicular pattern. FL frequently involves lymph nodes, but also spleen, bone marrow, and peripheral blood and Waldeyer's ring. FL with leukemic presentation is uncommon and has not been well characterized from Taiwan yet.

Methods: We retrospectively searched for cases of FL with leukemic presentation in our institution from January 2000 to October 2018. We characterized the leukemic cell by flow cytometric immunophenotyping and biopsies by immunohistochemistry and fluorescence in situ hybridization (FISH). Clinical history was reviewed.

Result: During this period, there were a total of 210 cases of FL. Among these, 13 (6.2%) cases presented with leukemic phase. All these cases were de novo neoplasms, without a prior history of lymphoma. There were 7 males and 6 females with a median age of 52 (range, 34-75). The median leukemic cell count was 11.40 x 103/μL (range, 6.08-154.6 x 103/μL). In one case, the leukemic cells were large with vesicular nuclei and open chromatin, while that in the remaining 12 cases the leukemic cells were small with irregular nuclear contours and condensed chromatin. All cases had concurrent tumors: one had only marrow disease, the remaining 12 patients had involvement of lymph node (n=11), bone marrow (n=11), spleen (n=8), nasopharynx (n=2), and other rare sites. Excluding one case with incomplete data, the FLIPI scores were 1 (n=2), 2 (n=2), 3 (n=3), 4 (n=4), and 5 (n=1), respectively. Histologically, the concurrent FL were mostly low-grade (n=12; 92%), with the remaining case with grade 3A disease. Interestingly, the case with large leukemic cells (Case no. 12) had a concurrent primary splenic low-grade FL and a double-hit (rearranged BCL2 and MYC genes) large B-cell lymphoma, of germinal center B-cell phenotype and also a double-expresser (positive for both bcl-2 and myc proteins), in the marrow. CD10 was expressed in the leukemic cells in 38% (5/13) cases by flow cytometry and in 77% (10/13) cases in tumor tissues (p= 0.0471, Chi-squared test). Reciprocal translocation of IGH/BCL2 was identified in 85% (11/13) cases. Eight patients were treated with R-COP, 3 with R-CHOP, and 1 with rituximab alone. In a median follow-up time of 32 months (range, 3-129), 6 patients were in complete remission, 4 alive with disease, 2 died of disease, and one died of dengue fever after the third course of chemotherapy. The 2- and 5-year survival rates were at 100% (7/7) and 83% (5/6), respectively.

Conclusions: In this study, we characterized the clinicopathological, immunophenotypical, and genetic features of a series of de novo FL with leukemic presentation in Taiwan. All patients had concurrent nodal and/or tissue tumors, without any cases with leukemic phase alone, which might suggest that these patients sought medical help too late. The lower CD10 expression rate of the leukemic cells as compared to their tissue counterpart might be due to different epitopes for detection in flow cytometry and immunohistochemistry. Alternatively, loss of CD10 expression might play a role in the pathogenesis of leukemic change. The rate of IGH/BCL2 reciprocal translocation was comparable to nodal FL. The clinical course of FL with leukemic presentation could be aggressive, but a significant proportion of the patients obtained complete remission with chemotherapy. Studies on larger number of patients are warranted for a better understanding of the impact of leukemic change in patients with FL.

Keyword: B-cell Leukemia, Follicular Lymphoma, Leukemic Change, Leukemic Phase, Lymphocytosis

PP-060

Milk- alkali syndrome with pulmonary calcification in diffused large B cell lymphoma: A case report

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Background: Historically, the milk-alkali syndrome (MAS) developed as an adverse reaction of treatment for peptic ulcer disease. MAS consists of a triad of hypercalcemia, metabolic alkalosis and variable degrees of renal insufficiency. The complications associated with MAS are metastatic calcifications, pancreatitis and reversible cardiac conduction abnormalities. But all including clinical and subclinical signs and symptoms are paraneoplastic syndrome and its sequences

Methods: Descriptive study: Case report

Result: Clinically, the patient without history of using herbal drugs presented in a cute hypercalcemia crisis associated with low parathyroid hormone, polyuria, dyspnea and fever. Subclinically, hypochlorid metabolic alkalosis in aterial blood gas and pre renal failure were our initial concerns. Serum phosphorus value was normal . There was not osteolytic bone involvement in bone X-ray. Pulmonary computer tomography showed diffused ground – glass opacity. 99 m- methyl diphosphonate (99mTc-MDP) single photon emission computed tomography (SPECT) bone scan showed increased tracer uptake in lung, as same as in bone. There is not any biological causes detected. Pulmonary calcification is result of thoracoscopic lung biopsy . Contrast to hypercalcemia's rapid response to hydration and steroid, the pulmonary damage could not improve.

Conclusions: MAS is rare in pediatric oncology. This case provided us a clust of signs and symptoms which are different from common syndromes in childhood cancer.

Keyword: Milk-Alkali Syndrome, Mas, Hypercalcemia, Metabolic Alkalosis, Pulmonary Calcification

PP-061

Asian variant of intravascular large B-cell lymphoma

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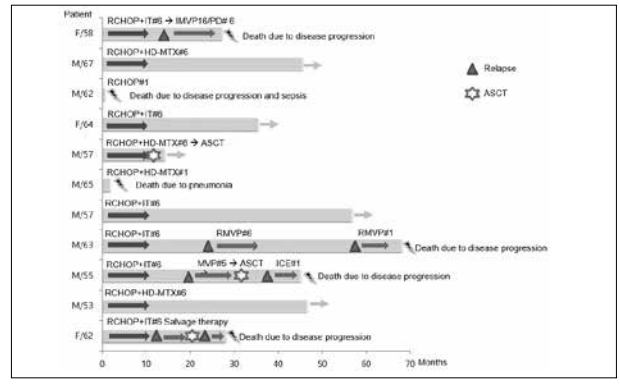
Background: There are limited data about the influence of the central nervous system (CNS) involvement on the prognosis for patients with the Asian variant of intravascular large B-cell lymphoma (IVLBCL).

Methods: We analyzed 46 patients who were diagnosed with IVLBCL between 2001 and 2018. All patients were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

Result: CNS involvement was diagnosed by cerebrospinal fluid analysis (n = 6) and brain imaging (n = 5) in 11 patients at diagnosis, and four cases with CNS relapse were found. Thus, 15 patients had CNS involvement (15/46, 33%). The clinical characteristics were not different between patients with and without CNS involvement, but all patients with CNS involvement belonged to the high-risk group of CNS-International Prognostic Index (IPI). Thirty-one patients achieved a complete response (67%, 31/46) whereas eight patients showed disease progression and six patients died after the first or second cycle of R-CHOP. CNS-directed therapy such as high-dose methotrexate was combined with R-CHOP for patients with CNS involvement, and five patients were alive without relapse. The median overall survival of all patients was 45.0 months, and overall survival was not different according to the involvement of CNS.

Conclusions: The treatment outcome of patients with the Asian variant of IVLBCL is still not satisfactory. The prediction of CNS involvement based on the clinical features including CNS-IPI score might not serve to identify patients at high risk of CNS involvement, either. Thus, more effective strategies for diagnosis and treatment should be developed.

Keyword: Intravascular B-cell Lymphoma, Asian Variant, Central Nervous System



PP-062

Clinical impact of prognostic nutritional index in diffuse large B cell lymphoma

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Background: We evaluated the association between the prognostic nutritional index (PNI) and the clinical features of diffuse large B cell lymphoma (DLBCL) and developed a novel prognostic model using a nomogram including the PNI and other biomarkers for cancer cachexia.

Methods: A total of 228 DLBCL patients treated with first-line R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) were retrospectively reviewed. PNI was calculated as 10 × serum levels of albumin (g/dL) + 0.005 × absolute lymphocyte count (/mm3). Patients were categorized into low- and high-PNI groups based on a cut-off value of 40. The nomogram for predicting overall survival (OS) was constructed using a Cox regression model.

Result: PNI was positively correlated with skeletal muscle index, body mass index, and serum levels of albumin. The low-PNI group had a lower complete response rate (60.3% vs. 87.6%), increased treatment-related toxicity, and more frequent treatment discontinuation (43.5% vs. 8.8%) than the high-PNI group. The median OS was shorter in the low-PNI group than the high-PNI group (15.6 months vs. not reached; $p < 0.001$). Multivariate Cox regression analyses showed that PNI, sarcopenia, and the international prognostic index (IPI) were independent prognostic factors for OS. The nomogram developed using this regression model showed excellent discriminatory ability for predicting OS (c-index, 0.80) compared to the IPI alone (c-index, 0.75). Low PNI was associated with adverse clinical features of DLBCL.

Conclusions: The proposed nomogram supports the clinical impact of cachexia on survival and may contribute to individualized therapy in DLBCL.

Keyword: Lymphoma, Cachexia, Nutrition Assessment, Sarcopenia, Serum Albumin, Lymphocyte Count

PP-063

Clinical characteristics and outcome of acquired immune deficiency syndrome (AIDS) related lymphomas (ARL) in hospital Ampang

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Background: Patients with Human Immunodefiency Virus (HIV) have a higher risk of developing Non-Hodgkin lymphomas (NHL). The World Health Organization (WHO) recognises NHL as an Acquired Immune Deficiency Syndrome (AIDS) defining illness, known as AIDS related lymphomas (ARL). The clinical manifestations of ARL are more advanced in stage, with B symptoms, and more likely to involve extra nodal and unusual sites. Outcome of ARL has improved during recent years due to the introduction of combination anti-retroviral therapy (cART). Early initiation of cART has reduced the risk of developing ARL and also improves the complete remission (CR) rates and overall survival (OS) rates in those treated with chemotherapy and autologous stem cell transplant.

Methods: This is a retrospective analytical study. We included patients with HIV and NHL, treated from January 2010 to December 2017. Data were obtained through the electronic medical records and database, including demographic data, clinical and laboratory characteristics, complications, treatment and outcome, were analysed.

Result: 45 patients were analysed. The mean age at diagnosis was 42 years old and 91% are males (n=41). 75% of patients (n=34) have advanced disease. Diffuse Large B Cell Lymphoma (DLBCL) is the most common subtype (67%, n=30). Most of them were on combination anti-retroviral therapy cART (87%, n=39) and given chemotherapy (83%, n=36), but less than half achieve an overall response rate (ORR) of at least a partial response (39%, n=14). The median overall survival (OS) is 6 months.

Conclusions: The outcome of our patients with ARL is poor despite most of them being initiated on cART. The advance stage of presentation of ARL contributes to the poorer outcome compared to their HIV negative counterparts. With the current emphasis on early initiation of CART upon diagnosis of HIV regardless of CD4 count, it remains to be seen if that would further improve the outcome of these patients.

Keyword: Human Immunodefiency Virus (HIV), Non-Hodgkin Lymphomas (NHL), AIDS Related Lymphomas (ARL)

Table 1. Baseline characteristics

Characteristics	N (%)
Total	45 (100%)
Age (years)	
< 40	17 (38%)
≥ 40	28 (62%)
SEX	
Male	41 (91%)
Female	4 (9%)
PS (ECOG)	
>2	21 (46%)
0-2	24 (53%)
LYMPHOMA SUBTYPE	
Diffuse large B cell (DLBCL)	30 (67%)
Burkitts Lymphoma	8 (18%)
Primary CNS Lymphoma	2 (4%)
Plasmablastic Lymphoma	2 (4%)
ALCL	1 (2%)
MALT	1 (2%)
Castleman's disease	1 (2%)
ADVANCE STAGE	
>stage IIB	28 (64%)
<stage IIA	16 (36%)
Bulky disease (>7cm)	20 (44%)
CHEMOTHERAPY REGIME	
MTX based	11 (24%)
EPOCH	4 (9%)
CHOP	20 (44%)
No treatment	9 (20%)
Prephase treatment only	1 (2%)
CD 4 COUNT	
< 50	13 (29%)
50-199	14 (31%)
> 200	15 (33%)
Unknown	3 (7%)
Best Response (For treated patients, n=36)	
Complete response (CR)	11 (31%)
Partial response (PR)	3 (8%)
Refractory	22 (61%)

PP-064

Necropotosis was restored in chronic lymphocytic leukemia by inhibiting LTB-NF-KB-LEF1 pathway

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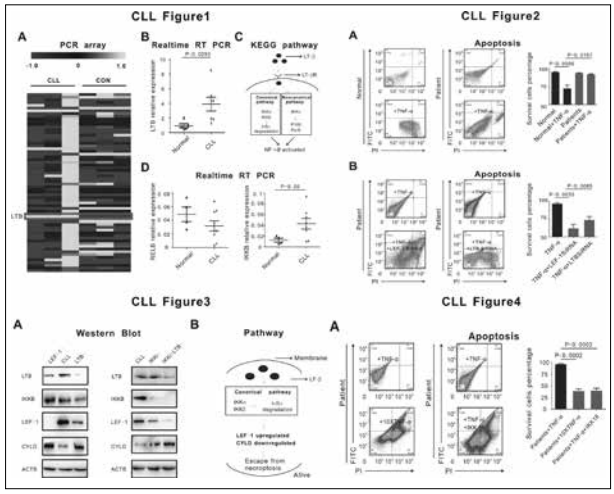
Background: Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in western countries. Although CLL develops relatively slow, it is very difficult to be completely cured. Small B lymphocytes progressively accumulate in CLL, which is largely attributed to defective apoptosis. A cell may die through apoptosis or necrosis pathway, but when cells are in apoptotic-deficient conditions, necroptosis acts as the main cell death program. We have demonstrated that necroptosis was blocked in CLL cells and necroptosis induced by tumor necrosis factors alpha (TNF-α) was inhibited by LEF1. However, it is difficult to find drugs specifically targeting LEF1. Lymphotoxin-β (LTB) is a member of TNF family protein which activates NF-κB pathway to induce these responses, and anti-tumor process or tumor genesis are also regulated by LTB. The relationship between CLL and LTB is still unclear.

Methods: Peripheral blood mononuclear cells (PBMCs) of patients diagnosed as CLL and normal volunteers were isolated from blood samples by Ficoll-isopaque centrifugation. Genes' expression was analyzed by real-time quantitative RT-PCR. SiRNAs was used to knockdown genes. Proteins' expression was measured by Western Blot. Cell apoptosis was assessed by the Annexin-V-PE kit. Differences of gene expression among groups were assessed by the Mann-Whitney U test. Experimental results were obtained from three separate experiments and determined using a t-test to compare variance.

Result: Cytokine and inflammatory reaction PCR arrays including 3 CLL patients and 3 normal volunteers. LTB ranked at the top of the gene list. LTB expressed much higher in patients and Realtime RT-PCR was used to validate it's differentiate expression between patients and normal volunteers. Expression of LTB was much higher in 9 CLL patients than 8 normal volunteers. LTB was involved in NF-κB pathway and it might be able to activate this pathway by either canonical or noncanonical way. The result showed that IKKB was significantly upregulated in CLL patients, whereas RelB only slightly downregulated comparing with volunteer controls, which indicated that LTB induce activation of NF-κB canonical pathway in CLL cells. Measured by flow cytometry, necroptosis was generated by 30ng/ml TNF-α and 20μM zVAD in B lymphocytes of normal volunteers. However, in CLL cells, necroptosis could not be induced in the same microenvironment. When LEF1 was knocked down, necroptosis of CLL cells were restored significantly. Interestingly, after knocking down LTB, necroptosis was also restored. Western Blot showed that when LEF1 was knocked down, expression of CYLD was increased, which indicated necroptosis restored with IKKβ did not change significantly. While knocking down LTB led to not only increased CYLD, but also decreased the expression of IKKB in CLL cells. Furthermore, IKK16 was used to block IKKβ of CLL cells. IKKB blocking did not regulate the expression of LTB, but expression of LEF1 decreased and CYLD increased significantly.

Conclusions: When large amount of TNF-α and NF-κB pathway inhibitors were added to CLL therapeutic regimens, CLL cells may restore necroptosis through LTB-NF-κB pathway. Under the assistance of these new strategies, these malignant cells might be killed more easily by chemotherapeutics.

Keyword: Chronic Lymphocytic Leukemia (CLL), LTB- NF-KB Pathway, Necroptosis



PP-065

Prevalence and immunophenotypic characteristics of monoclonal B-cell lymphocytosis in Korea

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Background: Monoclonal B- cell lymphocytosis (MBL), known as a precursor condition of chronic lymphocytic leukemia/small lymphocytic lymphoma, is defined by the presence of fewer than 5.0×10^9/L clonal B lymphocytes in the absence of clinical signs and symptoms of malignancy and infectious/autoimmune disease. Based on the immunophenotypic characteristic of clonal B lymphocytes, it was subdivided into three categories: (1) CLL-like MBL (CD5+CD20dim+CD23+slglow), (2) atypical CLL-like MBL (CD5+CD20bright+ CD23-) and (3) CD5-MBL. Most epidemiologic studies about MBL were performed targeting on limited geographical regions. To our knowledge, little is known about the prevalence of MBL in Asia. Therefore, we aimed to investigate the frequency and immunophenotypic characteristic of MBL in healthy subjects older than 40 years in Korea, using a multicolor flow cytometry assay.

Methods: This prospective study was performed with residual peripheral blood samples from healthy subjects older than 40 years who visited the Health Promotion Center, Samsung Medical Center, Seoul, Korea between March 2018 and November 2018. Inclusion criteria were: (1) Patients had no previous history of malignancy, autoimmune disease and infectious disease; (2) Samples had a lymphocytosis (>4.0×10^9/L) without possible causes. The selected samples were immunophenotyped using high-sensitive flow cytometry based on following 8-color monoclonal antibodies: CD45/CD10/CD19/CD20/CD23/kappa/lambda light chain.

Result: During the 9-month study period, total 65 EDTA peripheral blood samples from 39 males and 26 females were collected. Median age of the 65 healthy subjects was 55 years (range 40-81 years). The median cell count of absolute lymphocyte was 4.3 ×10^9/L (range 4.0 - 6.7 ×10^9/L). Among 65 healthy subjects, the overall MBL prevalence was 3.1% (2/65); one CLL-like MBL and atypical CLL-like MBL. Case 1 was 68-year-old man without any evidence of malignancy and infectious status. The peripheral white blood cell count was 8.3 ×10^9/L with 29.5% B lymphocytes, of them the absolute count of MBL was 2.2 ×10^9/L. This case 1 showed CLL-like MBL (CD5+CD23+) with abnormal kappa/lambda restriction pattern and low expression of CD20. The other case 2 was 53-year-old man who showed leukocytosis (10.3 ×10^9/L) with clonal B cells with abnormal kappa/lambda restriction pattern and strongly positive for CD5 and CD20, but negative for CD23 expression.

Conclusions: This study is the first MBL prevalence study in East Asian population that demonstrates lower prevalence (3.1%) of MBL compared to other studies conducted with similar sensitive method and aged group. Further study should be conducted to determine progression potential to CLL or other lymphoproliferative disease on two MBL cases detected in this study.

Keyword: Chronic Lymphocytic Leukemia, Monoclonal B-cell Lymphocytosis, Prevalence, Flow Cytometry, Korea

PP-066

Event free survival at 24 months is a surrogate end point for subsequent overall survival in peripheral T-cell lymphoma

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Background: Despite the progress of chemotherapeutic agent, peripheral T-cell lymphoma (PTCL) still have poor prognosis. To evaluate the surrogate marker for overall survival (OS) in PTCL, we investigated the role of event free survival (EFS) at 24 months (EFS24), and then assessed the predictive factor for EFS24.

Methods: Newly diagnosed PTCL patients who treated with anthracycline containing chemotherapy were analyzed. EFS was defined the time from the date of diagnosis to progression, re-treatment or death from any cause.

Result: Total 178 patients were included, median follow up was 16.0 months (range, 0 to 107), 63 (35.4%) patients remained event free status at 24 months. Subsequent OS of the patients who achieve EFS24 was not different to age, sex matched general population (P = 0.0576) while the patients who could not achieve EFS24 showed poor survival (P < 0.001). After matching the baseline characteristics compared to DLBCL cohort, subsequent survival of the patients who achieve EFS24 did not show statistical difference between PTCL and DLBCL (P = 0.0577). Patients who were event free status at 24 months could have a chance for favorable survival like general population. Advanced stage is the single predictive factor for EFS24 by multivariable analysis.

Conclusions: EFS24 could stratify the subsequent OS in PTCL patients. PTCL patients who achieve EFS24 showed similar subsequent OS compared to general population or DLBCL. Advanced stage at diagnosis is the negative predictive factor for EFS24 in PTCL, these group of patients are needed to receive the new therapeutic strategy.

Keyword: Periperal T-cell Lymphoma, Event Free Survival, Diffuse Large B-cell Lymphoma

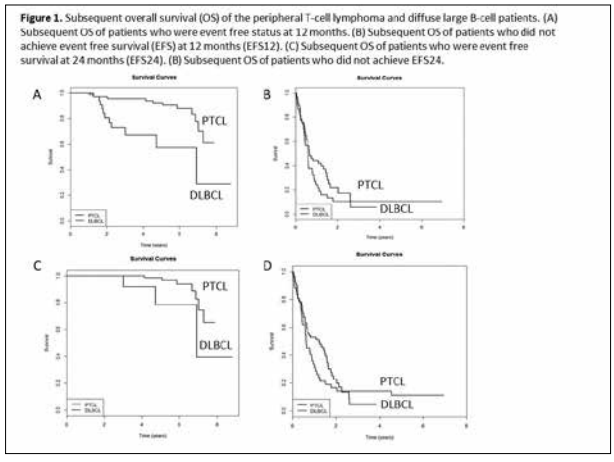

Figure 1. Subsequent overall survival (OS) of the peripheral T-cell lymphoma and diffuse large B-cell patients. (A) Subsequent OS of patients who were event free status at 12 months. (B) Subsequent OS of patients who did not achieve event free survival (EFS) at 12 months (EFS12). (C) Subsequent OS of patients who were event free survival at 24 months (EFS24). (B) Subsequent OS of patients who did not achieve EFS24.

PP-067

Prurigo nodularis and hodgkin's lymphoma – A rare association

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Background: Prurigo nodularis (PN) is characterized by multiple pruritic, hyperkeratotic nodules on the extensor surfaces of the lower extremities. The largest cohort to date by Iking et al. revealed that PN is associated with a systemic condition in 87% of cases. Hence, clinicians when encountering unexplained cutaneous lesions should prompt a search for systemic conditions. Here we report a case of PN secondary to Hodgkin's Lymphoma. To our knowledge, in Malaysia there is by far no reported case of PN secondary to lymphoma in literatures, whereas a local cohort in Singapore by Tan et al. did not report any association of lymphoma either.

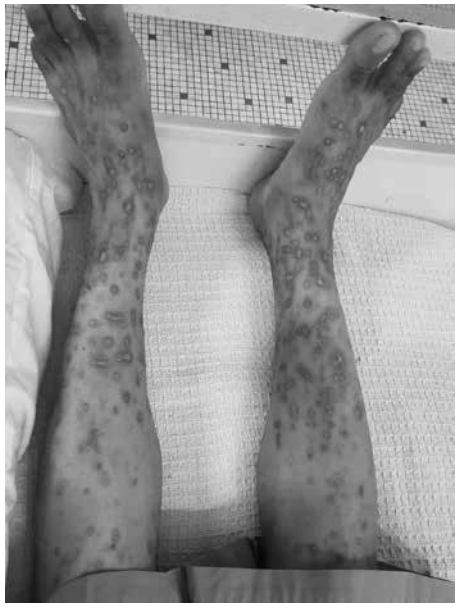
Methods: (Case Report) A 30-year-old man experienced rashes over both lower limbs since April 2018. The rashes appeared on both dorsum of the foot, and gradually involved the shins. The rashes were symmetrical, erythematous, nodular, hyperkeratotic, and pruritic with scratch marks (figure 1). He visited four general practitioners in three months, given multiple courses of topical steroid, antibiotic, antifungal, emollient, and antihistamines. These medications temporarily relieved the pruritus yet the lesions persisted. He did not have fever and constitutional symptoms. In July 2018, he developed right cervical lymphadenopathy and features of superior vena cava (SVC) obstruction. Further workup revealed a mediastinal mass on chest X-ray. Cervical lymph node biopsy was done followed by computered tomography (CT). The histopathological examination of the cervical lymph node showed features classical of Reed-Sternberg cells consistent with Hodgkin's Lymphoma. CT imaging revealed a large anterior mediastinal mass measured 6.4 x 6.1 x 11.2 cm, complicated by SVC obstruction and tumour thrombus in the right internal jugular vein (IJV). There were multiple enlarged right cervical and supraclavicular nodes seen. These findings concluded a stage 2a disease. His rashes were reviewed by the dermatology team and diagnosed as prurigo nodularis (PN). He was started on low molecular weight heparin for the IJV tumour thrombus, and chemotherapy escalated BEACOPP protocol consisting of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisolone. The dermatology team started him on topical emollient, steroid, and oral antihistamine for his PN. After four cycles of chemotherapy,

his pruritus resolved. The PN rashes on the lower limb appeared less erythematous, fainted, with no scratch mark. Repeated CT showed partial response (PR).

Result: (Discussion) Lymphoma is known to associate with cutaneous manifestations. Our index patient suffered from intense pruritic rashes of PN months before developing cervical lymphadenopathy. This case illustrated the sinister cutaneous presentation of lymphoma, and making the correct underlying diagnosis becomes very challenging. Bearing in mind PN is frequently associated with underlying systemic conditions, clinicians should have a low threshold to prompt a search of systemic illnesses and refer to appropriate specialties when encountering such skin lesions, in order to make an early precise diagnosis followed by management.

Conclusions: Cutaneous manifestations such as PN can be the initial and only presentation of lymphoma. Clinicians should have a broad list of differential diagnosis when encountering difficult rashes like our index case, followed by appropriate consultations and referrals.

Keyword: Prurigo Nodularis, Hodgkin's Lymphoma, Cutaneous Manifestation of Lymphoma, Paraneoplastic Skin Lesions



PP-068

The protection effect of moringa extract from lymphoma cell metastasis through decreasing ICAM-1 in Internal carotid artery of metabolic syndrome rats

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Background: Metabolic syndrome has been associated with chronic inflammation due to the increased production of reactive oxygen species (ROS) that impact on increase of ICAM-1 expression. High ICAM-1 participate in the dissemination of lymphoma cells to target organs in the late stages of the metastatic process by mediating firm cell to cell contact to arrest in the circulation. Moringa seeds contains secondary metabolites that can decrease ICAM-1 through inhibition of ROS production. This study aimed to determine the effect of Moringa seeds extract against ICAM-1 expression on internal carotid artery of metabolic syndrome rats (Rattus norvegicus).

Methods: This was laboratory experimental using posttest only group design held in Gadjah Mada University and pathology anatomy laboratory of Sebelas Maret University. The sample are 28 male rats (Rattus norvegicus) that divided into 4 groups: K1 as the control were fed with standard pellet, K2 were metabolic syndrome rats model without moringa seed extract, K3 were metabolic syndrome rats model and given Moringa seeds extract at dose 150mg/KgBW and K4 were metabolic syndrome rats model and given Moringa seeds extract at dose 200mg/KgBW. ICAM-1 expression measured with intensity distribution score (IDS). Effect of Moringa seeds extract to ICAM-1 expression on internal carotid artery were analyzed with Kruskal-Wallis and Mann-Whitney posthoc test.

Result: The mean value of IDS ICAM-1 expression in K1: 2.33, K2: 159.29, K3: 88.83, K4: 46.00. ICAM-1 expression in the internal carotid artery then analyzed by Kruskal-Wallis test. Kruskal-Wallis test showed that there were significant differences of ICAM-1 expression between 4 groups of liver tissue ($p<0.05$). Then the Mann-Whitney post hoc test showed significance differences between four groups ($p<0.05$).

Conclusions: Moringa oleifera seeds extract at dose of 150 mg/kgBW and dose of 200 mg/kgBW potentially lowered ICAM-1 on carotid interna artery of metabolic syndrome rats (Rattus norvegicus).

Keyword: Moringa Oleifera Seeds, ICAM-1, Metabolic Syndrome

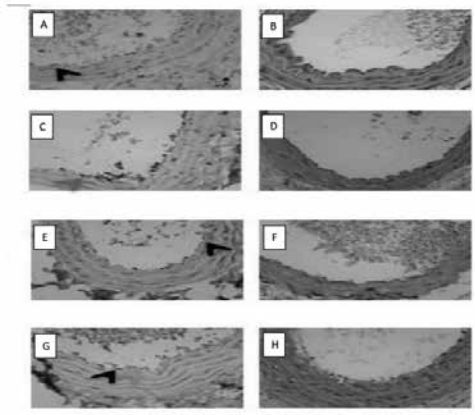

Figure 1. ICAM-1 expression in the internal carotid artery. Observed with a microscope magnified 400 times.

With:

A. Control, IHC

B. Control, HE

C. Metabolic syndrome without extract, IHC

D. Metabolic syndrome without extract, HE

E. Moringa seed extract dose 150 mg / kg, IHC

F. Moringa seed extract dose of 150 mg / kg, HE

G. Moringa seed extract dose 200 mg / kg, IHC

H. Moringa seed extract dose 200 mg / kg body weight, HE

Table 1. Average ICAM-1 expression in the internal carotid artery

Group	N	Average IDS expression for ICAM-1
K 1	6	2.33
K 2	7	159.29
K 3	6	88.83
K 4	7	46.00

Table 2. The Mann-Whitney post hoc test of ICAM-1 expression in internal carotid artery

Group	Sig. value	Significance
K1 and K2	0.002	Significant
K1 and K3	0.003	Significant
K1 and K4	0.008	Significant
K2 and K3	0.022	Significant
K2 and K4	0.002	Significant
K3 and K4	0.012	Significant

PP-069

Ibrutinib vs real-world (RW) treatment outcomes in chronic lymphocytic leukemia by Del11q status: Adjusted comparison of clinical trial and RW data

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Background: Ibrutinib, a first-in-class, oral, covalent inhibitor of Bruton's tyrosine kinase, is approved in many countries for treatment-naïve (TN) and previously treated chronic lymphocytic leukemia (CLL), supported by improved response rates, progression-free survival (PFS), and overall survival (OS) versus chlorambucil in RESONATE-2™ (NCT01722487; Burger JA, et al. N Engl J Med. 2015;373:2425-2437) and ofatumumab in RESONATE™ (NCT01578707; Byrd JC, et al. N Engl J Med. 2014;371:213-223). We analyzed survival outcomes for ibrutinib versus RW treatments for TN and relapsed/refractory (R/R) CLL by del11q status, an adverse prognostic factor linked with poor patient outcomes despite conventional chemoimmunotherapy. An adjusted comparison restricted to patients with confirmed del11q status was conducted using patient-level data from RESONATE-2™ and RESONATE™ and RW databases from 2 countries.

Methods: The Lyon-Sud RW database holds medical records for patients with CLL diagnosed between 1980 and 2017 from the Centre Hospitalier Lyon-Sud, France; the Chronic Lymphocytic Leukemia Registry (CLLEAR) RW database holds medical records for patients with CLL diagnosed between 1988 and 2017 from 7 academic centers in the Czech Republic. TN CLL database patients were selected using RESONATE-2™ criteria (which excluded those aged < 65 years or del17p positive). For the R/R group, patients ≥ 18 years of age or those with del17p were allowed per RESONATE™ inclusion criteria. PFS and OS outcomes by del11q status were compared between the ibrutinib arms of RESONATE-2™/RESONATE™ and physicians' choice (PC) treatment in the pooled RW

databases (excluding ibrutinib). A multivariate Cox proportional hazards model was fitted on pooled randomized controlled trial/RW data to estimate adjusted hazard ratios (HRs) for effect of ibrutinib versus RW PC treatment using age, sex, and treatment line as covariates. The unit of observation for the RW databases was the treatment line (rather than patient) number; RW patients receiving multiple lines of therapy contributed to multiple observations, and baseline was defined as the line-specific treatment start date.

Result: For the RW TN (first-line [1L]) cohort, 466 treatment lines were analyzed; 134 (28.8%) patients were del11q positive. In RESONATE-2™, 29/136 (21.3%) TN patients were del11q positive. For second-line (2L) PC treatment in the RW R/R cohort, 385 treatment lines were analyzed; 135 (35.1%) were from del11q-positive patients. In RESONATE™, 13 (37.1%) 2L patients were del11q positive. For 2L or later (2L+) treatment in the RW R/R cohort, 727 treatment lines were analyzed; 291 (40.0%) were from del11q positive patients. In RESONATE™, 63/195 (32.3%) 2L+ patients were del11q positive. The Table shows adjusted HRs for PFS and OS for 1L, 2L, and 2L+ ibrutinib versus RW PC treatment of patients with/without del11q.

Conclusions: Adjusted comparisons of the registration trial (RESONATE-2™/RESONATE™) and RW patient-level data suggest that OS and PFS improvements with ibrutinib versus PC therapies are pronounced for patients with CLL harboring del11q compared with those who are del11q negative. The findings inform physicians of the comparative effectiveness of ibrutinib in the RW for patients with this high-risk cytogenetic abnormality.

Keyword: Chronic Lymphocytic Leukemia, Real-World Evidence, Ibrutinib, Del11q, Survival

Table. Summary of Adjusted HRs for OS and PFS for Ibrutinib Versus RW PC Therapy by del11q Status[a] and Treatment Line Setting

End Point / Treatment Line Setting	(Treatment Lines, n) Adjusted HR (95% CI); *p* Value	
	del11q Positive	del11q Negative
PFS		
1L	(n = 134) 0.02 (0.00-0.17); *p* = 0.0002	(n = 332) 0.34 (0.20-0.57); *p* < 0.0001
2L	(n = 135) 0.03 (0.00-0.21); *p* = 0.0003	(n = 250) 0.27 (0.14-0.51); *p* < 0.0001
2L+	(n = 291) 0.13 (0.08-0.20); *p* < 0.0001	(n = 436) 0.20 (0.14-0.29); *p* < 0.0001
OS		
1L	(n = 134) NE[b]	(n = 332) 0.74 (0.37-1.49); *p* = 0.3957
2L	(n = 135) 0.08 (0.01-0.46); *p* = 0.0050	(n = 250) 0.50 (0.24-1.05); *p* = 0.0670
2L+	(n = 291) 0.15 (0.08-0.26); *p* < 0.0001	(n = 436) 0.33 (0.21-0.52); *p* < 0.0001

[a]138 treatment lines from the TN setting, 218 treatment lines from the R/R (2L+) setting, and 110 treatment lines from the R/R 2L setting were not analyzed due to missing del11q status in the RW databases.
[b]Due to no deaths on ibrutinib in this group.
1L, first line; 2L, second line; 2L+, second line or later; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PC, physicians' choice; PFS, progression-free survival; R/R, relapsed/refractory; RW, real world; TN, treatment naive.

PP-070

A case of EBV-Positive NK/T cell lymphoma progressed from severe mosquito bite allergy

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Background: A severe mosquito bite allergy is one of Chronic active EBV infection (CAEBV). It might be misdiagnosed as a cellulitis. CAEBV including severe mosquito bite allergy can progress to systemic EBV-positive NK/T cell lymphoma which has very fulminant and fatal clinical course. We report a case of EBV-positive NK/T cell lymphoma progressed from severe mosquito bite allergy. To the best of our knowledge, this is the first case reported in Korea. In March 2018, a 17-years old boy was admitted for his unknown upper arm mass lesion with necrosis. He had a severe mosquito bite allergy 5 years ago at the fifth grade. Two months ago, he visited the dermatology clinic for his right upper arm mass lesion, and received a skin excision, but the skin necrosis got worse. The skin biopsy at the right upper arm was performed in the general hospital, and revealed NK/T-cell lymphoma in the background of CAEBV of T-and NK-cell type. He showed high titers of EBV-VCA IgG (396 U/mL) and EBV-EA IgG (82.0 U/mL) with WBC 2.1× 109/L with left shift (3% myelocytes), Hb 13.3 g/dL and platelet 118× 109/L. The bone marrow (BM) study disclosed the marked interstitial infiltration of neoplastic lymphoid cells. The immunohistochemistry of BM biopsy revealed the positivity for CD3, CD8 and CD56, and the EBV in situ hybridization showed strong positivity. So the BM involvement of NK/T cell lymphoma was diagnosed. PET-CT showed several hypermetabolic lesions in the right upper limb, lung, omentum, mesentery and right iliac bone, compatible with NK/T cell lymphoma. He is being treated with SMILE chemotherapy.

Keyword: NK/T Cell Lymphoma, EBV, Severe Mosquito Bite Allergy, Chronic Active EBV Infection

PP-071

Efficacy of Ibrutinib-Rituximab versus Real-World (RW) regimens for waldenström's macroglobulinemia: Adjusted comparison of clinical trial and RW data

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Background: Ibrutinib, a first-in-class, oral, covalent inhibitor of Bruton's tyrosine kinase, is approved in several countries as monotherapy for adults with Waldenström's macroglobulinemia (WM). In the phase 3 iNNOVATE trial (NCT02165397; Dimopoulos MA, et al. N Engl J Med. 2018;378:2399-2410), adding ibrutinib to rituximab (IR) led to a statistically significant improvement in progression-free survival (PFS) compared with placebo-rituximab in both treatment-naïve (TN) and relapsed/refractory (R/R) patients. This analysis examined the relative treatment effect of IR vs other RW treatment regimens used in daily clinical practice in TN and R/R WM. An adjusted comparison was conducted using patient-level data (PLD) from iNNOVATE and the French Lyon-Sud RW database.

Methods: The Lyon-Sud database holds medical records for patients with WM diagnosed between 1980 and 2017 from the Centre Hospitalier Lyon-Sud. PFS and overall survival (OS) outcomes were compared between the IR arm of iNNOVATE and RW physicians' choice (PC) treatment in Lyon-Sud (excluding RW ibrutinib). Kaplan-Meier survival curves by patient cohort were generated for PFS and OS. A multivariate Cox proportional hazards model was fitted on the pooled PLD from both sources to estimate adjusted hazard ratios (HRs) for effect of IR on PFS and OS vs RW treatment, with age, sex, and treatment line as covariates. Treatment line was the unit of observation for the RW databases; RW patients receiving multiple treatment lines contributed to multiple observations. Baseline was defined as the line-specific treatment start date.

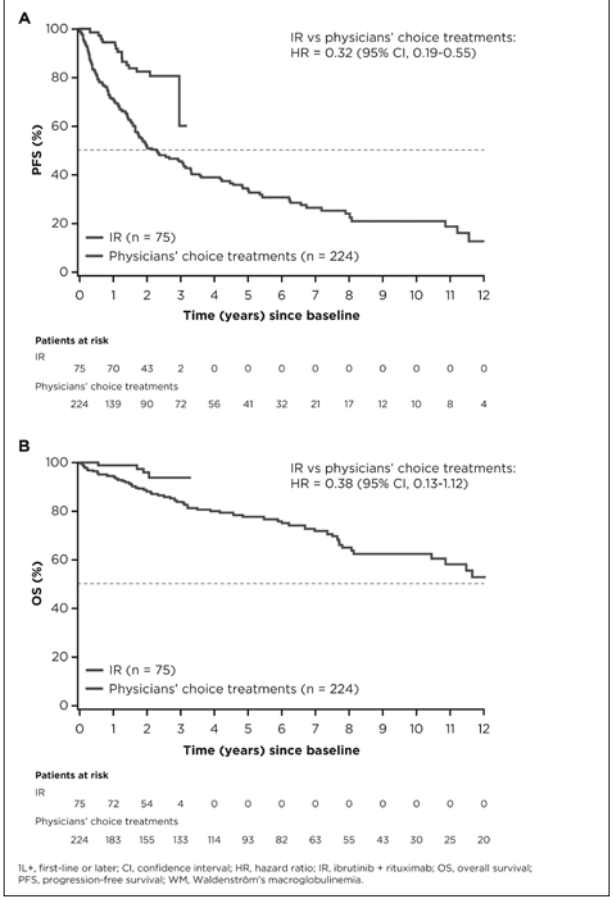
Results: Overall, 242 treatment lines were identified and 224 were analyzed. Baseline characteristics were comparable between the IR arm of iNNOVATE (n=75) and the RW cohort; median follow-up was 26.7 and 68.5 months, respectively.

Non-ibrutinib PC regimens in the RW cohort included rituximab (n=51 treatment lines), chemotherapy (n=66; including chlorambucil, n=31), rituximab-cyclophosphamide-dexamethasone (n=35), rituximab-CHOP/CHOP-like (n=21), rituximab-chlorambucil (n=15), fludarabine-cyclophosphamide-rituximab (n=14), bendamustine-rituximab (n=10), other rituximab-containing chemoimmunotherapy (n=10), and rituximab-targeted agent (n=2). Two ibrutinib lines were excluded from the RW cohort analysis. The Figure shows the observed first line or later (1L+) Kaplan-Meier curves for IR vs RW PC therapy for all analyzed patients with WM (unadjusted HRs: 0.32 [95% confidence interval (CI), 0.19-0.55] for PFS [A] and 0.38 [95% CI, 0.13-1.09] for OS [B]). After adjusting for differences in patient characteristics, HRs (1L+ therapy) became 0.28 (95% CI, 0.16-0.48; p<0.001) for PFS and 0.29 (95% CI, 0.09-0.93; p=0.037) for OS. For 1L treatment only (Lyon-Sud n=109; iNNOVATE n=34), adjusted HRs were 0.25 (95% CI, 0.09-0.70; p<0.009) for PFS and 0.20 (95% CI, 0.02-2.00; p=0.170) for OS; respective unadjusted HRs were 0.31 (95% CI, 0.12-0.78) and 0.30 (95% CI, 0.04-2.34). For the second line or later setting (Lyon-Sud n=115; iNNOVATE n=41), adjusted HRs were 0.28 (95% CI, 0.15-0.56; p<0.001) for PFS and 0.34 (95% CI, 0.08-1.35; p=0.126) for OS; respective unadjusted HRs were 0.31 (95% CI, 0.16-0.61) and 0.39 (95% CI, 0.12-1.31).

Conclusions: Comparisons of clinical trial and RW PLD suggest that IR significantly improves both PFS and OS vs RW PC regimens as 1L+ therapy. These results help inform physicians on the standard of care for WM in clinical practice.

Keyword: B-cell Lymphoma, Waldenström's Macroglobulinemia, Ibrutinib, Rituximab, Real-World Evidence, Survival

Figure. Kaplan-Meier curves for PFS (A) and OS (B) for WM patients treated with IR in iNNOVATE and physicians' choice treatments in Lyon-Sud (1L+)



1L+, first-line or later; CI, confidence interval; HR, hazard ratio; IR, ibrutinib + rituximab; OS, overall survival; PFS, progression-free survival; WM, Waldenström's macroglobulinemia.

PP-072

Treatment outcomes of adult primary mediastinal B-cell lymphoma (PMBCL) treated with dose-adjusted R-EPOCH as frontline therapy in tertiary hospital

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Background: PMBCL is a subtype form of diffuse large B-cell lymphoma that is potentially curable despite its' aggressiveness. In fact, excellent outcomes have recently been reported using infusional dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisolone and rituximab (DA-R-EPOCH) without radiotherapy. On the basis of the results, we evaluate the clinical outcomes of DA-R-EPOCH regimen as frontline treatment of PMBCL as well as the treatment-related complications.

Methods: We analyzed a cohort of 6 primary mediastinal large B-cell lymphoma (PMLBL) patients who had completed 6-8 cycles of DA-R-EPOCH by November 2018 in Hospital Melaka, Malaysia. These six PMBCL patients were diagnosed from 2017 and all had bulky disease with mean measurement of 11.5cm.

Result: DA-R-EPOCH treatment with an escalation dose of level 3, representing a 144% of the starting dose were given and 40mg/m2 of doxorubicin were received for at least one cycle. Cumulative doses of anthracycline were range from 416 to 430mg per square meter; which falls between the range in other reported studies. A few retrospective studies have long suggested that patients with PMBCL have improved outcomes with the receipt of regimens of increased dose intensity. The six patients in our cohort were able to achieve partial response (PR) at the end of treatment. The average of mediastinal residual disease size was 7.3cm. Five out of six patients had been scheduled for radiotherapy consolidation and one patient refused radiotherapy. Hospitalization due to treatment-related complication were reported for four patients. Three of the patients admitted to ICU (Intensive Care Unit) due to infected chemoport. Another patient reported acquired Varicella zoster virus (VZV) during the chemotherapy. He also had sinus tachycardia probably related to anthracycline with prolonged QTC and was able to be controlled by tablet carvedillol during treatment. Toxicity was evaluated during administration of all the cycles of DA-R-EPOCH. Absolute neutrophil counts of less than 500 cells per cubic milliliter occurred in 35% of the cycles compared to the reported 50% in other study. This could be due to the higher GCSF dose used (10μg/kg/day) in the patients. However, all patients tolerated 144% for the subsequent cycles of chemotherapy. The use of neutrophil-based dose adjustment maximized the delivered dose and limited the incidence of febrile neutropenia to 30% of the total cycles. The infusional schedule of doxorubicin allow for delivery of high maximal and cumulative doses of doxorubicin.

Conclusions: DA-R-EPOCH demonstrates a reasonable treatment approach for adults with PMBCL. Our results indicated that PMBCL patients on DA-R-EPOCH regimen had a partial response and may not necessary obviate the need for radiotherapy. This is a preliminary result as 3 more patients are ongoing DA-R-EPOCH treatment. More data are needed to provide confirmatory evidence.

Keyword: Primary Mediastinal B-cell lymphoma, Dose Adjusted R-EPOCH, Frontline Therapy, Clinical Outcome, Response Rate

PP-073

Triple improvement in the clinical, laboratory, and radiologic manifestations of multicentric castleman disease after treatment with siltuximab

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Background: Multicentric Castleman disease (MCD) constitutes about 30% of all cases of Castleman disease, which characterized by systemic symptoms including fever, chills, fatigue, anorexia, cachexia, and enlarged lymph nodes in multiple anatomical sites. The associated laboratory test abnormalities include cytopenias, hypoalbuminemia, and increased concentration of acute-phase proteins such as C-reactive protein (CRP). These signs and symptoms are driven by the dysregulated excess production of interleukin-6, which plays a central role in the pathophysiology of MCD. Siltuximab is a human-mouse chimeric immunoglobulin G1κ monoclonal antibody against human IL-6. A multicenter, randomized, controlled phase 2 trial of siltuximab treatment in patients with MCD showed superior outcomes and tolerable safety and efficacy.

Methods: We enrolled 15 patients diagnosed with MCD and eligible for siltuximab treatment based on patient history, physical examination, assessment of laboratory abnormalities, pathological diagnosis, and radiological imaging. The primary endpoint was durable improvement in clinical symptoms, signs, and radiologic findings for at least three months during treatment. The median age was 44 years (range 24 – 76), and 60.0% of the patients were men. All patients had symptomatic disease consisting of one or more of the following manifestations: fatigue (66.7%), peripheral sensory neuropathy (53.3%), sustained fever (46.7%), peripheral edema (33.3%), and multiple palpable lymph nodes (26.7%). The 60.0% of patients received previous treatment with either corticosteroid or chemotherapy before commencing siltuximab therapy. Computed tomography (CT) imaging was done at diagnosis and every three months, along with laboratory evaluation. Disease signs and symptoms were assessed at each cycle on day 1, and all tumor and symptomatic responses were confirmed on repeat assessment.

Result: After a median duration of 9 months (range, 1 – 95) of siltuximab treatment, symptomatic responses occurred in 11 of 15 patients (64.7%), and the median time to durable symptomatic response 22 days (range, 17 – 56). On laboratory evaluation after the first 3 months of siltuximab treatment, the mean hemoglobin recovery (from 10.5 to 13.1 g/dL; p=0.03), ESR normalization (from 72.5 to 21.9 mm/hr; p<0.01), and serum albumin recovery (from 3.2 g/dL to 4.0 g/dL; p=0.001) were statistically significant. Three patients (20.0%) achieved complete remission and seven patients (46.7%) achieved partial remission. The remaining 3 patients had stable disease with symptomatic relief and ongoing siltuximab treatment cycles. Unfortunately, two patients (13.3%) discontinued siltuximab due to poor general condition and poor response, respectively. The most common adverse event was infection (26.7%), mostly upper respiratory infection, followed by maculopapular rash (20.0%) and NCI CTCAE grade 3 or higher nephropathy (13.4%) or hepatopathy (13.4%).

Conclusions: Siltuximab with best supportive care resulted in improvement in symptoms, laboratory parameters, and imaging findings in our hospital cohort of patients with symptomatic MCD. Furthermore, siltuximab had a favorable safety profile and prolonged treatment with siltuximab was well tolerated with no evidence of new or cumulative toxic effects or treatment discontinuations and a low rate of serious adverse events. Despite the small number of MCD patients enrolled for siltuximab treatment in this study, the results are encouraging; large multicenter studies are needed to further elucidate the clinical outcomes and adverse events associated with siltuximab.

Keyword: Multicentric Castleman Disease, Siltuximab, Interleukin-6

PP-074

A 15-year-old male diagnosed with mantle cell lymphoma, presenting with mediastinal mass

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Background: Mantle cell lymphoma (MCL) is one of the mature B cell non-Hodgkin lymphomas (NHL). While it is often discussed together with the clinically indolent forms of NHL, its behavior is more often that of an aggressive disease. MCL comprises about 7 percent of adult non-Hodgkin lymphomas in the United States and Europe with an incidence of approximately 4 to 8 cases per million persons per year. Incidence increases with age and appears to be increasing overall in the United State. Approximately three-quarters of patients are male and median age at diagnosis is 68 years.

Methods: We report unusual case of mantle cell lymphoma presenting with mediastinal mass in 15-year-old male.

Result: The 15-year-old boy visit hospital presenting with prolong cough and dyspnea. Chest x-ray showed pleural effusion on right lung field and mediastinal widening. Chest CT showed that there was about 12 cm, enhancing lobulating anterior mediastinal mass with heterogenous density. There was multiple right pleural mass with large amount of effusion. Pleural fluid analysis showed exudate pattern, there is atypical lymphoid cell consistent with malignant lymphoma. Biopsy of mediastinal mass showed diffuse effacement of medium to large atypical lymphoid cells. Many of them show cytoplasmic immunoglobulin deposition with Dutcher body. The atypical lymphoid cells reveal positivity for cyclin D1. The histologic and immunohistochemical findings are more favor mantle cell lymphoma. Fluorescence in situ hybridization for t(11:14)(q13;q32) IGH/CCND1 showed positive fusion signal in biopsy sample. PET-MR showed FDG uptake in mediastinal mass, pleural wall, and multiple lymph node (infraclavicular, paraaortic, celiac). We start chemotherapy with of CCG 5961. After COP reduction followed by 2 cycle of COPADM, mediastinal mass and lymphadenopathy disappeared.

Conclusions: We report a case of a 15 - year - old male with a medullary lymph node metastasis. This is a case of mantle cell lymphoma occurring at the youngest age.

Keyword: Mantle Cell Lymphoma, Non Hodgkin Lymphoma, Adolescent

PP-075

Treatment abandonment amongst patients with hematological malignancy in TYA age group

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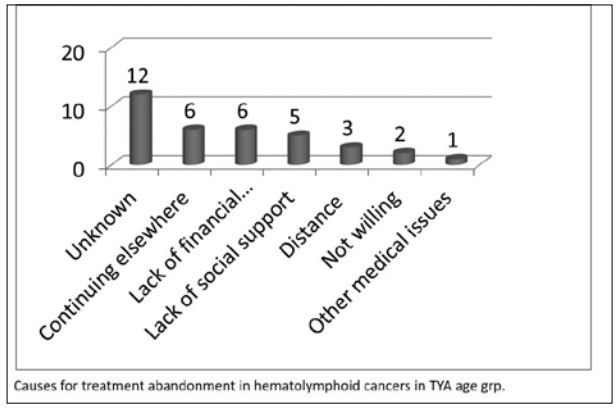
Background: Treatment abandonment is a major cause of treatment failure in cancer patients in teen and young adult (TYA) age group. It is important to understand the reasons for treatment abandonment to design measures to reduce abandonments. Reduction in abandonments will improve survival outcomes in TYA patients with cancer. The present study was conducted to look at factors for treatment abandonment among TYA patients with hematological malignancies treated at our hospital.

Methods: This was a retrospective study of patients in the age group of 15-29 yrs with hematological malignancy who were treated at Cancer Institute, Chennai, from January 2013 to December 2015. Abandonment was defined as patient not taking the next course of treatment for reasons other than death, disease progression or toxicity. Abandonment was correlated with factors like income, employment, social-support, type of cancer, distance and gender.

Result: The study included 300 patients, among whom 212 (70%) were males. The median age of the patient was 21yrs (15-29). The most common malignancy was Acute lymphoblastic leukemia followed by Non hodgkins lymphoma. One hundred and four (34%) patients were employed, 80 (26%) were married and 35 (13%) had income more than Rs10000. One ninty two (64%) patients came to the hospital from a distance of more than 150 kilometers. Among the 300 patients treatment interruption was observed in 141(47%) patients, the reasons for treatment interruption were death in 61 (43%), progression in 41(29%), toxicity in 3(2%) and abandonment in 36(26%) patients. The reasons for abandonment were, lack of financial support in 6/36 (16%), distance from the hospital in 3/36(8%), lack of social support in 5/36 (13%) patients. 5/36 (13%) patients were continuing treatment in other hospital and reasons were not known in 12/36 (33%) patients. Gender, distance, state, type of cancer, marital status, educational qualification, income and employment did not correlate with treatment abandonment.

Conclusions: One fourth of all treatment interruptions in TYA patients are due to treatment abandonments. The reasons for treatment abandonments are multifactorial. Financial and social support and access to health care near the place of residence can reduce treatment abandonments and improve survival outcomes in TYA cancer patients.

Keyword: Abandonment, Hematolymphoid Cancer, TYA



Causes for treatment abandonment in hematolymphoid cancers in TYA age grp.

PP-076

Effect of the dose of rituximab on survival outcomes of the DLBCL treated with rituximab-CHOP; Based on the national health information database

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Background: The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been shown to improve outcome in patients with diffuse large B-cell lymphoma (DLBCL). However, the impact of body surface area (BSA) on survival in DLBCL is controversial. We evaluated whether dose of rituximab or BSA were associated with overall survival (OS) in Korean DLBCL patients.

Methods: Data were extracted from the national health information database (NHID). We identified 5,688 newly diagnosed adult patients with DLBCL from 2006 to 2014 who received rituximab-CHOP as frontline chemotherapy. We excluded patients who were given rituximab-CHOP less than 4 times or more than 8 times. Student's t test was used for numerical comparison between two groups, and chi-square test was applied for categorical variables. Survival was estimated using the Kaplan-Meier

method, with statistical comparison using the log-rank statistic. Cox proportional hazard regression models were used for univariate and multivariate analysis with following variables; age, sex, rituximab-CHOP frequency, total rituximab dose, and mean rituximab dose.

Result: The median age at diagnosis was 58 years (range, 20-98 years), and the male to female ratio was 1.3:1. The median period from diagnosis to first rituximab administration was 7.2 days (range, 0-60 days). Four to five times rituximab-CHOP was given to 2,201 patients (38.7%), and 6 to 8 times was 3,487 patients (61.3%). Patients received 4 times, 6 times, and 8 times rituximab therapy were 993 (17.5%), 2,568 (45.1%), and 597 (10.5%), respectively. The median mean dose of rituximab was 606.2 mg (range, 100-1,000 mg) and median total dose was 6,733.8 mg (range, 400-16,800 mg). Weight and height before chemotherapy were available in 4,048 patients (71.1%). Median body surface area (BSA) was 1.69 (1.13-2.45)/m2, and median body mass index (BMI) was 24.02 (11.1-39.8) kg/m2. With 39.3 months (range, 2.1-144.8) of median follow up, 1,761 patients (30.96%) were expired. In survival analysis, patients age 60 years or less had longer OS than age more than 60 years (38.9 months vs. 31.0 months, p<0.001), and patients received 6-8 times rituximab-CHOP chemotherapy showed favorable survival outcome than 4-5 times (40.1 months vs. 27.9 months, p<0.001). Although there was no significant difference between 6 times and 8 times group for OS, 4 times group showed significant worse survival outcome than others (26.1 monthsa vs. 40.1 monthsb vs. 42.5 monthsc, p<0.001, a<b.c). Higher rituximab mean dose (<600 mg vs. ≥600 mg; 26.4 months vs. 36.6 months, p<0.001) and total rituximab dose (<7,200 mg vs. ≥7,200 mg; 28.2 months vs. 41.1 months, p<0.001) were associated with better survival outcome. Patients with less than 1.69 m2 of BSA showed 33.6 months for OS, which were shorter than patients with BSA >1.69 m2 (36.4 months, p<0.014). In multivariable analysis, age≤60 years (vs. >60 years), female (vs. male), receiving rituximab-CHOP chemotherapy 6-8 times (vs. 4-5 times), and mean rituximab dose ≥600 mg (vs. <600 mg) were associated better OS (p-values of all variables were <0.001).

Conclusions: In this study, young and female patients who received rituximab-CHOP chemotherapy more than 6 times or more than 600 mg of mean rituximab dose were showed favorable survival outcome in DLBCL patients who were treated with rituximab-CHOP chemotherapy.

Keyword: Diffuse Large B-cell Lymphoma, Dose, Rituximab, Overall Survival

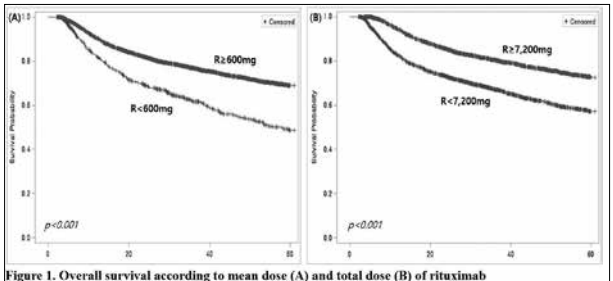

Figure 1. Overall survival according to mean dose (A) and total dose (B) of rituximab

PP-077

Clinical impact of ibrutinib in refractory or relapsed mantle cell lymphoma: Single-center experience in clinical practice

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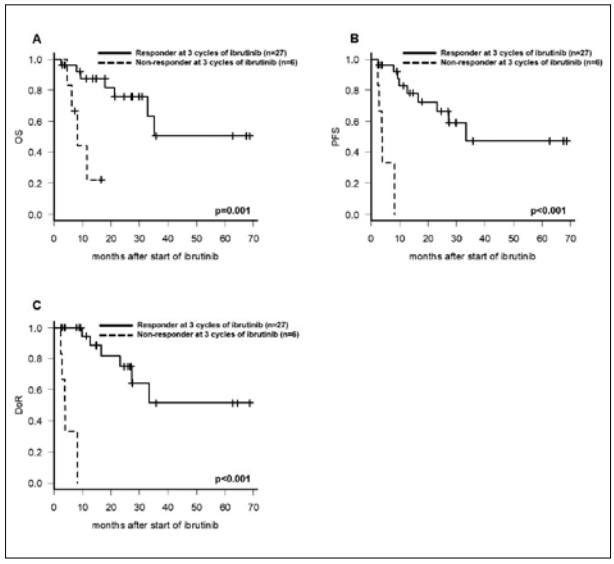
Background: Ibrutinib is highly effective in patients with relapsed or refractory mantle cell lymphoma (MCL) in clinical trials. Nevertheless, these significant advances of improved survival outcomes in the salvage setting, non-response to ibrutinib is still troublesome and dismal prognosis. So, we conducted to identify prognostic factors to predict the response of ibrutinib monotherapy in patients with relapsed or refractory MCL retrospectively.

Methods: In consecutive 33 refractory of relapsed MCL patients who were treated with ibrutinib in a salvage setting were analyzed.

Result: The median overall survival (OS), progression-free survival (PFS), time-to-progression (TTP) after initiation of ibrutinib was 35.1 months, 27.4 months, and 33.4 months, respectively. Risk factor analysis showed that high-risk by biologic MIPI and non-response to ibrutinib at first 3 cycles were statistically significantly associated with the inferior OS. Poor PFS was associated with high-risk biologic MIPI, prior bendamustine-exposure, and non-response of ibrutinib at first 3 cycles. After ibrutinib failure, primary non-responder was the poorer outcomes than the non-consistent responder. And overall response rate (ORR) for the first salvage therapy was only 33% with a median TTP of 3.2 months, and there was no effective therapeutic strategy except for allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Conclusions: Ibrutinib responder showed favorable survival outcomes. However, the non-responders had a dismal prognosis, and selective patients such as inconsistent responder were needed to prepare for allo-HSCT in advance.

Keyword: Ibrutinib, Mantle Cell Lymphoma, Responder, Allogeneic HSCT



relapse / refractoriness, primary patients). PR / CR were obtained in 7 patients, progression in 3. A course of DexaBEAM as a 2–3 line therapy was used in 8 patients, and a general response (GS) would be achieved in 62.5%. The highest efficacy was obtained in the group of 5 patients who received auto-TSCC in PR: complete remission was observed in 4 of 5 patients, relapse was verified in 1 patient.

Conclusions: Patients with ALCL ALK + have a favorable prognosis when using high-dosage chemotherapy programs, but, given the good prospects for using less intensive regimens, a randomized prospective study is needed. The question of the choice of the induction chemotherapy regimen in patients with ACL ALK- to achieve PR or CR with subsequent auto-TSCC remains unresolved. In patients who have not achieved OO, use of the Dexa-BEAM regimen with subsequent auto-TSCC or supportive therapy is possible as 2nd line therapy.

Keyword: Anaplastic Cell Lymphoma, NHL-BFM-90 Protocol, Auto-TSCC

PP-078

Results and prospects for the treatment of anaplastic cell lymphoma in adult patients

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Background: Evaluation of the results of high-dose treatment programs in ACL ALK + and ACL ALK-AL, as well as the results of various treatment schemes as a rescue therapy.

Methods: A retrospective analysis of patients with ACL ALK + and ACL ALK-observed at the Department of Hematology of the Tashkent Medical Academy from 2002 to 2015.

Result: The study included 68 patients with ACL (38 with ACL ALK + and 26 with ACL ALK-). 38 patients with ACCL ALK + received standardized treatment according to the NHL-BFM-90 protocol - OS and RRT were 90 and 83%, respectively, and the median survival rate was 67 months. Twenty two patients with ACL ALK-2 completed two protocols of high-dose chemotherapy: OS and RRV were 40 and 28%, respectively. The NHL-BFM-90 protocol was used in 16 patients - a general response (PR / CR) was achieved in 8 (50%) of 16 patients, but in 6 there were progresses, in 3 - relapses. Thus, OM and BSV were 37.5 and 31%, respectively. 10 patients received treatment according to the TL-REZ-09 protocol (4 with

PP-079

Genetic and non-genetic risk factors of bleomycin-Induced pulmonary toxicity in south indian patients with hodgkin lymphoma

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Background: Bleomycin is an anticancer antibiotic used in the treatment of Germ-cell tumours (GCTs) and Hodgkin Lymphoma (HL). Bleomycin causes life threatening pulmonary toxicity and occurs in 2-46% of the treated patients with mortality rate of up to 3%. Cumulative bleomycin dose, granulocyte-colony stimulating factor (G-CSF), glomerular filtration rate (GFR) and age more than 40 are some of the risk factors which have been found to be associated with bleomycin-induced pulmonary toxicity (BPT). As there is inter-patient variability in susceptibility to this toxicity we hypothesise that polymorphisms in XPO5, BLMH and HFE genes may be associated with toxicity.

Methods: After obtaining institute ethics committee approval 176 cases with HL were screened and 122 patients who were given

bleomycin-based regimen were analysed. Diagnosis of BPT was done using computed tomography (CT) scan and x-ray reports. Symptoms such as dyspnoea and dry cough were also noted. Base line characteristics were noted from their case records and XPO5, BLMH and HFE gene polymorphisms were genotyped using real-time PCR. BPT was graded according CTCAE V.4.0. Chi-square test and logistic regression analysis was done using SPSS V.20.

Result: Out of 122 patients, 51 (42%) patients developed BPT. G1 grade (Asymptomatic) patients were 18, G2 (Symptomatic) were 21, G3 (Severe symptoms) were 7, G4 (Life-threatening respiratory compromise) were 5 and all 5 five patients eventually died. Age>35 years, advanced stage, GFR ≤80 (ml min-1), albumin≤3.5 g/dL, mediastinal mass and Hb<10.5 g/dL were associated with BPT. In regression model only Hb<10.5 g/dL was found to be significant whereas XPO5, BLMH and HFE gene polymorphisms were not associated with toxicity.

Conclusions: We report incidence of bleomycin-induced pulmonary toxicity to be 42% in HL patients of south Indian origin. We found that Hb<10.5 g/dL was an independent risk factor for bleomycin-induced pulmonary toxicity and it was not dose dependent in south Indian population.

Keyword: Hodgkin Lymphoma, Bleomycin, Pulmonary Toxicity, Risk Factors

PP-080

A rare case of high grade nodal marginal zone B cell lymphoma with diffuse bone marrow involvement and igm-type monoclonal paraproteinemia

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Background: IgM-type monoclonal paraproteinemia is reported to be present in patients with various subtype of lymphoma but approximately 60% and 20% of cases is found in patients with lymphoplasmacytic lymphoma (LPL)/Waldenstrom's macroglobulinemia (WM) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Other type of non-Hodgkin lymphoma with serum monoclonal IgM paraprotein is reported to occur rarely and we report here a rare case with nodal marginal zone B cell lymphoma (NMZBCL) with diffuse bone marrow (BM) involvement and IgM-type monoclonal paraproteinemia.

Result: A 60 years-old woman visited author's institution at December 2018 with the symptom of fever, cough, and epigastric pain lasting for one week. Her computerized tomography (CT) scan results showed the presence of hepatosplenomegaly, multiple lymphadenopathy involving bilateral cervical, axillary, upper mediastinum lymph node (LN) and whole body Positron Emission Tomography (PET)-CT scan results showed diffusely increased metabolism with marrow expansion and multiple hypermetabolic LNs in bilateral cervical, axillary, mediastinal, and abdominal areas. Her hemogram results at first visit were as follows: white blood cells, 14.6 × 109/L, Hb, 9.8 g/dL, and platelets, 73 × 109/L. The peripheral blood smear (PBS) revealed the presence of medium to large sized neoplastic lymphoid cells with the frequency of 32%. The BM aspiration showed normocellular marrow with increased infiltration of large sized neoplastic lymphoid cells (8.5%) and plasma cells (4.5%), and BM biopsy showed normocellular marrow (cellularity 60%) with diffuse infiltration of large sized neoplastic lymphoid cells, accompanied with increased infiltration of small sized reactive lymphocytes. Subsequently performed immunohistochemical (IHC) stain in BM biopsy section showed the presence of large sized neoplastic lymphoid cells with membranous positive on CD20, nuclear positive on both BCL-6 and MUM1 but negative on CD10 and CD30. In addition, increased small-sized reactive lymphocytes showed positive on CD3 IHC stain and increased plasma cells showed positive on CD138 IHC stain. Interestingly, serum electrophoresis/immunofixation results showed the presence of monoclonal gammopathy, IgM kappa type with M-protein of 5.6 g/L. Excisional biopsy specimen obtained from left axillary LN showed the increase of reactive T cells with positivity on CD3, CD4 and CD8 IHC stains, and also showed the presence of small sized neoplastic lymphoid cells with transformed large sized cells exhibiting positive results on CD20, BCL-2, Ki-67 (40%) IHC stains but negative results on CD10, Cyclin D1 and EBV in situ hybridization IHC stains. With these results, the pathologic diagnosis of NMZBCL, high grade was made and she was planned to treat with intravenous methylprednisolone at 1 mg/kg for every 12 hours at first, followed by rituximab-bendamustine based chemotherapy.

Conclusions: The most common lymphoma associated with IgM-type monoclonal paraproteinemia is LPL/WM with the frequency of approximately 60%, followed by CLL/SLL with the frequency of approximately 20%. Although some marginal zone B cell lymphoma with IgM-type monoclonal paraproteinemia was reported but most cases of them was reported to be extranodal and splenic subtype. To date, only 2 cases with NMZBCL with IgM-type monoclonal paraproteinemia have been reported. We report here a rare case with NMZBCL with diffuse bone marrow (BM) involvement and IgM-type monoclonal paraproteinemia.

Keyword: Bone Marrow Involvement, IgM-Type Monoclonal Paraproteinemia, Nodal Marginal Zone B Cell Lymphoma

PP-081

9-year-old boy diagnosed with X-linked lymphoproliferative disease type 1 - Case report

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Background: Familial hemophagocytic lymphohistiocytosis (FHL) is a rare heritable disorder of immune regulation that is typically characterized by sudden onset of severe systemic illness. Functional impairment or absence of 1 or more of several proteins that participate in lymphocyte cytotoxicity underlies the disease.

Methods: We report 9-year-old boy who was diagnosed with X-linked lymphoproliferative disease type 1 (XLP1) in genetic presenting with HLH.

Result: A 9-year-old boy presented with fever for 2 weeks. The patient had a tonsillar whitish patch, cervical lymphadenopathy, skin rash, hepatosplenomegaly at the time of admission. He has fever, cytopenia, increased ferritin, TG and solubleIL-2 receptor level, decreased fibrinogen and NK cell activity. EBV PCR was positive and EBV Quantitative PCR is 48,400 copies/ml. Neck CT showed multiple cervical lymph node enlargement, and abdomen CT showed gallbladder wall edema, ascites, and hepatosplenomegaly. Hemophagocytic histiocyte and atypical lymphocyte was increased in bone marrow. Hemophagocytic lymphohistiocytosis was diagnosed and treatment was started according to the HLH-2004 protocol. CSF study showed pleocytosis, atypical lymphoid cell, hemophagocytosis, EBV PCR positive findings and increased protein. No pathologic mutation of the PFR or UNC13D gene was found in the patient. Fever was improved two weeks after the start of the treatment, and blood test was improved, but he started to fever again from the third week and showed disorientation and mentality change. Brain MRI showed encephalopathy with multifocal high signal intensity in flair image. After then, initial therapy was restarted to increase dexamethasone to 10 mg/m2 and VP-16 was given twice a week. Intrathecal methotrexate and steroid therapy also added. Methylprednisolone pulse therapy, anti-thymocyte globulin(thymoglobulin) treatment did not effective. Antiviral agent (ganciclovir) against to EBV virus did not effective to reduce EBV viral load. Eventually, the patient died due to respiratory failure due to central nervous involvement. Several months after the patient death, genetic test found that there was exon2-4 deletion in the SH2D1A gene. He finally diagnosed with XLP1.

Conclusions: XLP1 features include hemophagocytic lymphohistiocytosis (HLH), lymphomas, and dysgammaglobulinemias. Molecular cloning of the causative gene, SH2D1A, has provided insights into the nature of the disease, as well as characterizing several features of normal immune cell function. A common cause of familial HLH is PFR, UNC13D gene abnormalities in Korea. Finding genetic abnormalities early in the diagnosis of HLH patients is crucial in determining the treatment and prognosis of patients.

Keyword: HLH, XLP1, CNS Involvement

PP-082

Multi-gene sequencing of hemophagocytic lymphohistiocytosis in pediatric patients: Gene profiles and its correlation with bone marrow findings

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Background: Diagnostic criteria of primary hemophagocytic lymphohistiocytosis (HLH) includes defects in genes involved in the cytolytic activity of natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), and dysregulated activation of lymphocytes. Regarding to gene defect, it is difficult to tell the difference between secondary HLH and familial HHL, any case of HLH should be considered for genetic testing to confirm the diagnosis. Thirteen defective genes (PRF1, UNC13D, STX11, STXBP2, RAB27A, LYST, AP3B1, SH2D1A, XIAP, ITK, CD27, MAGT1 and SLC7A7) have been identified. We investigated defective genes in 10 pediatric patients diagnosed with HLH.

Methods: Ten patients diagnosed with HLH were enrolled between January 2013 and December 2014. We performed multi-gene target sequencing consisted of 11 HLH related genes (PRF1, UNC13D, STX11, STXBP2, RAB27A, LYST, AP3B1, SH2D1A, XIAP, ITK and MAGT1) and 87 hematologic neoplasm associated genes. Sanger sequencing was conducted for verification. Laboratory results and histologic findings in bone marrow were retrospectively reviewed, targeting number of histiocytes, hemophagocytic histiocytes, lymphocytes and cellularity.

Result: Among 10 patients diagnosed with HLH, 5 patients was diagnosed with primary HLH (5/10, 50%) and 5 patients was diagnosed with secondary HLH (5/10, 50%). Median ages were 4.5 year (range 0-16). NGS revealed defective genes in 5 patients including 4 patients in primary HLH and 1 patient in secondary HLH (5/10, 50%); PRF1, UNC13D and STXBP2. Meanwhile, 50% showed no mutations in HLH related genes. Among 3 genes, novel mutations in STXBP2 (c.1099-2A>G, p.?, heterozygote and c.1348-2A>G, p.?, heterozygote) was identified. WBC count was significantly higher in mutated HLH (p = 0.028, 3.13x109/L in mutated HLH vs 1.97 x109/L in non-mutated HLH). Lymphocyte% in peripheral blood was significantly higher in mutated HLH (p = 0.016, 75.0% in mutated HLH vs 30.6% in non-mutated HLH). Number of histiocytes and hemophagocytic histiocytes in bone marrow was higher in mutated HLH (p = 0.465, 7.5% in mutated HLH vs 3.4% in non-mutated HLH and p = 0.590, 1.2% in mutated HLH vs 0.3% in non-mutated HLH). Lymphocyte% in bone marrow was also higher in mutated HLH (p = 0.117, 40.8% in mutated HLH vs 21.3% in non-mutated HLH). BM cellularity was significantly higher in mutated HLH group (p = 0.018). Overall survival of mutated group was 42.1 months in mutated HLH and 35.2 months in non-mutated group (p = 0.904).

Conclusions: The present study revealed biologic difference between non-mutated HLH group and mutated HLH group; younger age, higher BM cellularity, higher lymphocyte and histiocytes count. Of note, among secondary HLH, a mutated patient with heterozygous carrier state was detected.

Keyword: Hemophagocytic Lymphohistiocytosis, Multi-Gene s Equencing, Familial Hemophagocytic Lymphohistiocytosis, Secondary Hemophagocytic Lymphohistiocytosis, Novel Mutation

Table 1.

	Non-mutated (n=5)	Mutated (n=5)	p value†
Age (year)	10.5 (2.0-16.0)	0.5 (0.0-1.1)	0.459
Sex (male: female)	2:3	3:2	1.000
CBC			
Hb (g/L)	87.0 (78.0-129.0)	88.0 (54.0-100.0)	0.602
WBC count (x10^9/L)	1.97 (0.68-2.08)	3.13 (2.00-3.72)	0.028
ANC (x10^9/L)	0.61 (0.25-1.81)	0.32 (0.16-1.81)	0.347
Platelets (x10^9/L)	75.0 (62.0-110.0)	35.0 (26.0-102.0)	0.175
Lymphocytes (%)	30.6 (5.3-56.0)	75.0 (40.0-85.0)	0.016
Lymphocyte count (x10^9/L)	0.32 (0.11-1.10)	2.12 (1.44-2.38)	0.009
Bone marrow			
Cellularity (%)	65.0 (40.0-80.0)	95.0 (90.0-100.0)	0.018
Histiocytes (%)	3.4 (0.9-6.2)	7.5 (0.6-13.7)	0.465
Hemophagocytes/ Histiocytes(%)	1.0 (0.0-3.0)	3.0 (0.0-7.0)	0.386
Hemophagocytes/TNC (%)	0.3 (0.0-2.7)	1.2 (0.0-3.3)	0.590
Lymphocytes (%)	21.3 (6.4-35.7)	40.8 (9.9-69.8)	0.117
Monocytes (%)	2.2 (0.9-3.6)	2.9 (0.8-6.9)	0.465
M:E ratio	2.9 (0.7-17.4)	1.9 (0.7-13.1)	0.602
HLH parameters			
Ferritin (ng/mL)	3699.3 (1565.0-60260.2)	2454.7 (254.6-41232.0)	0.465
Fibrinogen (mg/dL)	119.0 (65.0-161.0)	86.0 (67.0-397.0)	0.917
TG (mg/dL)	301.0 (48.0-1410.0)	186.0 (78.0-955.0)	0.917

Abbreviations: CBC, complete blood count; Hb, hemoglobin; WBC, white blood cell; ANC, absolute neutrophil count; TG, triglycerides, TNC, total nucleated cell; HLH, hemophagocyticlymphohistiocytosis.
†Small sample size reduces the statistical power of the study.

PP-083

Isolated splenic Rosai-Dorfman disease presenting as a fever of unknown origin in a 10-months-old child

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Background: Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare form of histiocytosis characterized by massive bilateral cervical adenopathy but may present with lymph node involvement in other sites. Less commonly, RDD may involve extra-nodal sites such as the skin, central nervous system, bone, liver, pancreas or spleen. In particular, there are only a few cases presenting with isolated splenic involvement by RDD. The patients with RDD may be mimicking the malignancy because they can be accompanied by malaise, weight loss, and fever of unknown

origin (FUO). Due to benign course of RDD and spontaneous remission in most cases, treatment for RDD is usually unnecessary. However, when the lesions progress or systemic symptoms persist, treatment including surgery, radiation, and medical agents may be required.

Methods: A 10-month-old Vietnamese girl who was presented with FUO. She had no any other signs or symptoms including peripheral adenopathy or hepatosplenomegaly. Her diagnostic workup was negative for infectious and autoimmune disorders. Laboratory test results were unremarkable except for leukocytosis and elevated erythrocyte sedimentation rate and C-reactive protein. Bone marrow examination showed normocellular marrow for her age without evidence of malignancy. CT scan revealed multiple rounded heterogeneous low-attenuation masses in the spleen. Four splenic masses, the largest one was 4.7 x 4.3 x 5.0 cm at inferior portion, were demonstrated heterogeneous hypointense with peripheral enhancement on T2-weighted magnetic resonance imaging. She continued to spike fevers during hospitalization. Although primary splenic masses is unusual cause of FUO, we elected to perform a diagnostic splenectomy because of persistent fever as well as considering the risk for bleeding or rupture in biopsy.

Result: There were CD68 and S-100 positive and CD1a negative histiocytic proliferation with emperipolesis, consistent with RDD in spleen and peripheral lymph nodes. The fever subsided eventually after splenectomy, she has been well for 6 months with only postsplenectomy thrombocytosis.

Conclusions: This case is the first RDD case of isolated splenic involvement without lymphadenopathy in children. In addition to, RDD may be included in differential diagnosis of obscure causes of FUO particularly in pediatric patients.

Keyword: Rosai-Dorfman Disease (RDD), Fever of Unknown Origin (FUO), Spleen, Children

PP-084

Multiple myeloma in teenage patient: A case report

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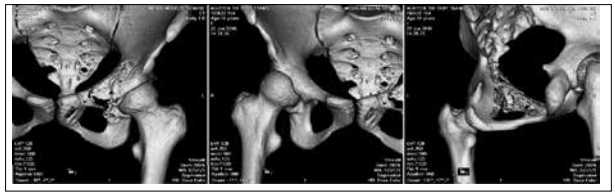
Background: Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction. Multiple myeloma is most common in the age group of 65 to 70. Less than 2% of patients are younger than 40 years of age at diagnosis and it is extremely rare in those younger than 30 years (0.3%). According to some reports in the world: the youngest recorded age is 19 years old. Now, we report a case with Multiple myeloma at 17 years old. Probably, this patient is the youngest in my country.

Methods: This is female patient, she was 17 years old at the diagnosis time. Date of first her admission in 12/2015 with chief complaint is hip – joint pain. About 1 month before hospitalization, the patient felt an increasing left hip – joint pain, she went to Orthopaedic Hospital and had CT scan, which found ilium tumor in the left wing. The results of tumor biopsy is plasmacytoma. After that, she was transferred to Blood Transfusion Hematology Hospital. At admission time, her ECOG score is 2. She has mild anemia and severe pain in left hip, walking on crutches. Laboratory findings included normocytic anemia of 10.9 g/dL, normal β-2 microglobulin calcium and creatinine. Serum electrophoresis revealed high levels of serum IgG (41.73g/dL) characterized as IgG Lambda monoclonal protein. Bone marrow biopsy and aspirate showed a hypercellular marrow with 7% infiltration of plasma cells. Base on International Myeloma Working Group, her diagnosis was Multiple myeloma, stage IIIA (according Durie – Salmon), stage I (according Revised – ISS) in standard – risk group. She was treatment with Bortezomib-Dexamethasone 4 cycles, then autologous stem cell transplant, and after that 2 cycles Bortezomib-Dexamethasone more for consolidation. Adjunctive treatment are: Biphosphonates each cycles beginning, analgesic drug, using crutches when walking and physical therapy. Prevention infection by using Acyclovir and Bactrim. Side effect was constipation in first cycle.

Result: After 4 cycles Bortezomib-Dexamethasone and after autotransplantation, she got rid of pain, walked normally and have no anemia. Serum immunofixation and protein electrophoresis are normal. Bone lesions in Xray and CTscan are not increasing after 4 cycles Bortezomib-Dexamethasone, especially, after autotransplantation her damaged bone was recreated. The patient achieved VGPR after 4 cycles of Bortezomib – Dexamethasone. After autologous stem cell transplant and 2 cycles of Bortezomib - Dexamthasone, she still achieved VGPR. Now: Her condition is stable. She has been received maintenance treatment with Thalidomide in the 25th month.

Conclusions: This is a case report about the youngest patient, who is diagnosed with Multiple myeloma with typical bone lesions in Viet Nam. Diagnostic imaging tools greatly assist in the diagnosis and evaluation of treatment response to patients. Combination of Bortezomib and adjunctive therapy (Biphosphonates, physical therapy) is a good treatment for bone damage due to disease. Clinical and biochemical improvement after chemotherapy and autologous stem cell transplant: reduction of pain, normal physical activity, imaging diagnostics showing no further bone damage but new bone formation.

Keyword: Multiple Myeloma, Teenage Patient, Bortezomib-Dexamethasone



PP-085

Multiple myeloma patients on novel agents: Effect of pneumococcal vaccination on incidence of infectious complications

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Background: Multiple myeloma (MM) is a neoplasm of the hematopoietic tissue with a predominant effect based on plasma cells, which affects older patients. In recent years, novel therapeutic agents have been actively introduced into clinical practice, resulting in improved survival rates in patients with MM. At the same time, the rates of infection-related mortality in MM patients remain impressive. For example, in a Swedish cohort of 9253 patients with MM it was found that 22% of patients die from infectious complications within the first year of diagnosis [1]. Pneumococcal infections remain significant causes of morbidity and mortality in hematologic patients receiving chemotherapy, especially in MM patients on novel agents, being one of the leading causes of pneumonias.

Methods: The aim of the conducted prospective study was to examine the clinical efficacy of 13-valent pneumococcal conjugate vaccine (PCV13) vaccination in patients with MM receiving novel agents. Therefore during the 2017-2018 years there were 17 patients vaccinated. Vaccination with PCV13 was recommended whenever possible between periods of chemotherapy and was performed three times with a minimum interval of 1 month. All patients expressed informed consent and commitment to vaccination. The cohort of MM patients matched by age, sex, hypogammaglobulinemia level and treatment regimen were used as comparative control group.

Result: Adverse events during vaccination in patients with MM were not recorded. The control group was recruited using the paired matching method in a 1: 1 ratio in the study. Despite the small sample size, a statistically significant effect of PCV13 vaccination on the incidence of febrile neutropenia episodes (p=0.0339) was observed. Meanwhile, there was a tendency to decrease in incidence of clinically-radiologically confirmed pneumonia in patients with MM after vaccination (p = 0.1344).

Conclusions: Implementation of PCV13 vaccination in MM patients between the periods of chemotherapy by novel agents has decreased the incidence of febrile neutropenia and showed a trend towards a decrease in incidence of pneumonias. Increasing the sample size of this ongoing study may give a more confident answer to the questions of clinical efficacy of further introduction of vaccination in adult patients with MM on novel agents. 1. Blimark, C. et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients / C. Blimark et al. // Haematologica. – 2015. – Vol. 100, № 1. – P. 107–113.

Keyword: Multiple Myeloma, Novel Agents, Infectious Complications, Pneumococcal Infection, Vaccination

PP-086

Detection of chromosome 13 (13q14) deletion among Sudanese patients with multiple myeloma using a molecular genetics fluorescent in situ hybridization

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Background: Multiple myeloma (MM) is a neoplastic plasma cell dyscrasia with an incidence of 4-4.5 per 100,000 population per year. It is regarded as the second most prevalent blood cancer (10%) after non-Hodgkin lymphoma.

Methods: 15 patients were enrolled in the study. 11 bone marrow samples were collected from MM patients at different stages of the disease and 4 samples were from patients with conditions other than MM as control. Plasma cells were counted from bone marrow smears and fluorescence-in-situ hybridization (FISH) was performed using Fluorophore labeled DLEU1 (13q14) LSI (local specific identifier) probe designed as a dual-colour assay to detect deletion at 13q14. Heparanized sample was taken for estimation of serum albumin in all patients.

Result: 13q14 deletion was detected in 6 (54.5%) MM patients while one (9.1%) patient showed monosomy. All relapsed MM (27.3%) had 13q14 deletion. Surprisingly almost all patients studied had normal albumin level.

Conclusions: In this study the detection rate of chromosomal abnormalities was successfully and significantly improved with FISH analysis using DLEU1 (13q14) LSI (local specific identifier) probe designed as a dual-color assay to detect deletion at 13q14. Chromsomal13q14 deletion was detected frequently (54.5%) among multiple myeloma patients and monosomy was detected in one (9.1%) patients. 13q14 deletion was significantly associated with a hyperproliferative stage of the disease (marrow plasma cell above 30%). All relapsed cases (27.3%) had deletion13q14. Whether the deletion is implicated in the pathogenesis of multiple myeloma needs to be elucidated.

Keyword: Multiple Myeloma, Fluorescence in-Situ Hybridization, FISH, DLEU1

PP-087

MGUS predicts worse prognosis in patients with coronary artery disease

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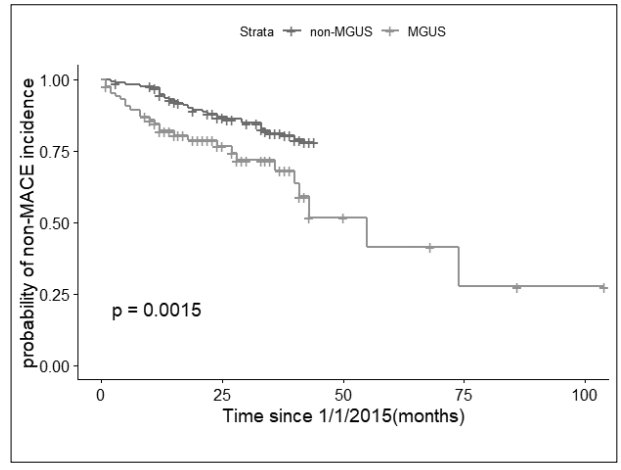
Background: Monoclonal gammopathy of undetermined significance (MGUS) is the premalignancy of multiple myeloma and accounts for about 50% of monoclonal gammopathy. MGUS is associated with numerous disorders, but there are very few articles focusing on the relationship between MGUS and coronary artery disease (CAD). This study is to evaluate the prognostic value of MGUS in patients with CAD.

Methods: We recruited 87 CAD patients with MGUS and 178 CAD patients without MGUS in Zhongshan Hospital from January 1, 2015 to December 31, 2017. Follow-up was performed by telephone and regular patient visits, with a median follow-up of 2.9 years. The end point was the occurrence of major adverse cardiac events (MACE). $p<0.05$ was considered to be statistically significant.

Result: We compared the biochemical data including gender, age, hypertension, diabetes, smoking status, serum glucose, Hb1Ac, eGFR, LDL, CRP, cTNT, NT-proBNP, PT, APTT, fibrinogen, and D-Dimer. Only age (p=0.026) and Hb1Ac (p=0.031) were considered to be statistically significant. Patients with MGUS had a higher incidence of MACE than those without MGUS (log-rank P=0.0015). After adjustment for other markers, MGUS was associated with increasing risk of MACE incident. (p=0.025, HR, 2.509[95%CI, 1.123, 5.604])

Conclusions: MGUS predicted worse prognosis in CAD patients, even after adjustment for other prognostic factors (including NT-proBNP) in the multivariate Cox model. Based on our research, MGUS might be added into the risk model of CAD and it is valuable and necessary to screen MGUS in CAD patients.

Keyword: MGUS, Coronary Artery Disease, Prognosis



PP-088

The value of abdominal fat aspiration and labial salivary gland biopsy in diagnosing immunoglobulin light chain amyloidosis

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Background: Light Chain Amyloidosis (AL) is a plasma cell disease with organ involvement causing by monoclonal immunoglobulin light chain, for which tissue biopsy stained with Congo red demonstrating amyloid deposits and verification of light chain composition is required for diagnosis. Different minimal invasive biopsy methods including abdominal fat aspiration, labial salivary galnd, and bone marrow biopsy have been reported, with the optimal biopsy strategy undetermined. Also, the correlation between IGVL gene usage and organ tropism has been studied, raising the possibility of association between biopsy site and organ involvement. Therefore, we evaluate the diagnostic performance and value of abdominal fat aspiration and labial salivary gland (LSG) biopsy in diagnosing AL amyloidosis with different organ involvement.

Methods: 59 patients diagnosed as AL amyloidosis from March 2017 to August 2018 in our centre were included in this retrospective study. Abdominal fat aspiration and LSG biopsies were respectively perfomed by one experienced hematologist and dentist by routine; other biopsies are done as needed. The biopsy results are confirmed by central Department of Pathology, with Congo red staining positive and immunoglobulin light chain composition verified by immunohistochemistry or immunofluorescence. Organ involvement is assessed according to NCCN guidelines. The diagnostic sensitivity of abdominal fat aspiration and LSG biopsy or both were compared, with information of organ involvement (cardiac and renal involvement) taking into consideration. Data analysis is done with SPSS 19.0. Quantitative and categorical data are analyzed with t-test and Chi square test.

Result: There were 43 males and 16 females with an average age of 63 (30-80) years old. Cardiac involvement and renal involvement were confirmed in 45 and 27 patients. 54 and 43 patients received abdominal fat aspiration and LSG biopsy respectively; 41 received both. The sensitivity for abdominal fat aspiration and LSG biopsy were 68.5% (37/54) and 62.8% (27/43) respectively, and 85.4% (35/41) for two methods combined. The sensitivity of LSG biopsy was significantly higher in patients with cardiac involvement than those who without (71.9% vs 30%, P=0.027), but no significant difference for abdominal fat aspiration (70.7% vs 58.3%, P=0.490) was found. The sensitivity for these two methods has no statistically significant difference in patients with or without renal involvement (fat aspiration 56.5% vs 75.9%, LSG 60% vs 61.9%, P>0.05), although a numerical difference was observed for fat aspiration.

Conclusions: The combination of abdominal fat aspiration and labial salivary gland (LSG) biopsy can increase the diagnostic sensitivity for AL amyloidosis, preventing the possibility of miss or delay of diagnosis. The value of LSG biopsy should be emphasized in cardiac involved patients, in whom its sensitivity is relatively high.

Keyword: Light Chain Amyloidosis, Biopsy, Abdominal Fat Aspiration, Labial Salivary Gland

No. Positive/No. Received（%）							
	All Patients N=59	Cardiac Involved	No Cardiac Involved	*P*	Renal Involved	No Renal Involved	*P*
Abdominal Fat Aspiration	37/54 (68.5)	29/41 (70.7)	7/12 (58.3)	0.490	13/23 (56.5)	22/29 (75.9)	0.234
LSG	27/43 (62.8)	23/32 (71.9)	3/10 (30)	0.027	12/20 (60)	13/21 (61.9)	1.000
Both	35/41 (85.4)	28/30 (93.3)	/	/	15/18 (83.3)	/	/

PP-089

Megakaryocytic expression of GATA-1, IL-6, and IL-8 in plasma cell neoplasm with dysmegakaryopoiesis

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Background: Dysmegakaryopoiesis is a diagnostic criterion for myelodysplastic syndrome (MDS), which accompanies thrombocytopenia. Recently, patients with plasma cell neoplasm (PCN) also reported dysmegakaryopoiesis; however, although they maintained normal platelet counts, the disease progressed, with most bone marrow cells being replaced by plasma cells. Several studies reported that dysmegakaryopoiesis was induced by inflammatory mechanisms; however, the exact mechanism underlying dysmegakaryopoiesis remains unknown. This study aimed to investigate whether changes in the

megakaryocytic expression of GATA-1; pro-inflammatory cytokines, including interleukin (IL)-6 and IL-8; and CD9 affect platelet counts and dysmegakaryopoiesis in patients with PCN and MDS.

Methods: In total, 114 patients were examined and categorized into the following four groups: Group 1 (MDS with dysmegakaryopoiesis), 34 patients; Group 2 (PCN without dysmegakaryopoiesis), 36 patients; Group 3 (PCN with dysmegakaryopoiesis), 19 patients; and Group 4 (normal control), 25 patients. GATA-1, IL-6, IL-8, and CD9 expression in megakaryocytes was assessed by immunohistochemical (IHC) staining of paraffin-embedded bone marrow sections. Localized expression of transcription factor and cytokines was observed in megakaryocytes.

Result: Expression of GATA-1, IL-6, and IL-8 significantly differed (all $p<0.05$). Decreased GATA-1 expression was identified in MDS. Decreased IL-6 expression was observed in PCN and MDS. Moreover, decreased IL-8 expression was associated with dysmegakaryopoiesis, regardless of whether platelet counts were maintained.

Conclusions: In conclusion, PCN with dysmegakaryopoiesis had normal platelet counts, and their megakaryocytes showed decreased IL-6 and IL-8 expression and normal GATA-1 expression. The differences in the megakaryocytic expression of cytokines in PCN and MDS with dysmegakaryopoiesis may be applicable to target therapy.

Keyword: Dysmegakaryopoiesis, GATA-1, IL-6, IL-8, Plasma Cell Neoplasm, Myelodysplastic Syndrome

Table Statistical comparison of IHC scoring among the four groups

		Mean rank	Median value	IQR	χ^2	*p value*
GATA-1 d	Group 1	42.44	0.74	0.22	11.095	0.011
	Group 2	68.03	0.87	0.15		
	Group 3	60.50	0.77	0.25		
	Group 4	60.54	0.80	0.32		
GATA-1 i	Group 1	40.47	1.21	0.59	13.299	0.004
	Group 2	67.28	1.66	0.76		
	Group 3	63.84	1.50	0.48		
	Group 4	61.76	1.50	0.59		
IL-6 d	Group 1	55.15	0.49	0.80	20.409	0.000
	Group 2	51.49	0.45	0.91		
	Group 3	40.74	0.30	0.50		
	Group 4	82.10	0.86	0.14		
IL-6 i	Group 1	52.00	0.70	0.71	25.326	0.000
	Group 2	59.60	0.87	1.17		
	Group 3	32.05	0.37	0.53		
	Group 4	81.30	1.23	0.67		
IL-8 d	Group 1	54.72	0.87	0.02	9.489	0.023
	Group 2	62.65	0.98	0.00		
	Group 3	44.24	0.90	0.07		
	Group 4	63.94	0.99	0.00		
IL-8 i	Group 1	44.62	0.97	0.17	13.623	0.003
	Group 2	71.10	1.34	0.55		
	Group 3	47.82	0.98	0.83		
	Group 4	62.80	1.20	0.29		
CD9 d	Group 1	56.12	1.00	0.00	1.734	0.629
	Group 2	57.96	1.00	0.00		
	Group 3	56.47	1.00	0.00		
	Group 4	59.50	1.00	0.00		
CD9 i	Group 1	74.71	2.97	0.14	45.550	0.000
	Group 2	62.57	2.91	0.28		
	Group 3	66.92	2.97	0.40		
	Group 4	19.64	2.13	0.45		

Group 1 (myelodysplastic syndrome with dysmegakaryopoiesis), Group 2 (plasma cell neoplasm [PCN] without dysmegakaryopoiesis), Group 3(PCN with dysmegakaryopoiesis), and Group 4 (normal controls).

IQR, Interquartile range; d, diffuseness score; i, intensity score.

PP-090

Bortezomib-based first line treatment for AL amyloidosis patients who are not candidate for stem cell transplantation

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Background: Systemic AL amyloidosis (AL) is characterised by deposition of misfolded immunoglobulin light chains within organs. Treatment for amyloidosis is generally derived from that for multiple myeloma (MM). Combinations of immunomodulatory drugs and proteasome inhibitors are standard frontline MM therapy, but there is little experience with such regimens in AL. For patients not receiving autologous stem cell transplantation (ASCT), bortezomib-based regimens have been first-line treatment in AL amyloidosis over the last few years. The purpose of this study is to investigate the efficacy of bortezomib-based regimens for patients with newly diagnosed AL amyloidosis

Methods: We performed a retrospective study of all newly diagnosed patients with AL treated at our center between 4/1/11 and 12/31/17. Data pertaining to demographics, diagnosis, treatment and follow-up were extracted from electronic medical records. Survival curves were constructed according to the Kaplan-Meier method and compared using the log rank test. All statistical analyses were performed by using the SPSS 24.0 software. Progression free survival (PFS) is defined as time from the date of diagnosis to disease progression or death. The primary endpoint was overall response rate and secondary endpoints were overall survival (OS) and PFS.

Result: A total 63 patients with newly diagnosed AL amyloidosis who did not receive ASCT were analyzed. Clinical characteristics are shown in Table 1. They included 32 men and 31 women with a median age of 66 years (range, 42–82). Autonomic nerve, Cardiac, peripheral nerve, renal, soft tissue, and liver involvement were found in 46 (73%),41 (65.1%), 23 (36.5%), 20 (31.7%), 16 (25.4%), 4(6.4%), respectively. The Mayo 2012 stage was: Stage 2 3.8%, Stage 3 30.8% and stage 4 65.4%. Hematological responses were: complete response (CR) 33.3 %, VGPR 19.0%, partial response (PR) 12.6% and no-response (NR) 17.4%. Organ response was 26.9% (n=17). With a median follow-up of 34 months, median OS was 44 months (95% CI 13-70) and median PFS was 12 months (95% CI 5-34). The rate of early death within 6 months was 28.5% (n=18). Patients were classified according to first-line treatment; bortezomib-based regimens (VMP, n=37; VD (Bortezomib and dexamethasone), n=9; VCD, n=8; VMD, n=8; VTD (Bortezomib with thalidomide and dexamethasone, n=1). Hematological responses of VMP, VD, VCD, VMD, and VTD were: 75.6%, 55.5%, 50.0%, 50.0%, 100%, respectively. Organ responses of VMP, VD, and VMD were: 35.1%, 22.2%, 25.0%, respectively.

Conclusions: These findings continue to support the emerging roles for bortezomib-based regimens for the purposes of improving response. There are no significant differences of efficacy between bortezomib based regimens.

Keyword: Bortezomib, Amyloidosis, Survival

Table 1. Baseline Characteristics

		N	%
		63	100
Age		66 (42-82)	
	> 65	36	57.1
Sex	M/F	32/31	50.8/49.2
Presenting Symptom	dyspnea	33	52.4
	edema	9	14.3
	proteinuria	5	7.9
	dizziness or syncope	3	4.8
	diarrhea	2	3.2
	ECOG PS 2 or more	14	22.2
	NYHA Fc G2 or more (n=63)	37	58.7
Organ involvement	Cardiac (n=63)	41	65.1
	Renal (n=63)	20	31.7
	Hepatic (n=63)	4	6.4
	Peripheral neuropathy (n=63)	23	36.5
	Autonomic neuropathy (n=63)	46	73.0
	Gastrointestinal (n=63)	11	17.5
	Pulmonary (n=63)	2	3.2
	soft tissue (n=63)	16	25.4
N of organ involvement	1	8	12.7
	2	20	31.7
	3 or more	35	55.6
Systolic Blood Pressure	<100	29	46.0
	≥100	34	54.0
Heavy chain	IgG	14	22.2
	IgA	6	9.5
	Light chain disease	40	63.5
	IgD	3	4.8
Light chain	Kappa	15	23.8
	Lambda	47	74.6
CRAB	Anemia (n=63)	15	23.8
	Hypercalcemia (n=63)	3	4.8
	Cr>2.0 (n=63)	21	33.9
	lytic bone lesion (n=63)	4	8.0
TYPE (n=50)	MM-CRAB	16	25.3
	MM-PC	26	41.2
	AL	8	12.6
NT-proBNP (n=62)	median	6238 (285-35000)	
	≥332 ng/L	61	98.4
	≥1800 ng/L	51	82.3
	≥8500 ng/L	23	37.1
troponin T (n=54)	median	0.074 (0.018-0.356)	
	≥0.025 ng/mL	51	94.4
	≥0.035 ng/mL	51	94.4
	≥0.06 ng/mL	38	70.4
troponin I (n=50)	median	0.231 (0.010-3.82)	
	≥0.1ng/mL	38	76.0
dFLC (n=63)	Median	189(0-11633)	
	≥180mg/L	49	77.8

PP-091

Health-related quality of life in relapsed/refractory multiple myeloma: Systematic review of randomized control trials

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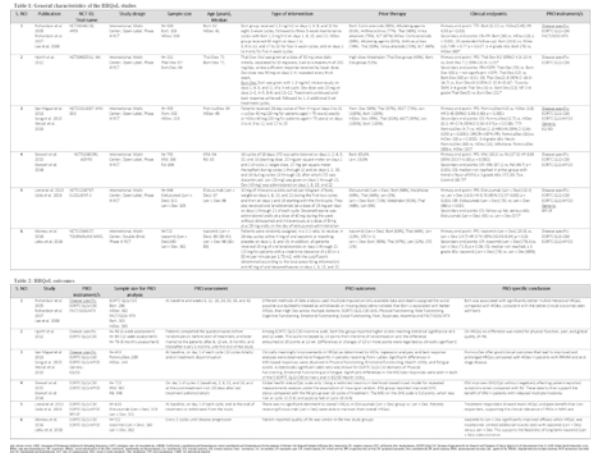
Background: Health-related quality of life (HRQoL) is becoming an increasingly important goal for the treatment of patients with Relapsed/Refractory Multiple Myeloma (RRMM). Availability of the appropriate HRQoL data improves healthcare decision-making and resource allocation by providing disease state utility value and health outcomes. We performed a systematic review to identify evidence from randomized control trial (RCT) reporting HRQOL in patients receiving treatments for RRMM.

Methods: A systematic search was conducted on Medline, Embase, and Cochrane databases (using Ovid platform), and ClinicalTrials.gov in Dec 2018. Eligible studies comprised RCTs reporting HRQoL in patients with RRMM. Data pertaining to demographics, clinical characteristics, patients reported outcomes tool (PRO) characteristics, and summary of findings was extracted.

Result: After screening 780 records, six RCTs reported in 13 articles qualified for inclusion. Four studies compared proteasome inhibitors (PIs) with placebo or active comparator, one study each compared immunomodulatory drugs and monoclonal antibodies with dexamethasone. While all the studies used disease-specific PRO tool i.e. EORTC QLQ-C30; four used it in conjunction with myeloma specific QLQ-MY20 instrument, and one with FACT/GOG-NTX. EQ-5D and BPI-SF were other accompanying generic PRO instruments used. All expect two studies used all the domains of the EORTC QLQ-C30 and QLQ-MY20. The HRQOL the by improved global health status (GHS) along with physical functioning and emotional functioning. Signifying that GHS can be considered important in patients with RRMM. Overall, the patients in the experimental arm did not indicate a worse HRQoL outcome or symptom severity compared to the control arm.

Conclusions: The evidence from RCTs on HRQoL in RRMM patients is scarce. Future RCTs in this area with the use of both generic and disease-specific PRO tool are recommended to better identify the patients focused outcomes and disease state utility.

Keyword: Multiple Myeloma, Quality of Life, Patient-Reported Outcomes, HRQoL, Systematic Review, Randomized Control Trial



PP-092

Prognostic impact of frailty in transplant-ineligible multiple myeloma patients treated with first-line bortezomib-based chemotherapy

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Background: Frail patients who are in a poor performance status and have serious comorbidities or abnormal laboratory results comprise about one-third of the transplant ineligible multiple myeloma (MM). These patients, most of the cases, are excluded from the clinical studies. By far, the outcome of the real world data according to the patients' fitness in transplant ineligible MM patients is limited.

Methods: Four hundred and fifteen patients with MM who have been treated with bortezomib, melphalan and prednisone (VMP) as a first-line treatment were retrospectively analyzed. 4 factors included

into the frailty scores were Age, ECOG PS (Eastern cooperative group performance status), eGFR (estimated glomerular filtration rate), and number of comorbidities (heart disease, lung disease, liver disease, cerebrovascular disease, diabetes mellitus). These factors were di- or trichotomized by the reference of previously published papers and the meaningful cut-offs in our data. The points given to each variables were after the following criteria: Age < 70 (point 0), 70-79 (point 1), ≥ 80 (point 2); ECOG PS 0-2 (point 0), 3-4 (point 2); eGFR ≥ 60 mL/min/1.73 m2 (point 0), < 60 mL/min/1.73 m2 (point 1); comorbidity 0-1 (point 0) and ≥ 2 (point 1). Patients were further classified by frailty scores: fit (points 0-2), unfit (points 3-5) and frail (point 6).

Result: The median follow-up duration was 26.72 months (range 0.37 – 180.20 months). Patient characteristics are listed in Table 1. All of the factors including the Age ≥ 80, ECOG PS 3-4, eGFR < 60 mL/min/1.73 m2, and comorbidity ≥ 2 were statistically significant for overall survival (OS) by univariate analysis. In multivariate analysis, ECOG PS 3-4 and eGFR < 60 mL/min/1.73 m2remained statistically significant for OS and Age ≥ 80 was marginally significant for OS (Figure 1 and Table 2). The response rates by the fit, unfit, and frail were as follows: 77.5% (148/191), 71.4% (55/77), and 0% (0/2) (P= 0.028). The 3-year overall survival rates by the frailty were 66%, 41%, and 0% in the fit, unfit or frail patients, respectively and showed statistically significant differences (Figure 2 and Table 3, P= 0.000). The comparison of the frailty score with international staging system (ISS) and revised ISS (R-ISS) revealed statistical significance of all of the prognostic systems affecting OS by the univariate analyses but R-ISS and frailty score remained significantly affecting OS.

Conclusions: Unfit and frail patients showed a significant decrease in OS compared to fit patients. But there was no difference between the unfit and fit patients in terms of response rate in MM patients who were transplant ineligible and have received bortezomib-containing regimen. Treatment of the unfit and frail patients needs more caution on toxicity management and appropriate dosing schedules to improve the survival outcome.

Keyword: Multiple Myeloma, Bortezomib, Frailty

Table 1. Univariate and multivariate analysis of overall survival according to the patient fitness

	Univariate analysis		Multivariate analysis	
	HR	P-value	HR	P-value
Age (years, n)				
< 80 (388)				
≥ 80 (20)	2.302 (1.122-4.726)	0.023	2.004 (0.960-4.181)	0.064
ECOG PS (n)				
0-2 (391)				
3-4 (19)	3.760 (2.014-7.022)	0.000	3.660 (1.922-6.970)	0.000
eGFR (mL/min/1.73m², n)				
≥ 60 (185)				
< 60 (144)	1.990 (1.348-2.937)	0.001	1.840 (1.231-2.749)	0.003
Comorbidities (n)				
0-1 (360)				
≥ 2 (49)	1.660 (1.003-2.746)	0.049	1.205 (0.651-2.230)	0.554

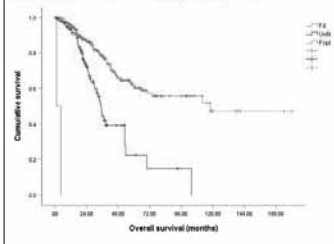
ECOG PS, eastern cooperative group performance status; eGFR, estimated glomerular filtration rate; HR, hazard ratio

Table 2. Univariate and multivariate analysis of overall survival according to the patient fitness and stage

	Univariate analysis		Multivariate analysis	
	HR	P-value	HR	P-value
ISS (n)				
I (75)				
II, III (326)	2.007 (1.213-3.322)	0.007	0.519 (0.259-1.037)	0.063
R-ISS (n)				
I (57)				
II, III (344)	3.481 (1.755-6.905)	0.000	5.744 (2.249-14.666)	0.000
Frailty score (n)				
fit (308)				
unfit/frail (102)	2.831 (1.948-4.114)	0.000	2.682 (1.830-3.931)	0.000

ISS, international staging system; R-ISS, revised international staging system; HR, hazard ratio

Figure 1. Overall survival according to frailty score



PP-093

Comparison of conventional cytogenetic analysis and fluorescence in situ hybridization in survival of newly diagnosed myeloma patients

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Background: Cytogenetic changes detected at the time of diagnosis in multiple myeloma patients are of significant importance in terms of prognoses. In this research, I investigated the frequencies of different types of chromosomal abnormalities and analyzed the patients' overall survival according to each types of abnormalities. Discordant detection results were also compared.

Methods: In this retrospective study, 98 patients with multiple myeloma diagnosed in Dong-A University hospital with results from

both conventional cytogenetic analysis and fluorescence in situ hybridization were enrolled. The comparison group was defined as patients with normal karyotypes. Patients'clinical and laboratory data such as hemoglobin, platelet, calcium, albumin, creatinine, beta-2 microglobulin, International staging system, monoclonal protein, chemotherapy, stem cell transplantation were retrieved from medical records. G-banding method was used for conventional cytogenetic analysis and the types of probes for FISH were: del(1p32)/dup(1q21), t(4;14)(p16;q32), t(6;14)(p21;q32), t(11;14)(q13;q32), CEP12, 13q34.3, IGH(14q32), t(14;16)(q32;q23), t(4;20)(q32;q12), and TP53.

Result: The median age of study population was 66 years old and the median survival period of patients was 24.5 months, with 40 surviving patients during study period. 82.6% of patients presented with abnormal genetic results. Between normal and abnormal karyotype groups, only anemia (P=0.01) had statistical significance. Among clinical and laboratory factors except for cytogenetic aberrations, old age (>65 years) (P=0.02) was the most independent risk factor for overall survival. Common cytogenetic abnormalities in our study population were -13/del(13q) (17.9%), dup(1q21)(13.8%), hyperdiploidy (11.93%), t(11;14) (9.2%), and among them, -13/del(13q) (P=0.03), hypodiploidy (P=0.008) and dup(1q21) (P=0.01) only correlated with adverse clinical impact. Thirty-three cases (33.7%) showed different detection results between G-banding and FISH. Patients with 1q21 gain lived shorter when detected by metaphase analysis.

Conclusions: The shortcomings of this study are that this retrospective study is done on a small number of patients in a single institution, and the numbers of FISH probes observed were not constant. I found 3 types of chromosomal abnormalities that adversely predicted patients'overall survival. In cases of discordant results between metaphase analysis and interphase FISH, 1q21 gain predicted shorter overall survival when detected by metaphase analysis.

Keyword: Multiple Myeloma, Somatic Variants, Survival, Conventional Cytogenetic Analysis, Fluorescence in Situ Hybridization

PP-094

Orthotopic heart transplant facilitated autologous hematopoietic stem cell transplantation for light-chain amyloidosis

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Background: Dominant cardiac involvement by primary systemic amyloidosis (AL) precludes effective AL treatment and is associated with short survival. We evaluated long term outcomes of these patients receiving orthotopic heart transplantation (OHT) and autologous hematopoietic stem cell transplantation (ASCT).

Methods: Between January 2009 and July 2018, total of 14 patients who presented with severe cardiac dysfunction as their major manifestation of AL underwent OHT. Eight of these 14 patients received ASCT. All patients had end stage heart failure and developed cardiogenic shock requiring intra-aortic balloon pump support (median 20 days, range 10-165) as a bridge to OHT.

Result: The median age at AL presentation was 54 years (42-63) in 7 females and 7 males. At median follow-up of 55 months (1-104) from OHT, 10 (71 %) patients are alive (table-1). Two patients died of post-operative complications at 1 and 7 months post OHT; 2 patient died 36 and 104 months after OHT (23 and 91 months post ASCT) of AL progression. Eight patients received ASCT at median of 13 months (13-34) after OHT. Treatment for disseminated cryptococcus delayed ASCT in one patient (#8). One patient awaits ASCT in June 2018. In the remaining 3 patients ASCT was not feasible due; to low DLCO (n=2) and prior ASCT (n=1). All 8 patients with ASCT were on tacrolimus and prednisone at the time of stem cell mobilization and hematopoietic transplant; two patients were also receiving mycophenolate mofetil and valganciclovir. We collected 4.0, 5.7, 6.1, 6.2 and 9.6 x 106/kg CD-34+ cells in 2 days after filgrastim administration (5 ug/kg, twice, daily) and plerixafor (16 mg/kg based on day- 4 CD-34+ counts) in 5 subjects. The fifth patient initially failed to mobilize but 4.3x106/kg CD-34+ cells were subsequently obtained after stopping mycophenolate mofetil for 4 weeks. The median creatinine clearance at the time of ASCT was 42 (30-53) ml/minute. All 8 patients received a renal adjusted dose of melphalan at 140mg/m2. Mycophenolate mofetil and valganciclovir were withheld during neutropenia until engraftment. No patients received post-transplant filgrastim. Median duration of hospitalization was 18 (15-20) days. Six patients achieved hematologic complete remission while 2 patients had a partial response following ASCT. Post ASCT reactivation of CMV was seen in 4 patients. Median survival from initial AL diagnosis is 44 (11-136) Months.

Conclusions: The strategy of OHT followed by ASCT is therefore feasible in select patients with dominant cardiac involvement and advanced heart failure.

Keyword: Amyloidosis, Light Chain, ASCT, Heart Transplant, Stem Cell Transplant

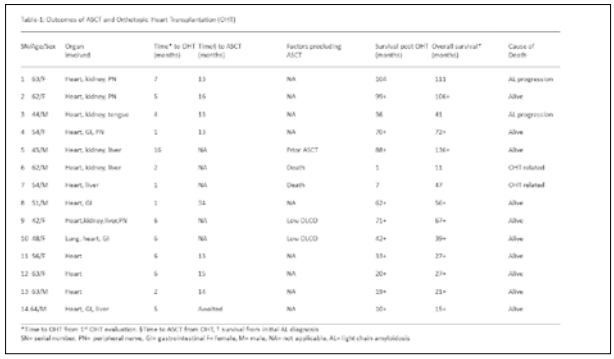

Table 1. Outcomes of ASCT and Orthotopic Heart Transplantation (OHT)

SN/Age/Sex	Organ involved	Time* to OHT (months)	Time† to ASCT (months)	Factors precluding ASCT	Survival post OHT (months)	Overall survival* (months)	Cause of Death
1 63/F	Heart, kidney, PN	7	13	NA	104	133	AL progression
2 62/F	Heart, kidney, PN	5	16	NA	95+	106+	Alive
3 44/M	Heart, kidney, tongue	4	15	NA	56	63	AL progression
4 54/F	Heart, GI, PN	1	10	NA	70+	72+	Alive
5 45/M	Heart, kidney, liver	16	NA	Prior ASCT	88+	136+	Alive
6 62/M	Heart, kidney, liver	2	NA	Death	1	13	OHT related
7 54/M	Heart, liver	1	NA	Death	7	47	OHT related
8 51/M	Heart, GI	1	14	NA	62+	56+	Alive
9 42/F	Heart,kidney,liver,PN	9	NA	Low DLCO	71+	97+	Alive
10 68/F	Lung, heart, GI	6	NA	Low DLCO	42+	39+	Alive
11 56/F	Heart	6	15	NA	33+	37+	Alive
12 63/F	Heart	6	15	NA	20+	23+	Alive
13 63/M	Heart	2	14	NA	19+	23+	Alive
14 64/M	Heart, GI, liver	5	Awaited	NA	10+	15+	Alive

*Time to OHT from 1st OHT evaluation, †Time to ASCT from OHT, ‡ survival from initial AL diagnosis
SN= serial number, PN= peripheral nerve, GI= gastrointestinal F= female, M= male, NA= not applicable, AL= light chain amyloidosis

PP-095

Changes in blood viscosity and yield stress before and after phlebotomy

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Background: Hematocrit (Hct) has been used as a conventional parameter to evaluate the effect of phlebotomy. There have been limited studies on blood viscosity in relation to phlebotomy. We investigated the changes in blood viscosity before and after phlebotomy in polycythemia patients.

Methods: In 40 polycythemia patients undergoing phlebotomy (phlebotomy events, n = 50), systolic blood viscosity (SBV), diastolic blood viscosity (DBV), and yield stress (YS) were measured and calculated using scanning capillary tube viscometer (Hemovister, Ubiosis, Seongnam, Korea). We compared the median values of Hct, SBV, DBV, and YS immediately before and after phlebotomy using Wilcoxon signed-rank test. The association between Hct, SBV, DBV, and YS was evaluated using Pearson's correlation and multivariate linear regression analyses.

Result: Among 50 phlebotomy events, Hct, SBV, DBV, and YS decreased significantly after phlebotomy (all $P < 0.01$). Post-Hct (%) highly correlated with post-SBV (cP, centipoise), post-DBV (cP), and post-YS (cP) (all $r \geq 0.8$, $P < 0.001$). In multivariate linear regression analysis, post-Hct (%) significantly predicted post-SBV (cP) and post-DBV (cP) ($P < 0.05$, all); post-DBV significantly predicted post-YS ($P < 0.001$). Delta Hct (%), delta SBV (cP), delta DBV (cP), and delta YS (cP) all showed variable distributions.

Conclusions: The changes in SBV, DBV, and YS were variable after phlebotomy. These findings may provide fundamental data to understand the changes in blood viscosity and to expand therapeutic targets in phlebotomy.

Keyword: Hematocrit, Phlebotomy, Viscosity, Polycythemia, Yield Stress

PP-096

Do we need the revised 2016 WHO polycythemia vera diagnostic criteria for better diagnosis of posttransplantation erythrocytosis?

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Background: Posttransplantation erythrocytosis (PTE) has been arbitrarily defined as persistent elevation of hemoglobin (Hb) and hematocrit (Hct) to > 17.0 g/dL and > 51%, respectively, after kidney transplantation (so-called "traditional PTE diagnostic criteria"). A significant increase in Hct was shown to increase viscosity of the blood and cause thrombosis and cardiovascular events. The World Health Organization (WHO) lowered the diagnostic Hb/Hct threshold values for diagnosis of polycythemia vera (PV) in 2016, which has markedly changed the diagnostic landscape of this disorder, and consequently the options for treatment and outcome. In the present study, we retrospectively evaluated whether the revised WHO Hb/Hct criteria for PV is more relevant than the traditional PTE diagnostic criteria in terms of predicting cardiovascular events.

Methods: The medical records of patients undergoing kidney transplantation at Chungnam National University Hospital in Daejeon, South Korea, between June 2000 and December 2016 were retrospectively reviewed. PTE was diagnosed according to the traditional criteria and the 2016 WHO criteria, and the patients were divided into three groups: patients meeting Hb/Hct criteria at least once (all PTE), patients with PTE lasting for more than 3 months (PTE > 3 m), and patients with PTE lasting for more than 6 months (PTE >

6 m). Each group was compared to non-PTE patients and age-, sex-, graft function-, and follow-up duration-matched controls.

Result: A total of 237 patients (158 males, 79 females) with a median age of 56 years (range: 18–84 years) were followed up for a median of 70.4 months (range: 4–221 months). The incidence rates of all PTE, PTE > 3 m, and PTE > 6 m were 16.0%, 10.1%, and 7.6%, respectively, according to the traditional criteria, and 24.1%, 19.8%, and 16.0%, respectively, according to the 2016 WHO criteria. During follow-up, 19 patients developed cardiovascular events (8 cardiac, 7 cerebrovascular, 3 peripheral vascular, and 1 other). The incidence rates of cardiovascular events in the all PTE group and PTE > 3 m group did not differ from those in non-PTE patients, regardless of the diagnostic criteria used. Cardiovascular events tended to be more frequent in the 2016 WHO criteria PTE > 6 m group (15.4% vs. 6.5%, P=0.064), and were significantly more frequent in the traditional criteria PTE > 6 m group (22.2% vs. 6.8%, P=0.021) than in the non-PTE group. The incidence rates of cardiovascular events in the 2016 WHO criteria PTE groups did not differ from controls, regardless of subgroup: all PTE (10.5% vs. 5.5%, P=0.324), PTE > 3 m (13.3% vs. 4.5%, P=0.147), and PTE > 6 m (15.4% vs. 8.3%, P=0.348). On the other hand, cardiovascular events tended to be more frequent in the traditional criteria all PTE group (15.8% vs. 2.9%, P=0.061), and were significantly more frequent in the traditional criteria PTE > 3 m group (16.7% vs. 0%, P=0.041) and the traditional criteria PTE > 6 m group (22.2% vs. 0%, P=0.034) compared to the controls.

Conclusions: The revised 2016 WHO Hb/Hct criteria for diagnosis of PV do not provide additional information over the traditional PTE diagnostic criteria in terms of cardiovascular events.

Keyword: Erythrocytosis, Kidney Transplantation, Polycythemia Vera, WHO

PP-097

Characteristics and survival of atypical chronic myeloid leukemia; Based on national health information database

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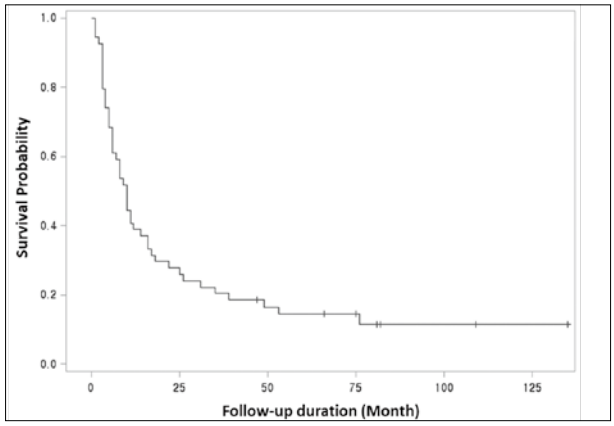
Background: BCR/ABL negative or atypical chronic myeloid leukemia (aCML) is rare hematologic malignancy with an estimated incidence of 1–2% of BCR/ABL positive CML. The rarity of the disease has largely precluded conduction of any prospective study to optimize treatment strategy of BCR/ABL negative CML, consequently, BCR/ABL negative CML has been managed with palliative therapy. A population-based study on the outcome of atypical CML is rare. Thus, we analyzed characteristics and outcomes of aCML using the national health information database (NHID).

Methods: We included patients who were diagnosed with aCML (ICD 10, C922) between 2004-2015. We excluded following patients; 1) age <20, 2) who received chemotherapy before aCML diagnosis, 3) C922 was recoded just once during the follow up period. Student's t test (Mann-Whitney test) was used for numerical comparison between two groups, chi-square test (Fisher exact test) was applied for categorical variables. Overall survival (OS) was calculated by Kaplan-Meier methods, using SAS version 9.2.

Result: Over 11 years, only 54 aCML patients were identified. Median age at diagnosis was 73 years old, age≤50 was 7 (13%) patients, 50< age ≤70 was 11 (20.4%) patients, and age >70 years, 36 (66.7%) patients. Sixty-five % were male. Thirty-five patients (64.8%) were paying high insurance premium, and 20 patients (37%) were treated at institution located in Seoul area. Most patients were received transfusion (91%), 59% (n=32) needed both RBC and platelet transfusion, and 31.5% (n=17) received only RBC transfusion. Packed RBC was transfused mean 3.1 times every month. Hydroxyurea was given to 93% of patients. Seven patients (13%) were received decitabine and 8 (14.8%) were treated with cytarabine. No one received azacytidine or underwent hematopoietic stem cell transplantation. With 10 (1-135) months of median follow up, 47 patients were expired, and their median OS was 10 (6-14) months (Figure 1). Limitations of this study include inability to determine the effect of therapy or differences in clinical features at presentation.

Conclusions: Based on national health information database, atypical CML in Korea is rare, and only 54 patients were diagnosed between 2004-2015. With 10 (1-135) months of median follow up, OS was poor showing that median OS was 10 (6-14) month. Thus, collaborative efforts to find a treatment target and development of new therapy should be needed.

Keyword: Atypical Chronic Myeloid Leukemia, Overall Survival, The National Health Information Database



PP-098

Clinical application of next-generation sequencing in myeloproliferative neoplasms: Genetic profiles and prognostic significance

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Background: Mutational landscape of myeloproliferative neoplasms (MPNs) has been discovered including three diagnostic driver mutations, JAK2, MPL, and CALR. Nowadays, next-generation sequencing (NGS), especially targeted panel sequencing, is widely applied in clinical laboratory to identify mutational profile in hematologic malignancies. Herein, we evaluated genetic profiles in MPNs using NGS and explored the clinical application in the single center cohort.

Methods: A total of 432 patients were included; 196 essential thrombocythemia (45.37%), 112 polycythemia vera (25.9%), 72 primary myelofibrosis (16.7%), 14 other MPNs (3.2%) and 38 myelodysplastic/myeloproliferative neoplasms (MDS/MPN, 8.8%). JAK2 V617F, CALR and MPL 515 mutations were firstly analyzed using allele-specific PCR and fragment analysis. Targeted panel sequencing including 86 genes was performed. We analyzed relationships between genetic proflies and clinical outcomes including acute transformation, bone marrow fibrosis and death.

Result: Three driver mutations were detected in 82.4% of patients; JAK2 V617F in 64.8%, CALR in 15.7% and MPL in 1.9%. We also detected mutations in other genes through NGS which included ASXL1 (27.0%), TET2 (7.6%), KMT2C (3.2%), SRSF2 (2.9%), RUNX1 (2.9%), CSF3R (2.5%), ATM (2.2%), SETBP1 (1.8%), DNMT3A (1.8%), TP53 (1.8%), U2AF2 (1.8%), KMT2D (1.8%) and PTPN11 (1.8%). Among the three phenotypic subtypes, PMF showed shorter event free survival (EFS) than the others (hazard ratio: PMF-ET 2.62, PMF-PV and 2.97). In the aspect of genetic profile, TP53 mutation showed worst outcome followed by chromatin or spliceosome mutation (Median EFS: 77 and 99 months, 95% Confidential interval: 5.0-264 and 72-226, respectively). TP53 or chromatin/spliceosome mutations were detected in 34.4% (11/35) of triple negative MPN patients.

Conclusions: We demonstrated that NGS effectively identified mutations that were more relevant to the prognosis in MPN patients. Genetic profiles can improve a risk stratification to make efficient therapeutic plan including targeted therapy in MPN patients.

Keyword: Myeloproliferative Neoplasms, NGS, Prognosis, TP53

PP-099

Clinical effect of haploidentical hematopoietic stem cell transplantation combined with post-transplant cyclophosphamide for children with severe aplastic anemia

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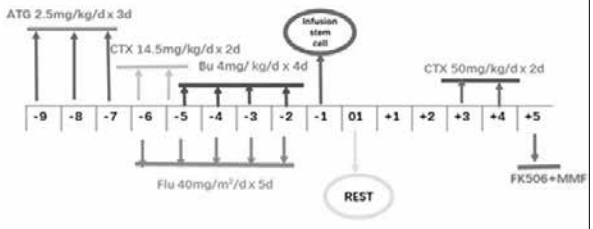
Background: Severe aplastic anemia (SAA) is a fatal bone marrow failure disease for pediatric patients. Hematopoietic stem cell transplantation (HSCT) with matched sibling donor (MSD) is still the first choice for children with SAA. However, most patients cannot find a suitable donor. Post-transplant graft-versus-host disease (GVHD) remains a severe complication. In recent years, many data confirms that the safety and efficacy by use of post-cyclophosphamide (PT/Cy) as GVHD prophylaxis in HSCT for patients without suitable donor. To investigate the efficacy and safety of HSCT in treatment of SAA with modified post-transplant cyclophosphamide (PT/Cy), we launched a novel approach for this group of patients.

Methods: From August 2015 to August 2018, 5 children diagnosed with SAA in our hospital were retrospectively analyzed. All patients were male. Donors were all from family members. HLA matching 6-8/12 loci were identical. Engrafts consisted of bone marrow (BM) and peripheral blood stem cells (PBSC). All patients received the same condition regimen including fludarabine, bulsufan, cyclophosphamide and thymoglobuline. As GVHD prophylaxis, intravenous infusion of 50mg/kg cyclophosphamide was given on day +3 to 4, low-dose tacrolimus (FK506) and oral mycophenolate mofetil (MMF) was given on day +5 post-transplant, if patients were without the risk of GVHD, FK506 was withdraw in 3 months post-HSCT and MMF on day +28.

Result: 80% (4/5) patients successfully achieved full donor' chemirism, only 1 patient occurred graft reject and performed second-HSCT with the change of donor. The median time of neutrophil and platelet engraftment was 13 (11~16) days and 26 (15~42) days, respectively. Only 1 patient developed acute GVHD (grade I), no patient developed acute GVHD (grade III ~ IV) and chronic GVHD. All 5 patients with a median followed up of 1.2 (range 0.5~3.0) years, All of them were well and alive.

Conclusions: Allo-HSCT combined with PT/Cy is an effective method for the treatment of pediatric SAA, and its safety are still need to be confirmed by a cohort number of cases.

Figure 1 Conditioning Regimen



PP-100

The outcome of immunotherapy by antithymocyte globulin and cyclosporine a for acquired aplastic anaemia during 10 years in Vietnam

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Background: Aplastic anaemia (AA) is one of the most common hematological diseases in children with many difficulties in management and prognosis. They are characterized by pancytopenia (anemia, gralunocytopenia, thrombocytopenia) and a hypocellular bone marrow. The incidence rate of AA in Europe amounts to approximately 2-3/ 10 6/ year and 4- 16 per 10 6 / year in parts of Asia. No difference between boy and girl.

Objective: Evaluate the efficacies of immunosuppressive therapy (IST) with horse antithymocyte globulin (ATG) and cyclosporine A (CSA) for childhood AA at NCH.

Methods: Prospective and retrospective study was carried on 30 patients of AA at Clinical Hematology Department from Jan 2007 to Aug 2017. A hypocellular bone marrow biopsy is required for the diagnosis of AA. All of these children were divided 3 subgroups as classification based on the degree of peripheral blood cytopenia: very severe AA- vSAA (n= 10), severe AA- SAA (n= 18) and non severe AA- nSAA (n= 2).

Result: 30 patients with 20 boys and 10 girls (2:1). Median age was 7.0 year old. Ten years followed up post immunosuppressive regimen, overall response rate is 73.3% (included 40%; 88.9% and 100% in vSAA; SAA and nSAA respectively, p= 0.013). Overall complete remission rate is 26.7% (0%; 33.3% and 100% in vSAA; SAA and nSAA respectively, p= 0.005). The time between diagnosis and treatmentis a prognostic factor associated with response to IST (p= 0.026). 10- year overall survival (116 months) is 48.3%. Relapse after treatment happened in 4 children (18.2%). MDS occurred in 1 child (3.3%).

Conclusions: IST that include ATG and CSA is good alternative for AA children who lack of an HLA match sibling donor with overall response rate is 73.3% and 10- year overall survival is 48.3%.

Keyword: Aplastic Anemia, Antithymocyte Globulin, Cyclosporine A., Children

PP-101

The incidence of severe chronic neutropenia in Korea and related clinical manifestations: A national health insurance database study

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Background: Severe chronic neutropenia (SCN) refers to a condition in which neutrophils under 500/uL over months or years. And generally, neutropenia due to previous hematologic disease, systemic autoimmune disease, and infectious disease are excluded in this category. These patients could develop chronic fever and recurrent, life-threatening infection due to a long-term immunodeficient state. Moreover, some of them could evolve to myelodysplastic syndrome (MDS) or leukemia. However, studies on the incidence and clinical progress in large-scale cohorts are still insufficient. Therefore, in this study, we used national health insurance data to investigate the epidemiologic feature and prognosis of SCN in Korea.

Methods: The Health Insurance Review and Assessment (HIRA) database recorded between 1 January 2011 and 31 December 2015, and Korean population data was utilized. The Severe CPN was defined based on ICD-10 code and according to the exclusion criteria, patients not cover the disease were excluded. After identifying patients with SCN, annual incidence according to age and sex, the most common comorbidities including inflammatory disease, MDS and/or acute leukemia, and mortality were investigated.

Result: Among the initially screened patients with severe neutropenia (N=2134), a total of 367 patients were enrolled for SCN. The annual incidence rate of SCN ranged from 0.12 to 0.17 per 100,000 person-year (PY) during the study period. The total incidence in women was higher than that of men (incidence: 0.17 vs. 0.12, RR: 1.46, 95% CI: 1.19-1.80), and especially, in middle-aged women had a relatively high incidence rate. The highest incidence was observed in the 0 to 4 year old group (1.12/100,000 PY), and there was no difference in the incidence of men and women in this age group. The most common accompanying diseases were upper and lower respiratory infection followed by otitis and intestinal infectious disease. A total of 12 patients (3.3%) were progressed to acute leukemia or MDS and 4 patients (1.1%) were died.

Conclusions: From this population-based study, the national incidence of SCN was estimated and their accompanying diseases were analyzed. Our data will provide a valuable information to assist in diagnosing SCN and predicting the disease course in the future.

Keyword: Neutropenia, Severe Chronic, Epidemiology, Incidence

PP-102

CD3/CD45RA depleted haploidentical transplant for SCID: First case in Vietnam

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Background: Severe combine immunodeficiency disease (SCID) is a genetic disorder characterized by the disturbed development of functional T cells and B cells, consequently, adaptive immune system are impaired and patients are affected by severe bacterial, viral or fungal infections early in life. If untreated, these patients die within one year due to severe, recurrent infections. The curable treatment for SCID is HLA-matched hematopoetic stem cell transplantation. However, seeking for HLA-matched donor is difficult and requiring time, moreover, SCID patient can't wait. Vietnam National Children's hospital is using haplo HLA matching hematopoetic stem cell transplantation for SCID patients.

Methods: 3 SCID patient who don't have matched HLA donor underwent hematopoetic stem cell transplantation with haplo HLA donor(father). Stem cells were harvested and manipulated with CD34+ selection or CD3/CD45RA depletion kit via CliniMacs system (Miltenyi) based on T-B-NK cells and genetic mutation.

Result: 2 T-B+NK- SCID used CD34+ selection and 1 T-B-NK+ used CD3/CD45RA depletion kit. Stem cells infusion were uneventful. Engraftment was around day D+60 post- transplant with CD34+ selection and D+14 with CD3/CD45RA depletion kit. Complications post- transplant were: infections, engraftment syndrome, CMV reactivation…, no sign of aGVHD. 1 patient is complete chimerism without IVG infusion, 1 patient is complete chimerism with IVIG infusion, 1 patient died post-transplant because of septicemia.

Conclusions: Haplo HLA typing hematopoetic stem cell transplantation is a high technique procedure with good result. This procedure will save many SCID patients, especially in Vietnam where lack of bone marrow and stem cells bank.

PP-103

Label-free and high-sensitive detection of pseudomonas aeruginosa from bacteremia using a surface plasmon resonance DNA-based biosensor

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Background: loop-mediated isothermal amplification (LAMP) of DNA is a sensitive and cost-effective method for rapid identification of pathogens without the need for sequencing. The reaction is conducted under isothermal conditions for 60 min in water bath or a heating block, which shows high potential to be exploited in SPR biosensor for real-time detection of pathogens. This paper aims to employ LAMP integrated with SPR assay in the examination of P. aeruginosa.

Methods: All the DNA of 25 P. aeruginosa were extracted by DNA extraction kit from Dongsheng Biotech according to its instruction. Additionally, a set of LAMP primers, including FIP, BIP, F3 and B3, was designed by using the software of Primer 5.0. Then, conventional LAMP amplification was performed for detection of oprl, meanwhile, agarose gel electrophoresis was employed for specific visualization of the amplicons. Afterwards, LAMP and SPR were fabricated to detect P. aeruginosa.

Result: Curve results of LAMP-SPR showed similar tendency with that of Q-PCR when DNA samples were positive in the detection loci. For assay of LAMP integrated with SPR, results could be achieved in 15 min in the form of sensorgram, in which the vertical and horizontal signal suggested positive and negative results for biosensor.

Conclusions: In this study, our data therefore provided evidence to support the use of SPR-DNA array for detection of P. aeruginosa with high sensitivity, specificity and rapidity.

Keyword: Surface Plasmon Resonance, Loop-Mediated Isothermal Amplification, Pseudomonas Aeruginosa

PP-104

Detection of staphylococcal bacteremia virulence factors using novel isothermal amplification with SPR biosensor methodology

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Background: MRSA is one of the most widely found pathogens in public healthcare worldwide, its rapid and accurate detection remains a major concern. In this study, two novel nucleic acids isothermal amplification assays, including loop-mediated isothermal amplification (LAMP) and Polymerase Spiral Reaction (PSR) have been used in combination with surface plasmon resonance (SPR) biosensor, for the detection of bacteremia MRSA strains and its virulence factors

Methods: A total of 19 MRSA Genomic DNA was extracted and conducted using LAMP and PSR amplification on the SPR platform for femA, mecA and its virulence factors, including sea, seb, sec, see and pvL. All primers for PSR and LAMP were designed by Primer Premier 5.0 or PrimerExplorer V5, respectively. Both of the isothermal amplification assays were carried out on the SPR sensor with specific chips to detect mentioned genes, in less reagents and shorter time about 15 min than that of conventional LAMP and PSR reactions.

Result: Results of conventional LAMP and PSR were measured by gel electrophoresis and typical ladder bands pattern was observed for 19 samples, suggesting all the examined MRSA strains had both femA and mecA genes. According to the LAMP-SPR and PSR-SPR results, 13, 6, 7, 7, 3 of 19 MRSA strains were positive for sea, seb, sec, see and pvL in accordance with conventional method, respectively.

Conclusions: In this study, our data therefore provided evidence to support the use of LAMP and PSR-SPR biosensor for detection of virulence genes in MRSA with high sensitivity, easy-operation and cost-effective.

Keyword: LAMP, PSR, SPR, MRSA, Virulence Factors

PP-105

Diagnostics under sky: Mitigation of gap in global health point-of-care diagnosis in extremely poor hematology laboratory linking frugal science

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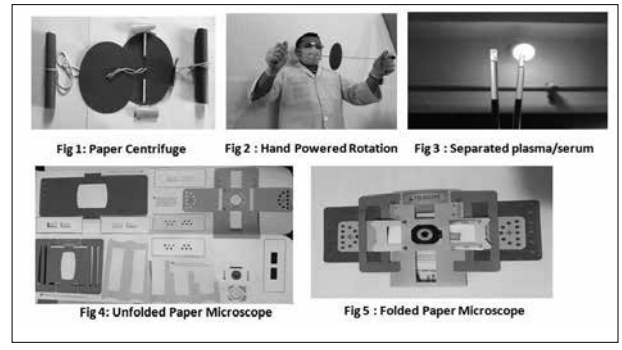
Background: Almost a billion of world population live with no any infrastructures such as healthcare, education, electricity despite the great advancement of technologies. Also at the same time we are witnessing a great overwhelming paradigm shift from central laboratory-based diagnosis to point-of-care based diagnosis. Centrifugation and microscopy are the workhorse of any modern diagnosis including hematology but modern diagnostic equipment harasses us in many ways such as cost of device, ease of use, electricity access, size and utilities. So, we study the prospects of some electricity-free frugal devices costing 1 dollar paper microscope, 0.5 dollar paper/plastic centrifuge which can be used under open sky for diagnosis intended to resource poor hematological setting at point-of-care level. Frugal science is the innovative approach and novel philosophy that encourage design, development and deployment of ultra affordable devices by cutting its original price thousands of times for developing world.

Methods: We assembled the device at point-of-care level so that it can be used promptly. 1 dollar electricity-free paper microscope with magnification 140X was assembled through folding and human sample blood was studied on site. Also 0.5 dollar costing plastic/paper centrifuge was fabricated on ancient whirligig toy principle, that resulted in a good separation of plasma/serum from the cellular blood components with ultra speed of more than one hundred thousand rotation per minute. Serum for infectious diseases such as HIV, hepatitis, malaria was tested using rapid diagnostic kits under open sky through point-of-care blood centrifugation. This resulted in a good separation of plasma from the cellular blood components.

Result: We found that the results were astonishing and comparable to modern methods using electric microscope and centrifuge to our claimed approach forming the promising novel alternatives for developing world and field testing. Through paper microscope it has been possible to study blood cells and blood parasites with or without coupling with smart phone while via paper/plastic centrifuge it is possible to achieve centrifugation in less than a minute for field testing of infectious diseases using rapid diagnostic kits. Also those devices weigh less than 50 gram, that easily fits in pocket being more cost effective, user friendly, light in nature and can be used anywhere, anytime.

Conclusions: A great barrier of access of scientific for developing world can be resolved through this novel approach by democratizing the access to diagnostic tools . There is a vast save of time, money, resources for immediate access and use of those devices in low-cost settings with no any requirements of special healthcare facilities supporting electricity-free testing under open sky

Keyword: Electricity-Free, Point-Of-Care test, Paper-Microscopy, Centrifugation, Diagnostics, Frugal science



PP-106

Acute kidney disease as a 90-day mortality predictor in hemato-oncologic patients with persistent acute kidney injury and vancomycin treatment

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Background: Acute kidney disease (AKD) has been newly proposed to define the course of disease after acute kidney injury (AKI). Vancomycin (VM) administration could deteriorate kidney function seriously. We investigated the prevalence of AKD and

association between AKD stages and clinical outcome in hemato-oncologic patients with persistent AKI and VM treatment.

Methods: In 120 hemato-oncologic patients with persistent AKI and VM treatment, we reviewed serum creatinine levels serially (from D0 to D90) and divided patients into five AKD stage groups. We analyzed the association between AKD stages and 90-day mortality and compared VM trough concentrations between initial therapeutic drug monitoring (TDM) and AKD event.

Result: AKD occurred in all patients. AKD stages were: stage 0, 2.5% (n = 3); stage 1, 25.8% (n = 31); stage 2, 30.8% (n = 37); stage 3, 30.0% (n = 36); and ongoing renal replacement therapy (RRT), 10.8% (n = 13). Except AKD stage 0, the 90-day mortality was: stage 1, 19.4% (n = 6); stage 2, 27.0% (n = 10); stage 3, 52.8% (n = 19); and ongoing RRT, 76.9% (n = 10). The higher AKD stage predicted the higher 90-day mortality (P <0.0001). VM trough concentrations in toxic levels were significantly different between initial TDM and AKD event (4/120 [3.3%] vs. 67/80 [83.8%], P < 0.0001).

Conclusions: This is the first study that showed AKD stage distributions and its clinical outcomes in the hemato-oncologic patients with persistent AKI and VM treatment. It is mandatory to monitor AKD for proper management and prognosis prediction in these patients.

Keyword: Acute Kidney Disease, Stage, Mortality, Predictor, Vancomycin, Hemato-Oncologic Patients

PP-107

Pattern of hematological disorders on bone marrow examination: A tertiary care hospital experience

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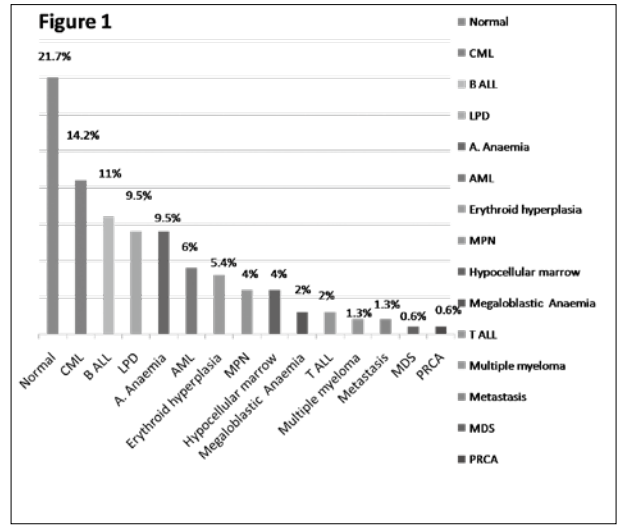
Background: Bone marrow examination is useful in the diagnosis of both hematological and non-hematological disorders. The two most important techniques used for the diagnosis of hematological disorders are bone marrow aspiration and trephine biopsy. Commonly it is done for the evaluation of unexplained cytopenias and malignant conditions likeleukemia. For bone marrow interpretation the history, clinical finding, peripheral blood picture and other laboratory findings are required.

Methods: This study was a Retrospective and prospective and carried out in the Haematology Department of CHK-Central Laboratory from July 2016 to August 2018. Bone marrow examination of 147 cases of suspected hematological disorders was carried out, who came to the laboratory for bone marrow biopsy request. Complete details of clinical history, physical examination, complete blood counts and demographic details were recorded.

Result: Among 147 cases studied, age of patients ranged from 02 to 75 yrs with mean age of 35 yrs ±17.3 and male predominance (1.3:1). Most of the patients presented with fever, Easy fatigability and generalized weakness. Out of 147 cases of bone marrow biopsy 21.7% cases showed Normal haematopoiesis. Erythroid Hyperplasia in 5.4% cases and Megaloblastic Anaemia in 2% cases. ITP in 3.4%, Hypocellular marrow in 4%, Aplastic Anaemia in 9.5% cases. Acute leukemia was seen in 28 cases with 12.9% cases of ALL and 6.1% cases of AML. CML was seen in 14.2%, MPN in 4% cases, LPD in 9.5% cases, Multiple myeloma in 1.3%. 01 case (0.6%) of granulomatous pathology and 01 case (0.6%) of Myelodysplastic syndrome were diagnosed exclusively on bone marrow biopsy. In addition metastatic deposits of adenocarcinoma were observed in 1.3% cases.

Conclusions: The present study showed the usefulness of bone marrow aspiration and trephine biopsy in evaluation of the bone marrow in routine haematological disorders and also for understanding disease progression.

Keyword: Leukemia, Haematological Disorders, Bone Marrow Biopsy



PP-108

Flow cytometry quantitation of acridine orange-stained malaria parasites

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Background: Quantitation of malaria parasites is essential for the treatment of patients. However, the currently used flow cytometry method can assess only the percentage of infected red blood cells (RBCs). Thus the aim of the present study is to optimize the flow cytometry approach for enumeration of total malaria parasites per microliter of the blood specimen.

Methods: Specimens were incubated with acridine orange (AO) and an RBC lysing solution. The numbers of malaria parasites were quantitated using the FACSCalibur analyzer and calibrated with size-standard bead and counting beads. The fluorescence of the AO-stained malaria parasites was examined using a fluorescent microscope. Electron microscopy was also used to study the ultrastructure of the malaria parasites in lysed RBC specimens.

Result: The number of malaria parasites was correlated with the percentage of infected RBCs obtained from manual counting ($r2 = 0.87$, $p < 0.0001$). A dilution assay demonstrated that the counting method was linear in the range between 60 to 36,700 particles/μL; however, stored specimens exhibited an increase in the number of malaria particles. The fluorescence of AO-stained malaria parasites was confirmed. An electron microscopic study demonstrated that different stages of malaria parasites existed in lysed RBC specimens in the form of membrane-bounded spherical cells.

Conclusions: The potential use of flow cytometry for enumeration of malaria parasites was demonstrated. The developed approach is reliable and straightforward for malaria parasite enumeration in the routine laboratory.

Keyword: Malaria, Parasites Particles, Flow Cytometry

PP-109

Platelet counting in thrombocytopenic samples using mindray BC-6800 plus

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Background: The performance of low PLT counting is crucial for clinical practice especially in transfusion management. We evaluated low PLT counting performance of Mindray BC-6800 Plus (BC-6800P, Mindray, Shenzhen, China) and compared it with that of Sysmex XN-9000 (XN, Sysmex, Kobe, Japan).

Methods: We observed precision of both PLT-I channels (PLT-I) in BC-6800P and XN in 11 consecutive samples (10.7 – 385.0 × 10^9/L) and 10 thrombocytopenic samples (6.7 - 20 × 10^9/L). We also observed precision of PLT-O channel with CR mode in BC-6800P (PLT-O/CR) and PLT-F channel in XN (PLT-F) in 10 thrombocytopenic samples. We analyzed correlation of PLT-Is in both analyzers in 2,339 clinical samples. We also analyzed correlation of PLT-O/CR and PLT-F in reflex tested ($n = 398$) and thrombocytopenic ($\leq 50 \times 10^9/L$, $n = 145$) samples.

Result: In 11 consecutive samples, precision of PLT-Is were all < 10% CV in both analyzers. In 10 thrombocytopenic samples, precision of PLT-Is ranged 8.0 – 26.7% in BC-6800P and 5.5 – 28.7% in XN; however, precision of PLT-O/CR and PLT-F ranged 2.1 – 7.2% in BC-6800P and 2.6 – 17.8% in XN. Correlation was very strong ($r < 0.900$, all) in all samples as well as reflex tested, and thrombocytopenic samples.

Conclusions: BC-6800P would be a promising and reliable option in clinical hematology laboratories and transfusion management with good analytical performance in PLT counting especially in thrombocytopenic samples.

Keyword: BC-6800 Plus, Platelet Counting, Thrombocytopenic Samples

PP-110

Evaluation of neutrophil gelatinase-associated lipocalin (NGAL), compared with IL-1β, IL-6, TNF-A and CRP in hematologic malignancy

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Background: The relation of NGAL to hematologic malignancies have been evaluated. Whereas NGAL have been known as an inflammatory factor. This study aimed to investigate the pattern of NGAL expression compared with several inflammatory factors (CRP, IL-1β, IL-6, and TNF-α) in hematologic malignancy.

Methods: Paired bone marrow (BM) aspirates and peripheral blood (PB) samples were collected from 41 patients and classified into five groups: myeloproliferative neoplasm (MPN), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), plasma cell neoplasm (PCN), and lymphoma without BM involvement which was used as controls. NGAL levels were measured using an immunoassay and western blotting. CRP levels were measured by an immunoassay, while cytokine levels (IL-1β, IL-6, & TNF-α) measured by western blotting.

Result: NGAL showed the highest levels in MPN group and the lowest levels in AML group, presenting lower levels in MDS group than those in control group. In contrast, CRP showed the highest level in AML and the lowest level in MPN. IL-1β showed much lower levels in AML, MPN and MDS groups than those in control group. IL-6 showed similar levels to or lower levels in AML, MPN and MDS groups than those in control group. TNF-α showed higher levels in AML, MPN and MDS groups than those in control group.

Conclusions: NGAL showed the distinct pattern compared with other inflammatory factors, while NGAL levels in hematologic malignancy entities seemed to be associated with the amount of normal neutrophil precursors and the degree of neutrophil maturation.

Keyword: NGAL, IL-1β, IL-6, TNF-A, Inflammation, Hematologic

PP-111

Cell population data of automated hematology analyzer Sysmex XN for sepsis

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Background: Cell population data (CPD) using multi-parametric algorithms are available in modern automated hematology analyzers. We investigated clinical utility of CPD obtained on Sysmex XN-9000 (Sysmex XN, Sysmex, Kobe, Japan) for risk stratification and mortality prediction in critically ill septic patients.

Methods: We enrolled 169 septic patients (sepsis, n = 85 and septic shock, n = 84) diagnosed by Sepsis-3 criteria. CPD was as follows; immature granulocytes (IG, number [#] and percentage [%]), neutrophil granularity intensity (NEUT-GI), neutrophil reactivity intensity (NEUT-RI), antibody synthesizing lymphocytes (AS-LYMP, # and %), reactive lymphocytes (RE-LYMP, # and %), and highly fluorescent lymphocytes (HFLC, # and %), reticulocyte hemoglobin equivalent (RET-He), RBC hemoglobin equivalent (RBC-He), difference of RET-He – RBC-He (Delta-He), reticulocytes, and immature reticulocytes fraction (IRF, # and %), and immature platelets fraction (IPF, # and %) for platelets. The CPD was analyzed according to the sepsis severity and 30-day mortality using Mann-Whitney U test and the receiver operating characteristic (ROC) curve analysis.

Result: The NEUT-RI, IRF%, and IPF% values were significantly higher in septic shock patients than septic patients, respectively (median: 53.6 FI vs 60.5 FI, 10.0% vs. 12.4%, and 3.1% vs. 4.4%, all $P < 0.05$, M-W test). These three parameters significantly predicted septic shock and 30-day mortality, respectively (AUC: 0.588 – 0.723 and 0.614 – 0.696, all $P < 0.05$, ROC curve analysis).

Conclusions: Cell population data such as The NEUT-RI, IRF%, and IPF% may provide useful information for risk stratification and mortality prediction of critically ill septic patients.

Keyword: Automated Hematology Analyzer, Sysmex XN, Sepsis, Cell Population Data, Mortality

PP-112

The effect of oral administration corticosteroid toward leukocytes number and differential count in mice (Mus Musculus) based on its duration

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Background: Corticosteroid is the derivate of steroid hormone which has important role to control inflammation response and widely use as anti-inflammation and anti-allergic. It has many side effects that will be worsen if be used without necessary indication, dosage, and duration. One of the effects was the decline of leukocytes number and differential count that affect the immunity.

Methods: This was an experimental study with Post Test Control Group Design. It was held in pharmacology laboratory, Andalas University on January – March 2016. The subjects were 18 mice (Mus musculus) consist of Group I as control, Group II was given corticosteroid 0,0026 mg/day for 7 days, and Group III was given corticosteroid 0,0026 mg/day for 14 days. Blood samples were taken from each group, respectively, to count the number of leukocytes and differential count. Data analysis used Oneway ANOVA test and Kruskal-Wallis Test.

Result: The average number of leukocyte in this study is 8,175.0 ± 2,646.08, 6,700.00 ± 871.78, and 5,083.3 ± 1,158.30 for Group I, Group II, Group III, respectively. The results show decline of leukocyte numbers in group that administered corticosteroid compared with the control. The assessment of differential count shown the increasing of neutrophils segment and decreasing of eosinophil, neutrophil bar, lymphocytes, and monocytes in corticosteroid given groups compare with control group. Generally, the average number in group which was given corticosteroid for 14 days was less than group which was administered corticosteroid for 7 days. Data analysis with ANOVA test show significant difference in the duration of corticosteroid intervention effect with leukocyte number's count in study groups (p=0.026). The different counts of leukocytes include Eosinophil, Bar neutrophil, Segmented neutrophil, Lymphocyte, and Monocyte. The effect of corticosteroid administration with differential counts are significant statistically with the p value are 0.001 for Eosinophil, Bar neutrophil, Segmented neutrophil, Lymphocyte, and 0.028 for Monocyte.

Conclusions: The conclusion was the administration of corticosteroid has the effect towards the leukocyte numbers and the differential count.

Keyword: Corticosteroid, Leukocytes Number, Differential Count, Immunity

PP-113

Hematologic scoring system for detection of neonatal sepsis

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Background: Neonatal sepsis still be a major cause of infants mortality mainly in developing country. Based on WHO's data there is 8.1% death among children under 5 years in 2016 in south-east asia region caused by sepsis (death rates per 1000 live births). Limited cost and facilities are some of the problems in the management of sepsis. A simple and cost-effective hematologic examination is needed to help clinician diagnosing the disease.

Methods: This study is a literature review study of scientific manuscripts and scientific articles about hematology scoring systems in diagnosis of neonatal sepsis.

Result: Several studies about hematologic scoring systems have been collected. A prospective study by Selimovic et al., (2010) reveals that the predictive score for EONS is useful in diagnostic evaluation of neonates suspected for EONS. A prospective study by khair et al., (2010) reveals that Rodwell Score > 4 has a sensitivity of 100%, specificity of 60%, with PPV 26% and NPV 100 %. Score > 4 were more reliable as a screening tool for sepsis than any of the individual hematological parameter. A clinical trial study by Shirazi et al., (2010) reveals that the CRP was positive in 23% of proven septic babies and in 16% of babies with probable sepsis. Thrombocytopenia had a sensitivity of 61% and a specificity of 82 %. A Prospective study by Narashima et al., (2011) reveals that abnormal I:T followed by an abnormal I:M were the most sensitive indicators in identifying infants with sepsis. A cross sectional study by Makkar et al., (2013) reveals that sensitivities of the various screening parameters were found to be satisfactory in identifying early onset neonatal sepsis. A clinical trial by Majumdar et al., (2013) reveals that abnormal I:T ratio followed by an abnormal I:M

ratio were the most sensitive indicators in identifying infants with sepsis. A cross sectional study by Iskandar et al., (2015) reveals that Rodwel's HSS have high sensitivity and mild specificity for diagnose EONS. A cross sectional study by Meirina et al., (2015) reveals that HSS score > 4 had sensitivity 80% and specificity 90%. A cross sectional study by Pramana et al., (2016) reveals that HSS can be used to early diagnose of neonatal sepsis with sensitivity 80.9% and specificity 92.7%. A cohort study by Ramadhani et al., (2016) reveals that score HSS > 2 can be used to be predict mortality of early-onset neonatal sepsis. Moreover a novel study by Indonesian researcher (Adriani et al.,) in 2018 found that the score of ≥2 on hematologic scoring system had 100% sensitivity, 25.8 % specificity for diagnosis of bacteremia in infants at risk and suspected EONS. In addition the study in the same year from Nur'izzati et al., reveals that HSS score: 14 (41.2%) patients were sepsis unlikely, 11 (32.3%) possible sepsis, and 9 (26.5%)very likely sepsis as a profile HSS in neonatal sepsis suspected.

Conclusions: Hematologic Scoring Systems can be used as a diagnostic tool for neonatal sepsis. it's rapid, cost-effective, and easy to perform mainly in developing country.

Keyword: Hematologic Scoring System, Neonatal Sepsis, Early Diagnosis

PP-114

Screening of dysplastic neutrophils using cell population data using Sysmex XN-1000 analyzer

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Background: Dysplasia in the myeloid series is defined by hypogranular neutrophils and/or neutrophils with nuclear abnormality. Presence of dysplastic neutrophils (dysNE) is identified subjectively by microscopic examination and affected by staining quality. The cell population data (CPD) obtained during CBC assessed on the hematology analyzer XN-1000 (Sysmex, Kobe, Japan) reflects cell's morphology including granularity, size, and nuclear shape. It would be valuable if we can screen dysNE using instrument. We analyzed samples from patients with various diseases to explore whether neutrophils' CPDs are useful to screen the presence of dysNE.

Methods: Total 1,687 blood samples from 100 MDS, 226 AML, 14 APL, 145 ALL, 61 CML-CP, 4 CML-BC, 14 CMMoL, 68 MM and 937 patients with other diseases, and 118 healthy controls were analyzed. Microscopically dysNE were found in 176 samples (dysNE group) and remaining 1,511 samples showed normal appearing neutrophils (non-dysNE group). Blood samples were collected in standardized EDTA tubes and analyzed for CBC-DIFF on a XN-1000 instrument. Three kinds of neutrophil CPD (NE-SSC, NE-SFL, NE-FSC) were collected. The CPD parameters of each group were compared using Mann–Whitney test. To find out the range set of CPD for screening of dysNE, the CPD values were displayed in ascending order and the range was set manually by eliminating as many other cases as possible and holding cases with dysNE. The CPD of the remaining cases were analyzed.

Result: All three neutrophil CPD values were significantly different between dysNE and non-dysNE groups ($p < 0.0001$). Using NE-SSC < 140, 136 of 176 dysNE samples (sensitivity 77.3%) and 60 of 1,511 non-dysNE samples (specificity 96.0%) were identified. There were no remained samples from normal healthy cases, and all of remained samples except 2 samples from chronic renal disease were from patients with hematologic malignancies (58 samples). The NE-SFL < 75 eliminates only 8 more cases, including 1 dysNE case and NE-FSC did not increase sensitivity or specificity.

Conclusions: Although some samples from patients with various hematologic malignancies could be contaminated to the suggested range of NE-SSC, screening of presence of dysNE is possible using NE-SSC < 140(sensitivity 77.3%, specificity 96.0%) obtained during CBC by XN-1000. It would be useful to flag 'dysplastic neutrophils'

Keyword: Dysplastic Neutrophils, Sysmex XN, Cell Population Data

PP-115

A case of spurious white blood cell count from automated Sysmex XN hematology analyzer: Difference between WNR and WDF channels

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Background: Most clinical laboratories have automated hematology analyzers for complete blood cell count (CBC). The CBC is critical for clinicians to determine their patient's clinical status and therefore its result should be accurate and precise. Among CBC data, white blood cell (WBC) count is one of the most important parameters. But in some cases, spurious WBC counts can occur. We encountered a case that showed incorrect WBC count from a Sysmex XN hematology analyzer (Sysmex Corporation, Kobe, Japan). A 56-year-old men visited our center in October 2018, for the follow up of hepatocellular carcinoma with lung metastases. He started sorafenib 3 months before and nivolumab 2 days before his blood was drawn for lab tests. The initial WBC count measured by Sysmex XN was $0.02x10^3$/μL and the differential count was not available. A blood smear slide was automatically prepared and reviewed according to the laboratory protocol. It was found that the WBC count in the blood smear was much higher than that of CBC result, and there was no WBC aggregation. Few hypersegmented neutrophils were shown and monocytes were slightly activated. Therefore we reviewed the raw data of the hematology analyzer, and we found the big difference between two channels (WNR and WDF) of the analyzer. The WBC count of WNR channel was very low, but that of WDF channel was $7.16x10^3$/μL, neutrophil $5.02x10^3$/μL, lymphocyte $1.32x10^3$/μL, monocyte $0.75x10^3$/μL, eosinophil $0.07x10^3$/μL. The viscosity of the blood and the neutrophil respiratory burst activity were within normal limits. The two channels of Sysmex XN hematology analayzer treat patient's blood differently. WNR channel treats with more acidic reagent (Lysercell WNR) than WDF channel (Lysercell WDF) does. We assume that more acidic reagent of WNR channel may cause more lysis of WBCs, especially abnormal WBCs damaged by cytotoxic drugs given to the patient, which are more fragile than normal WBCs. In conclusion, all clinical laboratories operating hematology analyzers should be alert for this phenomenon. If the analyzer shows 'Difference between channels', it is important to check the raw results of the machine, prepare the blood smear, review carefully by the microscopy, and report the accurate result.

Keyword: WBC, Hematology Analyzer, Sysmex XN

PP-116

Atypical chronic lymphocytic leukemia has a worse prognosis than CLL and clinically and laboratory different from B-cell prolymphocytic leukemia

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Background: Chronic lymphocytic leukemia (CLL) is a neoplasm composed of monomorphic small mature B cells that coexpress CD5 and CD23. The finding of ≥55% prolymphocytes defines B-cell prolymphocytic leukemia (B-PLL), and cases with 15–55% of the prolymphocytes called atypical CLL (aCLL, previously called CLL/PL). The aim of this study was evaluation of the clinical and prognostic significance of aCLL.

Methods: We reviewed the medical records, peripheral blood, and bone marrow findings of 121 patients with untreated CLL (n=101), aCLL (n=9), and B-PLL (n=11) between January 1995 and June 2018. CLL and aCLL patients were classified as Binet stage A (<3 areas of lymphadenopathy, hemoglobin >10 g/dL, platelets >100k/?L), B (≥3 areas of lymphadenopathy, hemoglobin >10 g/dL, platelets >100 k/?L), or C (hemoglobin <10 g/dL or platelets <100k/?L). All patients underwent immunohistochemistry and/or flow cytometric immunophenotyping, among them; 107 patients underwent karyotyping, and 15 patients underwent fluorescent in situ hybridization.

Result: The median age at diagnosis was 63.5 years (range 2585), 68.0 (40-77) years, and 66.0 (29-78) years and the ratio of males to females was 2.0, 2.0, and 1.8 in CLL, aCLL, and B-PLL, respectively. Lymphadenopathy was more common in CLL (42%, 42/101) and aCLL (56%, 5/9) than in B-PLL (0%), whereas splenomegaly was more in B-PLL (100%) than CLL (25%, 25/101) and aCLL (33%, 3/9). (P=0.683 and 0.010, respectively). aCLL showed more severe anemia, elevated lactate dehydrogenase, and β2-microglobulin than CLL and B-PLL (P=0.001, 0.027, and 0.037, respectively). Binet stage A and B were more in CLL (51% and 26%) than in aCLL (30% and 0%), whereas Binet stage C was more in aCLL (70%) than CLL (23%). (P=0.013). Patients with B-PLL had an atypical immunophenotype with high frequencies of CD5 or CD23 negativity, FMC7 positivity, and strong CD22 positivity (P=0.672, 0.440, 0.004, and <0.001, respectively) (Table1). Especially in this study, patients with aCLL showed higher frequencies of FMC7 positivity and strong CD22 positivity than CLL in Western study (P=0.032 and <0.001, respectively). In B-PLL, normal karyotype was less common and complex karyotype was more common than CLL and aCLL (P=0.028). In the CLL group, cytogenetic abnormalities were observed in 35% of patients (33/94). The descending order of

frequency was trisomy 12 (11%, 10/94), 13q deletion (10%, 9/94), complex karyotype (7%, 7/94), 11q deletion (5%, 5/94), 14q deletion (2%, 2/94), and 17p deletion (1%, 1/94). In the aCLL group, cytogenetic abnormalities were present in 50% of patients (4/8), including 3 cases of trisomy 12, 2 cases of 14q deletion, 1 case of 13q deletion, 11q deletion, 17q deletion and complex karyotype. In the B-PLL group, cytogenetic abnormalities were observed in 80% of patients (8/10), of whom 4 had complex karyotypes. The overall survival rate at 10 years were 65.6%, 22.2%, and 46.3 % in patient with CLL, aCLL, and B-PLL, respectively (P=0.155). However, only OS of CLL and aCLL showed statistically significant difference (P=0.043).

Conclusions: CLL, aCLL, and B-PLL showed different clinical, immunophenotypic, and cytogenetic characteristics. aCLL has a worse prognosis than CLL; therefore, it is important to distinguish aCLL from CLL and B-PLL.

Keyword: Chronic Lymphocytic Leukemia, Atypical Chronic Lymphocytic Leukemia, B-cell Prolymphocytic Leukemia, Immunophenotype, Cytogenetics, Clinical Findings

Table1. The immunophenotypic features of patients with CLL, aCLL, and B-PLL in this study and that of patients with CLL in Western study

Marker	CLL in AMC (n=101)	Atypical CLL in AMC (n=9)	B-PLL in AMC (n=11)	CLL in Western Study† (n=400)	*P* value
Surface immunoglobulin					<0.001**
Kappa	28 % (26/93)	45 % (4/9)	55 % (6/11)	56 % (228/396)	
Lambda	35 % (33/93)	33 % (3/9)	45 % (5/11)	34 % (136/396)	
Negative/weak(±)	37 % (34/93)	22 % (2/9)	0 % (0/11)	8 % (32/396)	
CD5	94 % (94/100)	100 % (9/9)	36% (4/11)	92 % (366/398)	0.672
CD23	93 % (85/91)	100% (6/6)	50% (4/8)	94 % (352/376)	0.440
FMC7	38 % (25/90)	29% (2/7)	80 % (8/10)	19% (69/386)	0.004*
CD22					<0.001**
Weak (±)	11 % (7/66)	25 % (1/4)	0 % (0/8)	40 % (140/355)	
+/++	74 % (49/66)	25 % (1/4)	100 % (8/8)	7 % (26/355)	

†Leukemia. 1994;8:1640-5.

PP-117

Participation in the external quality assurance for international normalised ratio: Our experience

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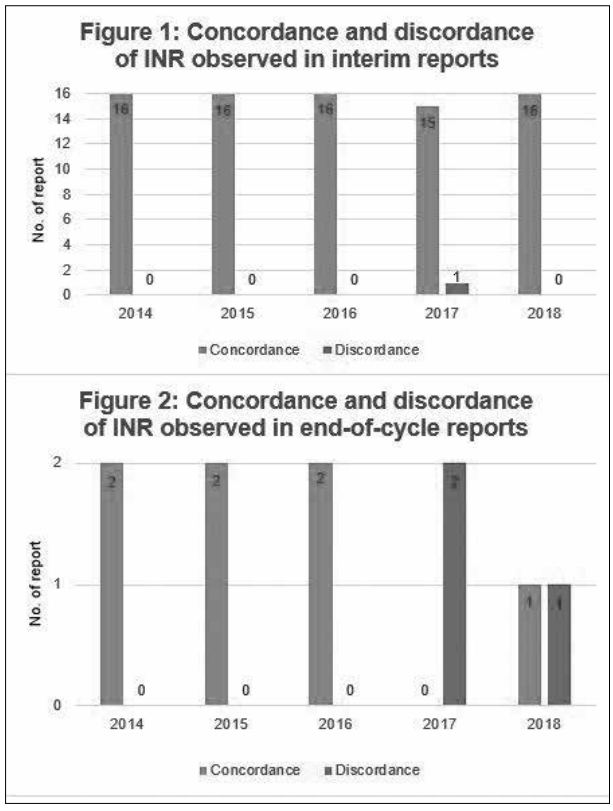
Background: The International Normalized Ratio (INR) is the most common coagulation test performed to monitor warfarin therapy. This test requires the use of thromboplastin reagent which is composed of tissue factor that prompts the coagulation cascade via the extrinsic pathway. Thromboplastin reagents vary in sensitivity level and this level of sensitivity is determined by its International Sensitivity Index (ISI) value. For diagnostic purpose, it is recommended to use the highly sensitive thromboplastin reagent which has an ISI value close to 1.0. We have subscribed to Royal College of Pathologists of Australasia Quality Assurance Programme (RCPAQAP) as part of ISO 15189 requirement for inter laboratory comparison for the past five year. INR is one of the tests in our subscription. Hence, we intend to evaluate our 5-year performance in external quality assurance (EQA) programme for INR.

Methods: Between 2014 and 2018, our laboratory has participated in RCPAQAP Haemostasis Module for our coagulation analysers, STA-Compact Diagnostica France which used thromboplastin reagent, STA Neoplastine® CI Plus for INR calculation. A total of eighty interim (each survey report) and ten end-of-cycle reports (EOC) were evaluated.

Result: Our laboratory managed to score 98.75% (79/80) and 70% (7/10) concordant analytical performance specification (APS) for interim and EOC reports respectively (Figure 1 and 2). For the past five years, we have used five different lot of thromboplastin reagents with ISI values, ranging from 1.21 to 1.31. The Mean Normal Prothrombin Time (MNPT) generated from these reagents varied from 12.4 to 13.2. Interim data for INR collected between 2014 and 2018 showed that our laboratory was able to maintain results within APS range except for one INR report (1/80) which was miscalculated. However, the EOC reports showed contradicting performance as 3/10 reports showed total error (TE) of >1.0. It was difficult to obtain INR results which fell within APS range in 2017. Fortunately, our results improved in 2018. The investigation into the cause of the TEs showed that there was a concern of inaccuracy. This eventually led us to re-examine our reagent preparation, MNPT establishment process and thromboplastin's ISI value. There was not so much change in reagent preparation technique, therefore we believe that we need to improve our method in determining a correct MNPT value. We also have to consider changing the thromboplastin reagent with an ISI value closer to 1.0. Although the College of Pathologists (CAP) recommends that laboratories should use thromboplastin reagents that are at least moderately sensitive (i.e. ISI <1.7), we still believe that the reagent may not be suitable for our reagent/instrument current combinations and can lead to inaccurate result.

Conclusions: This report illustrates the need to use thromboplastin with ISI closer to 1.0. Based on our experience, EQA programme is essential in monitoring the method of choice used in the laboratory. The programme when regularly evaluated and acted on, can have a positive impact on the quality of patient care.

Keyword: INR Monitoring, External Quality Assurance, Thromboplastin Sensitivity Level, ISI Value, INR Calculation, Laboratory Experience



PP-118

HDAC inhibitor martinostat-induced immunogenic cell death in chronic myeloid leukemia

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Background: Chronic myeloid leukemia (CML) expressing the BCR-ABL fusion gene is treated by Imatinib (Gleevec). Considering development of resistance mechanisms in over 30% of patients, novel therapeutic approaches are required. Here we investigated the effect of Martinostat a novel pan-histone deacetylase inhibitor (HDACi) acting at lower concentrations compared to clinically-used SAHA (Vorinostat).

Methods: Here, we investigated the effect of Martinostat on various CML cell lines by Trypan blue staining in a concentration range between 0 and 10μM after 24, 48 and 72 hours to quantify changes of proliferation and cell viability, compared to SAHA used as a control. Results were validated by western blot and colony formation assays. To assess activation of cell death, we conducted Annexin V (An V)- and/or Propidium Iodide (PI)-staining and flow cytometry. To investigate caspase-dependency of cell death, Hoechst staining in presence or absence of pan-caspase inhibitor zVAD was done. To confirm the caspase-3 activation in CML cells by Martinostat, we undertook western blot and luminescent caspase-3/7 activity assays. Expression of ectopic calreticulin was investigated by flow cytometry analysis. Regarding the synergistic effect of Martinostat and Imatinib in CML, An V- and/or PI staining, western blotting and luminescent caspase-3/7 activity assays were used.

Result: Regarding proliferation and viability, our results showed that Martinostat induced a cytotoxic effect on CML cell lines as proliferation and cell viability decreased dose-dependently with an IC50 of 0.87nM, considerably lower than SAHA (85.9nM). Compared to SAHA, Martinostat had a stronger effect on acetylation of histone and tubulin target proteins in a low concentration range (from 0nM to 500nM) compared with SAHA (from 0μM to 5μM) by western blot. Colony formation assays showed that the number of colonies treated by Martinostat decreased dramatically at a lower concentration range (0.05μM) compared with SAHA (2.5μM and 10μM). By An V - and/or propidium Iodide (PI) staining, we confirmed that Martinostat induced apoptosis (An V+ and PI+ was detected at 0.15μM and 0.25μM). By Hoechst staining with zVAD pre-treatment, we observed that Martinostat induced caspase-dependent cell death in CML. We further validated our results by western blots showing cleavage of caspase-3 and luminescent caspase-3/7 activity assays. Using flow cytometry analysis, the expression of ectopic calreticulin, a marker of immunogenic cell death, was detected, suggesting that Martinostat induced immunogenic cell death. We observed that co-treatment of Martinostat and Imatinib induced apoptosis in CML cells compared to single treatments by Annexin V- and/or PI staining. By western blot, we observed that co-treatments triggered cleavage of caspase-3 and also activation of other apoptotic proteins compared to single treatments. Moreover, the increase of caspase-3/7 activity was much higher after co-treatments compared to single treatments.

Conclusions: Based on these findings, we show that the HDAC inhibitor Martinostat possesses an interesting therapeutic potential against CML cells alone or in combination with Imatinib.

Keyword: Chronic Myeloid Leukemia, HDAC Inhibitor, Martinostat, Apoptosis

PP-119

Optimization of high resolution melting assays for detection of candidate SNPs associated with anemia: The nutrigenomics unit, FNRI-DOST experience

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Background: Anemia remained to be a public health concern in the Philippines over the last decade. During the post-genomic era, a number of genome-wide association studies were conducted and have reported SNPs associated with anemia and certain hematological parameters. This paper presents the development and optimization of high resolution melting assays that can be used in the routine detection of candidate susceptibility SNPs of anemia in the Nutrigenomics Laboratory of the Food and Nutrition Research Institute, Department of Science and Technology.

Methods: Genomic DNAs were extracted from venous blood samples. Sets of forward and reverse primers were designed following recommended guidelines. Real-time PCR reactions were then developed and optimized for the detection of SNPs in HFE (rs1800562 and rs1799945), TF (rs3811647 and rs1799852), and TMPRSS6 (rs855791 and rs4820268) using the high-resolution melting analysis feature of the BioRad CFX96 Real-Time PCR Detection System. Validation of the target loci were carried out using capillary sequencing and alignment against FASTA sequences using online bioinformatics tools.

Result: The best parameters of HRM assays that can detect the common candidate SNPs associated with anemia were successfully determined. PCR conditions were varied in evaluating each assay in terms of linearity and efficiency. Through analyses of the characteristic melt curve profiles and genotype discrimination, three genotypes of TMPRSS6 rs855791 and rs4820268 and TF rs3811647 and rs1799852 were found with varying frequencies among samples used. Conversely, one and two genotypes were detected for HFE rs1800562 and rs1799945, respectively. Melt curve data obtained in each HRM assay showed specific products, and the percent confidence of genotype clustering were at least 95%. Results obtained from all HRM assays had 100% concordance with the sequencing analyses results. Post-PCR electrophoresis runs and alignment against FASTA sequences demonstrated amplicon specificity and correct amplification of target loci, respectively.

Conclusions: In line with the establishment of the Nutrigenomics Unit of the FNRI-DOST, HRM assays can be considered as a reliable yet affordable alternative to the gold-standard sequencing technique. These methods can be used in the routine detection of candidate SNPs of anemia in Filipinos, of which a significant proportion of the population are continuously being afflicted with anemia. Hence, the findings also warrant the conduct of association studies among Filipinos in order to elucidate suitable gene markers in diagnosing anemia.

Keyword: TMPRSS6, TF, HFE, SNPs, HRM Assay, Anemia

PP-120

Comparison of gene expression profile in myeloid, lymphoblastic and mixed phenotype acute leukemia sharing minor BCR/ABL1 fusion using RNA sequencing

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Background: It is interesting that minor BCR/ABL1 is accompanied in acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and mixed phenotype acute leukemia (MPAL). Morphology and immunophenotyping are commonly used to diagnose the disease, however, it has not been well established how the same genetic aberration cause three different disease category. In this study, we tried to find specific gene expression profile according to disease category to clarify differences.

Methods: Twelve patients with minor BCR/ABL1 were enrolled; ALL (N=5), AML (N=3), MPAL (N=4) who were diagnosed in Seoul St. Mary's hospital. RNA was extracted from bone marrow specimen and gene expression analysis was performed using the TruSeq RNA sample prep Kit and Illumina HiSeq2500 sequencer (Illumina, CA). Filtered reads were then mapped to the human reference genome and fusion genes were detected using three different tools. Differentially expressed genes were analyzed using Gene Set Enrichment Analysis and Gene Ontology. We compared the expressed genes among diagnostic groups and selected overexpressed genes in each diagnosis. The significance of the selected genes were validated using public source databases including 197 AML, 206 ALL and 24 MPAL.

Result: Gene expression values were compared according to disease category. All minor BCR/ABL1 were identified and an additional fusion was found which was confirmed by Sanger sequencing. Grouping with gene expression profile excellently reflected phenotypic characters of three disease category. We developed experimental simulation model using scoring the selected genes showing significantly overexpressed in each disease category; 251 genes in AML, 117 genes in ALL group. Data from public source excellently consistent with results from developmental data.

Conclusions: RNA sequencing detected fusion genes reliably. Gene expression profiles were significantly different in AML, ALL and MPAL even though they shared same driver genetic aberration. Therefore, gene expression profile made it possible to group acute leukemia because it reflected disease specific phenotypic characters. Through the model developed in this study, a gene expression profile can be used to diagnose acute leukemia by disease specific profile as well as fusion gene detection especially in case showing ambiguous phenotype.

Keyword: Minor BCR/ABL1 Fusion, Phenotype Acute Leukemia, Gene Expression, RNAseq

PP-121

Synergistic apoptosis induced by a targeted combination treatment with midostaurin and ABT199 in the FLT3-ITD-positive and BCL2-overexpressing MV4-11

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Background: Acute myeloid leukemia (AML) is a heterogenous disease with low survival rate, and relapsed AML with FMS-like tyrosine kinase (FLT) 3 (FLT3)-internal tandem duplication (ITD) mutations worsens the prognosis of the patients. After an initial profiling of AML cell lines, we selected the cell line MV4-11 presenting both the FLT3-ITD mutation as well as overexpression of the anti-apoptotic BCL2 resistance protein.

Methods: We use AML cell lines U937, MV4-11, MOLM13, OCI-AML3 and CML cell line K562. To determine the cytotoxic and/or anti-proliferative effect of two agents, we use Hoechst/PI staining by microscopy and Annexin V/PI staining by cytometry. Combination index was calculated by CompuSyn software according to Chou-Talalay. The effect of the combination treatment was also validated in vitro by colony formation assays and in vivo by zebrafish xenografts.

Result: In an attempt to suggest a more efficient targeted chemotherapeutic approach, we determined sub-toxic doses of midostaurin targeting the FLT3-ITD and ABT199 (Venetoclax), a specific inhibitor of BCL2. Midostaurin induced significant levels of cell death at concentrations of 50 nM and above, whereas ABT-199 killed MV4-11 cells starting at a concentration of 5 nM. As the pan-caspase inhibitor zVAD-FMK (50 μM) was able to significantly protect cells against the effect of midostaurin or ABT199, we concluded that both agents trigger caspase-dependent apoptosis as single agents. Based on the CI calculation, the combination of midostaurin at 30 nM and ABT199 at 10 nM reached CI of 0.27 witnessing a strong synergistic effect. Whereas subtoxic doses of both compounds did not strongly affect viability of MV4-11 cells, a combination treatment synergistically triggered caspase-dependent apoptotic cell death compared to AML cells lines without FLT3 mutation or RPMI 1788 lymphocytes with a healthy phenotype. Importantly, the combination of midostaurin and ABT199 reduced the tumor formation in in vitro colony formation assays and in vivo zebrafish xenografts.

Conclusions: Importantly, the combination of midostaurin and ABT199 reduced the tumor formation in in vitro colony formation assays and in vivo zebrafish xenografts.

Keyword: FLT3 Mutation, BCL2 Overexpression, BCL2 Overexpression, Apoptosis, Targeted Therapy

PP-122

TMQ0153, a synthetic hydroquinone, induces autophagy followed by controlled necroptosis via mitochondrial dysfunction in chronic myelogenous leukemia

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Background: Hydroquinone (HQ) is a phenolic metabolite of benzene, which is used as a skin whitener. Insects synthesize this natural compound as a deterrent or by mushrooms as a toxin. Chronic myeloid leukemia (CML) results from a t(9;22)(q34;q11) translocation also called Philadelphia chromosome (Ph). Imatinib (STI571, Gleevec) is targeting the oncogenic BCR-ABL protein to treat patients with chronic myelogenous leukemia. However, these drugs trigger resistance of CML patients and do not completely eradicate BCR-ABL expressing cells . Novel drugs are required to improve CML therapies Studies aim to clarify the mechanisms by which the hydroquinone derivative, TMQ0153, triggers caspase-dependent apoptosis and autophagy-independent necroptosis depending on the concentration-used in human chronic myelogenous leukemia K562 cells.

Methods: Cytotoxic and anti-proliferative effects of TMQ0153 was conducted by Trypan blue assays. We ussed zebrafish models for in vivo xenografts and toxicity assays. We quantified cells with nuclear condensation by fluorescence microscopy after Hoechst/PI double staining with and without pan-caspase inhibitor zVAD to confirm caspase-dependency of TMQ0153-induced cell death. Cell morphology was investigated by Diff-quick and Cyto-ID staining. The accumulation of membrane-bound microtubule-associated protein light chain 3 (LC3)-II was observed by western blot. We investigated induction of necroptosis after pre-treatment with Receptor-interacting serine/threonine-protein kinase (RIP)-1 inhibitor necrostatin-1. ATP levels were investigated by CellTiter Glo assay.

Result: We screened a series of thirteen HQ derivatives (TMQ0022-0158) and assessed their effect on leukemia cell viability. We selected the compound TMQ0153 as the most potent compound on K562 cells. We then assessed its effect on leukemia cell viability including K562 cells with an IC50 of 35.4μM, 28.7μM and 26.1μM after 24, 48 and 72h. Colony formation assays supported cytotoxic effects of TMQ0153 in a 3D culture system. TMQ0153 induces apoptotic cell death at a lower concentration such as 20μM and non-apoptotic cell death at a higher concentration at 30-50μM after 8, 24, 48 and 72h. Pretreatment of pan-caspase inhibitor z-VAD demonstrated caspase-dependent apoptosis and caspase-independent non-apoptotic cell death of TMQ0153-treated K562 cells. Several investigations reported a relationship between autophagy and necroptosis. Results showed that TMQ0153 triggered formation of vesicles and also showed an accumulation of LC3II levels by western blots, altogether supporting the idea of autophagy induction by TMQ0153. In parallel, we investigated the formation of autophagosomes after treatment with TMQ0153. At 30μM, we observed non-apoptotic PI positive cell death. Inhibition of this cell demise was observed after pre-treatment with necrostatin-1. TMQ0153-triggered necroptosis also promoted biological stress that caused mitochondrial dysfunction and increased the levels of reactive oxygen species (ROS) concomitant with the depletion of intracellular ATP levels. Pre-treatment by Nec-1 could not prevent autophagy induction in K562 cells. We concluded that TMQ0153 induced an early autophagic reaction as a protective mode against necroptosis.

Conclusions: Based on these finding, TMQ0153 mediates a caspase-independent, but RIP1-dependent nonapoptotic necroptosis in K562 cells. This necroptosis is triggered by intracellular ATP depletion and increase of cytosolic Ca2+ levels. This necroptosis further triggers HMGB1 release and exposure of calreticulin as the marker of immunogenic cell death.

Keyword: Mitochondria, ROS, ATP, Autophagy, Necroptosis

PP-123

Burden and associated factors of anemia among pregnant women attending antenatal care in southern Ethiopia: Cross sectional study

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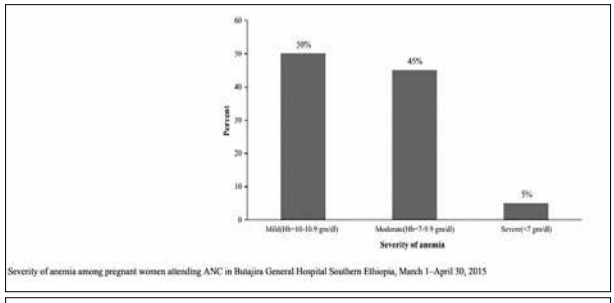
Background: Anemia is a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiologic needs, which varies by age, sex, altitude, smoking, and

pregnancy status. The study aim is to determine the prevalence and factors associated with anemia among pregnant women attending a hospital in southern Ethiopia using a structured interview administered questionnaire.

Methods: Facility-based cross-sectional study was conducted from March 01-April 30 2015 at Butajira General Hospital, Ethiopia. A total of 217 women responded to the questionnaire and provided blood and stool samples for analysis. Data were analyzed using Statistical packages for social sciences version 20 for windows.

Result and Conclusions: The overall burden of anemia in this study was 27.6%. Residence, ANC follow up, history of excess menstrual bleeding and inter-pregnancy interval were statistically associated with anemia among the pregnant women. Therefore, working in the identified gaps could reduce the current burden of anemia among pregnant women in the study area.



Severity of anemia among pregnant women attending ANC in Butajira General Hospital Southern Ethiopia, March 1–April 30, 2015

Multivariable logistic regression analysis of factors associated with anemia among pregnant women (n = 217) in Butajira General Hospital, Southern Ethiopia, March 1–April 30, 2015

Variables	Total (n = 217) n (%)	Anaemia		AOR (95% CI)	p value
		Yes (n = 60) n = (%)	No (n = 157) n = (%)		
Residence					
Urban	168 (77.4)	40 (18.4)	128 (58.9)	0.167 (0.041–0.682)	*0.013* *
Rural	49 (22.6)	20 (9.2)	29 (13.3)	1r	
History of Malaria prior to data collection time					
Yes	54 (24.9)	24 (11)	30 (13.8)	1r	0.525
No	163 (75.1)	36 (16.5)	127 (58.5)	1.622 (0.365–7.211)	
History of excess menstrual bleeding					
Yes	53 (24.4)	16 (7.3)	9 (4.1)	1r	*<0.001* *
No	164 (75.6)	44 (20.2)	148 (68.2)	0.028 (0.006–0.135)	
ANC follow up					
Yes	171 (78.8)	24 (9.2)	147 (67.7)	0.082 (0.018–0.370)	*<0.001* *
No	46 (21.2)	36 (16.5)	10 (4.6)	1r	
Consumption of AFS					
Yes	105 (48.4)	21 (9.6)	84 (38.7)	1.264 (0.365–4.380)	0.712
No	112 (51.6)	39 (17.9)	73 (33.6)	1r	
Inter pregnancy interval (years)					
<2	57 (26.3)	46 (21.1)	11 (5)	1r	*0.016* *
≥2	108 (49.8)	5 (2.3)	103 (47.4)	0.133 (0.026–0.685)	
Intestinal parasite					

1r set as reference, *AFS* animal food sources

* p < 0.05

PP-124

Molecular genetic modifier of glucose-6-phosphate dehydrogenase gene

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Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the genetic related erythrocytic enzyme disorder affecting oxidative stress defensive mechanism in human erythrocyte. The clinical manifestations of G6PD deficiency are neonatal jaundice and acute hemolytic anemia. The genetic alteration in G6PD gene characterized by mutations in protein coding region is the causative mechanism of G6PD deficiency in race specific manner. Therefore G6PD variants genotyping is the potential molecular tool for G6PD deficiency diagnosis beside screening tests such as methemoglobin reduction test and fluorescent spot test which are widely used in routine hematological laboratory. Considering 140 G6PD mutations deposited in G6PD mutation database (G6PD-MutDB) and 400 biochemical variants identified, this suggests genetic heterogeneity regulating G6PD phenotypic expression. World health Organization (WHO) recommends the investigation of G6PD residual enzymatic activity as a descriptor of G6PD deficiency and clinical classes. However G6PD genetic variant found and G6PD enzyme activity in female show no consistency correlation. The X-chromosome mosaicism is the only theory uses to describe this phenomenon.

Methods: In this study we therefore hypothesized that the genetic modifier mechanism might coordinately regulate inter-individual difference in G6PD enzyme activity. Sterol regulatory element binding protein-1 (SREBP1) is the transcription factor regulating G6PD gene expression. The SREBP1 genetic variation might explain the variation in G6PD activity. We recruited 30 G6PD subjects and 30 healthy subjects from the G6PD screening of 211 subjects.

Result: We found that the common G6PD variants in Thai population are Viangchan and Mahidol. The bioinformatics approach has been used to predict the functional single nucleotide polymorphism (SNP) residing in SREBP1 gene. We performed DNA sequencing to screen for SNP at 3'untranslated region (3'UTR) which is proposed to be binding site of regulatory RNA in post-transcriptional regulation. Three common SNPs namely rs2297508,

rs13306739 and rs11868035 have been identified with minor allele frequency > 10%. These three SNPs are in completed linkage disequilibrium (D' =1 and r2 = 1). However no association has been observed between 3'UTR SNP and G6PD enzymatic activity. Interestingly, novel SNP located in 3'UTR of SREBP1 gene has been discovered in one G6PD heterozygous female with Viangchan variant who has high G6PD activity (120% enzyme activity).

Conclusions: In further study the gene-gene interaction between G6PD mutation and SREBP1 SNP would be analyzed in order to fully elucidate the role of SREBP1SNP as genetic modifier of G6PD gene expression. The combination of molecular diagnostic approach and conventional hematological tests should be routinely used to definitively diagnosis G6PD deficiency. The molecular genetics study should be applied to clarify the interaction between G6PD and related functional gene in order to develop effective tool for detecting G6PD deficiency.

Keyword: G6PD, SREBP1, Molecular Diagnostic, Enzyme Activity, Gene-Gene Interaction

PP-125

Macrocytic anemia associated infantile tremor syndrome and vitamin D

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Background: Infantile tremor syndrome characterized by macrocytic anemia, dark knuckel skin pigmentation, tremors, physical, and mental regression, commonly between 9 months to 3 years age children on prolonged breast fed of vegetarian mothers, though the exact etiopathology is obscure. but Vitamin B12, folic acid deficiency is well documented with megaloblastic findings. and therapeutic improvement with early therapy Its prevalence is not documented in developed world but reported from various places in India(0.87-1.02% admissions) with decline in recent years with socioecon0mic well being We studied possible etiological associated vitamin D deficiency, common prevalence, evidenced with its therapeutic effect of immunomedulation, nerve conduction and neurotransmitter dendretic pathway activation along with haemopiotic maturation.property

Methods: 4 male children age 9 months to 2 years clinically diagnosis of infantile tremor syndrome who presented with macrocytic anemia low B12 (less than 200ng/ml) and Vitamin D (less than 20ng/ml) were included in this study , were treated with Vitamin B12, folic acid and Vitamin D in therapeutic doses and were evaluated

Result: All 4 children studied on follow up showed remarkable clinical disappearance tremors in 1-2 days, improved social motor activities. haematological improvement in 3-4 with dermatological improvement in 7-10 days observed

Conclusions: The present study, though small, has shown early therapeutic effect of vitamin D supplementation in management of infantile tremor syndrome associated megaloblastic anemia with its immunomedulatory, neurotransmitter and neuronal maturity and haematological maturation properties. Further more elaborative large studies may done

Keyword: Infantile Tremor Syndrome, Vitamin D

PP-126

Smartphone-based diagnosis in glucose-6-phosphate dehydrogenase deficiency

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Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme deficiency in humans, affecting 400 million people worldwide. Most persons with G6PD deficiency are asymptomatic, but exposure to oxidant drugs may induce haemolysis. The quantitative standard method is biochemical assay, which requires specialized equipment and high cost, thus cannot be used at point-of-care or in the field. We therefore developed a point-of-care Smartphone-based platform called "sG6PD" that can quickly identify a patient with G6PD deficiency.

Methods: The principle of testing is a colorimetric assay, based on reduction of tetra-nitro blue tetrazolium (TNBT) to color of formazan crystals by the G6PD enzyme on paper. Detection was achieved by capturing the colour using a mobile phone and the colour intensity was analysed using image processing technique. The colour intensities were analysed and the calculated mean colour intensity value was imported into the linear equation for

reporting the G6PD activity (IU/gHb). We compared the performance of sG6PD assay with the standard biochemical assay using blood samples of 280 G6PD normal and 300 G6PD deficient individuals.

Result: The result of G6PD activity measured by sG6PD assay and the standard method were highly correlated (r2 = 0.98, P<0.01). The limit of agreement was –0.63-1.25 IU/gHb. The standard deviation of the difference between the two measurements was 1.04 IU/gHb. The sensitivity and specificity of sG6PD assay were 97% and 99%, respectively.

Conclusions: This study demonstrates the feasibility of using sG6PD. sG6PD assay offers the potential to deliver a rapid diagnosis of G6PD deficiency with a simple test and low cost ($0.1/test) that can be performed at the point-of-care in resource-limited settings.

Keyword: Glucose-6-Phosphate Dehydrogenase Deficiency, Smartphone-Based Diagnosis, Biochemical Assay, Tetra-Nitro Blue Tetrazolium, Colorimetric Assay

PP-127

Microparticles-derived miRNAs serves as a novel diagnosis marker for glucose-6-phosphate dehydrogenase deficiency

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Background: Microparticles (MPs) are small membrane-bound structures that are secreted by various cell types, including red blood cells, white blood cells, endothelial cells and platelets. Recent studies have shown that MPs are important for cell-to-cell communication, locally and distantly; horizontally transferring DNA, mRNA, microRNA (miRNA), proteins and lipids. The miRNA function has been previously highlighted in erythropoiesis and hematological disorders. However, the analysis of MPs-derived miRNAs in patient with Glucose-6-phosphate dehydrogenase deficiency (G6PD) never been addressed.

Methods: In order to identify potential miRNAs involve G6PD, we initially applied computational approach for selecting candidate miRNA from 500 miRNAs in the human genome. The comparative bioinformatics study showed potential candidate miRNA; miR-16, miR-24, miR-138, miR-195 and miR-451. We further confirmed the association of G6PD activity with all these 5 selected miRNAs isolated from circulating MPs in 405 samples of G6PD deficient individuals and 410 samples of G6PD normal individuals using qRT-PCR. MPs were quantified by annexin V labeling and counted by flow cytometry.

Result: G6PD deficient individuals showed an increase in circulating MPs concentrations as compared to G6PD normal individuals (18561/uL (16865-20532/uL) vs (559 (335-875/ uL), P < 0.01). MPs concentrations were significantly increased with the severity of G6PD deficiency. Median MPs concentrations from individuals with severe G6PD deficiency and individuals with moderate G6PD deficiency were 25641/uL (21216-32132/uL) and 10984/uL (10685-22107/uL), respectively (P < 0.01). Moreover, a high expression level of MiR-138 derived MPs in G6PD deficient individuals compared with healthy was shown.

Conclusions: This study demonstrates a sensitive and specific biomarker for a miRNAs contained within circulating MPs could serve as biomarkers for the diagnosis of G6PD deficiency. However, further study is warranted to understand the targets affected by MiR-138 in pathophysiology of G6PD deficiency.

Keyword: Microparticles, MicroRNA, Glucose-6-Phosphate Dehydrogenase Deficiency

PP-128

Association of hematologic parameters with TMPRSS6 gene variations in iron deficiency anemia patients

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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.

Methods: 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.

Result: 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.

Conclusions: 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

PP-129

The effect of moringa seeds extract as anti anemia of chronic disease through decreasing IL-6 expression in liver tissue of metabolic syndrome rats

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Background: Metabolic syndrome correlate with chronic inflammation that impact on increasing of Interleukin-6 (IL-6) expression. IL-6 is a multifunctional cytokine that regulates the hepatic acute-phase response, the immune response, inflammation, and hematopoiesis. IL-6 appears to be the central mediator of anemia of chronic disease in a range of inflammatory diseases through increased generation of hepcidin that can cause a significant decrease in serum iron level. Moringa seeds (Moringa oleifera, Lam.) contains plenty secondary metabolites which is rich in antioxidant can decrease IL-6 expression. This study aimed to determine the effect of Moringa seeds extract against IL-6 expression on liver tissue of metabolic syndrome rats (Rattus norvegicus).

Methods: This was laboratory experimental research using posttest only group design. The sample are 28 male rats (Rattus norvegicus) that divided into 4 groups: K1 (control) were fed with standard pellet, K2 were metabolic syndrome rats model without moringa seed extract, K3 were metabolic syndrome rats model and given Moringa seeds extract at dose 150mg/KgBW and K4 were metabolic syndrome rats model and given Moringa seeds extract at dose 200mg/KgBW. IL-6 expression measured with intensity distribution score (IDS). Effect of Moringa seeds extract to IL-6 expression on hepatic tissue were analyzed with Kruskal-Wallis and Mann-Whitney posthoc test.

Result: The mean value of IDS IL-6 expression in K1: 22.12, K2: 201.34, K3: 151.63, K4: 148.58. IL-6 expression in the hepatic tissue then analyzed by Kruskal-Wallis test. Kruskal-Wallis test showed that there were significant differences of IL-6 expression between 4 groups of liver tissue ($p<0.05$). Then Mann-Whitney posthoc test showed significant differences of IL-6 expression between each group ($p < 0.05$) except in K3 and K4 ($p > 0.05$).

Conclusions: Moringa oleifera seeds extract at dose of 150 mg/kgBW and dose of 200 mg/kgBW potentially lowered IL-6 expression on liver tissue of metabolic syndrome rats (Rattus norvegicus).

Keyword: Moringa Oleifera Seeds Extract, IL-6 Expression on Liver Tissue, Anemia of Chronic Disease, Metabolic Syndrome

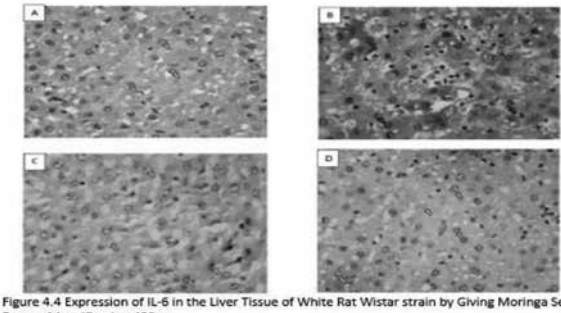

Figure 4.4 Expression of IL-6 in the Liver Tissue of White Rat Wistar strain by Giving Moringa Seed Extract.Magnification 400x;

With:

A. K1 shows liver tissue with negative IL-6 expression;
B. K2 shows liver tissue with moderate and strong IL-6 expression;
C. K3 shows liver tissue with weak and negative IL-6 expression;
D. K4 shows liver tissue with weak and negative IL-6 expression.

: negative expression
: weak expression
: medium expression
: strong expression

Table 1. Saphiro-Wilk Test Results IL-6 Expression in the Liver Tissues of Each Group.

Group	N	Sig. value
KI	6	0. 418
K2	7	0. 858
K3	6	0. 235
K4	7	0 905

Tabel 2.Mann-Whitney test results expression of IL-6 on liver tissue after give by Moringa Seed Extract

Group	Sig. value	Significance
K1 and K2	0.001	Significant
K1 and K3	0.002	Significant
K1 and K4	0.001	Significant
K2 and K3	0.001	Significant
K2 and K4	0.001	Significant
K3 and K4	0.073	Not Significant

PP-130

Thalassemia major patients presenting with raised HbF and a fast moving Hb

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Background: The thalassemias are characterized by reduced (hemoglobin) Hb level and hence anemia, the characteristic presenting symptom of the disease. Genetic modifiers that reduce the alpha/non-alpha chain imbalance have been seen to reduce infirmity in beta thalassemia patients.

Methods: In the present study, we conducted the HPLC analysis of blood samples of transfusion dependent thalassemia patients, of the Gwalior Chambal region of central India

Result: The study revealed HbA levels below the reference range in all the patients. The concentration of HbA was maximum in IVS1,5 homozygotes and was lowest in patients presenting with the codon 30 (G→A) mutation. A fast-moving hemoglobin comprising >2.5% to14% of the total hemoglobin was detected in 67% of the cases and fetal hemoglobin (HbF) was high in all these patients ranging from 3 to nearly 50%. The levels of HbF and the early eluting hemoglobin were inversely proportional to that of HbA and were highest in patients presenting with the codon 30 (G→A) anomaly.

Conclusions: Despite high HbF and the apparent co-inheritance of alpha thalassemia, the clinical presentation of the subjects is severe requiring transfusions at intervals of fifteen to thirty days.

Keyword: Alpha Thalassemia, Fetal Hemoglobin, HPLC Analysis, Central India, Genetic Modifiers

PP-131

Exploring the β-thalassaemia mutations in western rajasthan with clinical expression

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Background: In India, β-thalassaemia is the most common monogenic disorder. The disease is characterized by its genetic heterogeneity at the molecular level, and more than 300 mutations of the β globin gene have been characterized all over the world, however, five mutations, codon 8/9 (+G), codon 41/42 (–TCTT), IVS I-1 (G→T), IVS I-5(G→C), and 619 bp deletion at 3' end of β-globin gene, account for about 85-90% of β-thalassaemia mutations in Indian population. The aim of the present study was to screen known cases of β-thalassaemia in the Western part of Rajasthan state.

Methods: The study included 144 known cases of β-thalassaemia of all clinical phenotypes including β-thalassaemia major, β-thalassaemia minor and β-thalassaemia intermedia. Cases were diagnosed based on clinical features, haematology investigations including haemogram and Hb-HPLC (Haemoglobin-High performance liquid chromatography). Blood samples from all these cases were taken for mutation analysis. DNA was purified from anticoagulated whole blood using DNA Purification Kit. The mutations were characterized by the polymerase chain reaction method employing allele specific priming technique (AMRS) to study the five thalassaemia mutations including IVS-I-5 (G→C), IVS-I-1(G→T), CD 41/42 (-TCTT), CD 8/9 (+G) and 619 bp deletion from the 3' end of the β-globin gene using a total of seven different primers.

Result: Of all 144 cases, 74 (51.38% of all) cases were of β-thalassaemia major, five (3.4% of all) cases were of β-thalassaemia intermedia and 65 (45.14% of all) cases were of β-thalassaemia minor. Mutation analysis revealed that five common mutations were present in 130 (90.27% of all) cases. Among identified mutations, highest frequency of mutation was of IVS-I-5 (G→C) identified in 73 cases (50.7% of all cases). In 11 (7.63% of all) cases, more than one mutation was identified.

Conclusions: β-thalassaemias are common in Western part of Rajasthan state of India, however, there have been very few studies focusing this part of the country. In this study, we screened known cases of thalassaemia for five common mutations and found that these mutations are common in this part of the country also. These observations might help in forming the basis for comprehensive diagnostic database that would not only be useful for genetic counseling but also for prenatal diagnosis.

Keyword: B-Thalassaemia, Mutations, Haemogram, Hb-HPLC, Western Rajasthan

PP-132

A case of δ-thalassemia in Korea

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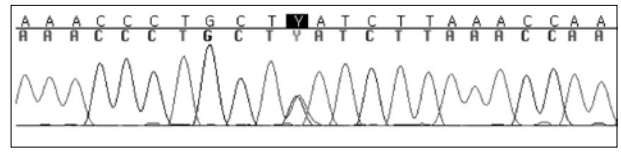
Background: Thalassemia is a genetic disorder of hemoglobin synthesis. It is known to be rare in Korea and, in particular, δ-thalassemia has not been reported yet. Here, we present the first patient who had δ-thalassemia in Korea.

Methods: A 46-year-old Korean male visited Incheon Health Screening Clinic of Korea Association of Health Promotion for the regular check-up. He had microcytosis and hypochromasia [mean corpuscular volume 79.2 fL, mean corpuscular Hb 25.5 pg, and Hb 15.9 g/dL]. Iron study of the patient showed the normal results [Fe 108 μg/dL, UIBC 272 μg/dL, TIBC 480 μg/dL, and Ferritin 175.6 ng/mL]. Hemoglobin analysis using capillary electrophoresis was done and direct sequencing of the HBB and HBD gene was performed.

Result: Hemoglobin electrophoresis showed the presence of a probable δ-globin chain variant (HbA 97.8%, HbF or Hb variant 0.8%, HbA2 1.4%). By Sanger sequencing, a variant, HBD: c.-127T>C, heterozygote was detected (Figure). Multiplex Ligation-dependent Probe Amplification for HBB gene was done and it showed no deletion or duplication.

Conclusions: δ defects have been reported to have no clinical significance, but this case shows that δ-globin variant can result in δ-thalassemia. Because the prevalence of thalassemia is increasing in Korea, δ-thalassemia should also be considered one of the differential diagnosis of patients with low mean corpuscular volume.

Keyword: Thalassemia, HBD Gene, Hemoglobin A2, Korea



PP-133

Parvovirus B19-associated neutropenia and thrombocytopenia without anemia

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Background: Parvovirus B19 infection can be symptomless or cause a benign and short-lived condition such as erythema. While the most representative hematologic manifestation is pure red cell aplasia (PRCA), neutropenia and/or thrombocytopenia without anemia have been rarely reported. Here, we describe two cases with Parvovirus B19 infection presenting as neutropenia and thrombocytopenia.

Methods: Patients' clinical and laboratory information was reviewed. Parvovirus B19 PCR was performed by in-house method.

Result: A 47-year-old female (Patient 1) and a 37-year-old female (Patient 2) presented with neutropenia and thrombocytopenia, not anemia. They had no underlying disease. Initial complete blood count (CBC) findings were as follows: in Patient 1, white blood cells (WBC) 0.95×106/L, absolute neutrophil count (ANC) 0.52×106/L, hemoglobin (Hb) 11.6 g/dl, platelets 87×109/L, reticulocyte count 0.28%; in Patient 2, WBC 2.92×106/L, ANC 1.18×106/L, Hb 14.7 g/dl, platelets 64×109/L, reticulocyte count 0.078%. They underwent bone marrow study and similar findings were observed. Erythroid progenitor cells were almost absent, leaving only a few pronormoblasts, suggesting PRCA. Also, histiocytic hyperplasia with rare hemophagocytosis was observed. Parvovirus PCR was performed and positive result was obtained. Patients' CBC recovered spontaneously within 10 days.

Conclusions: Even without anemia, neutropenia and thrombocytopenia can occur in association with parvovirus B19 infection. Therefore, parvovirus B19 infection should be considered in patients with neutropenia and thrombocytopenia without underlying disease.

Keyword: Parvovirus B19, Neutropenia, Thrombocytopenia, Pure Red Cell Aplasia, Korea

PP-134

Attenuation of anemia by retnla in LPS-induced inflammatory response

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Background: Anemia of inflammation is a common feature of inflammatory disorders, including chronic kidney disease, infections, and rheumatoid arthritis. Retnla is highly up-regulated in various inflammatory states, especially those involving asthma, intestinal inflammation, and parasitic diseases, and regulates the pathogenesis of those diseases. However, the role of Retnla in anemia of inflammation is unknown.

Methods: To explore the roles of Retnla in anemia of inflammation in vivo, we generated mouse model of the disease by injecting 0.25 mg/kg lipopolysaccharides (LPS) intraperitoneally into Retnla-deficient and wild-type (WT) mice daily for 10 days. Research data was expressed as differences between LPS-treated Retnla-deficient and WT mice by a two-tailed non-parametric Mann–Whitney U-test using GraphPad Instat program.

Result: The results of the study are as follows: The results of the study are as follows: LPS-treated Retnla-deficient mice had significantly lower hemoglobin contents, hematocrit levels and red blood cell indices including mean corpuscular volume, mean corpuscular hemoglobin than WT controls. This decrease was accompanied by significant increase in total white blood cell and monocyte counts in the blood. However, there was no significant difference in mRNA levels of hepatic hepcidin and renal erythropoietin between the two animal groups.

Conclusions: Taken together, these results indicates that Retnla deficiency exacerbates the anemia by increasing inflammation, suggesting therapeutic value of Retnla in the treatment of anemia of inflammation.

Keyword: Resistin-Like Molecule Alpha, Anemia of Inflammation, Lipopolysaccharide, Red Blood Cell, Hepcidin, Erythropoietin

Parameters	Wild-type mice	Relmα-deficient mice	*P* value
RBCs (×10^{12}/L)	9.72 ± 0.46	9.43 ± 0.39	0.15
Hb (g/dL)	14.13 ± 0.7	13.45 ± 0.64	0.04
HCT (%)	46.6 ± 2	44.38 ± 1.72	0.02
MCV (fL)	47.92 ± 0.36	47.04 ± 0.62	0.002
MCH (pg)	14.52 ± 0.19	14.25 ± 0.24	0.01
MCHC (g/dL)	30.32 ± 0.38	30.28 ± 0.51	0.86
RDW (%)	15.4 ± 1.02	15.2 ± 0.85	0.65
Reticulocytes (×10^{9}/L)	622.96 ± 161.01	692.28 ± 210.93	0.44
Reticulocytes (%)	6.44 ± 1.79	7.34 ± 2.25	0.36

PP-135

Glucose-6-phosphate dehydrogenase deficiency in newborns in Birjand, Iran

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Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common X-linked recessive hereditary disorders in the world, therefore Newborn G6PD deficiency screening has been recognized as an essential component of public health care in most developed and some Mediterranean countries. This study aimed at determining the prevalence of G6PD deficiency in newborns in Birjand city, Iran. Accordingly, the asymptomatic carrier parents will be informed and educated about favism.

Methods: A total of 2,421 blood samples collected from newborns in Vali-e-asr Hospital of Birjand city. The study population consisted of 1281 (52.91%) males and 1140 (47.09%) females. The specimens were characterized in terms of G6PD deficiency using fluorescent spot test.

Result: G6PD deficiency was observed in 94 (3.88%) out of 2440 newborns whose G6PD levels were measured. 74 were male and 20 were female newborns. In comparison with females, a greater proportion of males showed enzyme deficiency (78.72% Vs 21.28%). The difference was statistically significant

Conclusions: In this study, the prevalence of G6PD deficiency was lower than northern and southeastern provinces of Iran; however, it was higher than that reported for Mashhad city (0.8%). These differences may be related to demographic and geographical locations.

Keyword: G6pd Deficiency, Newborn, Iran

PP-136

Screening of α-thalassemia using cord blood in Bangladesh

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Background: α-thalassemia, perhaps the most common monogenic disorders, is an autosomal recessive condition characterized by a microcytic hypochromic anemia, commonly affecting Southeast Asian people where Bangladesh lies. However, there is a huge lack in the knowledge regarding the prevalence, etiology and screening of the disorder in the country.

Methods: To address this issue and to encourage newborn screening programs in the country, a comprehensive study was conducted using cord blood (CB) samples collected from two tertiary hospitals of Mymensingh and Kishoreganj districts of Bangladesh. A total of 99 healthy newborns were enrolled and clinical and sub-clinical information, hematological features of CB, serum iron levels were analyzed and thalassemic condition was screened using osmotic fragility testing (OFT) and gap-PCR (Polymerase Chain Reaction).

Result: The study revealed that, 16% of the studied subjects were α-thalassemia carriers and the –SEA type deletions were prevalent in 75% α-thalassemic subjects. Compared to the normal newborns, the α-thalassemic carrier newborns had significantly lower age of mother, gestation period, birth weight. Significantly lower values for erythrocyte counts, platelet counts were observed while higher values for leukocyte, neutrophil and lymphocyte parts were observed. An elevated erythrocyte sedimentation rate was also observed in the CB of α-thalassemia carrier newborns. A higher serum iron levels were determined, meaning that the α-thalassemic condition was not due to iron deficiencies. This study provides partial information regarding the reference ranges of hematological aspects and serum iron levels in the CB. Furthermore, a paradigm for newborn screening and genetic counseling practice in the context of Bangladesh were described.

Conclusions: This study presents important insights on the epidemiology and etiology of α-thalassemias in Bangladesh. It also puts forward to a paradigm for newborn screening and genetic counseling practice in the country, which could also be adopted by other low and lower-middle income countries.

Keyword: Alpha-Thalassemia, Complete Blood Counts, Serum Iron, Osmotic Fragility Test, Gap-PCR, Genetic Counseling

PP-137

Knowledge trend of anemia in adolescents in Indonesia

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Background: Anemia is one of the health problems in Indonesia that has not been fully addressed. The prevalence of anemia in female adolescents in Indonesia is still high, amounting to 22.7%. The impact of anemia may not be immediately visible, but it can last a long time and affects the subsequent lives of adolescents. Anemia in an adolescent girls can have a long impact on her and also for the child she is born with later.

Methods: The method used was the analysis of secondary data on the survey of adolescent reproduction health in 2007-2017. The sample used was adolescents aged 13 to 24 years who are not married.

Result: The results of the study show that 88% of adolescents' answers are incorrect about anemia. In addition, 67% or almost half the adolescents do not know at all about the causes of anemia. Other than that, teenagers who answered correctly about how to deal with anemia were still inaccurate, namely around 46%.

Conclusions: It can be implied that the awareness of understanding of adolescents in Indonesia regarding anemia is still very low. Therefore, it is very important to manage adolescent reproduction health programs related to a development of materials and information to adolescents about anemia problems.

Keyword: Anemia, Adolescence, Reproductive Health, Indonesia

PP-138

Successful sirolimus treatment of pure red cell aplasia in patients with renal insufficiency

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Background: Pure red cell aplasia (PRCA) is a kind of anemia defined by severe reticulocytopenia and reduction of erythroid precursors in bone marrow. Cyclosporine is the first line therapy, but nephrotoxicity is a significant side effect of it. Therefore, a new therapy should be found for PRCA patients with chronic renal insufficiency.

Methods: Twelve PRCA patients with renal insufficiency from May, 2014 to November, 2018 in Peking Union Medical College Hospital were enrolled in this study. Six patients have tried cyclosporine treatment before, but they can't continue because of renal insufficiency. Another six patients were at their initial treatment with sirolimus. All patients were administered with sirolimus at the dose of 1-3mg/d for at least 1.5 months. Clinical data were collected before and after sirolimus therapy at different time points. Patients were followed at the medium time of 14.5-month.

Result: All twelve patients responded to sirolimus with 58.3% complete response during sirolimus therapy. 90.9% patients reported creatinine level decreased or remained in the experimental period, while only 1 patient reported continually increase of creatinine during one-year therapy. Most side effects weren't related to renal function, including infections, oral mucositis and increase of triglyceride. Most patients remain stable during the follow-up period.

Conclusions: Sirolimus was effective and tolerable for PRCA associated with renal insufficiency, and sirolimus were safe for most of patients with renal insufficiency.

Keyword: Pure Red Cell Aplasia, Renal Insufficiency, Cyclosporine, Sirolimus, Initial Treatment

PP-139

Local wisdom and anemia prevention: Study of the use of herbs as an alternative treatment for rural communities in West Sulawesi, Indonesia

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Background: Anemia is one of a health problem in Indonesia. Among Southeast Asian countries, Indonesia is referred to as one of the countries with a large number of sufferers. These sufferers are not only in urban areas but also in rural areas. Based on data from the 2013 Basic Health Research (Riskesdas), the number of anemia sufferers in Indonesia consisted of 26.4 percent of children, 12.4 percent of men aged 13-18 years, 16.6 percent of men over 15 years, 22.7 percent of women were 13-18 years old, 22.7 percent were female money from 15-49 years and 37.1 percent in pregnant women.

Methods: This study uses qualitative method with case study. The author collected data in form of interviews, observation, and documentation. Here, author explored the habits of community how to prevent anemia.

Result: The phenomena learned from this incident was not only the behavior of people that used alternative medicine to prevent anemia, but also the effectiveness of this traditional treatment based on the local wisdom. The study findings indicated that 1) rural communities were more likely to prefer to use herbs in preventing anemia, 2) alternative medicine is chosen because it is not only economically cheap, but also safe from the influence of chemicals.

Conclusions: Based on the result of the study, it can be concluded that the majority of rural communities in West Sulawesi are more likely to use alternative treatments to prevent anemia.

Keyword: Anemia, Local Wisdom, Herbs, Alternative Treatment, Rural Communities

PP-140

The influence of socio-economic factors on prevelence of anemia among women of reproductive age in ASEAN-5

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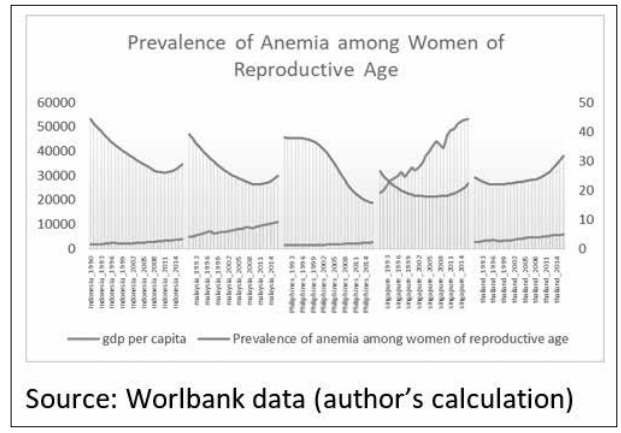
Background: Anemia is one of the most important diseases to pay attention, especially for women in reproductive age. The high rate of anemia in women in reproductive age in the ASEAN-5 which is ranked above 100 in the world has become focus of this study.

Methods: This study analyzes the effect of GDP per capita, the literacy rate of adult women, and the participation rate of women working in ASEAN-5 (Indonesia, Malaysia, Philippines, Thailand and Singapore). Secondary analysis is done by using panel data for the period 1991-2016 and random effect method.

Result: The results of the graph show that on average the level of anemia had a decreased in all five countries but had an increase in 2011-2016, except Thailand. Thailand have an increase in anemia each year. Meanwhile, the results of the regression show that the level of participation of working women has a positive and significant effect on anemia in the women in reproductive age while the GDP per capita and the literacy rate of adult women negatively affect anemia in the women in reproductive age.

Conclusions: It is expected that the government try to increase the GDP per capita, the level of education of female to decrease anemia of the women, and the need for special attention regarding women working in ASEAN-5.

Keyword: Anemia, Women in Reproductive Age, GDP per Capita, Literacy Rate, Women Working, ASEAN-5



Source: Worlbank data (author's calculation)

PP-141

The problem of identification of population objects during the unification of data from multiple sources when working with a hemophilia register

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Background: Development of methods for mutual identification of information records about population objects, construction of a measure of proximity of identification information, construction of procedures for preliminary sorting and combining records, probably related to one object for further expert verification. The practical purpose is the initial preliminary filling of the electronic database of the hemophilia register.

Methods: Data sources for register pre-filling: data from the register of patients with hemophilia of NGOs, data of the Hematology Department of the Tashkent Medical Academy. Data analysis and development of algorithms is carried out using standard statistical analysis methods, heuristic algorithms for analyzing string variables.

Result: A preliminary analysis of the available sources of data on patients with hemophilia patients shows the difficulty of automatically identifying objects from source databases due to the discrepancy in the structure of the collected information and the methods for updating it. Full identification and unequivocal decision to enter into the master register can be made solely on the basis of manual examination and update of current personal information. Nevertheless, the application of the developed identification techniques can significantly reduce the amount of manual work of data verification and initial input of basic information about the patient. In addition, a preliminary assessment of the population characteristics will allow optimizing the planned work of the register and studies based on it.

Conclusions: The development of adequate mathematically sound methods of register management and the use of multiple data sources should lead to a significant improvement in the quality of the register and an increase in the completeness of the description of the target population, reducing the cost of time-consuming manual data entry and verification operations

Keyword: Hemophilia, Register Management, Preliminary Analysis

PP-142

Prevalence of anaemia in western region of Nepal: A hospital based study

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Background: Anaemia is a common public health problem all over the world. It is due to inadequate intake of, Iron, vitamin B 12, Folic acid. Infants, children and women are more susceptible due to increased requirement. Thus the aim of this study is to rule out the frequency of anaemia in a western region of Nepal.

Methods: This is a crosssectional study. This study was carried out in the department of Pathology Manipal Teaching Hospital and laboratory unit of Kaski Sewa Hospital & Research Center, Pokhara, Nepal between 15 January to October 25, 2018. A total of 110 participants were included in this study out of which 20 (18.1%) were males and (90) 81.8% were females. All the participants haematological parameters (haemoglobin, red blood cell count, packed cell volume and Mean Corpuscular Volume, Mean Corpuscular Haemoglobin, and Mean Corpuscular Haemoglobin Concentration were measured in a coulter counter XN- 450, Sysmex (Japan). Iron and TIBC were measured in a semi-autoanalyzer Dialab DTN- by end point method provided by clinical coral systems. Ferritin was measured in a Chemiluminiscence Immuno Assay (CLIA) Maglumi 600, snibe. Statistical analysis were analyzed in a Statistical Package for Social Sciences (SPSS) version 17.

Result: The mean age of the participant was 36.7 ± 15.3. The mean haemoglobin concentration was found to be 10.7 ± 1.34 gm/dl. The mean serum iron, and TIBC levels were found to be 43.8± 33.9, 336.9 ± 149.6 respectively. The mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) and Red cell distribution width RDW were found to be 77.7±7.17, 25.6±2.94, 32.9±1.69 and 40.5±5.74 respectively. This study found 11.81 % mild anaemia, 59.9% moderate and 29.09% severe anaemia. Most of the severe anaemia participant shows microcytic hypochromic RBC in peripheral smear. We also found a low Iron level than normal in iron deficient group.

Conclusions: This study found 11.81 % mild anaemia, 59.9% moderate and 29.09% severe anaemia. Our study shows that females were most commonly affected. Most of the iron deficiency anaemia cases were severe. Severe anaemia group of the participant shows decreased iron level in the serum and increased total iron binding ca-

pacity. However, a larger sample size is an ongoing study is desirable to know the actual prevalence status of anaemia.

Keyword: Iron Deficiency Anaemia, Haemoglobin, Microcytic, Red Blood Cell

Table 2 : Prevalence of anaemia

Severity of anaemia	Frequency	Percentage (%)
Mild anaemia (Hb between 10.5- 12 gm/dl)	13	11.81 %
Moderate anaemia (Hb 8.5-10 gm/dl)	65	59.09 %
Severe anaemia (Hb < 8 gm/dl)	32	29.09 %
	Total 110	

PP-144

Chlorophyll as a considerable treatment for anemia through increases hemoglobin levels in anemia white rat model

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Background: Chlorophyll is mostly present in green vegetables. People have used chlorophyll as a health supplement for many years. It is chemically similar to hemoglobin, a protein that is essential in red blood cells as it carries oxygen around a person's body. Anemia is a disease that can be caused by the less number of hemoglobin in blood. This study aimed to prove that the consumption of chlorophyll could be used as a treatment for anemia through increasing the hemoglobin levels.

Methods: This experimental laboratory study used a pre-test-posttest control group design. 35 female rats, as sample, were divided into 5 groups. First, 3ml of blood was taken through retro orbital vein. G1 is an anemia model without chlorophyll treatment (control), G2 was treated by 0.6 mg of chlorophyll once daily, G3 was treated by 1.2 mg of chlorophyll once daily, G4 was treated by 0.6 mg of chlorophyll twice daily, and G5 was treated by 1.2 mg of chlorophyll twice daily, for 14 days. The blood was then taken again at day 15th. Data were analysed using Friedman test and then Wilcoxon test as post hoc.

Result: Friedman test result showed significant difference between control group (G1) and treated group (G2, G3, G4, G5) with p=0.0001. Wilcoxon test showed that increasing the dosage of chlorophyll had no significant differences (p>0.05).

Conclusions: Consuming chlorophyll could increase the hemoglobin levels in blood significantly. Essentially, chlorophyll helps the body turn free-form iron into red blood cells, thereby providing an effective way to treat anemia.

Keyword: Anemia, Hemoglobin, Chlorophyll

PP-145

Effect of carica papaya leaf extract on platelet counts in patient of dengue

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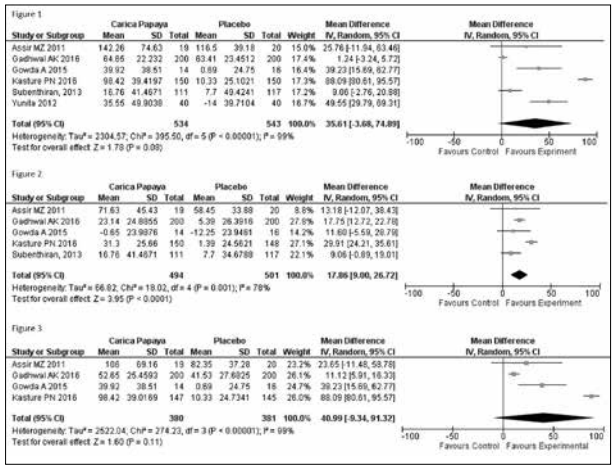
Background: Decrease in platelets is an important sign of dengue infection. Fall in platelet count in the dengue patients is associated with the hemorrhagic complications. Role of platelet infusion is in dengue patients is controversial. Leaf extract of Carica papaya is considered to be a new therapy for improvement of platelet counts in such patients. There are few clinical trials which shows very good effect on platelet numbers after consumption of leaf extract while few others shows not much impressive effect or no effect. There was a need of systematical analysis of available evidence in the form of systematic review and meta-analysis to evaluate the effect of Carica Papaya on platelet counts in dengue. This systematic review and meta-analysis were designed to search the available evidence related to the efficacy of Carica papaya leaf extract in platelet count in dengue and to synthesize the evidence in meaningful form through meta-analysis.

Methods: Randomized controlled trials related to the efficacy and safety of Carica papaya leaf extract in dengue were searched from PubMed, Cochrane Clinical Trial Registry, and Google Scholar. Primary endpoint was effect on platelet counts. Data related to primary endpoint were pooled together and analyzed by review manager (RevMen) software. The random effect model was used. The bias was analyzed by the Cochrane risk of bias tool.

Result: There were total six clinical trials found to be suitable for meta-analysis. Risk of bias for majority of clinical trials were moderate to low. Carica papaya leaf extract was not found to be associated with increase in platelet count in the overall analysis (mean difference [MD] 35.61 = [95% CI -3.68 to 74.89 P = 0.08]) and analysis after 4th day (MD = 40.99 [95% CI -9.34 to 91.32; P = 0.11]) (Figure 1 and 3) however there was significant increase in platelet count after 48 hours in Carica Papaya group as compared to placebo (MD = 17.86 [95% CI 9.0 to 26.72; P = <0.001]). (Figure 2) There was significant heterogeneity observed for all comparisons.

Conclusions: There is no clear evidence favoring the use of Carica papaya leaf extract to increase platelet in dengue. It may increase the platelet in short term but overall there is no clinically meaningful effect.

Keyword: Dengue, Carica papaya, Platelets, Leaf extract



PP-146

Platelet indices and their value in differentiating the causes of thrombocytopenia

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Background: The causes of thrombocytopenia can be categorised into hypoproliferative in bone marrow or hyperdestructive in peripheral blood by invasive bone marrow examination. Recently, platelet indices in Full Blood Count (FBC) are considered to be able to differentiate the cause of thrombocytopenia. In this study, we aim to evaluation the value of Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) in diagnosis of thrombocytopenia.

Methods: Cross-descriptive. 250 childrens with thrombocytopenia were given FBC and bone marrow examination to diagnose the cause of the disease at National Children's Hospital, Vietnam. 180 cases were identified as bone marrow disease (group I - including acute leukemia, aplastic anemia, hemophagocytic lymphohistiocytosis, bone marrow metastasis) and 70 cases of peripheral thrombocytopenia (group II - including Idiopathic thrombocytopenic purpura and sepsis).

Result: The platelet indices of group I: Platelet count was (52.5 ± 24.8)x109/L, MPV was 8.2±1.3 fL, PDW was 45.1± 22.6%. The platelet indices of group II: Platelet count was (51.6±21.5)x 109/L, MPV was 11.8±2.5 fL, PDW was 64.5±18.8%. There were no statistically significant differences in platelet counts in two groups but both MPV and PDW in the two groups had statistically significant differences (p<0.0001). For diagnosis of peripheral thrombocytopenia, MPV > 9.5fL had a sensitivity of 82.3% and a specificity of 88.5% and PDW >50% had a sensitivity of 89.4% and a specificity of 61.2%.

Conclusions: Interpretation of platelet indices (MPV, PDW) can help differentiating the causes of thrombocytopenia. These indicators are simple, inexpensive and always available in the full blood count test. In particular, a number of thrombocytopenia patients can be avoided having to undergo an unnecessary invasive bone marrow examination.

Keyword: Thrombocytopenia, Platelet indices, PDW, MPV

PP-147

Perioperative management and outcomes in children with congenital bleeding disorders: A retrospective review at a single hemophilia treatment center

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Background: Establishing hemostasis for surgical procedures in children with inherited bleeding disorders is challenging. Providers are often hesitant to undertake surgeries in children with bleeding disorders out of fear of bleeding complications. However, appropriate presurgery/preprocedure factor replacement can decrease

pre-, peri-, and postoperative bleeding complications and allow almost any necessary surgical procedure to proceed. We review the results of surgical procedures in children with inherited bleeding disorders at our center and review the preoperative management and hemorrhagic complications.

Methods: We conducted a retrospective electronic medical record review from October 2006 to November 2018. Primary focus was review of factor replacement strategies and bleeding complications.

Result: In total, 152 procedures were performed in 99 children at our center. The distribution of bleeding disorders is as follows; hemophilia A 79, hemophilia B 15, Von Willebrand disease 3 and FVII deficiency 2. The median age of the patients was 13 years (range, 0~18). Duration of hospitalization was median 8 days (range, 0~44) and period from surgery to discharge was median 7 days (range, 0~42). Nineteen procedures (12.5%) in 8 children were performed in the presence of high titer inhibitors to coagulation factor. Procedures included synovectomy (84/152, 55.3%), nonsynovectomy orthopaedic procedures (22/152, 14.5%), central venous catheter placement or revision (9/152, 5.9%), otolaryngology procedures (7/152, 4.6%), circumcision (6/152, 3.9%), laparoscopic appendectomy (5/152, 3.3%) and miscellaneous (19/152, 12.5%). All patients received preoperative factor replacement (100% in hemophilia patients) followed by various factor replacement regimens postoperatively. No deaths or life-threatening bleeding occurred with any procedure. Seven of 152 procedures (4.6%) were complicated by bleeding. Tonsillectomy was the most common procedure complicated by hemorrhage 3 of 7 (42.9%).

Conclusions: Surgical procedures are safe in children with bleeding disorders with adequate planning and factor replacement. Bleeding remains a problem in a subset of patients and requires ongoing hematological involvement and oversight. Delayed bleeding following tonsillectomy was especially common and suggests a need for close follow-up and ongoing factor coverage for this group of patients.

Keyword: Congenital Bleeding Disorder, Surgery, Hemophilia, Perioperative

PP-148

Reference intervals for platelet dense granules using whole mount electron microscopy

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Background: Platelet function tests are essential for the evaluation of common bleeding disorders. Platelet dense granule deficiency is evaluated only by some specialized laboratories because they may not be detected by screening level of tests. In this study, we measured the number of electron-dense platelet granules in control group using whole mount preparation by transmission electron microscopy. This method involves an assessment of unfixed platelets to evaluate and quantify the number of dense granules contained in platelets.

Methods: The platelet-rich plasma (PRP) samples were obtained from blood anticoagulated with 3.2% sodium citrate. Control samples were acquired from adults who showed all normal results to regular health screening tests. 10 uL PRP were spotted to Formvar-coated grids, rapidly blotted, rinsed with 10 uL distilled water 3 times, air dried. Images of platelet whole mount were acquired using a Hitachi H-7650 electron microscope. We prepared 3 grids per each control and obtained an average number of dense granules per platelet.

Result: We counted the dense granules in each of 25 to 30 platelets at approximately 10,000x magnification. The granules came in all different sizes and shapes, usually appearing round and dense black. Some dense granules were enclosed by membranes in the hyaloplasm. From 20 control samples, the average numbers of dense granules per platelet ranged from 2.5 to 9.7 (mean 4.5 and median 5.7). Representative photographs were also taken with a digitalized camera.

Conclusions: The calcium and phosphorus content of dense granules makes these structures electron-dense, allowing dense granules to be visualized in platelets without fixation or special stains. This method is known to detect dense-granule deficiency due to diverse disorders. The electron microscope is generally regarded as a sophisticated instrument used for basic research. However, ul-

tra structural methods with whole mount platelet preparation can be now a straightforward tool for the clinical diagnosis of platelet disorders.

Keyword: Platelets, Dense granules, Platelet Function Tests, Electron Microscop, Reference Interval

PP-149

Platelet parameters and inflammation in anemic and non-anemic patients with type 2 diabetes and early CKD

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Background: Patients with diabetic nephropathy are known to be prone to anemia and other hematologic abnormalities even at early stages of chronic kidney disease (CKD). They result mainly from erythropoietin deficiency and systemic inflammation. The aim of this study was to assess interconnections between platelet parameters and inflammation in anemic and non-anemic patients with type 2 diabetes (T2DM) and early CKD.

Methods: We investigated 65 patients with T2DM and CKD stages 1-3 (30 anemic and 35 non-anemic subjects). Patients with a history of bleedings, malignancies, primary hematological and rheumatic diseases were not included. In addition to routine clinical tests we measured serum levels of erythropoietin (EPO), homocysteine, IL-6, IL-18 and interferon gamma (IFNg). Mann-Whitney U-test and Spearmen's correlation coefficient (rs) were used for statistical analysis.

Result: Mean values of platelet count (PLT), plateletcrit (PCT) and mean platelet volume (MPV) were not significantly different between the groups. Platelet distribution width (PDW) was slightly lower (within the reference range) in anemic patients (p=0.046). Increased PCT was the most prevalent abnormality of platelet parameters (7.7% of all patients, with no significant differences between the groups). In both groups platelet indices didn't correlate with hemoglobin level, concentrations of EPO, IL-18 and IFNg. In anemic patients PLT correlated with serum homocysteine level (rs=-0.543, p=0.005) and eGFR CKD-EPI (rs=0.422, p=0.028), MPV - with serum homocysteine level (rs=0.479, p=0.024), PCT - with serum IL-6 level (rs=-0.489, p=0.018) and eGFR CKD-EPI (rs=0.430, p=0.032). Meanwhile, in the non-anemic group PLT and PCT correlated only with the level of albuminuria (rs=-0.421, p=0.012, and rs=-0.359, p=0.037, respectively), but not with other abovementioned parameters.

Conclusions: The results of the study suggest that anemic and non-anemic patients with T2DM and early CKD have different correlates of platelet indices. Only anemic subjects are characterized by interconnections between platelets parameters, IL-6 and homocysteine (independently of hemoglobin and EPO levels). The reported study was supported by Russian foundation of basic research (RFBR) according to the research project No.17-54-04080.

Keyword: Platetets, Diabetes, Inflammation, Nephropathy, Anemia, Erythropoietin

PP-150

Parameters of coagulation and fibrinolysis in patients with diabetes type 2 and chronic kidney disease

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Background: Diabetes type 2 (DT2) is a growing epidemic and is the most common cause of chronic kidney disease (CKD) which associated with an increased risk for cardiovascular and thrombotic complications. The present study aimed to investigate the markers of endogenous coagulation/fibrinolysis, vascular endothelial cell function, and their relationships in type 2 diabetic patients with CKD.

Methods: We investigated 65 patients both sexes with DT2 aged 56.54 ± 4.17 years. Control group included 50 healthy subjects the same age. Coagulation and fibrinolysis parameters were measured in DT2 and control groups. GFR was estimated using the modification of diet in renal disease (MDRD) equation.

Result: We found significantly increased the plasma levels of fibrinogen, antithrombin III (AT III), plasminogen activator inhibitor-1 (PAI-1) and prothrombin time in the type 2 diabetic patients compared with the control group. There was an inverse association between AT III levels and plasma LDL-C levels, plasma triglycerides and D-dimer levels. PAI-1 levels and factor V activity in diabetic patients with CKD were significantly higher than those of the diabetic patients without CKD. The plasma PAI-1, platelet count and factor VII activity were also increased in DT2 patients with CKD compared with the diabetic patients without CKD. von Willebrand factor antigen and factor VII activity were inversely correlated with eGFR (r=−0.369, p=0.02; r=−0.451, p=0.01). Multivariable linear regression analysis revealed significant associations between decreased eGFR and higher von Willebrand factor antigen and factor VII activity in DT2 patients and CKD.

Conclusions: Our data demonstrated that patients with type 2 diabetes mellitus and CKD are more prone to develop hypercoagulation state, thereby indicating that activation of coagulation with a reduced fibrinolytic activity may contribute to the increased risk of vascular disease in type 2 diabetic patients. Therefore, routine examinations of coagulation and fibrinolysis parameters are important to assess coagulation impairment in DT2 in order to prevent thromboembolic cardiovascular disease in type 2 diabetes mellitus and chronic kidney disease.

Keyword: Diabetes Type 2, Chronic Kidney Disease, Coagulation, Fibrinolysis

PP-151

The prognostic value of mean platelet volume in venous thromboembolism

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Background: Platelet has been known as an important factor of a cascade of coagulation and hemostasis. Increasing of platelet activity, shown as more platelet adhesion and aggregation, can be presented by increasing its size and yield to a higher vascular thrombotic event. Recent studies revealed that mean platelet volume (MPV), the inexpensive and accurate measurement of platelet size obtained from routine hematologic examination, was strongly associated with cardiovascular events comprising stroke and myocardial infraction. However, there was limited evidence considering the promising benefit of MPV to predict venous thromboembolism (VTE). Therefore, the more robust evidence remains to be elucidated. The objective of this study was to analyze the association of MVP and VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE).

Methods: We systematically searched major medical databases (EMBASE, PUBMED, Science Direct, Cochrane, Springer, Scopus, ProQuest, Clinicaltrial.gov, and Lilacs) for observational study which investigated the association of MVP and VTE published until December 2018. The primary outcome was a prediction of MPV on VTE occurrence involving DVT and PE. The secondary outcomes were PE-related mortality, and weighted mean difference (WMD) of MPV value between cases and control. We applied predefined protocol without language restriction based on PRISMA guideline and used RevMan 5.3 (fixed-effects and random-effects model based on heterogeneity test) to provide pooled measures for Risk Ratio (RR), 95% Confidence Interval (95%CI), and WMD.

Result: We included 21 studies into pool estimation of a meta-analysis involving 2,584 cases and 28,166 controls. A higher value of MVP has an association with increase risk of VTE compared to lower MPV (Pooled OR 2.62, 95% CI [1.5 – 2.31], p=0.0007, I^2=96%). Subgroup analysis showed both risk of DVT (Pooled OR 1.87, 95% CI [1.42 – 2.47], p<0.00001, I^2=62%) and PE (Pooled OR 4.19, 95% CI [1.4 – 12.5], p=0.01, I^2=97%) have a similar significant association with higher MPV. Mean value of MPV was significantly different between PE group and control group with WMD 0.84 fL (95% CI [0.46 – 1.23], p<0.00001, I^2=95%). PE-related mortality group has also significantly higher mean value of MVP in comparison to survivor group with WMD 1.16 fL (95% CI [1.03 – 1.29], p<0.00001, I^2=0%). Mean MPV value of DVT group was also significantly different with control group (WMD 0.81 fL, 95% CI [0.53 – 1.09], p<0.00001, I^2=88%).

Conclusions: Higher MPV value was associated with the occurrence of VTE, including DVT, PE, and PE-related mortality. Therefore, this promising finding of MPV could be useful as simple and inexpensive measurement, particularly in healthcare of rural area.

Keyword: Mean Platelet Volume, Venous Thromboembolism, Pulmonary Embolism, Deep Vein Thrombosis

PP-152

The prognostic role of red cell distribution width in venous thromboembolism and related mortality

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Background: Red cell distribution width (RDW) is a measure of red blood cell size variation and heterogeneity. It is calculated from routine hematology laboratory examination and traditionally used to classify the anemia. Recent meta-analyses demonstrated this low-cost and simple measurement could be strong a independent predictor of morbidity and mortality in coronary artery disease, chronic heart failure, and atrial fibrillation. Nevertheless, there is no meta-analysis evaluating the role of RDW in prediction of the occurrence of venous thromboembolism (VTE), the third most common cardiovascular disease, and related mortality. This study aimed to investigate the association of RDW and VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE) and related mortality.

Methods: Major medical databases (EMBASE, PUBMED, Science Direct, Cochrane, Springer, Scopus, ProQuest, and Lilacs) were systematically searched for observational study which assessed the association of RDW and VTE published until December 2018. The primary endpoints were RDW prediction of VTE incidence comprising DVT and PE. Secondary end points were short-term, long-term mortality after PE, and weighted mean difference (WMD) of RDW value between cases and control. The databases were searched with predefined protocol without language restriction based on PRISMA guideline. The analysis was performed in RevMan 5.3 (fixed-effects and random-effects model based on heterogeneity test) to provide pooled measures for Risk Ratio (RR), 95% Confidence Interval (95%CI), and WMD.

Result: Twenty one studies were enrolled including 6,646 cases and 58,617 controls. Higher RDW was indicated as independent predictors for VTE compared to lower RDW (Pooled RR 1.82, 95% CI [1.43 – 2.31], p<0.00001, I^2=89%). Risk of DVT and PE was also significantly increased with higher RDW in comparison to lower RDW with pooled RR 1.52 (95% CI [1.36 – 1.7], p<0.00001, I^2=54%) and pooled RR 2.05 (95% CI [1.29 – 3.26], p=0.002, I^2=92%), respectively. There was also an association between higher RDW and risk of mortality after PE episode with pooled RR 1.31 (95% CI [1.11 – 1.54], p=0.001, I^2=66%). Subgroup analysis showed that both short (30-day) and long-term (>1 year) mortality were significantly associated with higher RDW (pooled RR 1.79 (95% CI [1.02 – 3.13], p=0.04, I^2=54%) and pooled RR 1.15 (95% CI [1.01 – 1.3], p=0.03, I^2=18%), respectively). In comparison with lower RDW, higher RDW was also revealed a significant association with unprovoked VTE (Pooled RR 2.18 (95% CI [1.13 – 4.19], p=0.02, I^2=79%). VTE-group had a higher mean of RDW compared to control with WMD of RDW 1.13% (95% CI [0.72 – 1.54], p<0.00001, I^2=93%). Subgroup analysis showed WMD of RDW between PE-group and control was 0.99% (95% CI [0.67 – 1.31], p<0.00001, I^2=32%) and between DVT-group and control was 1.28% (95% CI [0.49 – 2.08], p<0.00001, I^2=87%). Among PE patients, PE-related mortality group had also higher mean of RDW in comparison to survivor group with WMD of RDW 2.04% (95% CI [1.54 – 2.55], p<0.00001, I^2=69%).

Conclusions: Higher RDW value was associated with the occurrence of VTE, including DVT, PE, unprovoked VTE, and PE-related mortality. Therefore, the use of the potential role of RDW should be emphasized since it is low-cost and simple to obtain, even in the low-resource setting.

Keyword: Red Cell Distribution Width, Venous Thromboembolism, Deep Vein Thrombosis, Pulmonary Embolism

PP-153

Long-term expansion of Gata1^{low} Meg-erythroid cells increased cell division while maintained differentiation potential

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Background: GATA1 is a key hematopoietic transcription factor that promotes meg-erythroid progenitors (MEP) to generate megakaryocytes or erythroid cells. It has been shown that murine cell lines with knockout or knockdown of GATA1, G1ME or G1ME2 cells respectively, represent MEP-like cells and expand while

thrombopoietin (Tpo) maintained. Specifically, G1ME2 cells can be differentiated to functional megakaryocytes and platelets by physiological level of GATA1 restoration. Therefore, it is suggested to be a proof-of-principle for development of physiologically relevant MEP cell lines as well as a good model to study hematopoiesis.

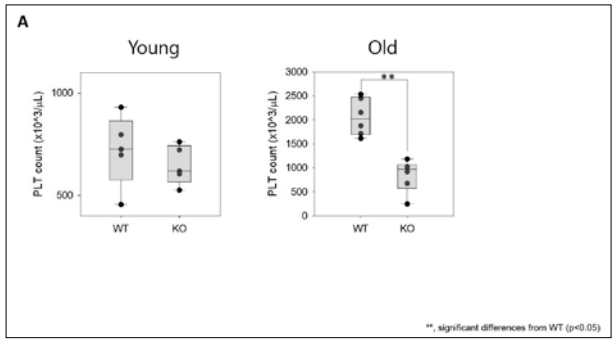
Previous studies using the GATA1low mice model (GATA-1.05/X) represented increased incidence of myelodysplastic syndrome (MDS) and leukemogenesis. Interestingly, myeloproliferative disorder was more obvious when GATA1 gene expression is at approximately 5%, as opposed to when GATA1 is knockout. The authors indicated that this is because accumulation of hematopoietic precursors with low level of GATA1 could be highly related to disease progression, however, cells undergo apoptosis with no GATA1 expression. Recently, we found that the rate of cell replication was accelerated after certain days (i.e. 100 days) of GATA1low G1ME2 cells expansion. The mechanisms of GATA1 regulation during hematopoiesis are required to understand this phenotype and this study will be applicable to many GATA1-related human blood disorders.

Methods: The TRE-GATA1 shRNA expressing mESCs and G1ME2 cells were kindly provided from the Children's hospital of Philadelphia. G1ME2 cells are generated and maintained in serum free differentiation media with 0.5 mg/mL doxycycline (dox), 100 ng/mL murine stem cell factor (mScf), 20 ng/mL mTpo. Cells were replenished with fresh media every 2-3 days in 3-5 x 105 cells/mL concentration. When differentiation to megakaryocyte or erythroid cells, dox was washed and resuspended in the same media but dox.

Result: Long-term expanded G1ME2 cells with dox (> 90 days; late) showed faster replication than short-term cultured G1ME2 cells with dox (< 50 days; early). The PI staining results also indicated that the late G1ME2 culture consist of more cells with S phase. Interestingly, G1ME2 cells gradually lose the MEP marker, CD41 with subtle increase of myeloid cell marker, CD11b, presumably due to low expression of GATA1 in CD41+ cells. Notably, late G1ME2 cells could differentiate to comparable mature megakaryocytes and produce proplatelets by dox removal, suggesting that this cell system is a good model for immortalized platelet precursors.

Conclusions: The G1ME2 cells can be used to study molecular mechanism of GATA1 regulation. Longer period of culture with low level of GATA1 in MEP-like cells represented accelerated proliferation, higher viability, similar or mildly delayed differentiation potential compared to short-term expanded G1ME2 cells. These results recapitulate the previous findings from GATA1low mice model, suggesting that the molecular mechanism of progression of MDS can be further studied in vitro. Importantly, our recent results showed that G1ME2 cell system is indeed a good model for MEP cell line establishment, which further proposes the development of platelet cell therapeutics in vitro.

Keyword: Thioredoxin-Interacting Protein, Megakaryopoiesis, Platelets, Thrombopoiesis



PP-154

Analysis of genetic factors in Korean adult patients with atypical hemolytic uremic syndrome

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Background: Atypical hemolytic uremic syndrome (aHUS) is a rare syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Recent reports showed that inherited genetic defects are related with the disease and prognosis. Herein, we investigated the molecular profile of adult Korean aHUS patients.

Methods: The study subjects were 768 patients diagnosed with thrombotic microangiopathy (TMA) from 2012 to 2017. The diagnosis of aHUS was clinically made according to the recent guidelines which exclude TMA patients having ADAMTS13 activity <10%, STEC-HUS, and secondary etiology of TMA. Molecular genetic workup included the initial screening of hotspot mutations in CFH and C3 genes by RFLP tests in all patients. Among mutation-negative patients by RFLP, 36 patients with a high index of suspicion were selected for whole exome sequencing (WES). For in silico analysis of variants, SIFT, PolyPhen-2 and MutationTaster were used. Variants were confirmed by using Sanger sequencing, and were classified based on the 2015 ACMG standards and guidelines.

Result: In the cohort, total 31 mutant alleles were found in 25 patients with aHUS (10 patients by the RFLP. screening and 15 patients by WES). Mutated genes were CFH (9/31, 29%), C3 (7/31, 22.6%), THBD (5/31, 16.1%), PLG (3/31, 9.7%), CFHR2 (2/31, 6.5%), CFHR4 (2/31, 6.5%), CFHR5 (2/31, 6.5%), and C4BPA (1/31, 3.2%). Five patients (20%; 5/25) had more than two mutant alleles. R425C and S562L of C3 and D486Y of THBD were recurrently identified variants of uncertain significance (VUS), with higher frequencies in our aHUS cohort than in the general Korean population. A patient had a pathogenic variant in the C4BPA gene, which is the first case in the literature.

Conclusions: This is the largest epidemiologic study on the genetic etiology in Korean adult patients with aHUS. Further studies are required to delineate the clinical implications of these genetic variants in Korean population.

Keyword: Atypical HUS, Epidemiology, Whole Exome Sequencing, Ethnicity

PP-155

Hereditary platelet function disorder from RASGRP2 mutations identified by whole exome sequencing

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Background: Hereditary platelet function disorders (PFDs) are a genetically heterogeneous group of disorders. Among them, PFD from RASGRP2 mutations is an autosomal recessive disorder and is rare with less than 20 families reported in the literature. Here, we report a Korean family with PFD from RASGRP2 mutations identified by whole exome sequencing (WES).

Methods: The proband was 41-year-old pregnant woman with a history of bleeding diathesis. Her platelet count, PT and aPTT was within normal ranges. Rapid platelet function test by PFA-100 showed significantly prolonged closure times (collagen/epi >300s and collagen/ADP 141s). Platelet aggregation test showed markedly decreased aggregation response to ADP and epinephrine, and relatively preserved response to ristocetin. The expression of glycoprotein IIb/IIIa on platelets were not decreased on flow cytometric analysis. For genetic analysis, WES was done and >70 genes associated with platelet disorders were screened with priority. The variants were classified based on the 2015 ACMG guideline. ClinVar, Human Gene Mutation Database, and in silico analysis including polyphen2 and SIFT were used. All potential pathogenic variants were confirmed by Sanger sequencing.

Result: WES data revealed two heterozygous variants in the RASGRP2 gene (c.659G>A [R220Q] and c.1142C>T [S381F]). S381F was a previously reported variant in a patient with PFD. R220Q was a novel variant and was predicted as damaging by in silico analyses. Family study showed R220Q and S381F were inherited from her father and mother, respectively. She was diagnosed as having hereditary PFD from RASGRP2 mutations. RASGRP2 codes for the protein CalDAG-GEFI, a guanine nucleotide exchange factor for the small GTPase Rap1proteins, which are signaling proteins critical to the inside-out activation of alphaIIbbeta3 of platelets.

Mutation in the gene cause PFD with similar presentation with Glanzmann thrombasthenia. After 39 weeks of pregnancy, she delivered a healthy baby by cesarean section uneventfully. During the operation, 2 units of single donor platelets were transfused to control bleeding.

Conclusions: We herein reported a rare PFD from RASGRP2 mutations identified by WES. In patients suspected to have Glanzmann thrombasthenia, the possibility of PFD form RASGRP2 mutations needs to be considered.

Keyword: Platelet, RASGRP2, Whole Exome Sequencing

PP-156

Cryopreservation of peripheral blood stem cell using mechanical freezers : Initial experience from an Indian tertiary care hospital

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Background: Cell therapies based on hematopoietic stem cells (HSCs) have become the standard of care for a large number of clinical indications, and the number of patients and disorders being treated using HSCs continue to grow. Here, we report an analysis of first 10 cryopreservation of peripheral-blood stem-cell (PBSC) at our center in terms of CD 34+ viability and cell engraftments in those patients.

Methods: Peripheral blood stem cells (PBSCs) were collected from auotologus donors using P1YA kits on Com.tec (Fresenius kabi). A solution made up of 10% DMSO, 20% human serum albumin (HSA) with 6% HES was used for cryopreservation of cells. Whole procedure was done under fully aseptic technique using laminar air flow. A mechanical freezer (Thermo Scientific) was used to store stem cells at -800 Celsius.

Result: All 10 patients were posted for re-transplant (2nd /3rd) and heavily pre treated with chemotherapy. Average time duration of storage for cryopreserved stem cells was 27 days (range 10 to 56 days). The initial yield of the products before cryopreservation ranged from 3 X 106 to 10.2 X 106 per Kg of the patient (mean dose 7.85 X 106 per Kg) which decrease to a mean of 5.85 X 106 per Kg post thawing of frozen stem cells. Stem cells viability after thawing ranged from 77 percent to 90 percent of total CD 34+ cells. All the patients had neutrophil and platelet engraftment before they were discharged. Days taken for engraftment of neutrophil ranged from 10 to 15 days (mean 11.5 days) whereas for platelets, it ranged from 14 to 43 days (mean 23.5 days)

Conclusions: Peripheral blood stem cells can be cryopreserved using a solution of 10% DMSO, 20% albumin with 6% HES up till 8 weeks without significant decrease in number and viability of CD34+ cells.

Keyword: Stem cell, Cryopreseravation, Harvesting

PP-157

Modified post-transplant cyclophosphamide allogeneic HSCT combined with decitabine-based reduction, busulfan and melphalan conditioning regimen in children with juvenile myelomonocytic leukemia

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Background: Hematopoietic stem cell transplantation (HSCT) is curative option for most of juvenile myelomonocytic leukemia (JMML). This disease is a particular responsiveness to epigenetic therapy such as decitabine. An emerging concept with intriguing potential is the combination of hypomethylating therapy and HSCT. Post-transplant cyclophosphamide (PT/Cy) is an effective method to control the occurrence of GVHD.

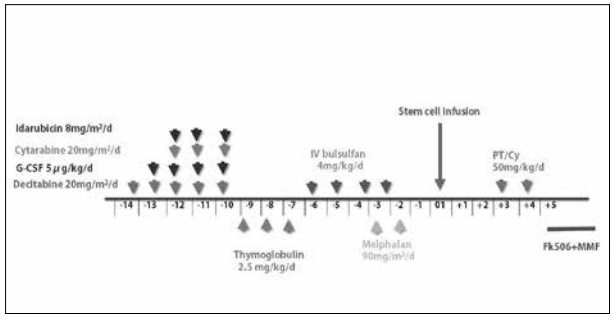
Methods: Between March 2015 to March 2018, 6 patients diagnosed as JMML without suitable donors, subsequently received decitabine of 20 mg/m2 for five days (Day -14 to -11) followed by cytarabine of 2 g/m2/d for 3 days (Day -12 to –10), idarubicin of 8 mg/m2/d for 3 days (Day -12 to -10), and G-CSF 5μg/kg/d for 4 days (Day -13 to -10) and followed by myeloablative conditioning regimen (MAC) consisted with thymoglobulin (2.5 mg/kg/day) administered for 3 days (Day -9 to -7), Bu (4 mg/kg/d for 4 days) on days -6, -5, -4, -3, and Melphalan (90 mg/m2 /d for 2 days) was

performed on days -3 and -2. Post-transplant cyclophosphamide (50 mg/kg/d) on day +3, +4 was given as GVHD prophylaxis.

Result: With a median 2.5 years follow-up (range 0.5-3.8), all patients received complete remission and with full donor chimerism. Only one patient developed acute GVHD (grade I-II), no patient developed acute GVHD (grade III-IV) and chronic GVHD, and rapid immune reconstitution was observed.

Conclusions: Modified PT/Cy conditioning regimen combined with decitabine and followed by bulsufan and melphalan based MAC provided a novel method for JMML patients.

Keyword: Haploidentical Transplantation, Post-Transplant Cyclophosphamide, JMML, Decitabine



PP-158

The correlation and predictive value of immature platelet fraction to plasma platelet recovery in patients receiving autoSCT

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Background: Engraftment is a critical milestone of the hematopoietic stem cell transplantation process. The immature platelet fraction (IPF) are considered early indicators of bone marrow recovery. The objective of this study was to assess this parameter as predictors of autologous stem cell transplantation.

Methods: The cross-sectional study was conducted at Ampang Hospital from June 2016 to December 2016, and included 23 autologous transplant patients with various hematologic malignancies. The results of post-transplant IPF and PLT were traced from the hematology laboratory, and validated by a hematologist before analysis. The role of IPF towards post-transplant PLT recovery was investigated by using parameters such as transient increase in IPF (%), time to transient increase in IPF (days), and 7 days mean IPF (%), towards PLT engraftment (days), lowest PLT, time to lowest PLT (days), PLT recovery (%), and PLT recovery time (days) from transplant day and lowest PLT. The degree of correlation was determined based on the Cohen's convention (1988). Patients with incomplete results (more than 50% missing data) were excluded from the analysis.

Result: The median age of the cohort was 37 years, ranging from 18 to 67 years. The conditioning regimens used for autologous transplant included BEAM (69.6%), high dose melphalan (21.7%) and Bu/TT/Cy (8.7%). The mean day for PLT engraftment was 11.4, ranging from 10.7 – 12.0 days after autologous transplantation. The cohort presented a mean value of 5.43% for transient increase in IPF, 4.7 days for time to transient increase in IPF, and 3.67% for 7 days IPF. The mean values in relation to PLT recovery were 14.40 x 109/L for lowest PLT, 5.3 days for time to lowest PLT, 225% for PLT recovery, and 6.9 days for PLT recovery time from transplant day and 1.7 days for PLT recovery time from lowest PLT. Statistically significant and positive correlations were found in the transient increase in IPF towards the PLT recovery time from the lowest PLT achieved in transplant patients ($r = 0.6141$, $p = 0.0114$); in the transient increase in IPF towards the PLT recovery time from transplant day ($r = 0.6028$, $p = 0.0135$); in post-transplant 7 days mean IPF towards the PLT recovery time from the lowest PLT achieved in transplant patients ($r = 0.7450$, $p = 0.0014$). A negative correlation was found in the time to the transient increase in IPF towards the PLT recovery time from the lowest PLT ($r = –0.5245$, $p = 0.0370$). The degree of the above correlations were considered strong ($|r| > 0.5$).

Conclusions: The generation and release of IPF, as part of hematopoietic activity seemed to be predictive and correlated with the PLT recovery time. A transient increase in the IPF preceded the PLT recovery by approximately 2 days and may be used to predict PLT recovery in patients receiving autologous transplantation. The longest time to have a transient increase in the IPF, the shortest time required for PLT to bounced back from its lowest level.

Keyword: Immature Platelet Fraction, IPF, Plasma Platelet, Platelet

PP-159

Survival by time to start of defibrotide in veno-occlusive disease/sinusoidal obstruction syndrome post hematopoietic stem cell transplant in adults

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Background: Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of hematopoietic stem cell transplant (HSCT) or nontransplant chemotherapy. VOD/SOS with multi-organ dysfunction (MOD; eg, renal or pulmonary dysfunction) may be associated with >80% mortality post-HSCT if left untreated. Defibrotide (DF) is approved to treat severe hepatic VOD/SOS post-HSCT in patients aged >1 month in the European Union and to treat hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT in the US and Canada. The European Society for Blood and Marrow Transplantation encourages prompt diagnosis of VOD/SOS, when it may be the most amenable to treatment with DF. Prior to US approval, DF was available through an international compassionate-use program (CUP; 1998–2009) and an expanded-access protocol (T-IND; 2007–2016).

Methods: For this post hoc analysis, data from the CUP and T-IND were pooled to investigate whether time to DF treatment initiation after VOD/SOS diagnosis had an impact on Day +100 survival. In the CUP (N=710) and T-IND (N=1137), VOD/SOS was diagnosed by Baltimore or modified Seattle criteria or biopsy (CUP enrollment also included hemodynamic, ultrasound, or histologic evidence of VOD/SOS). Both studies included patients with and without MOD. Adults (≥18 years) with VOD/SOS post-HSCT who received DF 25 mg/kg/day dosage were pooled (CUP, n=125; T-IND, n=412). The analyses examined (1) initiation of DF treatment before/after Days 1, 2, 3, 4, 7, and 14 post-diagnosis (Fisher's exact test) and (2) starting DF treatment on a particular day post-diagnosis: 0, 1, 2, 3, 4, 5, 6, 7, 8–14, and ≥15 (Cochran-Armitage test for trend). Causes of delay were not assessed.

Result: Of 534 pooled adults (aged ≥18) receiving 25 mg/kg/day and having reported timing data (3 patients did not have time to dosing), 300 (56%) had MOD. DF was initiated by Day 1 in 273 (51%) patients. In the analysis of DF initiation before or after Days 1, 2, 3, 4, 7, and 14, earlier treatment initiation showed numerically higher survival rates for all cut points. Cochran-Armitage test for trend in the overall group suggested that Day +100 survival was higher with earlier treatment initiation post-diagnosis (Table). Adverse events (AEs) were not pooled, as AEs in the CUP were only consistently reported for certain events. Treatment-related AEs in ≥2% of patients in the T-IND (n=412) were gastrointestinal hemorrhage, 3.6%; epistaxis, 3.4%; and hematuria, pulmonary hemorrhage, and hypotension, 2.2%, and in the CUP (n=125), gastrointestinal hemorrhage, 2.4%.

Conclusions: The results from this pooled post hoc analysis of post-HSCT adults aged 18 or older suggest that earlier DF treatment initiation after VOD/SOS diagnosis may improve Day +100 survival outcomes, although no specific day post-diagnosis provides a clinically meaningful cutoff for better outcome. The results are consistent with studies showing higher efficacy with earlier DF treatment and support further evaluation of the adult HSCT population. The safety profile for these patients was consistent with other DF VOD/SOS studies in adults. Support: Jazz Pharmaceuticals.

Table. Survival at Day +100 Post-HSCT by Days to Initiation of Defibrotide

Days	All Adults[a] (N=534)	
	Total Starting Defibrotide, n (%)	Alive, n (%)
0	146 (27.3)	79 (54.1)
1	127 (23.8)	64 (50.4)
2	70 (13.1)	35 (50.0)
3	44 (8.2)	12 (27.3)
4	32 (6.0)	13 (40.6)
5	27 (5.1)	13 (48.1)
6	15 (2.8)	6 (40.0)
7	10 (1.9)	3 (30.0)
8–14	38 (7.1)	16 (42.1)
≥15	25 (4.7)	9 (36.0)
Nominal *P*	.011	

[a]14 patients with negative time to dosing adjusted to 0.

PP-160

Initial evaluation of the efficacy of autologous stem cell transplantation in non-Hodgkin lymphoma at HCMC Blood Transfusion Hematology Hospital

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Background: Non-Hodgkin lymphoma(NHL) is a common cancer of lymph nodes. In addition of chemotherapy, autologous stem cell transplantation could be a therapeutic choice for high-risk or relapsed/refractory patients. The main aim of this study is to initially evaluate efficacy and safety of autologous stem cell transplantation in NHL at HCMC Blood Transfusion Hematology Hospital.

Methods: Retrospective case series study from Jan 2011 to Jan 2018. Twenty four NHL patients with autologous stem cell transplantation were analyzed. Five conditioning regimens were used, including BEAM, BEAC, BeEAM, BuCyE and R-LEED. We evaluated pre- and post-transplant responses according to standardized criteria for NHL, including clinical examination and positron emission tomography (PET) scan. Progression-free survival (PFS) and overal survival (OS) were presented using Kaplan-Meier survival analysis

Result: Median age was 42.5 years. High proportion of patients were diagnosed as diffuse large B cell lymphoma and in the intermediate-high or high risk group according to IPI scores. Eighteen of 24 (75%) patients received upfront autologous stem cell transplantation as a consolidation therapy. Median recovery time of neutrophils was 9 days and platelets was 13 days. Grade 3 or 4 hematologic toxicities occurred in most of patients. Diarrhea, mucositis and febrile neutropenia were the most common non-hematologic toxicities. Overall survival (OS) and progression-free survival (PFS) at 2 years was 83.3% and 58.5%, respectively. Transplant-related mortality was 5.8%. The median rates of overall survival were similar in the groups of conditioning regimens. However, we considered that PFS was significantly lower in the BuCyE regimen group

Conclusions: Our report shows high efficacy and safety of autologous stem cell transplantation in high-risk NHL. BeEAM may be a good alternative conditioning regimen when BCNU has not been available in Vietnam

Keyword: Non-Hodgkin Lymphoma, Autologous, Stem Cell Transplantation

PP-161

Evaluation of the bacterial and fungal infection status in HSCT patients in HCMC Blood Transfusion and Hematology Hospital

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Background: Bacterial and fungal infection are the major threat to hematopoietic stem cell transplantation (HSCT) patients and is one of the main causes that contribute to the increased complication and mortality. The aim of this study is to investigate the characteristics of bacterial and fungal infection and isolated pathogens in hematopoietic stem cell transplantation at our institution.

Methods: This study is retrospective descriptions of 113 hematopoietic transplantation recipients from 1/2015 to 3/2018 at HCMC Blood Transfusion and Hematology Hospital, both autologous and allogeneic HSCT. We collected and analyzed the data about conditioning regimens, number of infection episodes, the date when infection occured, isolated pathogens and antibiotic / antifungal susceptibility … within first 100 days after transplant.

Result: The median age at the time of transplantation was 44 (range, 4-66). There were 64 autologous (56.6%) and 49 allogeneic (43.4%) patients. The most common indication for HSCT was hematologic malignancies such as multiple myeloma (31.9%), acute myeloid leukemia (24.8%), non-Hodgkin Lymphoma (17.7%). There were 20 patients receiving nonmyeloablative HSCT. 108/113 patients (95.5%) were infection following HSCT with 166 infection episodes. Most infections occurred during the neutropenic period. About one-third of patients had two or more infection episodes. There were 17 patients with positive blood culture, including 3 fungal and 14 bacterial bloodstream infections. 26 infection episodes (15.6%) had isolated pathogen. Gram-negative bloodstream infection was more frequent than Gram-positive (50.4% vs 34.5%). On the other hand, the rate of fungal bloodstream infection was 15.3%. We considered that 50% of Gram-negative bacteria were resistant to Carbapenem and Amikacin. Gram-positive pathogens were still sensitive to both Vancomycin and Teicoplanin. The rate of Amphotericin B susceptibility in fungal infection was 75%. Transplant-related mortality (TRM) at day 100 after transplantation was 4%.

Conclusions: The incidence of bloodstream infection was still high, especially during neutropenia. These results will help guide initial antibiotic treatment and develop strategies to prevent bacterial and fungal infection in the future.

Keyword: Infection, Stem Cell Transplantation, Sepsis

PP-162

Recovery of specific subsets of NK and T cells highly associated with GVHD after haploidentical stem cell transplantation in acute leukemia

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Background: In the allogeneic hematopoietic stem cell transplantation, recent studies showed that T cell and natural killer (NK) cells recovery are implicated in the graft-versus-host disease (GVHD) and graft versus leukemia (GVL) effects. However, the significance of specific subsets of NK and T cell recovery in relation to transplantation outcomes remains to be elucidated in the haploidentical stem cell transplantation (haplo-HSCT).

Methods: Clinical data of patients with acute leukemia (n = 50) who underwent their first haplo-HSCT between 2009 and 2018 were analyzed. Peripheral blood mononuclear cells obtained from 30 patients were examined by multiparametric flow cytometric analysis. PD-1 and Tim-3 expression were examined in CD4+ and CD8+ T-cells and NK cell receptor (NKG2D, NKG2A, NKG2C, DNAM1 and NKp46) expression were analyzed in NK cells, respectively, at the 3 determined times (prior to conditioning therapy, day 30 and day 90 after haplo-HSCT).

Result: Median age at haplo-HSCT was 38 years (range, 21-62) and median follow-up duration was 34.8 months. Myeloablative conditioning was used for 14% and reduced intensity regimen for 86% of patients. GVHD prophylaxis was based on post-transplant cyclophosphamide for 7 (14%) or on anti-thymocyte-globulin for 41 (82%). Incidence of grade II-IV acute GVHD was 44% and chronic GVHD was 48%. In multivariate analysis, early CMV replication (P = 0.017), chronic GVHD (P = 0.013) and dose of infused T cells ≥ 3.2 x 10^8 /kg (P = 0.016) were significantly associated with lower 3-year cumulative incidence of relapse after haplo-HSCT. Longitudinal analysis of immune reconstitution after haplo-HSCT showed that the incidence of acute GVHD was associated with a delayed expansion of the NK cell population and incidence of chronic GVHD was associated with the extent of CD4+ T cell reconstitution. The incidence of acute GVHD was significantly higher in patients with lower (<30cells/uL) counts of CD56bright CD16neg cell at day+30 (100% vs 50%, P = 0.026), particularly in NKG2A-positive NK cell subsets (P = 0.005). The high dose of infused T cells was associated with the increased expansion of CD4+PD-1- T cells (P = 0.031 at day 30 and P = 0.017 at day 90). Of note, the incidence of chronic GVHD was significantly higher in patients with higher (>140cells/uL) counts of CD4+PD-1- T cell at day 30 (100% vs 38.8%, P = 0.008). Among CD4+ T cell, PD-1-/PD-1+ ratio over than 4.5 was significantly associated with increased chronic GVHD (P = 0.005).

Conclusions: Our findings suggest that the higher CD56brightCD-16neg NK cell count at day 30 after haplo-HSCT was significantly associated with decreased incidence of acute GVHD. High dose of infused T cells was associated with increased reconstitution of CD4+ PD-1- T cells and high CD4+ T cell counts, particularly in PD-1- subset, are associated with increased incidence of chronic GVHD. These findings should be further validated for elucidating the roles of these immune effectors cells in the development of GVHD and GVL effect in haplo-HSCT for acute leukemia.

Keyword: NK/T Cell Subset, GVHD, Haplo-HSCT

PP-163

Autologous hematopoietic stem cell transplantation in acute myeloid leukaemia: Long-term outcome

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Background: Autologous Hematopoietic Stem Cell Transplantation (AutoSCT) for Acute Myeloid Leukaemia (AML) is increasing becoming a viable option for an increasing number of patients

due to limited availability of matched sibling or unrelated donor for Allogeneic Hematopoietic Stem Cell Transplantation (AlloSCT). We examined the relevant long-term outcomes in our local patient cohort.

Methods: We retrospectively reviewed the data for all AutoSCT done for AML in our centre over a 17-years period between 1st January 2001 until 31st Dec 2017 from our electronic record. Patients with Acute Promyelocytic Leukaemia (APML) were excluded from this analysis. Patients were further stratified based on the number of high risk features present; not achieving complete remission (CR) following induction chemotherapy, high presenting total white cell count (WBC > 100 x 106/ml, adverse cytogenetics (example: complex cytogenetics) and adverse molecular mutations (example: FLT3-ITD & MLL gene arrangement). Outcome data including mortality (Overall survival (OS) and non-relapse mortality (NRM)) and morbidity (leukaemia free survival (LFS)) were recorded and analysed.

Result: A total of 64 patients were identified. Median age at diagnosis is 34-years old. The cohort comprised of 34 males and 30 females. The overall median OS and median LFS is 3.9 years and 2.2 years respectively. The NRM is 1.6% (1/64). There was no difference in the median OS and median LFS for the patients achieving CR following induction chemotherapy and those not in CR following induction chemotherapy; 4.4 years versus 3.9 years (Log-rank, p=0.9) and 3.4 years versus 2.1 years (Log-rank, p=0.9) respectively. The median OS were statistically significant for patients with zero versus one and two and more high risk features present; 10.2 years versus 3.7 years versus 2.2 years (Log-rank, p=0.4) respectively. However, the median LFS were not statistically significant for these three patient cohorts; 3.6 years versus 1.9 years versus 1.4 years (Log-rank, p=0.7) respectively.

Conclusions: In our patient cohort, AutoSCT appeared to be a feasible option for patents with AML without matched sibling or unrelated donor available.

Keyword: Acute Myeloid Leukaemia, Autologous Hematopoietic Stem Cell Transplantation

PP-164

Impact of CMV prophylaxis on rates of rehospitalization in adult CMV seropositive allogeneic HSCT recipients: Experience from the letermovir phase 3 clinical trial

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Background: In a Phase III randomized, double-blind, placebo-controlled study of CMV-seropositive post-HSCT recipients, letermovir prophylaxis significantly reduced the incidence of clinically significant CMV infection through week 24. The objectives of this analysis was to assess the impact of CMV prophylaxis on rates of rehospitalization in adult CMV seropositive allogeneic HSCT recipients from the letermovir phase 3 clinical trial

Methods: Rehospitalization was recorded as an exploratory endpoint in the clinical trial at end of treatment(Week14), time of primary endpoint(Week24) and through an extended follow-up period(Week48). CMV-related rehospitalization was assessed in the trial. Prespecified analyses describe the observed rates of rehospitalization for the letermovir and placebo groups at the specified times. Fine-Gray cumulative incidence function(CIF) regression models were used to explore the rate of all-cause, and CMV-related rehospitalization accounting for the competing risk of mortality. A multiple linear regression model was used to describe the cumulative length of stay(LOS) for all-cause rehospitalizations that occurred through Week48 (excluding time of initial transplant stay).

Result: Observed rates of all-cause rehospitalization were lower for the letermovir group compared to placebo at end of treatment(36.6%vs.47.6%), time of primary endpoint(48.6%vs.55.3%), and through extended follow-up(55.7%vs.60.6%). The CIF regression model demonstrated rates of all-cause rehospitalization were significantly lower through Week 14(HR=0.72;p=0.021) but did not reach significance at Week24 (HR=0.81;p=0.109) or Week 48(HR=0.84;p=0.173); and CMV-related rehospitalizations were significantly reduced at Week 14(0.6%vs.7.1%;HR=0.09;p=0.001), Week 24(2.8%vs.7.6%;HR= 0.36;p=0.015), and Week 48(3.1% vs.8.8%;HR=0.34;p=0.007). The adjusted mean cumulative LOS was shorter for letermovir than placebo but did not reach statistical significance(3.1 fewer days p= 0.333).

Conclusions: Letermovir was shown to significantly reduce the rate of clinically significant CMV infection in a placebo-controlled randomized clinical trial. These analyses suggest that there is also a reduction in the rate and cumulative days of rehospitalization. This trial was not sufficiently powered to detect differences in this exploratory endpoint. Nonetheless, these data provide valuable insights into the economic burden of CMV. Real world data and findings from future clinical trials are needed to better understand the nature of the association between CMV and rehospitalizations.

Keyword: Cmv Infection, Hematopoietic Stem Cell Transplantation, Cytomegalovirus, Cmv Prophylaxis, HSCT

PP-166

Lkb1 modulates regulatory T cell homeostasis during acute GVHD

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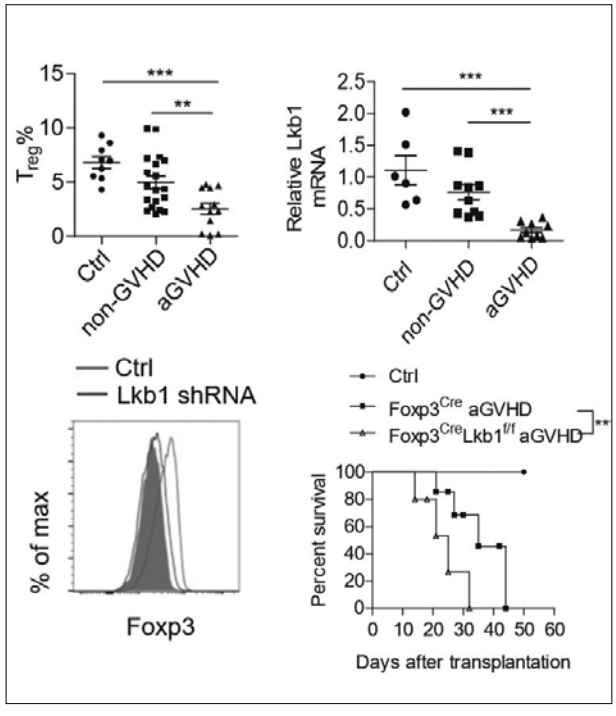
Background: Acute graft-versus-host disease (aGVHD) is a major complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT) which has negative impact on the morbidity and mortality of the patients. Accumulating evidences suggest that abnormalities of Foxp3+ Regulatory T (Treg) cells contributed to the pathogenesis of GVHD, but the underlying molecular mechanisms still remain largely unknown.

Methods: In this study, we enrolled all the 40 patients treated with allogeneic HSCT at the Institute of Hematology, Chinese Academy of Medical Sciences between 2016 and 2018, as well as 10 age-matched healthy adults as control samples. The ratio of Tregs in PB and BM of healthy controls (HCs) and patients with and without aGVHD was determined by flow cytometry. The transcription profile between Tregs from patients with or without acute GVHD was measured, the pathway enrichment analyses were performed by the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database and gene-set enrichment analysis (GSEA). The expression of Lkb1 at transcript levels and protein levels was measured by real-time PCR and analyzed by the NanoPro1000TM system. A series of functional assays in vitro were performed to assess the function and stability of Tregs from patients with and without aGVHD. Meanwhile, to assume the affect of Lkb1 on GVHD outcome, we established a murine transplant model, which recipient Balb/c animals were transplanted with the same amount of mixture made by BM, CD4+CD25-Tcon cells from C57BL/6 and CD4+ Foxp3 YFP+ Tregs from either Foxp3CreLkb1f/f or Foxp3Cre mice.

Result: In this study, we demonstrated that BM had decreased frequencies of Tregs, accompanied with a reversed lower ratio of Tregs frequencies between BM and PB in aGVHD patients. Meanwhile, the number and function of Tregs in bone marrow also affected hematopoietic reconstitution. Futhermore, to elucidate these mechanisms which regulate Tregs homeostasis, we examined the role of Lkb1 on Tregs in patients with aGVHD and in aGVHD murine model. Studies demonstrated that Lkb1-deficient Tregs lost Foxp3 expression and weaken suppressor function during aGVHD. Transcriptional profiling and pathway analysis revealed that NF-kB signaling activation and the impairment of a wide spectrum of immunosuppressive genes in aGVHD Tregs. Further mice experiments suggested that CNS2 methylation might lead to the instability of Tregs in aGVHD group. Transplantation with marrow grafts from Foxp3CreLkb1f/fmice exacerbates GVHD lethality.

Conclusions: These studies indicate that Lkb1 is a critical homeostatic regulator for Tregs during aGVHD. Targeting of Lkb1 therefore represents a novel therapeutic strategy that promote immune tolerance to mitigates the severity of aGVHD.

Keyword: Acute Graft-Versus-Host Disease, Regulatory T Cells, Lkb1, Hematopoietic Stem Cell Transplantation



PP-167

Phase II study of imatinib mesylate and mycophenolate mofetil in children with steroid-refractory sclerotic type chronic graft-versus-host disease

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Background: Chronic graft-versus-host disease (cGVHD) is the most common late complication following allogeneic stem cell transplantation. There is no standard therapy for those who fail to respond to steroids, and steroid-refractory cGVHD is associated with high morbidity. In this study, we evaluated the efficacy and safety of imatinib mesylate (Gleevec) and mycophenolate mofetil (MMF) to treat steroid-refractory sclerotic/fibrotic type cGVHD.

Methods: In non-randomized, open-label, single-arm, multi-center, prospective phase II study, we enrolled patients with steroid-refractory sclerotic/fibrotic type cGVHD. Participants were treated with MMF at a dose of 15-20mg/kg (maximum 1g) bid and Gleevec at the initial dose of 260 mg/m2/day (maximum 400mg). The primary endpoints was overall (complete and partial) response rate of steroid-refractory sclerotic/fibrotic cGVHD to Gleevec plus MMF at 1 year. Secondary endpoints included safety, quality of life, discontinuation of steroid and overall survival rate.

Result: A total of 13 patients were enrolled between October 2013 and July 2017. The median age was 10.4 years (range 5.0-20.1 years). Five of the 13 patients had previously experienced acute GVHD. The diagnoses were acute lymphoblastic leukemia in 5, acute myeloid leukemia in 3, chronic granulomatous disease in 3, neuroblastoma in 1 and hemophagocytic lymphohistiocytosis in 1 patient. Nine of the 13 patients achieved partial response (PR), 2 showed stable diseases (SD), and 1 died of pulmonary infection and progression of chronic lung GVHD. The remaining 1 patient died of primary disease progression. The overall response rate was 69.2 %. Nine of the 13 patients were able to reduce or discontinue steroids. Among 13 patients, 6 patients showed improvements in Lee cGVHD symptom scale score to assess quality of life. Common adverse events included grade 1-2 liver enzyme, creatinine elevations and fever.

Conclusions: Although limited by a small sample size, Gleevec plus MMF for cGVHD showed promising results with acceptable toxicity.

Keyword: Imatinib Mesylate, Chronic Graft Versus Host Disease, Mycophenolate Mofetil, Chilren

PP-168

Role of platelet-rich plasma in healing diabetic and leprosy foot ulcers in resource poor setting

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Background: Foot ulcers are a major complication of diabetes mellitus and leprosy, often leading to amputation. Trophic ulcers secondary to leprosy pose a great stigma to the patients and remain a challenge to the treating dermatologists. The discovery of Platelet Rich Plasma (PRP) with its favourable role in wound healing is a boon for the patients. PRP introduces the growth factors directly into the wound and aids in rapid healing.

Methods: To determine whether autologous PRP promotes the healing of chronic wounds as compare with conventional therapy Study among the 32 patients having chronic wound. Participants were divided in to two groups: a study group in which PRP was used and a control group receiving standard therapy. After wound bed preparation, activated PRP was sprayed over the ulcer and occlusive dressings were applied. Same procedure was repeated every week until complete re-epithelisation or up to six sittings whichever occurred earlier. Wound assessment was carried out according to the Bates-Jensen Wound Assessment Tool at weekly for 4 times.

Result: After application of PRP, there was significant improvement in mean wound score and significant percent improvement in wound score in the study group ($p< 0.0001$). Complete healing occurred in all patients in the study group in (mean score and standard deviation) 36.7±3 days compared with 60.6±3.7 days in

the control group (p< 0.0001). There were no unwanted side effects in patients using the PRP in this study.

Conclusions: Both DM and leprosy wound healing time is shorten as compared with conventional therapy. Neuropathic ulcers in leprosy represent a therapeutic challenge for clinicians. Chronic ulcers affect patient health, emotional state and quality of life, causing considerable morbidity and mortality in addition to contributing to significant health care costs. PRP therapy leads to faster rate of induction of granulation tissue with rapid healing. Healing had no direct statistical correlation with the size, site and duration of ulcer, the leprosy spectrum and associated motor deformities. It is a simple, safe and cost effective in-office procedure, albeit requiring an optimal set-up and expertise. PRP therapy has been growing as a viable treatment alternative for chronic ulcers in resource poor setting. However, stronger scientific evidence is required to support its potential benefit for use in chronic wounds.

Keyword: PRP, Chronic Wound, Resource Poor

PP-169

Curative effect and optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome of higher risk groups

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only potential curative therapy for myelodysplastic syndromes (MDS). To choose the right time to transplant, reduce the risk of transplantation and achieve the maximum benefit is very important.

Methods: We retrospectively analyzed 135 patients undergoing allo-HSCT for primary adult MDS or secondary acute myeloid leukemia (sAML) evolving from MDS of relatively high-risk groups according to the revised International Prognostic Scoring System (IPSS-R) between January 2010 and May 2018 in our hospital.

Result: Among the 135 patients,133 patients were transplanted successfully. The 3-year overall survival(OS) rate and disease-free survival (DFS) rate was 76.8%±4.2% and 76.7%±4.3% respectively. The 3-year cumulative relapse rate (RR) and the non-relapse mortality (NRM) rate was 13.9%±0.1% and 18.4%±0.1% respectively. The incidence of grade II–IV acute graft versus host disease (aGVHD) was 25.2%±0.1% and the incidence of grade III-IV aGVHD was 15.6%±0.1%. For the patients who survived more than 100 days after allo-HCT, the 2 years cumulative incidence of chronic graft versus host disease (cGVHD) was 33.4%±0.2%. Univariate analysis showed that the hematopoietic cell transplantation comorbidity index complications index (HCI-CT) and grade III-IV aGVHD are the high risk factors for OS(81.2±4.5%vs62.8±10%, P=0.027 and 81.9±4.4%vs51.1±11.8%, P<0.001). Multivariate analysis demonstated that the time from diagnosis to transplantation more than six months and grade III-IV aGVHD are independent risk factors for OS(HR=2.578, P=0.02, 95% CI:1.159~5.732 and HR=1.693, P<0.001, 95% CI:1.294~2.215). Chemotherapy before transplantation did not improve OS or DFS for patients with bone marrow blast cells more than 10% at the time of diagnosis.

Conclusions: Allo-HSCT is an effective treatment for MDS patients of relatively high-risk groups.HCI-CT ≥3 is a poor prognostic factors, the time span from diagnosis to transplantation more than six months and grade III-IV aGVHD are independent risk factors. For intermediate and high risk IPSS-R MDS patients, transplantation before the disease progression can achieve better prognosis. It's not necessary to do chemotherapy before transplantation for patients with bone marrow blast cells more than 10% at the time of diagnosis.

Keyword: Allogeneic Hematopoietic Stem Cell Transplantation, Myelodysplastic Syndromes, Curative Effect

		N	OS	P value
Age	<50y	112	78.1±4.4%	0.63
	≥50y	23	67.6±13%	
IRSS-R	intermediate	56	83.3±5.1%	0.451
	high	43	82.2±6.1%	
	very high	36	64.7±9.3%	
Bone Marrow Blast Cell	<5%	52	83.5±5.3%	0.077
before Transplantation	5-10%	31	92.4±5.3%	
	≥10%	49	65.6±7.8%	
HCT-CI	<3	106	81.2±4.5%	0.027
	≥3	27	62.8±10%	
Time from Diagnosis to	<6m	87	81.8±4.8%	0.075
Transplantation	≥6m	48	67.7±7.8	
III-IV aGVHD	yes	21	51.1±11.8%	0.000
	no	113	81.9±4.4%	
cGVHD	yes	43	84.8±6.4%	0.069
	no	91	74.3±5.3%	

Table 1 Univariate analysis of factors influencing survival

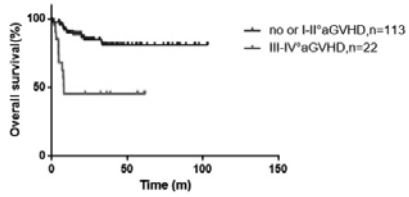

Figure 1 Occurance of III-IV°aGVHD or not affect overall survival

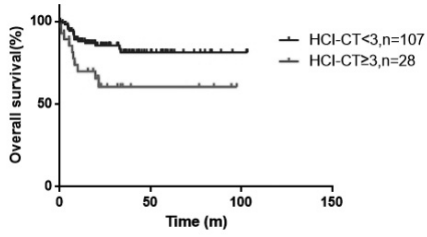

Figure 2 The HCI-CT of patients before transplantation on overall survival (P=0.027)

Background: Sickle Cell Anemia (SCA) is an autosomal recessive haemoglobinopathy resulting from a single gene mutation in beta-globin chain. It is a life threatening and debilitating condition especially in developing countries. As the global survival of SCA patients increased due to advances in management, the prevalence of chronic complications including Sickle Cell Nephropathy also increased; so early detection and management of these complications become mandatory. This study aimed to investigate the estimated Glomerular Filtration Rate (eGFR), proteinuria and serum uric acid as markers of renal involvement in Sudanese adults with Sickle Cell Anaemia and the association between these parameters and clinical severity score of sickle cell disease.

Methods: This was a cross-sectional hospital based study included 32 adult Sudanese patients diagnosed with SCA using…. and 23 controls For each participant; Informed consent was obtained, a structured questionnaire was administered and blood and urine samples were taken for serum uric acid level, urea, creatinine and urine for protein/creatinine ratio. Severity score and eGFR was calculated for sickle cell anaemia patients.

Result: Hyper-filtration was manifested in 75% of Sickle cell anaemia group. Protein/Creatinine Ratio (PCR) was significantly higher (P value > 0.001) in sickle cell anaemia group compared to controls. Hyperuricemia was found only in 6.3% of sickle cell group. There was no association between the severity score and renal manifestations in the sickle cell anaemia group.

Conclusions: Hyper-filtration and proteinuria were the most prevalent renal manifestations in SCA group. Further studies are recommended to determine the predictors of renal complications and early management of them.

Keyword: Sickle Cell Anemia, Glomerular Hyperfiltration, Proteiuria, Uric Acid

PP-170

Renal parameters and their associations with clinical severity score among adult Sudanese patients with sickle cell anemia

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PP-171

Autonomic activity and haemodynamic characteristics in relation to clinical severity of sickle cell anaemia among steady state adults

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Background: Autonomic Nervous System had been recently speculated as a contributor in Sickle Cell Anaemia (SCA) pathophysiology. Cardiovascular complications are a major cause of morbidity and mortality in SCA. This study evaluated the relationships between autonomic activity, haemodynamic characteristics and the clinical severity of SCA among adult patients.

Methods: A cross-sectional analytical hospital-based study, was conducted in the Military Hospital, Omdurman, Sudan including 35 patients and 25 healthy adults as comparative group. A standardized data collection tool was used to collect background variables, haemodynamic and laboratory measurements. The clinical severity score of SCA was calculated using an online calculator. The autonomic activity and haemodynamic measures were evaluated by analysing Heart Rate Variability and Pulse Wave respectively using SphygmoCor® Software 9.0. The data were summarized and analysed by SPSS 23. Multiple linear regression was applied to generate a model predicting SCA clinical severity using explanatory variables from autonomic activity and haemodynamic measurements. All tests used were considered as statistically significant when $p < 0.05$.

Result: Total Power (overall autonomic supply) was lower among patients, High Frequency Maximum (parasympathetic supply) was significantly higher among SCA patients ($p < 0.001$). Augmentation Pressure, Augmentation Index and Aortic Pulse Pressure were significantly higher among SCA patients ($p = 0.002$, 0.012 and 0.013 respectively). A highly statistically significant model was formulated to predict the clinical severity of SCA, with F test (7, 27) = 9.182, $p < 0.001$ and $R = 0.839$.

Conclusions: Autonomic activity and haemodynamic measurements significantly predicted the clinical severity of SCA.

Keyword: Sickle Cell Anaemia Severity, Heart Rate Variability, Pulse Wave Analysis

PP-172

A somatic cell nuclear transfer methodology for replacement of hematological malignant cells population in the myeloproliferative disorders

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Background: Localized malignancies originating in the human bone marrow are known to spread to the body by spilling into the circulation. Collectively these leukemic disorders have a high mortality rate. Diagnosis occurs usually after organ involvement and chemotherapy, radiation and bone-marrow transplantation are the current treatment options, which are associated with severe side effects and the mortality rate remains high despite current treatment modalities.

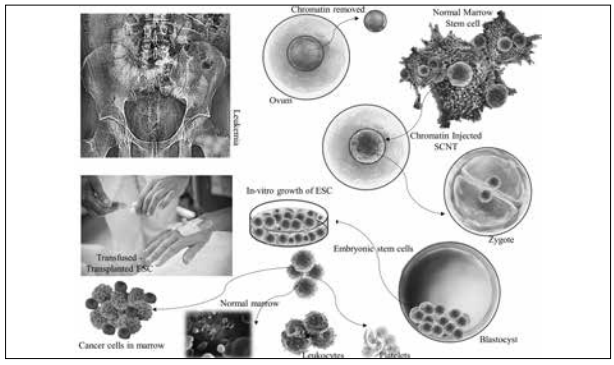
Methods: One line of treatment could be generation of population of in vitro allogeneic hematopoietic stem cells by somatic cell nuclear transfer (SCNT). This methodology would involve transfer of the chromatin from healthy hematopoietic stem cells to a healthy ovum following removal of its chromatin. The method would generate in vitro blastocysts, which would yield the cells from inner cell mass acting as embryonic stem cells (ESC) with a chromatin of hematopoietic origin. Given the fact that the ESC rapidly proliferates and have the epigenetic memory of the hematopoietic linage, large population of in vitro ESC could be produced for bone marrow transplantation following complete bone marrow radiation therapy of the affected marrow in the leukemia affected patients. This method is named as "Allogeneic SCNT transplantation for myeloproliferative disorders", which describes the utility of SCNT in leukemia.

Result: This method would first result in development of large volumes of ESC with epigenetic memory of hematopoietic origin that in the next phase would be transplanted to the affected patients. The method is expected to show results that are superior to conventional bone marrow transplantation in that, the ESC is known to have inhibitory effects on malignant cell proliferation and at the same time would be the source of the blood cell lines. The transplanted ESC with epigenetic memory of hematopoietic origin are expected to undergo self-replication as well as inherent differentiation into diverse formed elements of the blood.

Conclusions: "Allogeneic transplantation for myeloproliferative disorders" offers a dual advantage of not only restoring the formed elements of the blood and at the same time exert a cellular an-

ticancer effect. Given that the current therapies have failed to reduce the mortality rates in leukemias, the proposed transplantation of ESC produced by SCNT is expected to offer hope for patients suffering myeloproliferative disorders.

Keyword: Myeloproliferative Disorders, Somatic Cell Nuclear Transfer, Allogeneic Bone Marrow Transplant, Embryonic Stem Cells, Epigenetic Memory



PP-173

Adipose-derived stem cells therapy in diabetic osteoarthritis

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Background: Diabetes mellitus (DM) is a metabolic disorder distinguished by hyperglycaemia which develops as a consequence of defects in insulin secretion, insulin action, or both. The classic target organs affected with hyperglycaemic state include brain, heart and kidney, causing nephropathy, cardiomyopathy and nephropathy, respectively. However, the data about knee osteoarthritis (KOA) as a diabetic complication is still lacking. Therefore, we firstly established diabetic KOA and, later investigated adipose-derived stem cells (ADSC) therapy against this comorbid condition.

Methods: Th diabetes in C57BL/6J mice was estabished through administration of streptozotocin and the KOA characteristics in the knee-joint of was investigated through hematoxylin & eosin (structure), collagen type 2 staining (type II collagen) and safranin O (proteoglycan content), and expression of cartilage specific proteins (type II collagen, aggrecan). After confirming the presence of KOA, 1×106 ADSC were intra-articularly injected to assess its therapeutic efficacy. Specifically, the accumulation of advanced glycation end product with their receptors, oxidative stress, inflammation and expression of matrix metalloproteinase were determined.

Result: The diabetic mice showed osteoarthritic histopathologic characteristics which was demonstrated through loss of proteoglycan and articular cartilage in knee-joint, with highly accumulated advanced glycation end product and their receptors. Malondialdehyde and nuclear factor kappa B were also increased, implying oxidative stress and stimulated inflammatory signalling, respectively. Further, the magnitude of matrix metalloproteinase were also upregulated. Notwithstanding, the ADSC suppressed osteoarthritic characteristics by 4 weeks, and reduced the glycation, malondialdehyde, nuclear factor kappa B and matrix metalloproteinase in knee-joint.

Conclusions: ADSCs demonstrated anti-osteoarthritic activities in hyperglycemic mice through inhibting glycation, oxidative and inflammatory activities.

Keyword: Osteoarthritis, Stem Cell, Hyperglycemia

PP-174

Adipose tissue derived stromal-vascular-fraction enriched platelet-rich-plasma therapy reverses the effects of androgenetic alopecia

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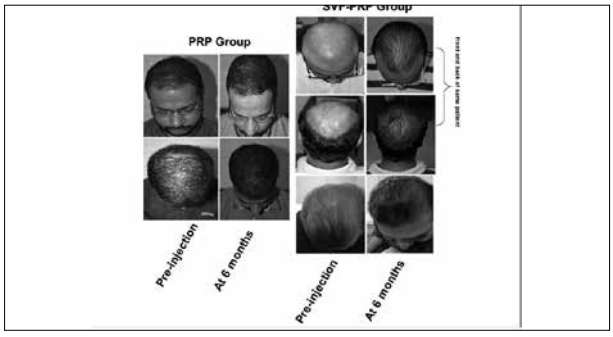
Background: Since antiquity, humans have been trying to devise remedies to cover or cure androgenic alopecia (AGA). Unfortunately, to date all the strategies to negate the effects of AGA have limitations and thus require new treatment options. The current study aims to ascertain effectiveness of autologous adipose tissue derived stromal vascular fraction (SVF) enriched platelet rich plasma (PRP) in reversing the effects of AGA.

Methods: In PRP-group, patients were injected with PRP only while in SVF-PRP group, a mixture of PRP and SVF was injected in scalp at bald areas of AGA-patients. The patients in both groups were assessed using various parameters such as physician- and patient -global assessment scores, pull test, trichoscan and photographs of affected areas.

Result: Mean hair density in PRP-group was significantly increased. Overall, increase in hair density in PRP-group was 21.96% and in the SVF-PRP group it was 56.84%. Similarly, pull test indicated a 33.65% and 80.57% reduction in pulled hair in PRP and SVF-PRP groups, respectively. Mean physician and patient global assessment score were significantly improved after addition of SVF in PRP as compared to PRP alone.

Conclusions: The use of a mixture of SVF and PRP helps reversing the effects of androgenetic alopecia more efficiently as compared to PRP only.

Keyword: Androgenetic Alopecia, Platelet Rich Plasma, Stromal Vascular Fraction, Stem Cells, SVF, PRP



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To determine the frequency and types of RBC alloimmunization in multitransfused oncology patients at a teaching hospital in Lahore, Pakistan

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Background: Blood transfusion is common nowadays in management of various diseases especially oncology patients. Blood grouping and cross matching is done in routine practice before transfusion against Major blood groups (i.e., ABO & Rh blood groups). Alloantibodies can be produced against Minor blood groups. These Alloantibodies can cause acute or delayed hemolytic transfusion reactions. These hemolytic reactions cause anemia as well as other related complications. Oncology patients can produce alloantibodies because of multiple transfusions from different donors. Pre transfusion antibody screening and identification in oncology patients can help them from unnecessary time required for identification of proper cross matched donor.

Methods: A total of 145 cases fulfilling the inclusion and exclusion were selected by non probability purposive sampling. Blood sample was taken and Plasma was separated with centrifugation. Routine blood testing for ABO and Rh grouping was done. The patient's plasma that was positive on initial screening for alloimmunization was further tested with Antibody Identification Panel.

Result: A total number of 145 patients with malignant disorders and who had received more than five transfusions were randomly selected. The red cell alloimmunization screening with three panel screening Kit was found to be positive in eight (8) patients out of total 145. The age analysis patients showed that the Mean age was 45.7 years. Among total 145 patients, 93 (64.2%) were males and 52 (35.8%) were female with a male to female ratio of 1.7:1. The frequency of Red cell alloimmunization is 5.5% (8/145). The alloantibodies for Rh were 6 (4.13%) and one patient positive each for Kell and Duffy having frequency of 0.68 % each. Alloantibodies are found to be Anti-D four (4) and each one (1) Anti- C, Anti-E, Anti-K and Anti Fya .

Conclusions: Multiple transfused patients should be screened against red cell alloantibodies, as the presence of these antibodies can lead to an inadequate haemoglobin level escalation as well as to transfusion reactions. RBC allo-antibodies may cause difficulty in obtaining compatible, antigen-negative RBCs blood in multi-transfused patients.

Keyword: Alloimmunization, Multitransfusion, Alloantibodies, Oncology

PP-176

An attempt to tailor wastage of blood products in the form of returned units

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Background: Wastage of blood products may have an atrocious outcome on health care system. With an improvement in overall health care system there is an emerging focus on limiting the cost and avoiding the practices which may lead to wastage of blood products. It is time to call for adopting the practices which minimize the wastage of such prized blood units to almost zero. To determine wastage rate of blood products in the form of returned blood products at a multidisciplinary institute To identify the reasons of returning blood product after allowable time.

Methods: Retrospective audit was conducted in the section of blood bank from Jan- Dec 2016 designed to determine rate of products returned to blood bank after dispatch, as a part of institutional wastage-reduction program. Reasons of return and key personnel and areas involved were identified.

Result: 3999(46.5%) of blood components were wasted in study duration out of which returned packed red cells after specified time contributed 7.8%(n=315). 3.2%(n=15) blood products were returned within 30 minutes and were taken back in inventory. Majority of these products were returned from Operating room 34%(n=159). In 93%(n=109) cases, nurses and physicians were oblivious of the acceptable duration of keeping blood products out of controlled temperature. For total of 116 patients, ordering multiple units at a time with an anticipation of excessive bleeding during procedure (37.9%, n=44), patient's apprehensions (24.1%, n=28) and unavailability of proper intravenous access (19.8%, n=23), were identified as key reasons behind delaying the transfusion.

Conclusions: Wastage of blood in the form of returned products was found to be significant. A multi-faceted plan was formulated as an important step towards hemovigilance in order to reduce the wastage in the form of small group educational sessions, flyers, new blood bag tags and transport box labels with 30 minutes rule messages on them. A re-audit is now planned to analyze the affect and outcome of these efforts

Keyword: Wastage, Returned, Blood Compoenent, Packed Red Cell, Platelets, Plasma

PP-177

Inappropriate use of fresh frozen plasma in a tertiary care hospital

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Background: Fresh frozen plasma (FFP) is a blood component prepared from whole blood by centrifugation or through apheresis, which is frozen within defined time limits for adequate preservation of clotting factors. The main indication of FFP transfusion is to correct congenital or acquired deficiencies of clotting factors (for which there is not a specific concentrate) and reversal of vitamin K antagonist. However it is commonly observed that there are high rates of inappropriate transfusion in terms of indication and dosage due to non-compliance with established guidelines. To determine the indications of FFP transfusion and to assess appropriateness of their dosage as defined by BCSH guidelines.

Methods: This was a retrospective review of data. Clinical charts of patient receiving FFP from June 2017-Dec 2017 were reviewed. Indications, baseline and post transfusion coagulation profile of patients were recorded. Laboratory data was retrieved from laboratory information system (LIS). The principle clinical audit standards that were applied to this preliminary project were adopted from BCSH guidelines

Result: During the study period, total 624 FFPs were arranged; out of which 402 units were transfused to 149 patients. There were 83 (55.7%) males and 66 (44.3%) females. Majority of patients were of paediatric age group (n=90, 60.4%) with mean age of 5.21±1.9 days while 59 (39.6%) were adults having mean age of 18.32±4.7 years. The most common unit requesting FFP was neonatal ICU from where 84 (56.3 %) requests were generated followed by general ICU (23.4%, n=35) and wards (20.1%, n=30). Main indications of transfusing FFP are tabulated in table 1. Weight based dosage (15ml/kg) was mainly followed in paediatric population (60.4%, n=90) while in adults, only 1 (0.67%) patient received appropriate dose. Rest of the patient received variable doses. 8.7% (n=13) cases had no record of pre-transfusion coagulation profile. In 37.5% (n=56) cases, coagulation screen was not repeated after FFP transfusion. Only in 41 (27.5%) cases, FFP transfusion was in accordance with BCSH guidelines. No transfusion reactions were recorded from the products released in the study duration.

Conclusions: The audit shows poor compliance with the standards. We recommend that hospital should have specialty specific

guidelines for the use of FFP which should define indications and appropriate dosage. Regular audits of compliance with local and international guidelines must be performed.

Keyword: Fresh Frozen Plasma, Audit

PP-178

Post donation notification, counseling and response rate of reactive blood donor: An important step to prevent reactive donor from re-donating blood

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Background: Provision of safe and adequate blood is a fundamental part of blood bank services. A crucial step in the prevention of transfusion transmitted infection is to notify and counsel reactive donors blood donors. Post donation notification and counseling of sero-positive blood donors not only protect the health of the donor but also prevent secondary transmission of infectious diseases. The aim of the study was to determine the response rate of reactive blood donor after notification of their screening status.

Methods: This is an observational study carried out in Patel Hospital Blood bank over a period of 05 months from July – November 2016 involving total 1539 donors. All sero-positive blood donors were informed by the blood bank staff about an abnormal test result with an advice to report to blood bank for counseling and for referral to respective department/clinics of the hospital for further management. The response rate of reactive donors after notification of their abnormal test results was evaluated.

Result: The total reactive donors were 82(5.3%). 54(66%) reactive donors could be contacted of which 39(72%) responded positively to the notification calls and attended counseling at the blood bank and 28(34%) reactive donors could not be contacted either due to incorrect/changed contact details or did not picked up call even after three attempts.

Conclusions: The response rate of the reactive donors was found to be 72%. The response rate of reactive blood donors in developing countries is quite low suggesting insufficient health care knowledge and a poor understanding of screening tests.

Keyword: Donor, Counselling

PP-179

Therapeutic plasma exchange in rat killer (Yellow Phosphorus) poisoning: Experience from South India

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Background: Accidental or suicidal consumption of rat killer poison, which contain yellow phosphorus (YP) component, could lead to death. YP could cause acute liver failure (ALF), cardiac arrhythmias, bone marrow depression and renal failure. Liver transplantation (LT) is the only successful treatment option in ALF once patient develops acute liver failure following consumption of YP, as of now. Therapeutic plasma exchange (TPE) provides a potential therapeutic option to support liver function and provide scope for regeneration in ALF. However, the role of TPE in YP poisoning in not yet reported. The purpose of the study is identify if the TPE reduces mortality and increase transplant free survival in patients with YP poisoning

Methods: This is a prospective study and was approved by institutional ethical committee. All adults who have consumed YP received standard medical therapy and TPE was indicated if INR >3, ALT or AST elevation>1000, Encephalopathy, or any significant changes in liver biopsy. The TPE was performed using centrifugal apheresis (Optia Spectra, Terumo BCT) for 5 consecutive days. 1.0 plasma volume exchange was performed with Fresh frozen plasma and 5% albumin as replacement fluid. All patients were monitored for any transfusion or procedure related adverse events and were given calcium prophylaxis. The patients were monitored for liver function test, renal function test, Arterial Ammonia, ABG, INR, and liver biopsy. Patients were also monitored for changes in Pre and post TPE (after 2 hours) cytokine levels

Result: During the study period (Dec 2015 – January 2018), 30 patients M:F 1:1, mean Age 28 (range 15-53) were admitted with YP poisoning induced ALF. Average time from YP intake to Admission was ranging from (1-10 days) average 3.7 days. Baseline Investigations showed elevated INR 4.0 (0.9 – 8.69), and raised liver enzymes AST 1567 (14 - 6139), ALT 669 (17- 2056). A total of 139 procedures were performed with average 5 Procedure (2 to 8 procedures) were performed in consecutive days with average 4840 (2769 - 8371) ml blood volume processed with average 2419 ml (1424- 3822) plasma exchange. There were 4 minor allergic reactions and no major adverse reactions during TPE procedures. Cytokine Analysis showed significant increase in anti- inflammatory cytokines IL-4 and IL-10 after plasmapheresis while the pro-inflammatory cytokine IL 6 ($p<0.02$) and fibrogenic cytokine TGF β ($p<0.02$) showed a significant decrease. The patients showed significant improvement in serum ALT and AST levels and coagulation status. 20 patients improved without need for Liver transplant and were discharged at average 9 days (5-30 days). 2 patients required urgent liver transplant 15 and 9 days respectively after poison intake. These 2 post LT patients had developed graft dysfunction in the postoperative period and improved after post LT TPE (1 and 5 cycles). The post TPE liver biopsies showed histological improvement in form of reduction in hepatocyte necrosis compared to pre TPE. 2 patients expired due to multi organ failure.

Conclusions: This is the first study highlighting the role of TPE as an effective treatment intervention for patients with Yellow phosphorus poisoning along with standard medical therapy. Our initial experience provides a strong recommendation for TPE in reducing mortality and improved survival in native livers in patients with YP poisoning.

Keyword: Yellow Phosphorus, Ratol, Liver Failure, Plasma Exchange, Alf, India

Table.
Effect of plasmapheresis (Pre and Post) on biochemical parameters and cytokine concentrations.

Parameters	Pre -TPE	Post TPE	p value
S. Bilirubin	4.9(0.7-13.5)	4.8 (0.5-11.4)	0.8
AST	1179 (27 -6079)	119.5(54-271)	0.02
ALT	889.5 (17-2056)	13.5 (49-221)	0.006
INR	4.4 (1.18- 10.4)	1.14 (1.1- 7.5)	0.02
Anti-inflammatory Cytokine	68 (26-113)	82 (32-126)	0.02
IL-4	11 (1-35)	29 (3-55)	0.0006
IL-10			
Pro inflammatory Cytokines	74.5 (4-502)	18 (5-87)	0.06
	83.5(1-300)	49.6 (6-230)	0.02
TNFα	23.5 (4-67)	13 (5-51)	0.02
IL-6			
Fibrogenic TGF-β			

PP-180

Correlation between the IgG subclasses with occurrence and severity of haemolytic disease of foetus and newborn

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Background: Hemolytic disease of fetus and new born (HDFN) is a leading cause of mortality and morbidity in the antenatal and neonatal periods. Maternal alloimmunization against paternal red cell antigens is the most important cause of HDFN. According to literature, HDFN cases with IgG1 and IgG3 have more severity when compared to IgG2 and IgG4. In present study, IgG subclass (IgG1 and IgG3) was identified using column agglutination test to evaluate the prevalence and clinical significance of IgG Subclasses in cases of HDFN. The findings might be helpful in early referral to higher centers and in determining prognosis of the case

Methods: Fourty-eight alloimmunized (only Anti D) antenatal cases were studied. "DAT IgG1/IgG3 ID- card (Bio-Rad) were used in IgG subclass determination. Pregnancy outcome was classified into unaffected or mild/ moderate/ severe HDFN. Subclass prevalence was calculated and HFDN severity was correlated with IgG subclass in the study population. A prior ethical clearance was taken from institute ethical board.

Result: Subclass distribution among 48 alloimmunized (with anti-D) women was 24% for IgG1, 16.6% for IgG3, 41.6% for IgG1+IgG3 and 14.5% had neither IgG1 nor IgG. HDFN severity was significantly higher when IgG1 was present alone or in combination with IgG3 (p value < 0.01). Disease occurrence and severity was also significantly higher in case of IgG1 or IgG3 present, alone or in combination (p value < 0.01).

Conclusions: The presence of IgG1 / IgG3 was significantly related to occurrence and severity of HDFN. Both disease occurrence and severity was significantly lower if neither IgG1 nor IgG3 was present. Therefore, alloimmunized antenatal women with IgG1/IgG3, alone or in combination require close and antenatal monitoring to detect HDFN features at early stage, timely and appropriate referral and intervention. It was recommended that IgG subclass determination to predict occurrence and severity of HDFN more accurately.

Keyword: HDFN, Rh Isoimmunization, IgG Subclass

Table 1: Association of IgG1 subclass with severe cases of HDFN

		Fetal outcome			Significance of difference (Fisher's Exact Test)
		Severe	Not severe	Total	
IgG1 OR IgG1+IgG3 Present	Yes	22 (a)	15(b)	37(a+b)	P value- 0.009
	No	2 (c)	9(d)	11(c+d)	
	Total	24(a+c)	24(b+d)	48 (n)	

PP-181

Overview of antibodies implicated in delayed hemolytic transfusion reaction

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Background: Multiple transfusions to patients expose them to various complications of blood transfusion including alloimmunization against red cell antigens, especially in thalassemia. One complication of alloimmunization is delayed hemolytic transfusion reaction (DHTR). Delayed hemolytic transfusion reactions (DHTRs) may occur when there is an antigen mismatch between transfused red blood cells and recipient antibodies where sensitized red blood cells are cleared by macrophages or complement activation leading to immunoglobulin G (IgG) mediated hemolysis. It occurs after alloimmunization to an RBC antigen(s) after a transfusion. Over time, the patient's antibody levels fall to undetectable levels. Subsequent re-exposure of the recipient to red blood cells that possess the antigen triggers an anamnestic response and subsequent hemolysis. The study was conducted to assess the antibody implicated in delayed haemolytic transfusion reactions.

Methods: A total of 19 episodes of delayed hemolytic transfusion reaction occurring in 17 patients were analyzed. The patients were given ABO matched cross match compatible red blood cell units. Delayed hemolytic transfusion reaction was considered when there was failure in rise of hemoglobin after transfusion, presence of jaundice, increase in the levels of bilirubin from baseline and the event occurring between 5 to 12 days of transfusion. Prior ethical permission was taken for conducting the study.

Result: The median time between red cell transfusion and diagnosis of delayed hemolytic transfusion reaction was 7 days. Out of the 19 episodes in 15 episodes there was no change in hemoglobin levels after red cell transfusion where as in 4 episodes the hemoglobin fell below the pre transfusion levels. The post transfusion direct antiglobulin test was positive in 5 events. The total antibodies implicated were 9 (Anti Jka: 6, Anti Jkb: 2, Anti Fya: 2, Anti Fyb: 1, Anti S: 1, Anti s: 1, Anti E: 2, Anti e: 1, Anti c: 1). Significant jaundice was noted on physical examination. Laboratory data showed lower mean levels of post transfusion hemoglobin was 7.4 g/dl versus 9.2 gm/dl pre-transfusion Hb. Similarly, the post transfusion levels of bilirubin (3.9 mg/dl v/s 1.4 mg/dl, and LDH (280 IU/L v/s 452 IU/L) were higher in comparison to pre-transfusion values.

Conclusions: The initial symptoms of delayed hemolytic transfusion reaction are often missed as in most of cases; no antibody is identified during testing. Delayed hemolytic transfusion reactions can be asymptomatic or mimic other conditions and may be misdiagnosed. In patients with known clinically significant antibodies, confirming on each pre-transfusion sample tested, that the evaluation for the presence of additional clinically significant antibodies has been correctly performed and appropriately phenotype red blood cell unit is issued. Failure to recognize this entity could lead to inappropriate treatment and future transfusions reactions.

Keyword: DHTR, Transfusion Reaction, Antibodies, Minor Antigens

PP-182

Retrospection of anti-blood group antibody proficiency testing data using geometric mean and standard deviation

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Background: Anti-blood group antibody titer is an important index for transfusion in ABO-incompatible HSCT. Laboratories use different test methods and external proficiency testing (PT) has contributed to the reduction of interlaboratory variance. Statistically, reporting results in titers as reciprocal of the last dilution has the unsought effect of increasing the arithmetic difference

between titers. Consensus for an external proficiency testing conducted by College of American Pathologists (CAP) is determined by mode titer and its four adjacent titers. Here we analyze five recent PT results and compare two consensus criteria of 'mode ± 2 titers' and 'geometric mean (GM) ± 2 geometric standard deviations (GSD)'.

Methods: Result summary from five most recent PT provided by CAP for anti-blood group antibody titer was used for statistical analyses. Target analytes of PT included anti-A and anti-D and test methods used were 'uniform procedures' and 'other procedure'. Test methods with more than 100 responses were selected for comparison. Uniform procedures for anti-A testing included tube testing at room temperature and tube testing at 37℃ with anti-IgG AHG. Uniform procedures for anti-D testing were tube testing at 37℃ with anti-IgG AHG and gel testing at 37℃ with anti-IgG AHG. Anti-D tube testing using saline at 37℃ with anti-IgG AHG was included as other procedure. A consensus was made when 80% or more participant results were within five titers (mode ± two titers). GM ± 2GSD was used as the alternative consensus criteria for comparison. All statistical analyses were done using SPSS 21 for Windows (SPSS Inc., Chicago, IL) and Microsoft Office Excel 16.0 (Microsoft, Redmond, WA).

Result: For anti-A, tube testing was more commonly used than gel testing, and uniform procedure was the common method of testing. Tube testing was also more common for anti-D testing and the most common method was tube testing at 37℃ with anti-IgG AHG in saline. Using PT evaluation criteria of mode ± 2 titers, mean percentage of participants with acceptable result was 97.59%. Using GM ± 2 GSD, the mean percentage of acceptable result was 94.7%. Difference between results of two criteria was statistically significant (CI 95%, $P < 0.000$) using paired t-test. Percentages of consensus inclusion was consistently lower in GM ± 2 GSD, except for 2016 ABT-B anti-D tube testing at 37℃ with anti-IgG AHG. GM ± 2 GSD included additional 1:128 titer in consensus, adding four responses as acceptable, which were previously out of consensus using mode ± 2 titers.

Conclusions: Efforts for standardization and reduction of interlaboratory variance in ABO antibody testing has yielded satisfactory agreements between participating laboratories, but the decision rate of accordance appears to be exceptionally high as seen from the five most recent PT summary. This results from using mode as the measure of central tendency which requires considerable allowable errors around the measurement. In contrast, geometric means are considered more robust and precise in visualizing the central tendency of a dataset presented in titers or ratios. While standardization of techniques and efforts for consistency remains important for reducing interlaboratory variance and maintaining consensus, a different statistical approach using GM and GSD can provide a goal towards which efforts for consistency should be directed.

Keyword: Blood Group Antibody, Proficiency, Consensus, Mode, Geometric, Standard Deviation

Table. Comparison of consensus range of titers using two criteria

Analyte	Procedure / Method	Survey (N)	Mode ± 2 Titers	% acceptable	GM ± 2GSD	% acceptable
Anti-A	Uniform	2016 ABT-A (120)	16-256	96.70	16-128	95.80
	Tube (RT)	2016 ABT-B (124)	32-512	98.40	64-256	89.50
		2017 ABT-A (122)	16-256	99.20	32-256	98.40
		2017 ABT-B (118)	32-512	100.00	64-256	90.70
		2018 ABT-A (116)	32-512	95.70	64-512	92.20
	Uniform	2016 ABT-A (114)	64-1024	98.20	64-512	93.90
	Tube (37°C) Anti-IgG AHG	2016 ABT-B (113)	64-1024	95.60	128-1024	81.40
		2017 ABT-A (115)	128-2048	96.50	128-1024	95.70
		2017 ABT-B (109)	32-512	97.20	64-512	95.40
		2018 ABT-A (101)	128-2048	95.00	128-1024	92.10
Anti-D	Uniform	2016 ABT-A (342)	64-1024	98.50	128-1024	96.50
	Tube (37°C) Anti-IgG AHG	**2016 ABT-B (334)**	**4-64**	**96.40**	**4-128**	**97.60**
		2017 ABT-A (333)	16-256	98.20	32-256	95.80
		2017 ABT-B (329)	16-256	98.50	16-256	98.50
		2018 ABT-A (318)	16-256	98.10	32-256	93.10
	Uniform	2016 ABT-A (130)	128-2048	99.20	256-1024	95.40
	Gel (37°C) Anti-IgG AHG	2016 ABT-B (129)	16-128	97.70	16-128	97.70
		2017 ABT-A (138)	64-1024	96.40	64-512	96.40
		2017 ABT-B (144)	64-1024	97.20	64-512	96.50
		2018 ABT-A (142)	32-512	97.90	64-512	97.90
	Other	2016 ABT-A (487)	64-1024	98.20	64-512	96.10
	Tube (37°C)	2016 ABT-B (487)	4-64	97.90	4-32	94.30
	Saline Anti-IgG AHG	2017 ABT-A (509)	16-256	98.40	32-256	95.70
		2017 ABT-B (510)	16-256	96.70	16-128	94.10
		2018 ABT-A (506)	16-256	98.00	16-128	96.00

Abbreviations: GM, geometric mean; GSD, geometric standard deviation; RT, room temperature; AHG, anti-human globulin; % acceptable, percentage of responses included within criteria

PP-183

Ensuring standard transfusion practices amidst staff nurses by implicating a framework of knowledge gap analysis and subsequent reformatory measures

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Background: Millions of patients receive transfusion everyday across the globe for various disorders. Precise knowledge for standard practices of transfusion is imperative for providing high quality patient care and safety. The study was aimed to evaluate the understanding of clinical transfusion practices amidst staff nurses and to rectify the subsequent erroneous undertakings.

Methods: A prospective, cross sectional study was structured to be conducted in two phases. The study period was stretched from 15th January to 30th November 2018 at Jinnah Medical and Dental College Hospital, Karachi. In phase one pre-tested questionnaire was used for assessment of knowledge of staff nurses (referring to standard operational procedures for blood product administration). In Phase Two, three stage plan was designed to take corrective action.

Result: Total of 65 registered staff nurses participated by filling questionnaire containing 13 questions with three different options. Six various areas of knowledge disparity were identified such as concerning positive patient identification, taking consent before transfusion, pre-transfusion blood sampling, ordering and receiving blood in clinical area and transportation of blood products. Interventions included three stage reformatory measures. In stage one educational workshops were carried out targeting in-house registered staff nurses, nursing students and nursing assistants with total of 150 participants. Educational flyers were circulated. In stage two clinical transfusion was implemented in nursing students' curriculum. In stage three (on going) it is planned to set up a constant surveillance system for clinical transfusion as a part of Hospital Hemovigilance.

Conclusions: Questionnaire based assessment of knowledge gave us an indirect reflection of clinical practices of transfusion by staff nurses and identified the target issues that were accosted in form of interactive and informative workshops, lectures and educational flyers.

Keyword: Transfusion, Staff Nurses, Standard Practices.

PP-184

Knowledge, attitudes and practices on blood transfusion of medical residents in a tertiary hospital: A questionnaire-based study

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Background: Blood transfusion remains to be one of the most common procedures performed in hospitals. It is an extremely efficient and perhaps life-saving procedure which is very much an essential part in the management of hematologic and non-hematologic cases. The knowledge of doctors on blood transfusion has a substantial influence on the rational utilization of blood products. The general objective of the study was to to assess the knowledge, attitudes and practices on blood transfusion of internal medicine residents for the Fiscal Year 2016 at the Philippine General Hospital, using the BEST-TEST validated questionnaire on transfusion medicine.

Methods: This is a descriptive cross-sectional study design, which included all 63 internal medicine residents undergoing training at the Philippine General Hospital for the year 2016. General data on demographics were collected, after which the participants were asked to answer the BEST-TEST validated questionnaire on transfusion medicine

Result: A total of 63 internal medicine residents with a mean age 27.9 ± 1.6 ranging from 25 to 33 years old and majority (61.9%) were between 28 to 30 years old were included in this study. Gender distribution is almost even (50.8% males). In terms of number of hours of training on transfusion medicine in medical school, a third had 4+ hours and a little more than half (50.8%) had 3+ hours. Majority (58.7%) of the internal medicine residents appraised their knowledge of transfusion medicine as intermediate, and almost all (98.4%) rated it as beginner to intermediate. BEST-TEST mean scores were 39.1%, 40.0%, and 41.0% for the first, second, and third year residents, respectively. There is no significant correlation between test scores of the residents and number of hours of training in transfusion medicine in medical school ($p = 0.694$) and in residency ($p = 0.927$). On the other hand, there is a significant correlation between the quality (perceived helpfulness) of residency training on transfusion medicine and test scores with the scores increasing as the year level increases.

Conclusions: Indeed, the results of this study has shown inadeqacy in the knowledge on transfusion medicine among internal medicine residents. Therefore, further training on transfusion medicine, maybe in the form of lecture series and seminars may help strengthen the knowledge of the residents.

Keyword: Blood, Transfusion, Knowledge, Residents

Correlation of training and perceived knowledge with exam scores (n = 63)

Question	Number	Mean	SE[1]	p-value[2]
Medical school hours				
None	1	10.0	-	0.694
1 – 2 hours	30	40.3	1.57	
>2 hours	32	40.6	1.27	
Residency hours				
None	10	39.0	1.80	0.927
1 – 2 hours	37	40.8	1.44	
>2 hours	16	38.8	2.52	
Quality of medical school training				
Not/slightly helpful	40	39.6	1.48	0.826
Moderately helpful	22	40.5	1.61	
Very/extremely helpful	1	45.0	-	
Quality of residency training				
Not/slightly helpful	32	37.8	1.68	0.041
Moderately helpful	28	42.0	1.39	
Very/extremely helpful	3	45.0	2.89	
Self-rated transfusion medicine knowledge	25	40.0	1.68	0.759
Beginner	37	39.9	1.48	
Intermediate	1	45.0	-	
Advanced				
Composite score of self-rated ability to manage transfusion				
Below median	30	39.0	1.7	0.470
Above median	33	40.9	1.4	

[1] Standard error
[2] Spearman's rank correlation used

PP-185

Correlation between packed red cells hematocrit with post-transfusion hemoglobin level in anemic patient at Badung mangusada district hospital, Bali

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Background: The demand for Packed Red Cells (PRC) unit transfusion on Badung Mangusada District Hospital is increasing annually. In some cases, there are discrepancies between increasing of hemoglobin level with the volume of PRC unit has given, which is the reason is unclear yet. Each unit PRC contains approximately 42.5 – 80 g of hemoglobin or 128 - 240 mL of pure red cells depending on the hemoglobin level of the donor, the starting whole blood collection volume, and the collection method or further processing. With the anticoagulant system using CPDA-1, hematocrit of red blood cells ranges from 65 – 80%. One PRC unit expected to increase hemoglobin level by 1 g/dL. In our hospital, there is no study of PRC quality before. So, this study objective is to evaluate the quality of PRC unit with measure the hematocrit level and evaluation of hemoglobin level 24 hours after transfusion.

Methods: anemic patients (hemoglobin < 10 g/dL) is enrolled in this research, with massive acute bleeding and hemolytic anemia exclusion. PRC hematocrit is checked pretransfusion. There is no PRC transfusion again in 24 hours. After that, we checked for the hemoglobin level.

Result: Twenty-four male and sixteen females enrolled in this research. The youngest is 14 years old, and the oldest is 90 years old. The underlying diseases are aplastic anemia, myelodysplastic syndrome, Type 1 Diabetes Mellitus, peptic ulcer, prostate cancer, multiple myeloma, hip fracture, colon malignancy, severe iron deficiency anemia, and other diagnoses. Mild, moderate and severe anemia are 9 (22.5%), 20 (50%) and 11 (27.5%) respectively. The mean of pretransfusion Hb is 6.77 g/dL. 16 PRC units (60%) had hematocrit level >65%, and the others are lower than 65%. The mean of hematocrit PRC and Hb post-transfusion are 59.71 % and 7.91 g/dL respectively. Average increased Hb level post-PRC transfusion is 1.14 g/dL. Female had higher increase of Hb post-transfusion than male (1.2 g/dL vs 1.1 g/dL); although there is no significant correlation ($p>0.05$; $r = 0.07$). There is a significant correlation between PRC hematocrit and Hb 24 hours post-transfusion among male ($p=0.016$; $r=0.469$). However, there is no correlation between PRC hematocrit and Hb level post-transfusion ($p=0.793$; $r=0.43$).

Conclusions: Mean of PRC hematocrit in Badung district hospital is 59.71%, slightly below national standard (65% -75%). However, the average hemoglobin increase is quite enough (1.14 g/dL). There is a correlation between PRC hematocrit level with hemoglobin level after transfusion in male ($p=0.016$; $r=0.469$), but not for overall subject ($p=0.793$; $r =- 0.43$).

Keyword: Packed Red Cells, Hematocrit, Hemoglobin

PP-186

Impact of voluntary non-remunerated blood donation: How the community responses in developing country

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Background: WHO is advocating a policy towards 100% voluntary non-remunerated blood donation by year 2020. Natural disaster prone country has always scarcity of blood and blood products is frequently encountered. Nepal has encounter many natural disaster including Earthquake, flood, fire

Aims: To determine knowledge, attitude and practices(KAP) of young students(100), elder people(100) about voluntary blood donation(VBD) in emergency conditions as well.

Methods: Cross-sectional study conducted in 2017Jan to 2018Jan. A pre- tested, semi-structured questionnaire was used as a study tool. After the collection of the baseline information, a brief interactive awareness session given by nurses, addressing VBD was organized for the participants and their willingness to donate blood was again noted at the conclusion of the session, level of knowledge was assessed by scoring scale

Result: Results: The proportion of young students having less knowledge was 33.1% with the mean score of 12.2±2 but the elder people having more knowledge and willing for blood donation. 89.8% intended to donate blood in future but only 11.9% had ever donated blood and out of which, 44.8% of donors were first timers. The elders having more donation and having VBD oral history in past. Female participants having less than male counterpart. Knowledge on blood safety and donation was significantly associated with blood donation status.

Conclusions: Conclusions: VBD is considered as backbone of blood safety and safe transfusion practices. There is a serious need to improve the recruitment and retention of VBD population to ensure a sustainable safe blood transfusion practice. Nursing allied health worker´s Awareness sessions on VBD should be held regularly to create positive attitude, and to remove misconceptions among the college students about VBD. Know your blood group status program is effective for future blood donors. Community should priorities for medical purpose for life saving the blood donation rather than aesthetic purpose

Keyword: Transfusion Blood, Developing Country, Knowledge

PP-187

Development of deep vein thrombosis after achieving remission in a patient with acquired hemophilia A

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Background: Acquired hemophilia A (AHA) is an uncommon autoimmune disease caused by immunoglobulin G antibodies against factor (F) VIII. Occurrence of clinical thrombosis is rare for congenital or acquired hemophilia. We report a case of acquired hemophilia A achieving remission with combination treatment of steroids and cyclophosphamide who subsequently developed deep vein thrombosis.

Methods: A 53-year-old Filipino male was admitted for left lower quadrant pain. Work-up revealed anemia, isolated activated partial thromboplastin time (APTT) prolongation, and left psoas hematoma on ultrasound. Diagnosis of Acquired Hemophilia A was confirmed with decreased Factor VIII (FVIII) levels and PTT mixing studies revealing presence of an inhibitor. Management for acute bleeding was supportive transfusion (Fresh Frozen Plasma or cryoprecipitate) and upon availability, bypassing agents (FEIBA and rFVIIa) and FVIII concentrates. For inhibitor eradication, Prednisone and Cyclophosphamide were used. The patient improved and discharged on maintenance steroids and factor concentrates given upon availability. Two months after treatment, he achieved partial remission (repeat FVIII was normal and interval scan demonstrated decrease in hematoma size). However, he was readmitted due to sudden left leg swelling. Venous duplex scan revealed deep vein thrombosis (DVT) of the distal external iliac, common femoral, deep femoral and popliteal veins. He was treated with low molecular weight heparin (LMWH) and bridging anti-coagulation. Upon discharge, he was maintained on Prednisone, which was tapered down gradually, and Warfarin 5mg daily, with INR target of 2 to 2.5. On his 10th month of Warfarin treatment, repeat venous duplex scan revealed full resolution of the DVT.

Result: The occurrence of thrombosis in the setting of hemophilia is a paradox with several proposed explanations. (1) Rapid increase in FVIII activation during the remission phase of AHA leads

to elevated FVIII levels, which predisposed the patient to both venous and arterial thrombosis in a dose-dependent manner. (2) Risk factors such as comorbid conditions, advancing age, medication use and infection are present. (3) Complications of long term glucocorticoid steroid therapy may lead to increased levels of Von Willebrand factor (vWF) thus promoting vWF-dependent thrombus formation leading to adverse vascular events increase in FVIII activation during remission phase leads to elevated FVIII levels, predisposing the patient to thrombosis in a dose-dependent manner. The thromboembolic risk among patients receiving bypassing agents is also recognized in literature. In the general hemophiliac population, thrombosis can occur with the administration of the bypassing agents activated prothrombin complex concentrate (aPCC) and recombinant factor VIIa (rVIIa). This risk of thrombosis appears to be higher among patients with AHA compared to those with congenital hemophilia. This observation may probably be linked to the presence of additional risk factors associated with aging and comorbidities among patients with AHA.

Conclusions: AHA patients with risk factors for thrombosis have substantial risk to develop it during the recovery phase of FVIII activity. Therefore, these patients should be monitored closely by clinical assessment and coagulation testing. Treatment of thrombosis must be carefully and vigilantly balanced with the high risk of bleeding innate among patients with hemophilia.

Keyword: Acquired Hemophilia A, Remission, Deep Vein Thrombosis

PP-188

Successful management and delivery in a pregnancy with secondary evans syndrome from systemic lupus erythematosus and antiphospholipid syndrome

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Background: Pregnancies complicated by Evans' syndrome are uncommon. Management is geared towards sufficient control of the underlying conditions however the therapeutic options are limited due to possible teratogenic effects of currently available medications. We present a case of a successfully managed pregnancy complicated by secondary Evans syndrome from Systemic Lupus Erythematosus with concurrent Antiphospholipid Syndrome.

Methods: A 24 year old Filipino female primigravida with history of ischemic stroke and recently diagnosed with Immune Thrombocytopenic Purpura presented at 27 weeks of gestation with 1 day history of hematemesis and melena. On admission, she was thrombocytopenic (4 x 109/L), anemic (97 g/dL), and had positive Coombs test. Subsequent testing for connective tissue disorders showed presence of both systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). Treatment with supportive blood transfusions, corticosteroids, IVIg and intralipid infusion in conjunction with heparin and aspirin were given. She underwent emergency LTCS at 34 weeks gestation and successfully delivered a baby boy weighing 2200 gms with no neonatal lupus and normal blood counts. She was discharged maintained on Prednisone at 1mkd and ASA 80mg/tab OD. Six months post-partum, her blood counts were normal and steroids tapered down gradually.

Result: Management is geared towards sufficient control of the underlying conditions however the therapeutic options are limited due to possible teratogenic effects of currently available medications. The use of comprehensive treatment with heparin, IVIg in conjunction with corticosteroids and aspirin were proven safe and effective for patients. The use of combination therapy was shown to have various functions including anti-inflammatory, antiplatelet, anticoagulation, inhibition of complement-mediated damage, modulation of cytokine production, regulation of endothelial cell function and assist in implantation and trophoblast invasion. Intralipid infusion was also given to the patient as alternative to IVIg due to constraint on medication availability. Studies suggest that intravenous intralipid administration may improve implantation and maintenance of pregnancy in patients with abnormal NK cell function due to suppression of NK cytotoxicity. Fetal outcome is generally favorable as long as underlying conditions are well managed. However, there are few cases reported wherein fetuses were affected by transplacental passage of antibodies which lead to morbidity and mortality in utero. Thus, it is crucial to do close surveillance in order to minimize the risk of adverse pregnancy outcome. Fortunately, the patient successfully delivered to a baby boy with no neonatal lupus and normal blood counts.

Conclusions: In our case, the sufficient control of the patient's underlying condition was vital for her successful pregnancy

outcome. The judicious use of comprehensive treatment with heparin, IVIg, intralipid infusion in conjunction with corticosteroids and aspirin were proven safe and effective. Moreover, the use of a multiple disciplinary approach and constant communication between co-managing services was essential for achieving a successful therapeutic management and delivery for the patient.

Keyword: Evans Syndrome, Systemic Lupus Erythematosus, Antiphospholipid Syndrome, Pregnancy

PP-189

On-demand versus low dose factor VIII prophylaxis treatment in hemophilia A patients: Differences in outcome and factor concentrates utilization

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Background: Long term prophylaxis FVIII is a standard of care in severe hemophilia patient to prevent joint bleeding and chronic arthropathy. This study was undertaken to assess the differences in annualized bleeding rate (ABR) and factor concentrates utilization between on-demand and prophylaxis treatment in severe hemophilia patients.

Methods: A retrospective study of 7 severe hemophilia patients in Hospital Melaka who received at least 6 months of on-demand treatment followed by at least 6 months of prophylaxis treatment was carried out. During on-demand treatment, subjects came to emergency department to receive factor concentrates. However in prophylaxis treatment arm, subjects allow to bring certain amount of factor concentrates home. The dose of prophylaxis FVIII was determined by the physician based on bleeding history. The data of treatment and outcome in the period of 6 months in both treatment arms were evaluated. Besides, a questionnaire was completed by subjects to evaluate patient's feedback on the differences of bleeding control, quality of life and preference between both treatments. The data was analyzed using SPSS version 20.

Results: Subject's age ranged from 23-53 years old with the mean of 33.4 years. The median FVIII dose in on-demand treatment is 15IU/Kg (IQR 15-20). In prophylaxis treatment arm, 1 subject was given prophylaxis FVIII 15IU/Kg weekly and another 6 subjects with the dose 15IU/Kg twice a week. However, there are 2 subjects changed their prophylaxis regimen from twice a week to three times a week due to inadequate control of bleeding. The mean ABR between on-demand and prophylaxis treatment is significantly different (p = 0.019, 95%CI 6.376, 49.624). The mean ABR in prophylaxis treatment arm is 8.86 (SD= 10.885), which is lower than on-demand arm with 36.86 (SD= 23.32). The mean number of hospital visit over 6 months in both arms showed significantly different (p= 0.033, 95%CI 2.04, 34.245) with the mean in prophylaxis arm is 6.86 (SD= 0.69), lower than on-demand arm with 25 (SD= 17.776). However, the median factor concentrates consumption over 6 months in prophylaxis arm is 56000 IU (IQR 33750-71000), higher than on-demand arm with the median of 33000 IU (IQR 3000- 45000). All subjects preferred prophylaxis treatment and agreed that prophylaxis treatment gave better control of bleeding. There are 71.5% of subjects agreed that prophylaxis treatment gave better quality of life and 85.7% of subject agreed that experienced pain relieve in shorter time in prophylaxis treatment arm.

Conclusion: Prophylaxis treatment significantly reduced ABR and gave better quality of life. However, it increased factor concentrate consumption.

Keyword: Hemophilia A, Prophylaxis, On-Demand, Annualized Bleeding Rate

PP-190

Evaluation of bone marrow study in patients with ewing sarcoma/primitive neuroectodermal tumors at a tertiary-care hospital

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Background: It is well-known that metastasis is the most important prognostic factor in Ewing sarcoma family tumor (ESFT). Due to the importance of bone marrow (BM) metastasis as a risk factor, BM examination still plays a big role in staging of ESFT. This study aimed to investigate the BM findings and other prognostic factors in ESFT at a tertiary-care hospital since January 2000.

Methods: All patients who were newly diagnosed with ESFT and underwent BM study were enrolled during 19 years from January 2000 to September 2018. The first BM study from enrolled patients were reviewed, and BM diagnosis was made from a combination of morphological findings of BM specimens including BM aspirates and biopsies, and immunohistochemistry (IHC) results. Electronic medical records of these patients were reviewed for previous history of ESFT, pathology results of primary lesion and primary tumor site, tumor size and metastasis.

Result: For 19 years, a total of 55 patients who were diagnosed with ESFT and underwent BM examination were identified. Unilateral BM study was performed for 10 patients, the other 45 patients received bilateral BM examination. Primary tumor sites were 9 extremity area, 31 chest/spine/head and neck area, 15 abdomen-pelvis area. Bone metastasis was observed in 10 patients: single in 3 patients, 2 to 5 in 3 patients, more than 5 in 4 patients. Only 2 cases showed lung metastasis. Only one of 53 IHC staining for CD99 of primary tumor specimen showed negativity unusually. BM metastasis was revealed in 7 patients. Three cases were diagnosed as BM metastasis only with morphological findings. Other 4 cases were assisted with IHC staining: 2 with CD56, one with CD99, one with vimentin. Bone scan didn't show distant bone metastasis in 2 cases with BM metastasis, of which, primary sites were sacrum and lumbar spine.

Conclusions: Not only morphological findings, but also IHC staining was helpful for diagnosing BM metastasis of ESFT. This study concludes that BM study in Ewing sarcoma is important for detecting metastasis although the utility of imaging modalities is rapidly improving.

Keyword: Ewing Sarcoma, Bone Marrow, Immunohistochemistry

PP-191

Bone marrow findings of IgG4-related disease; A case of bone marrow involvement of IgG4-related disease

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Background: Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibro-inflammatory disorder, named by International Multidisciplinary Study Group in 2012. The pathogenesis is not fully understood yet, but cytokines from type 2 helper T-cells and regulatory T-cells and autoimmune pathways are known to be pathogenic. The most important characteristics of IgG4-RD are increased serum IgG4 concentration, a number of IgG4 positive plasma cells in affected tissues, painless swollen affected organs and blood plasmablasts. IgG4-RD has distinct pathological features, which are also critical for the diagnosis. It includes lymphoplasmacytic infiltration especially positive for IgG4 immunohistochemistry (IHC), storiform fibrosis, obliterative phlebitis and eosinophilic hyperplasia. Although tissue biopsy findings are critical for the diagnosis, there is no reported case about bone marrow (BM) involvement of IgG4-RD. Therefore, we present a case of 63-year-old man diagnosed to have BM involvement of IgG4-RD which had been previously diagnosed by the kidney biopsy, His peripheral blood (PB) showed leukocytes 16,500/uL, hemoglobin 12.2 g/dL, platelet 45k/uL, eosinophil 51% and rare nucleated red cells (1/100 WBC). Plasma cell count (%) on BM aspirates was 16.8% and CD138 IHC revealed increased plasma cells with interstitial and nodular infiltration pattern. CD79a IHC was also turned out to be positive on increased plasma cells and few B-cells. IgG4 IHC showed the positivity of increased plasma cells on the both of BM biopsy and clot section. Moderate eosinophilic hyperplasia was also noted. We underwent the flow cytometric immunophenotyping with BM aspirate and PB. The atypical plasma cells of BM aspirates were brightly positive for CD38, negative to dimly positive for CD138, negative for CD56, intermediately and brightly positive for CD19, and positive for CD45. The atypical plasma cells were also identified in the blood (0.3760% among leukocytes). We suggest that BM evaluation with immunophenotyping including IgG4 IHC might be needed to diagnose IgG4-RD, especially for the patients with abnormal blood cell counts.

Keyword: Igg4-Related Disease, Bone Marrow, Immunophenotyping, Atypical Plasma Cells, Eosinophils

PP-192

Etiology, sensitivity profiles, clinical course of bloodstream infections in patients with hematological and oncological diseases

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Background: Blood stream Infections（BSI）are serious complications in hematology-oncology patients. This study aimed to analyze the prevalence of BSI, the positive rate of blood culture, the distribution of pathogen, sensitivity profiles, and the outcome of antimicrobial therapy in pediatric patients.

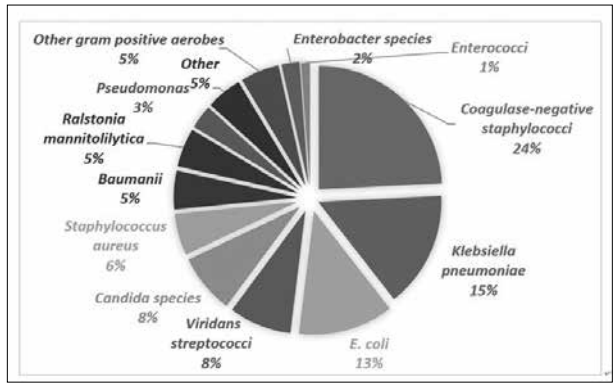
Methods: BSI of all patients admitted to pediatric hematology-oncology unit between January 2016 and December 2017 were reviewed. The data retrieved from the medical records included sex, age at the infection day, primary diseases, white blood cell count, neutropenia, level of C-reactive protein (CRP), procalcitonin, fibrinogen, D-Dimer and microbiology results of all clinical specimens. The incidence, laboratory and microbiology characteristics, poor outcome, and effectiveness of antimicrobial therapy were analyzed.

Result: There were 125 cases of BSI in 108 patients (mean age, 5.5 years), including 69 (55.2%) cases of nosocomial BSI. The overall rate of BSI in hematology and oncology unit was 18.8%. Ninety four（75.2%）episodes occurred in neutropenic patients. The age of patients was older in nosocomial BSIs and neutropenic group (p=0.018, p=0.034). HSCTs and AML were seen more often in nosocomial BSIs than in non-nosocomial BSIs. Solid tumors were seen more often in non-nosocomial and non-neutropenic BSIs. A total of 295 organisms (42 kinds) were isolated from 5,162 blood samples collected during the 2 study years, positive rate of blood culture was 5.8%. Gram-negative BSIs slightly predominated in hematology and oncology unit, but the most common pathogens were coagulase-negative staphylococci (CoNS 24.2%) followed by Klebsiella pneumonia (15.2%), Escherichia coli (12.5%), Viridans streptococci(8.2%) and Candida species (7.8%). (see Fig. 1). Procalcitonin was higher in gram-negative BSIs compared to gram-positive BSIs(P=0.001). There were no statistical differences in white blood cell count, neutropenia, level of CRP, fibrinogen and D-Dimer between gram-negative BSIs and gram-positive BSIs. The mortality of BSI was 6%. Antibiotic therapy was effective in 94% BSIs. The causative pathogen of death was E. coli（2/7）, Baumanii(2/7), Staphylococcus aureus(1/7), Bacillus cereus(1/7) and Candida tropicalis(1/7). All Gram-positive bacteria were susceptible to vancomycin, which was added to the empirical antibiotic therapy in case of persistent fever. CoNS were often resistant to many antibiotics, including penicillin, amoxicillin, amoxicillin/clavulanate, erythromycin, cotrimoxazole and azithromycin, but sensitive to gentamicin, rifampicin and levofloxacin. Viridans streptococci were susceptible to amoxicillin, but resistant to penicillins. The resistance rates of the gram-negative bacteria to ceftazidime, imipenem, piperacillin/tazobactam and aminoglycosides were low.

Conclusions: Gram-negative BSIs slightly predominated among pediatric hematology-oncology patients. CoNS and Klebsiella pneumoniae were the most common pathogens. Antibiotic therapy was effective.

Keyword: Children, Blood Stream Infection, Susceptibility, Hematology and Oncology, Etiology

Figure 1. Most common pathogens causing bloodstream infection in patients admitted in hematology and oncologyunit, Shenzhen Children's Hospital, China, 2016–2017.



PP-193

Evaluation of neutrophil extracellular traps as the circulating marker for patients with cardiocerebrovascular diseases

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Background: The neutrophil extracellular traps (NETs) are known to be induced by various factors such as microorganisms, antibodies, activated platelets and reactive oxygen species. In this study, we tried to identify circulating levels of the NETs in patients with cardiocerebrovascular disease and to confirm its suitability as a new circulating marker in detecting them.

Methods: We prospectively enrolled 95 patients with a diagnosis of acute coronary syndrome (ACS) (N=37) or acute ischemic stroke (AIS) (N=58) in Dong-A University Hospital, Busan, Korea. The control group was selected from healthy adults (N=25) who visited the hospital for health screening. The circulating levels of the NETs were evaluated by measuring plasma concentrations of double-stranded DNA (dsDNA) and DNA-histone complex. The dsDNA concentration was measured using a Synergy™ H1m

Hybrid Multi-Mode Microplate Reader (BioTek, Winooski, VT, USA) with Quant-iT™ PicoGreen® dsDNA reagent and kit (Molecular Probes, Eugene, OR, USA) and was analyzed in comparison with other clinical and laboratory markers. The DNA-histone complex was measured using a VersaMax™ Microplate Reader (Molecular Devices, Sunnyvale, CA, USA) with Cell Death Detection ELISAPLUS (Roche Diagnostics GmbH, Mannheim, Germany).

Result: The results of dsDNA concentrations for the enrolled patients with ACS or AIS and the control group were 743.28±323.10 pg/μL, 524.22±370.06 pg/μL, and 216.48±140.43 pg/μL, respectively. The concentrations of dsDNA were statistically higher in patients with ACS or AIS than those in the control group (both P<0.001). In the univariable and multivariable analyses, statistically significant risk factors were troponin I (TnI) level and dsDNA concentration in the ACS group (P=0.046 and P=0.015, respectively), and only dsDNA concentration in the AIS group (P=0.002). In the receiver operating characteristic curve analyses, the area under the curve values for TnI level and dsDNA concentration in the ACS group were 0.878 and 0.968, respectively, and the value for dsDNA concentration in the AIS group was 0.859. The measured values of DNA-histone complex in the ACS and AIS groups were not statistically different from those in the control group (P=0.364 and P=0.830, respectively).

Conclusions: The analysis of NETs in patients with cardiocerebrovascular disease has not been well studied; therefore, there are limitations for application to clinical fields. In this study, it was confirmed that the circulating level of the NETs increases in patients with ACS or AIS at initial presentation. Findings in this study show that the NETs could be used as a new circulating marker for the initial diagnosis of cardiocerebrovascular diseases, but further studies should be performed in this area.

Keyword: Neutrophil Extracellular Traps, Circulating Marker, Platelet Activation, Acute Coronary Syndrome, Acute Ischemic Stroke

PP-194

Current status of Korea Leukemia Bank

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Background: The Korea Leukemia Bank (KLB), one of the Korean National Research Resources Bank, was established in 2002. The KLB has developed diagnostic methods to acquire the fundamental information about leukemic cells from Korean patients, and equipped the information network to support the research projects in other laboratories. Aims of the KLB are to 1) establish and manage a synthetic leukemic cell and gene bank for the purpose of leukemia and cancer researches equipped with efficient information network, as it simultaneously 2) maximize the usage of material by developing new diagnostic methods to acquire the basic and distinctive information of leukemic cells in Korean population, that 3) construct an internationally competitive research foundation to perform multiple leukemia and cancer research.

Methods: The KLB has collected, preserved and characterized human leukemia cells and genome research biomaterials using conventional diagnostic methods such as cytogenetics, FISH, flow cytometry. In addition, the KLB has developed diagnostic metheds, ie, multiparametric flow cytometry, real-time quantitative PCR, and cDNA microarray.

Result: The KLB currently maintains a collection of over 100,000 specimens that have been isolated from Korean leukemic patients since 2002. The collection consists of three categories: Mononuclear Cells, Total RNA, and Genomic DNA. The KLB has distributed approximately 4,000 specimens to many other institutions: Domestic institutes, foreign institutes, corporations, pharmaceutical companies and university laboratories.

Conclusions: The utility of human leukemia cells and genome research biomaterials have contributed to about 30 publications, 16 patents and 6 technology transfers. It has also lead to new collaborations between us and academic and research institutions as well as the pharmaceutical industry. Their utilisation has also facilitated the successful application of research funding both from industry as well as national research funding agencies.

Keyword: Resources Bank, Leukemic Cell, Distribution

PP-195

A report of a new NFKB1 frameshift mutation contributing to primary immunodeficiency diseases

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Background: Primary immunodeficiency diseases (PID) are caused by gene defects that impair function of the innate or adaptive immune systems. An increasing number of patients have been identified with a causative monogenic defect. Heterozygous variants of NFKB1 cause a progressive defect in formation of immunoglobulin-producing B cells.

Methods: A patient with a 20-year history of diarrhea was recently hospitalized due to three months of interrupted fever. We highly suspect that he has primary immunodeficiency and collected blood samples from all family members to identify the gene mutation. The patient's father (I.2) died early and his mother (I.1) died of cerebral infarction this year. The patient has two brothers and two sisters. One brother (II.1) died of tuberculosis, the other (II.4) is healthy. One sister (II.3) died of stomach cancer, the other (II.2) has a history of left breast cancer. His son (III.1) is clinically asymptomatic. His wife (II.6) is healthy (Figure 1). We evaluated complement components and quantified immunoglobulin levels of the family members, and determined the B cell ratio of the patient. Next, we performed whole exon sequencing by next-generation sequencing and predicted the protein structure of the mutant gene.

Result: The patient has severely decreased levels of serum IgG, IgA, and IgM. His son has moderately reduced IgG levels, while others' immunoglobulin is normal. The patient's lymphocyte phenotyping suggests a decreased proportion of B lymphocytes (Table 1). Next-generation sequencing revealed all known gene mutations of this family. Using Phenolyzer software, we selected three candidate genes: RAG1, C2, and NFKB1. The patient (II.5), his sister (II.2), and his son (III.1) all have a heterozygous mutation of RAG1. Thus, we ruled out RAG1, as it does not conform to Mendel's laws in this family. C2 was also excluded due to the low haploinsufficiency score (0.178). Interestingly, the patient (II.5) and his son (III.1) both have a heterozygous mutation of NFKB1, while others do not. NFKB1 shows a high haploinsufficiency score (0.945), suggesting that the single functional copy of the gene may not produce enough protein. Thus, we hypothesize that NFKB1 is the disease-causing gene in this family. Further investigation revealed a heterozygous NFKB1 frameshift mutation (c.2053delG: p.G685fs) in the patient and his son. The novel frameshift mutation influences three transcriptomes with a similar coding sequence to the NFB1 gene. The NFKB1 gene consists of four regions. Our prediction of the protein structure suggests that the frameshift mutation occurred in the ankyrin repeats region. This mutation resulted in a loss of 283 amino acids and addition of 40 new amino acids. Prediction of the tertiary structure illustrated that the coding protein is terminated early. This is a novel mutation of NFKB1 that has not previously been reported in PID, and which forms a new protein structure (Figure 2).

Conclusions: Our findings broaden the scope of phenotypes caused by mutations in NFKB1. We suspect that this heterozygous mutation of NFKB1 may lead to fewer immunoglobulins produced. Onset was delayed for this patient, at the age of 20. His son is 25 years old now, with moderately reduced levels of IgG but without symptoms. We suspect that he may be ill in the future and recommended that he seek genetic counseling when he is ready to have a child.

Keyword: Primary Immunodeficiency Diseases, NFKB1, Frameshift Mutation

Table 1. Immunoglobulin and complement components levels of the family members, and lymphocyte subgroup ratio of the patient.

	Proband (II.5)	Son (III.1)	Sister (II.2)	Brother (II.4)
IgG (7-16g/L)	0.13	6.95	11.8	10.00
IgA (0.7-4g/L)	<0.26	1.51	2.17	3.05
IgM (0.4-2.3g/L)	<0.181	1.430	1.590	0.834
C3 (0.9-1.8g/L)	0.89	1.27	1.49	0.97
C4 (0.1-0.4g/L)	0.201	0.303	0.400	0.326
$CD3^+$ (55-80%)	90.0			
$CD3^+CD8^+$ (15-30%)	46.64			
$CD19^+$ (6-18%)	3.90			
$CD56^+CD16^+$ (8-12%)	5.58			

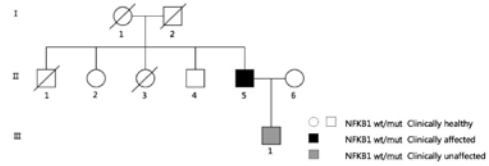

Figure 1. Pedigree of familial NFKB1 case.

Figure 2. Part of tertiary structure predictions of wild-type and mutant NFKB1. a. Part of tertiary structure prediction of wild-type NFKB1. b. Part of tertiary structure prediction of mutant NFKB1. c. Comparison of tertiary structure predictions of wild-type and mutant NFKB1.

PP-196

A case of occult macrophage activation syndrome that mimics of refeactory kawasaki disease

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Background: KD is an acute vasculitis predominantly occurring in children from 6 months to 5 years characterized by fever, conjuctivitis, polymorphous exanthema, cracked lips, changes in extremities, and cervical lymphadenopathy with predisposition to involved coronary ateries. MAS is an inflammatory reaction generated by excessive cytokine production, macrophage activation, and hemophagocytosis. MAS mainly presents with prolonged fever, rash, hepatosplenomegaly and hallmark features that include liver dysfunction, elevated lactate dehydrogenase (LDH), coagulopathy, hypofibrinogenemia, hyperferritinemia, hyertriglyceridemia, and pancytopenia. Among rheumatic disorder, MAS occurs most frequently in systemic juvenile idiopathic arthritis (sJIA) and has a 10% mortality risk. In recent years, this syndrome has been increasingly reported n patients with other rheumatic disorders such as KD.

Methods: We report a case of occult MAS that mimics of refractory KD. A 3-year old boy had been diagnosed as a KD and treated with IVIG (2g/kg/day) for 3 times, however, he had persistent fever. Despite the threatment, he has been transferred to a university hospital because of his continued fever.

Result: Laboratory data on his arrival at university hospital. WBC 39,400/mL Hb 8.6g/dL platelet 562,000/mm3 ESR 91mm/hr CRP 107.66mg/L procalcitonin 15.50ng/mL Iron 3 ug/dl TIBC 238ug/dl ferritin >2,000ng/mL Triglyceride 119mg/dl Fibrinogen 719mg/dL AST 45 IU/L ALT 17 IU/L LDH 904 IU/L Protein 7.9g/dl albumin 3.5g/dl Chest CT : diffuse GGO lesion in left lower lobe and right small pleural effusion. Multile enlarged enhancing lymph node both axillae. Abdomen CT : multiple small or mildly enlarged on mesenteric lymph nodes. Bone marrow biopsy : hypercellular marrow with increased of granulocytic precursors. Granulocytic reactive marrow. The EKG and echocardiogram were unremarkable.

Conclusions: The pulse methylprednisolone (30mg/kg/day) for 3 consecutive days with resolution of the fever. And the patient continued treatment with oral PD and cyclosporine. Laboratory data after MPD pulse WBC 11,400/mL Hb 10.6g/dL platelet 449,000/mm3 ESR 37mm/hr CRP 23.14mg/L procalcitonin 1.50ng/mL ferritin 599mg/mL LDH 695 IU/L The clinical and laboratory findings of occult MAS and KD are overlapped. Furthermore, histopathologic features of hemophagocytosis may not be present during the initial stages. MAS can result in progressive multiogan failure and fatal outcomes if not recognized, early recognition of MAS is often challenging given the lack of a single pathognomic clinical or laboratory features. They are treatedpromptly suggesting that they may have hadearly stage of MAS. If persistent fever and rash are observed in patient with IVIG, occult MAS should be considered. The question is occult MAS a rare and potentially fatal complication of Kawasaki disease?

Keyword: Macrophage Activation Syndrome, Refractory Kawasaki Disease

PP-197

Cutaneous manifestation among transfusion patients

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Background: The acute blood transfusion reactions are responsible for causing most serious adverse events. Awareness about various clinical features of acute and delayed transfusion reactions with an ability to assess the serious reactions on time can lead to a better prognosis

Methods: Aims: To find out the common adverse effects on blood transfusion Patients having cutaneous and after blood transfusion case reports during 2017Jan-2018 March. Total number of patients were 21. Among them 10 males and 11 females.

Result: Among them four percent had mild reactions (agitation, sweating, pallor, cold feeling, sense of weakness, nausea, pain in transfusion site), and only 3(1 males and 2 female, had more severe disorders, including urticaria with angioedema, ecchymossis, vomiting, loss of consciousness, and convulsive syncope.

Conclusions: Acute adverse reaction are although uncommon but we have to follow Evidence based management of it which helps to reduce mortality. creating awareness about haemovigilance by conducting continuing medical education (CMEs), and training to healthcare professionals would lead to improvement in reporting of transfusion reactions. Complacency and ignorance were the main factors which discouraged transfusion reaction reporting by doctors. Increasing awareness of haemovigilance

among doctors and training on reporting transfusion reactions would likely improve spontaneous reporting and help to strengthen the blood transfusion system

Keyword: Transfusion Blood, Skin, Reaction, Awareness, Developing Country

PP-199

Dipeptidyl peptidas-IV inhibition and hematological effect of alkaloids rich withania somnifera extract in type 2 diabetic mellitus; In-Vitro, In-Vivo

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Background: A novel approach in the treatment of type 2 diabetes mellitus (T2DM), based on incretin hormone which regulated by Dipeptidyl peptidase–IV (Dpp-IV). As such, we hypothesized that treatment of diabetes with DPP-IV inhibitors along with hematological effects from isolated alkaloids rich Withania somnifera (WS) extracts with different approached in-vitro; in-vivo; ex-vivo and tissue histology

Methods: Effects of DPP-IV inhibitors from WS in high sucrose diet along with dexamethasone induced T2DM was explored in-vivo in rat. Apart from serum glucose; DPP-IV inhibition activity, HbA1c, Insulin, hepatic and renal lipid peroxidation (LPO), superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) were measured with lipid profiles to correlate hematological effects of WS with tissue histology

Result: High sucrose diet with Dexamethasone administration (1 mg /kg BW 45 days) increased concentration of serum glucose, triglyceride, cholesterol and tissue LPO (renal, hepatic) with concomitant initial increase in tissue antioxidant to scavenging free radicals but after some time antioxidants such as SOD, CAT, GSH was decreased. However, after administration of alkaloid extract of WS, (in-vitro) DPP-IV inhibition increase in WS (74.39%), as compared to Sitagliptin (93.16%) with significant reduction in levels of glucose, TC, TG and the hematological parameters were remained unaltered except platelet count and TLC

Conclusions: DPP-IV inhibitors isolated from WS are novel antidiabetic agents with hematological protective effects in addition to their antioxidant properties. DPP-IV inhibition lower blood glucose by increasing endogenous levels of glucagon-like peptide-1, an incretin with fewer side effects.

Keyword: Dipeptidyl Peptidase –IV, Type 2 Diabetic Mellitus, Antioxidant, Hematology, Incretin

PP-200

Production of a chemotherapeutic enzyme drug for acute myeloid leukemia and acute lymphoblastic leukemia: L- asparaginase

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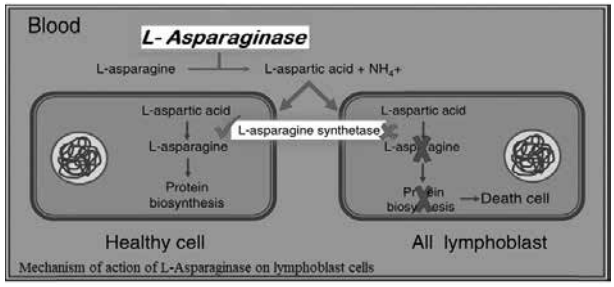
Background: L- Asparaginase is used as chemotherapeutic agent in treatment of Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML) and non-Hodgkin's lymphoma. The enzyme kills tumor cells by converting asparagine into aspartate. Tumor cells are lacks enzyme to synthesize the non-essential amino acid asparagine. Whereas, normal cells does. The present study was aimed at production of L-asparaginase using efficient microorganism.

Methods: Modified czapek Dox medium and modified M9 medium were used for screening of fungal and bacterial strains respectively. Two fungal and two bacterial species were screened for the production. Solely selected fungal strain was studied for production of L-asparaginase in sesame and coconut mixture oil extracted cake.

Result: Aspergillus niger ATCC 6275 exhibited significant variation in the production of L-Asparaginase in the influence of temperature, pH and carbon sources. The enzyme activity recorded was maximum at 72 hours of incubation period with an activity of 1.13 IU/ml of enzyme. The optimum pH and temperature for maximum enzyme production were 9 and 40°C respectively. Molasses (0.5%) proved to be the best carbon source for production of L-Asparaginase.

Conclusions: Aspergillus niger ATCC 6275 could be optimized for industrial scale production of L-Asparaginase. Cheap medium sources like oil-mill waste and molasses may be used for a cost effective production of this anti-cancer drug.

Keyword: Lymphoblastic Leukemia, Myeloid Leukemia, L-Asparaginase, Aspergillus Niger



Mechanism of action of L-Asparaginase on lymphoblast cells

PP-201

Factors associated with quality of life in patients with leukemia

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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.

Methods: 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.

Result: 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).

Conclusions: 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

PP-202

Systematic literature review and assessment of health-related quality of life in aggressive non-Hodgkin lymphoma survivors

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Background: Patients with aggressive non-Hodgkin lymphoma (NHL) treated with standard treatment regimens with substantial impact on patients' quality of life. However, several measures have been developed to assess the patients' health-related quality of

life (HRQoL) from diagnosis through survivors and still a comprehensive overview of their measurement properties is lacking. Therefore, this systematic literature review aimed to summarizes the current literature, which measuring the HRQoL of long-term survivors of aggressive NHL.

Methods: A systematic literature search was performed in PubMed/Medline to retrieve all the English articles published between January 2010 to November 2018. The eligible studies measure the HRQoL at least 2 years after NHL diagnosis. To evaluate the methodological quality of studies on measurement properties of HRQoL using the COSMIN checklist (COnsensus-based Standards for the selection of health status Measurement INstruments).

Result: Of 437 identified articles, a total of 11 studies met the inclusion criteria. Five different HRQoL instrument; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30), Functional Assessment of Cancer Therapy: General (FACT-G), Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym), Short Form Health Survey (SF-36, 12), and EuroQol five dimensions' questionnaire (EQ-5 D) used across the studies. None of the HRQoL instruments described the satisfactory results for all measurement properties. Majority of instruments received positive ratings for construct validity and content validity. Only two studies were tested adequately for internal consistency (Cronbach's alpha(s) ≥ 0.70) and reliability and had positive results. Responsiveness was not tested adequately for any of the instruments. Overall, the (EORTC) QLQ-C30, followed by the FACT-G and the FACT-Lym, reported to the best ratings for their measurement properties.

Conclusions: The current review identified several measurement instruments; however, the majority of measurement properties had not yet been adequately evaluated. Further well-designed studies with transparent reporting of methods warrant to support the use of HRQoL measures.

Keyword: Non-Hodgkin Lymphoma, Long-Term Survival, Health-Related Quality of Life, HRQoL, COSMIN

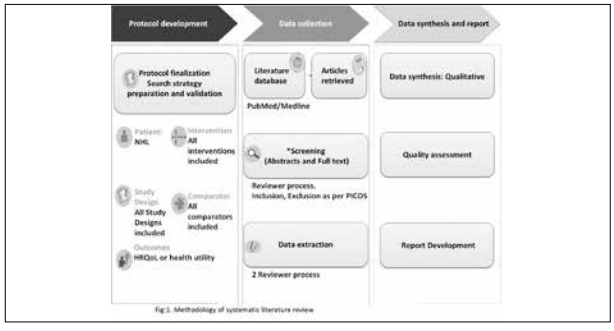

Fig 1. Methodology of systematic literature review

PP-203

Psychosocial counseling for prevention of sickle cell in a tribal population

Suresh Gemawat

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Background: The tribal communities with sickle cell disease constitute 0.9 to 1.3% in many part of India. Sickle cell disease is genetically transmitted hemo-globinopathy, Due to geographical and social barriers, relatively few primary and specialty care health facilities exist in tribal areas, With a large population, burgeoning birth rate, and consanguineous marriage practices, Epidemiological studies confirmed that sickle cell anemia is rampant in the tribal populace, the prevalence of homozygotes for the sickle gene calculated to be over 20% with an estimated five million individuals predicted as carriers. It is recommended that genetic health services be integrated The goal of preconception counseling is to identify potential or actual medical, psychological, or social conditions but inspite of great screening and therapeutic done by government primary health care and medical services fails prevent and combat the epidemic. We conducted health education in some Garasia tribal communities during their festive auspicious day of Akateez and parted psychoocial aspect of genetic premarital counseling session for young pre nuptial population

Methods: On the day of Akhateez, there are many marriages in the tribal Garacia belt of Sirohi. We talked on the sickle cell disease and counseling sessions were taken with the pre nuptial youths about the genetic counseling, its benefits to the community

Result: The youth were very eager and well appreciative about the screening and therapeutic well planned program of government health sevices. Our main objective to put forward psychosocial aspect in preventing consanguineous marriage counseling wa well perceived and accepted.

Conclusions: The prevalence of sickle cell disease a haemoglobinopathie is common worldwide, but the humen race is suffering differently because of various geographical and environmental and genetic factors. Preventing its spread by proper genetic counseling, with further genetic engineering may be a win win situation for the betterment of humanity .Our aim of putting forward pychosocial counseling during auspicious day of Akhateez wa to put forward a health education on largecommunity base. More large scale counseling session are sure to benefit in differet part of world and more scientific studies may be done

Keyword: Psychosocial Counselling, Sickel Cell, Tribal Community

PP-204

Incidence of cancer incidence in India: A analysis from cancer registries

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Background: Burden of cancer incidence in India is considerable. Cancer leads not only humanistic economic burden but also impact the healthcare system. It decreases both the quality and quantity of life. So, it is important to understand the cancer incidence in India to deal with this devastating disease.

Methods: We captured the latest available data from the Population-based cancer registries of India. The primary outcome of interest was to compute the crude incidence of cancer during 2012 – 2014, age-adjusted and truncated incidence rate per 100,000 populations. Secondary outcomes were to compute the cumulative incidence rate, cumulative risk. All the analysis was performed using STATA v12.

Result: A total number of 174,693 cancer cases (50% male) were reported during 2012 – 2014 from all the existing population-based registries in India. Aizawl district reported the highest crude incidence rate per 100,000 populations among both male (204.6 cases) and female (160.7 cases). The age-adjusted rate per 100,000 populations in male ranges from 40.9 to 230.4 cases, while in the female it was ranged from 52 to 207.7 cases. Overall, the truncated incidence rate per 100,000 populations ranged from 76.7 cases to 560.6 cases. Risk of developing cancer (cumulative risk) during the life period of 0-64 years of age was lying between 2.8% to 17.9%.

Conclusions: The present study concludes higher incidence of cancer in India. The government should frame policies to tackle the rising incidence.

Keyword: Cancer, Incidence, Epidemiology, Prevalence, India

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ABR; Annualized Bleeding Rate

| Study design | 연구 참여 12개월 이전에 12건 이상의 출혈 경험이 있는 6-65세의 중증 또는 중등증-중증 혈우병 B 환자 50명을 대상으로 베네픽스® 50 IU kg^{-1} 용량 주2회 투여 또는 100 IU kg^{-1} 용량 주1회 투여하는 예방요법과 보충요법의 유효성과 안전성을 비교한 다기관, 무작위 배정, 개방지표 연구.[2]

References **1.** 베네픽스®주 제품설명서(최종변경허가일: 2017년 2월 13일) **2.** Valentino LA, et al. Haemophilia. 2014 May;20(3):398-406 **3.** Pfizer; Data on file. **4.** BeneFIX® (nonacog alfa) Summary of Product Characteristics. March, 2017.

주요 안전성 정보 다른 정맥투여 단백질 제제와 마찬가지로 투여 후, 두통, 발열, 오한, 홍조, 오심, 구토, 기면 외 알레르기 증상 등의 반응이 일어날 수 있습니다. / IX인자 함유 제제로 치료받은 환자에게서 활성 중화항체(억제인자)가 발현될 수 있습니다. 이 약을 사용하는 환자에서 IX인자 억제인자가 발현되는지 모니터링 해야 합니다. / IX인자 억제인자를 지닌 환자의 경우, 차후 IX인자 투여 시 아낙필락시스의 위험성이 증가될 수 있습니다. 알레르기 반응이 나타난 환자에 대해서는 억제 인자 생성 여부를 평가해야 합니다. / 이 약은 동결을 피해야 합니다. 재구성된 약은 3시간 이내에 주사해야 하며 투여 전까지는 실온에서 보관 가능합니다. / IX인자를 함유한 다른 제제에서 관찰된 혈전증과 파종성 혈관내 응고(DIC), 혈전색전성 합병증을 유발할 가능성이 있으므로 간 질환자, 수술 후 환자, 신생아 또는 혈전색전증 및 파종성 혈관내 응고증(DIC)이 있는 환자에게 이 약 투여 시에는 주의해야 합니다.

베네픽스주® 제품요약정보 [제품명] 베네픽스®주(혈액응고인자 IX, 노나코그-알파(유전자재조합)) BeneFIX® Injection(Coagulation factor IX (Recombinant)) **[성분분량]** 표시역가 250IU (1 바이알 중): 노나코그-알파, 혈액응고인자 IX (유전자재조합) / 표시역가 500IU (1 바이알 중): 노나코그-알파, 혈액응고인자 IX (유전자재조합) / 표시역가 1000IU (1 바이알 중): 노나코그-알파, 혈액응고인자 IX (유전자재조합) / 표시역가 2000IU (1 바이알 중): 노나코그-알파, 혈액응고인자 IX (유전자재조합) / 표시역가 3000IU (1 바이알 중): 노나코그-알파 혈액응고인자 IX (유전자재조합) **[성상]** 흰색의 동결건조물이 충진된 바이알에 든 주사제이며, 첨부용제로 용해시 입자가 없는 맑고 무색투명한 액 **[효능·효과]** 혈우병 B(선천성 IX인자 결핍증 또는 크리스마스병(Christmas disease) 환자의 출혈 에피소드(episodes)의 억제 및 예방(외과적 수술 시 출혈억제 및 예방 포함) **[용법·용량]** 이 약은 혈우병B에 대한 치료경험이 있는 의사의 감독하에 투여하여야 합니다. 이 약을 포함한 모든 IX인자 제제는 각 개인에게 맞는 용량으로 투여하여야 합니다. 모든 IX인자 제제의 용량 및 투여 기간은 IX인자 결핍 정도, 출혈 부위 및 범위, 환자의 임상적 상태에 따라 결정됩니다. 이 약의 투여용량은 혈장 유래 IX인자 제제의 투여용량과 다를 수도 있습니다. 특히 수술의 경우, 요구되는 IX 인자 활성농도를 확보하기 위해서는 IX인자 활성평가를 이용한 정확한 모니터링을 해야 합니다. 투여용량을 적절히 조절하기 위해서는 환자의 임상적 상태뿐만 아니라 IX인자 활성도, 약력 학적 인자반감기 및 회복 수치를 고려하여야 합니다. **[용량계산식]** IX 인자의 IU 요구량(IU) = 체중(kg) x 요구되는 IX인자 증가치(% 또는 IU/dL) x 측정한 회복 수치의 역수(IU/dL당 IU/kg) 단, 억제인자가 존재할 경우는 더 많은 용량이 요구될 수도 있습니다. **[사용상의 주의사항]** 1. 다음 환자에게는 투여하지 말 것 1) 이 약 성분에 과민반응의 병력이 있는 환자 2) 햄스터 단백질에 과민반응의 병력이 있는 환자 2. 다음 환자에게는 신중히 투여 할 것 1) 과민반응: 이 약을 포함하여 모든 IX인자 제제에 대해 아나필락시스를 포함한 알레르기 형태의 과민반응이 보고되었습니다. **[이상반응]** 아래는 이전 치료경험이 있는 환자 및 이전에 치료를 받은 적이 없는 환자에 대한 임상시험에서 보고된 이상반응과 시판 후 사용에서 확인된 이상반응입니다. 매우 흔하게(≥1/10): 두통, 기침, 구토, 발열 / 흔하게(≥1/100~<1/10): IX인자 억제, 과민반응, 어지러움, 미각 이상, 정맥염, 저혈압, 홍조, 구역, 발진, 두드러기, 가슴불편감, 주입부위반응, 주입부위 통증 **[일반적 주의]** 1) 혈전증: II, VII, IX, X 인자를 함유한 사람 혈장 유래 IX인자 복합농출물의 투여는 병력적으로 혈전 색전성 합병증의 발생과 관련되어 있었습니다. 2)활성-중화항체(억제인자): IX인자를 함유한 제제로 치료받은 환자에게서는 활성 중화항체(억제인자)가 발견되었습니다. ※제품에 대한 자세한 정보는 최신의 제품설명서를 참고하시기 바라며, 홈페이지(www.pfizer.co.kr)를 통해 확인하실 수 있습니다. **[개정년월일]** 2017.02.13

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Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America[1]

What Is the Treatment for Candidemia in Nonneutropenic Patients?

Recommendations

1. An echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) is recommended as initial therapy (strong recommendation; high-quality evidence).
2. Fluconazole, intravenous or oral, 800mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have afluconazole-resistant Candida species (strong recommendation; high-quality evidence).

■ KOREAN REIMBURSEMENT GUIDELINE (updated 2015-134호)[2]

A. Candida infection
–proven invasive candidiasis Reimbursed in case of severe patients or azole pre-treated patients
B. Candida prophylaxis
–prophylaxis reimbursed in HSCT patient

■ INDICATION, DOSAGE AND DRUG PRICE[3]

1. Treatment of Patients with Candidemia, and Candidiasis		
Adult	2 vials 100mg/day	91,584 KRW/day
Pediatric	2 mg/kg/day (maximum 100mg daily)	
2. Treatment of Patients with Esophageal Candidiasis		
Adult	3 vials 150mg/day	137,376 KRW/day
Pediatric 30kg or less	3 mg/kg/day	
Pediatric greater than 30kg	2.5 mg/kg/day (maximum 150 mg daily)	
3. Prophylaxis of Candida Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation		
Adult	1 vial 50mg/day	45,792 KRW/day
Pediatric	1 mg/kg/day (maximum 50 mg daily)	

- A loading dose is not required. Infuse over 1 hour.
- Mycamine is indicated in adult and pediatric patients 4 months and older.

Reference: 1. IDSA 2. 보험 고시 2015-134호 3. 마이카민 제품설명서, 2015.12.09

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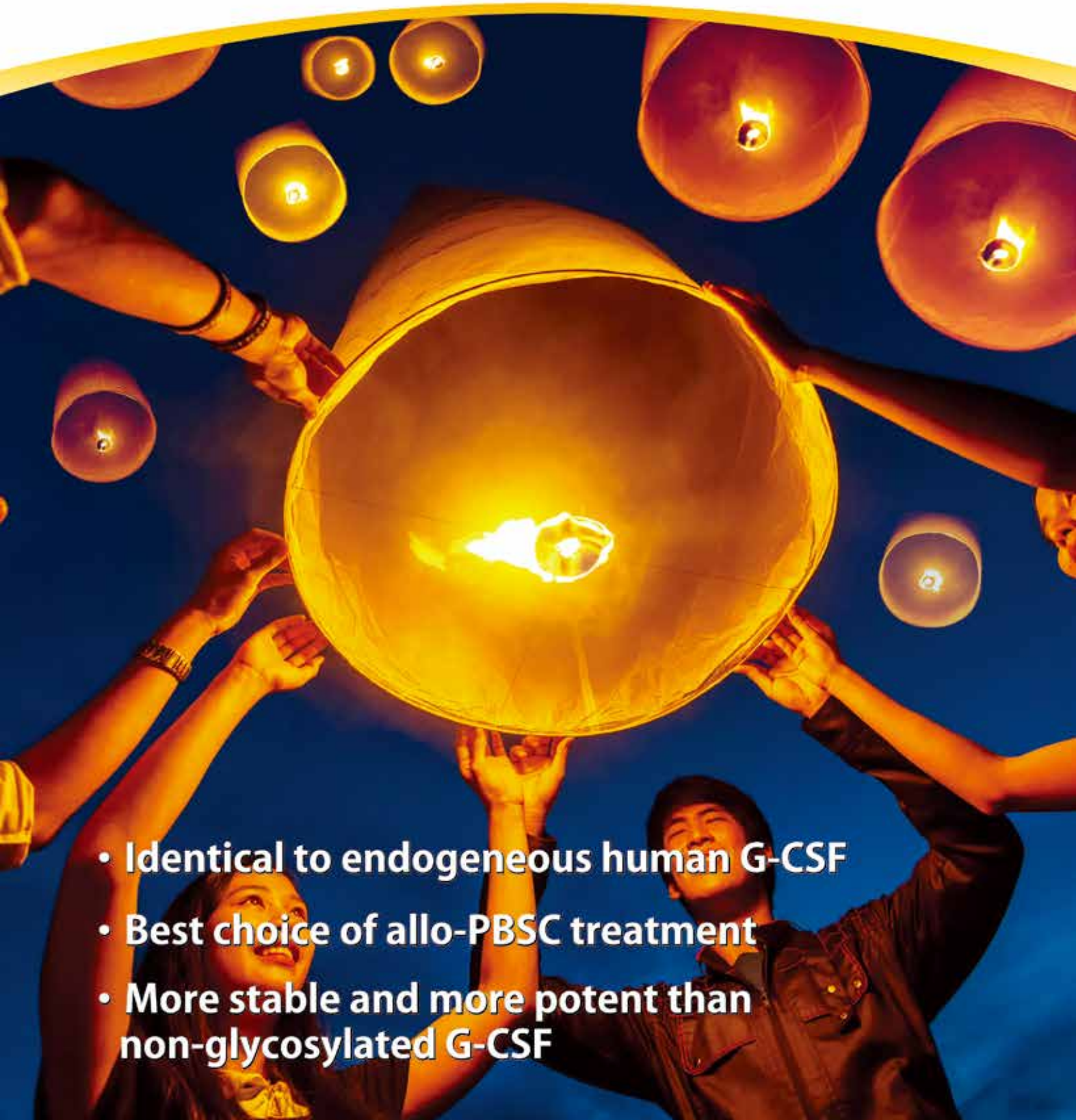

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REVLIMID® and POMALYST® are foundation treatments in Multiple Myeloma[1-6]

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Reference 1. Facon T et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018; 131(3):301–310. 2. Mc Carthy PL et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. J Clin Oncol. 2017 Oct 10;35(29):3279–3289. 3. Quach H et al. Mechanism of action of immunomodulatory drugs (IMIDS) in multiple myeloma. Leukemia. 2010 Jan;24(1):22–32. 4. Moreau P et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv52–iv61. 5. San Miguel JF et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica. 2015 Oct;100(10):1334–9 6. Raab MS et al. Multiple myeloma: practice patterns across Europe. Br J Haematol. 2016 Oct;175(1):66–76.

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Selected prescribing information

전문의약품

[제품명] 솔리리스주 **[조성]** 바이알(30mL)당 에쿨리주맙 300mg **[효능·효과]** **1) 발작성 야간 혈색소뇨증(PNH : Paroxysmal Nocturnal Hemoglobinuria)** 혈혈을 감소시키기 위한 발작성 야간 혈색소뇨증(PNH) 환자의 치료. 수혈 이력과 관계없이, 높은 질환 활성을 나타내는 임상 증상이 있는 환자의 유형에 관상적 이익이 확립되었다. **2) 비정형 용혈성 요독 증후군(aHUS : atypical Hemolytic Uremic Syndrome)** 보체 매개성 혈전성 미세혈관병증을 억제하기 위한 비정형 용혈성 요독 증후군(aHUS) 환자의 치료 **[용법·용량]** 심각한 감염에 대한 위험을 줄이기 위해서 환자들은 최신의 백신 접종 지침(Advisory Committee on Immunization Practices(ACIP) recommendations)에 따라 백신 접종을 해야 한다. 혈액투석(HD)이 한다. 6분간 • 용량 4회 참고. **1) 권장 용법·용량 - 발작성 야간 혈색소뇨증(PNH)** - 첫 4주간은 매 7일마다 600 mg을 투여한다. - 네 번째 용량 투여 7일 후에 다섯 번째 용량으로 900 mg을 투여하고, - 그 후부터는 매 14일마다 900 mg을 투여한다. 이 약은 생장 투여량과 일정에 맞게 투여, 혹은 예장된 혈장의 2일 전후로 투여되어야 한다. 적어혈성 교환 요법(plasma exchange 또는 plasmapheresis), 또는 신선 동결 혈장 투여(fresh frozen plasma infusion)와 같은 부수적 치료를 받는 경우 추가 용량 투여가 필요하다. **[사용상의 주의사항] 1. 경고** 수막구균 감염 위험 기한으로 인하여 이 약의 사용은 수막구균 감염에 대한 환자의 감수성을 증가시킨다. 이 약의 투여 환자에게서 치명적이고 생명을 위협하는 수막구균 감염이 발생하였다. 수막구균 감염은 어느 혈청군에 의해서도 발생할 수 있지만, 이 약의 투여 환자들은 혈청군Y로 등의 의한 질환이 빈생할 수 있다. 감염에 취약성을 낮추기 위하여, 이 약의 치료가 지연됨으로 인한 위험성이 수막구균 감염 질병의 위험성보다 큰 경우를 제외하고는 모든 환자들은 반드시 이 약의 투여 시작 최소한 2주 전에 수막구균 백신을 투여 받아야 한다. 만약 업급을 받지 않은 환자가 긴급히 이 약의 치료를 받아야 하면, 최대한 빨리 수막구균 백신을 투여 받도록 한다. 수막구균 백신 접종 이후 2주 미나 이 약을 투여할 경우, 수막구균 백신 접종 이후 2주 동안 적절한 예방적 항생요법으로 치료 받아야 한다. 혼합 병원성 수막구균 혈청군을 예방하기 위하여 가능하다면 혈청군 A, C, Y, W135, 와에 대한 백신이 권장된다. 환자들은 백신 사용을 위한 최신의 백신 접종 지침(ACIP recommendations)에 따라 백신을 접종 혹은 재접종 받아야 한다. 백신 접종은 보체를 다른 활성화시킬 수 있다. 결과적으로, PNH 및 aHUS를 포함한 모체 매개 질병을 가진 환자들은 폐렴구균(Pneumococcal 감염(예: 폐렴구균(TMA, pneumococcal 감염)과 같은, 그들의 고지 질환에 적절 및 증상이 증가하는 검사를 할 수 있다. 따라서, 지침에 따른 백신 접종 이후 질환의 증상에 대해 면밀히 관찰되어야 한다. 백신 접종은 수막구균 감염 위험을 줄일 수 있지만, 완전히 없애지는 않는다. 처방전 정정계 사용에 대한 공식 지침(예: 국내 없은 세균성 수막염의 임상진단지침 권고안 등)을 고려하여야 한다. 수막구균 감염의 초기에 질환나 증상이 나타나는 지 면밀히 관찰하고, 감염이 의심되면 즉시 검사받아야 한다. 환자는 의사한 질환와 징상 및 즉시 치료를 받는 절차에 대해 어느 한 분야라 하더, 담당 의사는 반드시 환자와 이 약의 치료의 위험과 이익을 상의하여야 한다. 수막구균 감염은 초기에 발견하고 치료하지 않으면 급격히 치명적이고 생명을 위협하게 된다. 중대한 수막구균 감염을 치료하는 환자는 이 약의 투여를 중지하도록 한다. **2. 투여금기** 이 이 약의 주성분 또는 대한 단백질 주는 계열 주성분분에 과민반응이 있는 환자. 고 치료되지 않은 중대한 수막구균(Neisseria meningitidis) 감염 환자. 고 수막구균(Neisseria meningitidis) 백신을 현재 접종하지 않은 환자 또는 백신 접종 이후 2주 동안 적절한 예방적 항생감염으로 치료를 받지 않은 환자(이 약의 치료를 늦추는 경우 수막구균 감염을 일으키는 경보다 중대하지 않은 감우) **3. 신중투여** 1) 기타 감염 적절치료로 인하여 이 약의 치료는 활성 감염 감염이 있는 환자들에게 주의하여 투여하여야 한다. 이 약은 일단 보체 활성을 차단하므로 환자들은 감염, 특히 Neisseria군 및 패상성 세균(encapsulated bacteria) 감염에 대한 감수성이 증가될 수 있다. 피증성 임균 감염을 포함하는 N. meningitidis 외의 Neisseria 종에 의한 중대한 감염이 보고되었다. 정맥투인 중대한 감염과 그 증상 및 징후에 대한 인식을 높이기 위하여 환자용 정보 안내서에 정보를 환자에게 제공해야 한다. 임을 예방에 관해 환자에게 조언해야 하고 위험성이 있는 환자는 정기적인 검사를 권고한다. 이목이, 관절염이 악화된 환자와 호중구 감소 환자에서 아스페르길루스 감염이 발생하였다. 이 약을 투여 받는 소아는 폐렴연쇄상구균(Streptococcus pneumoniae)과 인플루엔자 간균 B형(Haemophilus influenza type b)타입에 의해 중대한 감염을 일으킬 위험이 증가할 수 있다. 폐렴연쇄상구균(Streptococcus pneumoniae)과 인플루엔자 간균 B형(Haemophilus influenza type b)타입에 의한 감염을 예방하기 위해 최신의 백신 접종 지침에 따라 백신 접종을 받도록 한다. 전신 감염이 있는 환자에게 이 약을 투여할 시는 주의하도록 한다. 대골이수막염에 관련되고 유지 요법을 받는 환자에게 추가적인 백신 접종이 필요한 경우, 이 약 투여에 따른 백신 접종 시기를 신중히 고려하여야 한다. 고 실험실적 검사 결과 와 같이 혈액 이상 혈색소뇨증(PNH) : PNH 환자의 혈청 LDH(Lactate dehydrogenase)를 포함한 혈관 내 용혈의 징후 및 증상을 관찰하여야 한다. 이 약으로 치료 받는 PNH 환자는 LDH 수치를 확인하여 혈관 내 용혈을 관찰하여야 하며, 유지기간 동안 권장 투여일정(14~21일) 내에서 용혈 • 용량 조정이 필요할 수 있다(예 12일까지). 비정형 용혈성 요독 증후군(aHUS) : 이 약으로 치료 받는 aHUS 환자는 혈소판 수, 혈청 크레아티닌을 측정하여 미세혈관병증의 이상을 관찰하여야 하며, 유지기간 동안 권장 투여일정(14~21일) 내에서 용법 • 용량 조정이 필요할 수 있다(예 12일까지). **4. 주요 이상반응** 시판 후 보고 및 PNH, aHUS 임상시험에 참여한 302명의 환자에서 보고된 약물이상반응. 매우 흔하게(≥1/10) : 수두, 코인두염, 상기도감염, 바이러스성 기관지염, 구강 헤르페스, 요도 감염, 바이러스성 감염, 혈소판감소증, 백혈구감소증, 두통, 마비돌학시스 반응, 식욕감퇴, 현기증, 미각이상, 치통만, 호흡곤란, 기침, 비충혈, 인후두 통증, 오심, 설사, 구토, 구역, 복부통증, 변비, 소화불량, 발진, 탈모, 소양증, 관절통, 근육통, 근육경련, 뼈통증, 요통, 두 통증, 사지불대리의 통증, 부종, 가슴 불편감, 열, 모든 피곤한, 무력증 인플루엔자 유사질환, 콧소시염 등등. 모든 원상시험에서, 가장 흔하한 이상반응은 수막구균 패혈증이었고, 이는 이 약으로 치료받은 환자에서 수막구균 감염증의 중한 증상이었다. 수막구균 패혈증의 징후와 증상에 대해 환자에게 알리고 즉시 의료 조치 받을 것을 환자에게 권고해야 한다. Neisseria gonorrhoeae, Neisseria lactica / subflava Neisseria spp. unspecified로 인한 패혈증을 포함하여 Neisseria 종의 다른 사례들이 보고되었다. **[제조원]** 알렉시온 **[수입판매원]** 한독㈜ **[최종개정일]** 2018-10-01

ALEXION

(주)한독 서울시 강남구 테헤란로 132 Tel. 02)527-5114 Fax. 02) 527-5001 www.handok.co.kr

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- **CANCIDAS® was an effective antifungal therapy in patients with persistent fever and neutropenia.[1]**
  - CANCIDAS was as effective as liposomal amphotericin B when given as empirical antifungal therapy in patients with persistent fever and neutropenia.[1,a]
- **CANCIDAS® is indicated in adult and Pediatric patients (3 months of age and older) for ;**
  - Empirical Therapy for presumed fungal infections in febrile, neutropenic patients.
  - Treatment of Candidemia and the following *Candida* infections : intra-abdominal abscesses, peritonitis and pleural space infections.[†]
  - Treatment of Esophageal Candidiasis.
  - Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.[‡]

[a] The efficacy and safety of CANCIDAS has not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.[2]
[†] CANCIDAS has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*.[2]
[‡] CANCIDAS has not been studied as initial therapy for invasive aspergillosis.[2]

[a] In this double-blind study, febrile neutropenic (ANC <500 cells/mm³) patients were randomized to treatment with daily doses of CANCIDAS (50 mg/day following a 70-mg loading dose on day 1) or AmBisome (3 mg/kg/day). Primary efficacy analysis was conducted in the MITT population. Patients (N=1,095) were stratified based on risk category (high-risk patients had undergone allogeneic stem cell transplantation or had relapsed acute leukemia) and on receipt of prior antifungal prophylaxis. A total of 26.3% and 22.6% of patients were high risk in the CANCIDAS and AmBisome groups, respectively; 56.3% of patients received prior antifungal prophylaxis in both treatment groups. Patients who remained febrile or clinically deteriorated following 5 days of therapy could receive 70 mg/day of CANCIDAS or 5 mg/kg/day of AmBisome. Treatment was continued until the absolute neutrophil count was at least 500 per cubic millimeter and for up to72 hours thereafter. The on-site investigator determined the duration of therapy for patients with baseline or breakthrough fungal infections; however, it was recommended that treatment be given for at least 14 days and for at least 7 days after neutropenia and symptoms resolved.

The primary end point, overall favorable response, was defined as meeting 5 strictly defined criteria : successful treatment of any baseline fungal infection[b], absence of any breakthrough fungal infection[c] during therapy or within seven days after the completion of therapy, survival for seven days after the completion of therapy, no premature discontinuation of study therapy because of drug related toxicity or lack of efficacy, and resolution o fever (defined as a temperature below 38°C for at least 48 hours) during neutropenia.[1]

[b] Baseline infections were those present on or before day 2 of the study.
[c] Breakthrough infections were those with an onset on day 3 or later.

CANCIDAS® Selected Safety Information

1. CANCIDAS is indicated for : Empirical Therapy for presumed fungal infections in febrile, neutropenic patients. Treatment of Candidemia and the following Candida infections: intra-abdominal abscesses, peritonitis and pleural space infections. CANCIDAS has not been studied in endocarditis, osteomyelitis, and meningitis due to Candida. Treatment of Esophageal Candidiasis. Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies. CANCIDAS has not been studied as initial therapy for invasive aspergillosis. 2. Do not mix or co-infuse CANCIDAS with other medications, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medications. DO NOT USE DILUENTS CONTAINING DEXTROSE (-D-GLUCOSE), as CANCIDAS is not stable in diluents containing dextrose. 3. CANCIDAS is contraindicated in patients with hypersensitivity to any component of this product. 4. Clinical studies in adult healthy volunteers and adult patients show that liver ALT and AST were transient increased when CANCIDAS and cyclosporine were coadminintered (see 1. Wamings). Given the limitations of these data, CANCIDAS and cyclosporine should only be used concomitantly in those patients for whom the potential benefit outweighs the potential risk. Patients who develop abnormal liver function tests during concomitant therapy should be monitored and the risk/benefit of continuing therapy should be evaluated. 5. Possible histamine-mediated symptoms have been reported including reports of rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. Anaphylaxis has been reported during administration of CANCIDAS. 6. Reported clinical and laboratory abnormalities among all adult patients treated with CANCIDAS were typically mild and rarely led to discontinuation. The most common adverse reactions in adults (>1/100) were: pyrexia, headache, chills, nausea, diarrhea, vomiting, elevated liver values, phlebitis, dyspnoea, rash. 7.Reported clinical and laboratory abnormalities among all pediatric patients treated with CANCIDAS were typically mild and rarely led to discontinuation. The most common adverse reactions in adults (>1/100) were: pyrexia, headache, chills, elevated liver values, tachycardia, infusion site pruritus, hypotension, rash, itching. 8.CANCIDAS have drug interaction with tacrolimus, cyclosporine, rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, carbamazepine. 9. Podiatric Use: The safety and effectiveness of CANCIDAS in pediatric patients 3 months to 17 years of age are supported by additional data. The efficacy and safety of CANCIDAS has not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age. 10. Patients with Hepatic Insufficiency: Adult patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment. For adult patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), CANCIDAS 35mg daily is recommended. However, where recommended, a 70 mg loading dose should still be administered on Day 1 (see DOSAGE AND ADMINISTRATION). There is no clinical experience in adult patients with severe hepatic insufficiency (Child-Pugh score >9) and in pediatric patients with any degree of hepatic insufficiency. 11. Patients with Renal Insufficiency: No dosage adjustment is necessary for patients with renal insufficiency.

Before prescribing CANCIDAS, please consult the full Prescribing Information.

References : 1. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med*. 2004;351(14):1391 -1402.
2. CANCIDAS prescribing information, MFDS Korea.

MSD 한국엠에스디(유)

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SYMBENDA is a Reliable Backbone agent with significant activity in malignant lymphoma treatment [1]

Reference: D Genadry et al. Clin Cancer Res 2008;15(24) December 15, 2009

SYMBENDA®injection 25mg, 100mg

[Qualitative and Quantitative Composition] SYMBENDA 25mg API - Bendamustine hydrochloride (in freeze) 25mg SYMBENDA 100mg API - Bendamustine hydrochloride (in freeze) 100mg **[Pharmaceutical Form]** White, lyophilized microcrystalline powder in brown vial Powder for concentrate for solution for infusion **[Therapeutic Indications]** 1. Previously untreated follicular lymphoma in combination with rituximab 2. First-line treatment of chronic lymphocytic leukaemia (Binet stage II or C) in patients for whom fludarabine combination chemotherapy is not appropriate 3. Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment **[Posology and method of administration]** Infusion must be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents. Prior bone marrow function is related to increased chemotherapy-induced hematological toxicity. Treatment should not be started if leukocyte and/or platelet values have dropped to < 3,000/μl or < 75,000/μl, respectively. • For previously untreated follicular lymphoma in combination with rituximab : 90 mg/m² (body surface area) bendamustine hydrochloride on days 1 and 2, rituximab 375 mg/m² on day 1 i.v. every 4 weeks for up to 6 cycles • Monotherapy for chronic lymphocytic leukaemia : 100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2 every 4 weeks. • Multiple myeloma : 120 - 150 mg/m² body surface area bendamustine hydrochloride on days 1 and 2, 60 mg/m² body surface area prednisone i.v. or per os on days 1 to 4, every 4 weeks. Treatment should be terminated or delayed if leukocyte and/or platelet values have dropped to < 3,000/μl or < 75,000/μl, respectively. Treatment can be continued after leukocyte values have increased to> 4,000/μl and platelet values to> 100,000/μl. The leukocyte and platelet Nadir is reached after 14-20 days with regeneration after 3-5 weeks. During therapy free intervals strict monitoring of the blood count is recommended. (see general precautions) In case of non-hematological toxicity dose reductions have to be based on the worst c. T.C.® grades in the preceding cycle. A 50% dose reduction is recommended in case of C.T.C. grade 3 toxicity. An interruption of treatment is recommended in case of C.T.C. grade 4 toxicity. If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle. For special precaution for handling and administration, please refer to "6.6 Special precautions for handling." **[Contraindications]** 1. Hypersensitivity to the active substance or to any of the excipients 2. During breast feeding 3. Severe hepatic impairment (serum bilirubin> 3.0 mg/dl) 4. Jaundice 5. Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3,000/μl or < 75,000/μl, respectively) 6. Major surgery less than 30 days before start of treatment 7. Infections, especially involving leukocytopenia 8. Yellow fever vaccination **Special warnings and precautions for use** 1) Patients with cardiac disorders : During treatment with bendamustine hydrochloride the concentration of potassium in the blood must be closely monitored and potassium supplement must be given when K+ <3.5 mEq/l or <3.5mmol/L and ECG measurement must be performed. 2) Women of childbearing potential : Refer to 'Contraception' of 'General Precautions and Pregnancy and lactation' **Undesirable effects** The most common adverse reactions with bendamustine hydrochloride are hematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting). **[General Precautions]** 1) Myelosuppression : Patients treated with bendamustine hydrochloride may experience myelosuppression. In the event of treatment related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least weekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values> 4,000/μl or> 100,000/μl, respectively. 2) Infections : Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jiroveci pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV). Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 600/μl) and low CD4-positive T-cell (T-helper cell) counts (< 200/μl) for at least 7–9 months after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine is combined with rituximab. Patients with lymphopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections. In case of low CD4-positive T-cell counts (<200/μl) Pneumocystis jiroveci pneumonia (PJP) prophylaxis should be considered. All patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections. Patients with myelosuppression following bendamustine hydrochloride treatment should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms. Cytomegalovirus and herpes virus reactivation have been reported and may occur. Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received bendamustine hydrochloride. Some cases resulted in acute hepatic failure or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with bendamustine hydrochloride. Ex perts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B tests (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with bendamustine hydrochloride should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. 3) Skin reactions : A number of skin reactions have been reported. These events have included rash, severe cutaneous reactions and bullous exanthema. Cases of Stevens – Johnson syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), some fatal, have been re-ported with the use of bendamustine hydrochloride. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Events occurred when bendamustine was given as a single agent and in combination with other anticancer agents or allopurinol. Skin reactions may increase in severity with further treatment. If skin reactions are progressive, Symbenda should be withheld or discontinued. For severe skin reactions where a relationship to bendamustine hydrochloride is suspected, treatment should be discontinued. 4) Nausea, vomiting An antiemetic may be given for the symptomatic treatment of nausea and vomiting. 5) Tumour lysis syndrome : Tumour lysis syndrome associated with Symbenda treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of Symbenda and, without intervention, may lead to acute renal failure and death. Preventive measures include adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels and the use of hypouricemic agents (allopurinol and rasburicase) should be considered prior to therapy. There have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when benda-mustine and allopurinol were administered concomitantly. 6) Anaphylaxis : Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions. Patients who experienced Grade 3 or severe allergic-type reactions were typically not re-challenged. 7) Contraception - Bendamustine hydrochloride is teratogenic and mutagenic. Women should not become pregnant during treatment. Male patients should not father a child during and up to 6 months after treatment. They should seek advice about sperm conservation prior to treatment with bendamustine hydrochloride because of possible irreversible infertility. 8) Extravasation : An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit. 9) Effects on ability to drive and use machines : No studies on the effects on the ability to drive and use machines have been performed. However, ataxia, peripheral neuropathy and somnolence have been reported during treatment with Symbenda. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines. 10) Cardiac Events : Fatal cases of myocardial infarction and cardiac failure have been reported with bendamustine treatment. Patients with concurrent or history of cardiac disease should be observed closely. **[Recent information]** • For more information about this products, please contact Eisai Korea Inc., Tel. 02-3451-5500. • For any revised information of this package insert from printed date, please check homepage of Eisai Korea Inc., (www.eisaikorea.com) or Online drug library(http://drug.mfds.go.kr). **[Importer]** Eisai Korea Inc. 10F Revessant, 86-6 Bongeunsa-ro (Samseong-dong), Gangnam-gu, Seoul, Korea (Package Insert Update: 2018.09.12)

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Eisai

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KR-AMB0048_v1.0(2016.01.25)

AmBisome Injection (amphotericin B liposome for injection)

[Indications] Following systemic fungal infections sensitive to this drug; cryptococcosis, North American Blastomycosis, disseminated candidiasis, coccidioidomycosis, aspergillosis, mucormycosis and some cases of American mucocutaneous leishmaniasis Fever of unknown origin show in patients with neutropenia (Persistent fever of unknown origin which is not improved even after 96-hour treatment with antibiotics) Primary treatment of visceral leishmaniasis in immunocompetent adults and children Primary treatment of visceral leishmaniasis in immunocompromised patients (HIV-positive patients etc.) **[Dosage and Administration]** This drug should be administered via intravenous infusion for 30~60 mins. For doses greater than 5 mg/kg/day, intravenous infusion over 2 hour period is recommended. The recommended concentration in the intravenous infusion is 0.2~2.0 mg/mL of amphotericin B. The dosage of amphotericin B as AmBisome must be adjusted to the specific requirements of each patient. • Systemic fungal infections: Although 1.0 mg(liter)/kg/day is usually administered, the dosage can be gradually increased to 5.0 mg(liter)/kg/day, if required. • Fever of unknown origin show in patients with neutropenia: 1.0 mg(liter)/kg/day is administered as initial dose, which can be increased to 3.0 mg(liter)/kg/day according to symptoms. • Visceral leishmaniasis: 1.0~1.5 mg(liter)/kg/day is administered for 21 days or 3.0 mg(liter)/kg/day for 10 days. Maintenance therapy or responsive therapy is performed if required due to the risk of recurrence. [Warnings] This drug is not used for common clinically inapparent fungal infections due to its strong activity. A positive skin serum test for fungus is not sufficient for administration. In addition, it is not used for bacterial infections or viral diseases due to no efficacy. In the treatment of fever of unknown origin, it is not used for fever caused by infections due to usual viruses, parasites or mycobacterium. **[Contraindications]** Patients with the hypersensitivity to this drug or any component of the drug. **[General precautions]** It is recommended to check susceptibility for the prevention of the occurrence of resistant bacteria and to administer this drug for the minimum period required for the treatment. If a severe anaphylactic / anaphylactoid reaction occurs, the infusion should be immediately discontinued. It was found that the incidence rates of increased serum creatinine, hypokalemia and hypomagnesemia were notably higher in the high dose groups. Patient management should include routine laboratory evaluation of hepatic, renal and hematopoietic function. Amphotericin B has nephrotoxicity. Patients with diabetes should bear in mind that each vial contains 900 mg of white sugar. This drug should not be given during the dialysis. [Adverse Reactions] The following adverse reactions may be caused by this drug. Their incidences were based on a clinical trial. (1) 10% : Fever, coldness/chills, hypokalemia, nausea, vomiting (2) 1~<10%: Elevations in creatinine and BUN, hypomagnesemia, hypocalcemia, hyperglycemia, hyponatremia, increased ALP, bilirubinemia, abnormal liver function test results, diarrhea, abdominal pain, dyspnea, flushing/vasodilation, hypotension, headache, low back pain, chest pain, rapid pulse rate (tachycardia) and rash (3) 0.1~<1%: Convulsion, bronchiospasm, thrombocytopnea, anaphylactoid reaction, anemia and phlebitis (4) Frequency not known: anemia, anaphylactic reactions, hypersensitivity, cardiac arrest, arrhythmia, renal failure, renal insufficiency, angioneurotic edema, rhabdomyolysis(associated with hypokalemia) and musculoskeletal pain(described as arthralgia or bone pain) In post-marketing surveillance, anaphylactic reaction was uncommonly reported and angioedema was very rarely reported. Occasionally, there were cases of not severe hypersensitivity. Hematological changes, temporary hearing impairments, tinnitus, visual impairments, double vision, increase and decrease in blood pressure, arrhythmia, cardiac arrest, reversible increase of liver enzyme levels (transaminase), leukocytopenia, agranulocytosis, increase in leukocytes and eosinophil, and rarely reversible renal dysfunction may occur. Rhabdomyolysis accompanied by hypokalemia may be caused by amphotericin B. Therefore, if myalgia, feelings of burnout, increases in creatine kinase (CK, CPK) and increase of myoglobin in the blood and urine occur, administration should be discontinued and appropriate actions be taken. Interference with Phosphorous Chemistry Assays: False elevations of serum phosphate may occur when samples from patients receiving AmBisome are analyzed using the PHOSm assay. **[Use in pregnant women and nursing mothers & pediatric use]** The safety of this drug has not been established in pregnant women and nursing mothers. Safety and effectiveness in pediatric patients below the age of one month have not been established. **[Importer]** Gilead Sciences Korea (26 Eulji-ro 5-gil, Jung-gu, Seoul, 100-210, Korea, 02-6000-3330) **[Distributor]** yuhan Corp.

※ Please read full product information before prescription.

References : 1. Boswell et al. J Clin Pharmacol 1998;38:583-592. 2. Wingard et al. Clin Inf Dis 2000;31:1155-1163. 3. Lipid formulations of amphotericin B. In: Sabel JD, Vazquez JA,editors.Contemporary Diagnosis and Management of Fungal Infections.Handbook in Healthcare, 2006:18-19. 4. Walsh et al. N Engl J Med 1999;340:764-771 5. Lass-Flörl et al. Antimicrob Agents Chemother 2008;52:3637-3641. 6. Cornely et al. for the AmBiLoad Trial Study Group. Clin Infec Dis 2007;44:1289-1297.

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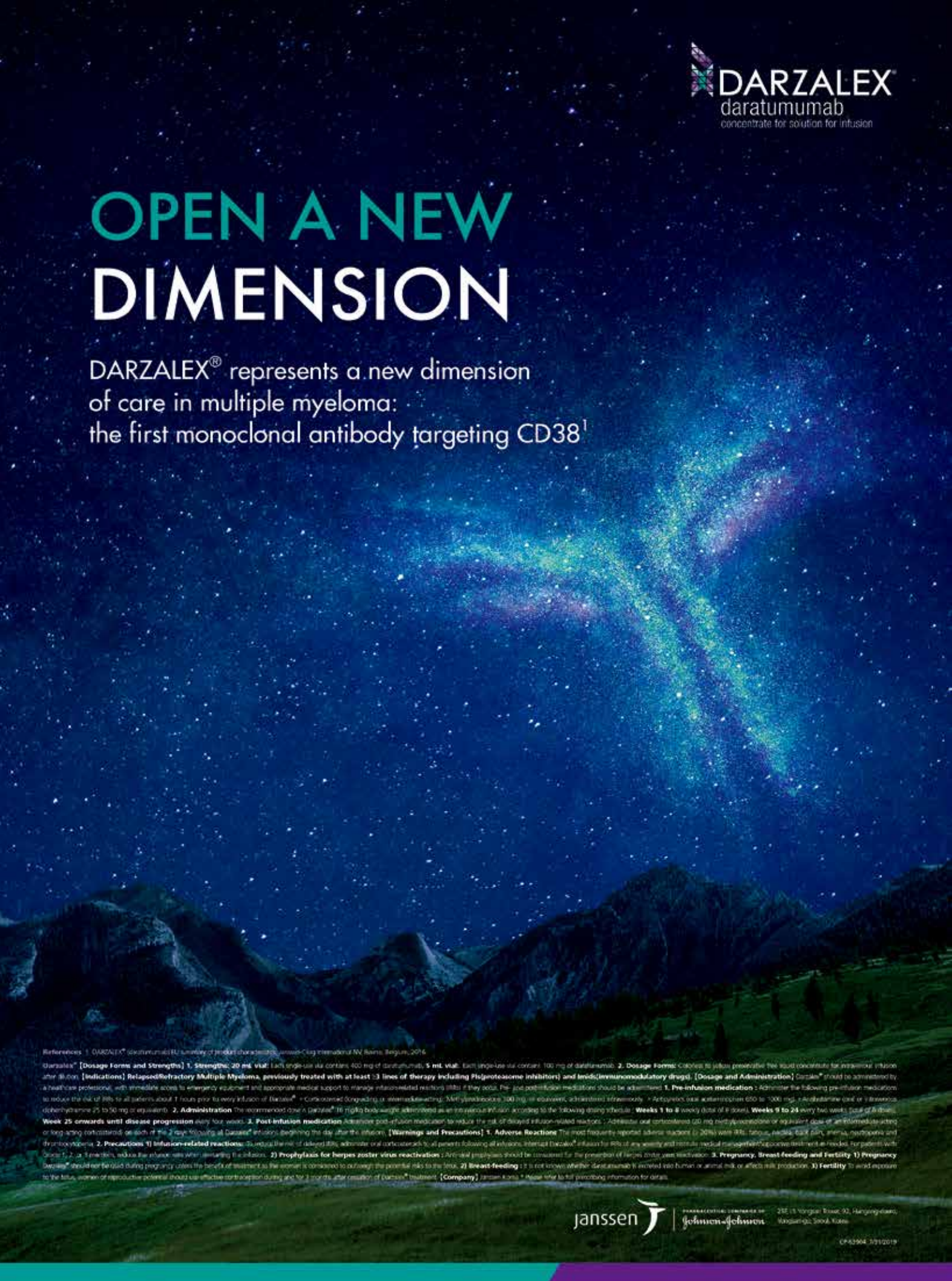
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References 1. DARZALEX® (daratumumab) EU summary of product characteristics. Janssen-Cilag International NV, Beerse, Belgium, 2016.
Darzalex® [Dosage Forms and Strengths] 1. Strengths: 20 mL vial: Each single-use vial contains 400 mg of daratumumab. 5 mL vial: Each single-use vial contains 100 mg of daratumumab. 2. Dosage Forms: Colorless to yellow preservative free liquid concentrate for intravenous infusion after dilution. [Indications] Relapsed/Refractory Multiple Myeloma, previously treated with at least ≥3 lines of therapy including PIs(proteasome inhibitors) and IMiDs(immunomodulatory drugs). [Dosage and Administration] Darzalex® should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions (IRRs) if they occur. Pre- and post-infusion medications should be administered. 1. Pre-infusion medication : Administer the following pre-infusion medications to reduce the risk of IRRs to all patients about 1 hours prior to every infusion of Darzalex®. • Corticosteroid (Long-acting or Intermediate-acting): Methylprednisolone 100 mg, or equivalent, administered intravenously. • Antipyretics (oral acetaminophen 650 to 1000 mg). • Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent). 2. Administration The recommended dose is Darzalex® 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule : Weeks 1 to 8 weekly dose of 8 doses, Weeks 9 to 24 every two weeks dose of 8 doses, Week 25 onwards until disease progression every four weeks. 3. Post-infusion medication Administer post-infusion medication to reduce the risk of delayed infusion-related reactions : Administer oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid) on days 2 and 3 following all Darzalex® infusions (beginning the day after the infusion). [Warnings and Precautions] 1. Adverse Reactions The most frequently reported adverse reactions (≥ 20%) were IRRs, fatigue, nausea, back pain, anemia, neutropenia and thrombocytopenia. 2. Precautions 1) Infusion-related reactions: To reduce the risk of delayed IRRs, administer oral corticosteroids to all patients following all infusions. Interrupt Darzalex® infusion for IRRs of any severity and institute medical management/supportive treatment as needed. For patients with Grade 1 or 2 IR reactions, reduce the infusion rate after restarting the infusion. 2) Prophylaxis for herpes zoster virus reactivation : Antiviral prophylaxis should be considered for the prevention of herpes zoster virus reactivation. 3. Pregnancy, Breast-feeding and Fertility 1) Pregnancy Category: Darzalex® should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. 2) Breast-feeding : It is not known whether daratumumab is excreted into human or animal milk or affects milk production. 3) Fertility To avoid exposure to the fetus, women of reproductive potential should use effective contraception during and for 3 months after cessation of Darzalex® treatment. [Company] Janssen Korea. * Please refer to full prescribing information for details.
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NAME OF THE MEDICINAL PRODUCT MabThera 1400 mg solution for subcutaneous injection **QUALITATIVE AND QUANTITATIVE COMPOSITION** Each vial contains 1400 mg/11.7 mL rituximab. **PHARMACEUTICAL FORM** Solution for injection. Clear to opalescent, colorless to yellowish liquid. **Indications** Non-Hodgkin's lymphoma (NHL) • Follicular lymphoma whose chemo-resistant or in their second or subsequent relapse after chemotherapy. • previously untreated follicular lymphoma in combination with chemotherapy. • maintenance therapy of follicular lymphoma patients responding to induction therapy. • CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. **Dosage and Administration** It is important to check the product labels to ensure that the appropriate formulation (IV or SC) and strength is being given to the patient, as prescribed. It is not for intravenous infusion. Before starting MabThera subcutaneous injections, all patients must always receive beforehand a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation (Chargrin®). MabThera 1400mg is allowed for Non-Hodgkin's lymphoma (NHL). MabThera 1400 mg solution for subcutaneous injection only were approximately 5 minutes. Premedication consisting of an anti-pyretic and an antihistamine, e.g. diphenhydramine, should always be given before each administration of MabThera. Premedication with glucocorticoids should be considered. If MabThera is not given in combination with glucocorticoid-containing chemotherapy, MabThera Roche SC should be injected subcutaneously into the abdominal wall and nevertheless areas, where the skin is red, bruised, tender, or hard or areas where there are moles or scars. No data are available on performing the injection in other sites of the body therefore injections should be restricted to the abdominal wall. During the treatment course with MabThera/Rituxan SC, other medications for subcutaneous administration should preferably be administered at different sites. **Posology** The recommended dose of MabThera/Rituxan SC solution for subcutaneous formulation used for adult patients is a subcutaneous injection of a fixed dose of 1400 mg regardless of the patient's body surface area. If patients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered. Therefore, the switch to MabThera subcutaneous form can only occur at the second or subsequent cycles of treatment. Follicular non-Hodgkin's lymphoma **Combination therapy** The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: first cycle with MabThera intravenous formulation 375 mg/m² body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle for up to 8 cycles. MabThera should be administered on day 1 of each chemotherapy cycle, after administration of the glucocorticoid component of the chemotherapy, if applicable. **Maintenance therapy - Previously untreated follicular lymphoma** The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 1400 mg once every 2 months, starting 2 months after the last dose of induction therapy, until disease progression or for a maximum period of two years (12 administrations in total). • **Relapsed/refractory follicular lymphoma** The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 1400 mg once every 3 months (starting 3 months after the last dose of induction therapy), until disease progression or for a maximum period of two years (8 administrations in total). Diffuse large B cell non-Hodgkin's lymphoma MabThera should be used in combination with CHOP chemotherapy. The recommended dose is: first cycle: MabThera intravenous formulation 375 mg/m² body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle, for total 8 cycles. MabThera is administered on day 1 of each chemotherapy cycle after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma. **Dose adjustments during treatment** No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied. **Contraindications** Hypersensitivity to the active substance or to murine proteins, hyaluronidase or to any of the other excipients. Active, severe infections. Patients in a severely immunocompromised state. Active hepatitis B patients. **Special warnings** The use of MabThera subcutaneous formulation as monotherapy in patients with stage III-IV follicular lymphoma who are in their second or subsequent relapse after chemotherapy cannot be recommended as the safety of the once weekly subcutaneous administration has not been established. **Progressive multifocal leukoencephalopathy** Use of MabThera may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these new symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated. If any do so exist, further evaluation, including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. If a patient develops PML, the dosing of MabThera must be permanently discontinued. Following reconstitution of the immune system in immunocompromised patients with PML, stabilization or improved outcome has been seen. It remains unknown if early detection of PML and discontinuation of MabThera therapy may lead to similar stabilization or improved outcome. **Infusion/Administration related reactions** MabThera is associated with administration related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions. The set of reactions which includes cytokine release syndrome, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They may not specifically related to the route of administration of MabThera and can be observed with both formulations. Severe infusion related reactions which fatal outcome have been reported during post-marketing use of the MabThera intravenous formulation, with an onset ranging within 30 minutes to 2 hours after starting the first MabThera intravenous infusion. They were characterized by pulmonary events, tumor lysis syndrome, fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms. Severe cytokine release syndrome is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest X-ray. The syndrome frequently manifests itself within one or two hours within the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumor lysis syndrome and pulmonary infiltration have been resolved, at a end out. Patients who resolved after complete resolution of signs and symptoms has rarely resulted in reported severe cytokine release syndrome. Like Chronic lymphocytic leukemia, Patients with a high tumor burden or with a high number ($\geq 25 \times 10^9$/L) of circulating malignant cells, who may be at a higher risk of especially severe cytokine release syndrome, should be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still $>25 \times 10^9$/L. Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, pure hypersensitivity reactions typically occur within minutes, after starting infusion. Medicines like the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MabThera. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome. Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release. Infusion related adverse reactions of all kinds have been observed in 77% of patients treated with MabThera intravenous formulation (including cytokine release syndrome accompanied by hypotension and dyspnea/dyspnea in 10.1% of patients). These symptoms are usually reversible with interruption of MabThera infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilator, and glucocorticoids if required. Administration related reactions have been observed in up to 50% of patients treated with MabThera subcutaneous formulation in clinical trials. The reactions occurring within 24 hours of the subcutaneous injection consisted primarily of erythema (redness), pain and injection site reactions, such as pain, swelling and redness and were generally of mild or moderate grade 1 or 2), and transient. Local cutaneous reactions were very common in patients receiving MabThera subcutaneous in clinical trials. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash. Some local cutaneous reactions occurred more than 24 hours after the MabThera subcutaneous administration. The majority of local cutaneous reactions following administration of MabThera subcutaneous formulations was mild or moderate and resolved without any specific treatment. Before starting MabThera subcutaneous injections, all patients must receive full dose of MabThera by intravenous infusion. The risk of experiencing an administration related reaction is the highest at first cycle. MabThera intravenous infusion would allow a better handling of the administration reactions by slowing or stopping the intravenous infusion. If patients were not able to receive one full MabThera intravenous infusion dose, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered. Therefore, switching to MabThera subcutaneous formulation is possible at the second or subsequent cycles of treatment. As with the intravenous formulation, MabThera subcutaneous formulation should be administered in an environment where full resuscitative facilities are immediately available and under the close supervision of an experienced healthcare professional. Premedication with an analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera subcutaneous formulation. Premedication with glucocorticoids should also be considered. Patients should be observed for at least 15 minutes following MabThera subcutaneous administration. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions. Patients should be instructed to contact their treating physician immediately if symptoms that are suggestive of severe hypersensitivity or cytokine release syndrome occur at any time after administration. **Cardiovascular Adverse Reactions** Myocardial infarction, atrial fibrillation, pulmonary edema and acute ventricular thrombocytopenia. Since hypotension may occur during MabThera administration, withholding anti-hypertensive medication 12 hours prior to giving MabThera should be considered. Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely. **Monitoring of blood counts** Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils $< 1 \times 10^9$/L and/or platelet counts $< 75 \times 10^9$/L as clinical experience in this population is limited. The MabThera intravenous formulation has been used in 23 patients who underwent autologous bone marrow transplantation and other risk groups with a presumption reduced bone marrow function without inducing myelotoxicity. Regular full blood counts, including neutrophil and platelet counts, should be performed during MabThera therapy. **Infections** Serious infections, including fatal, can occur during therapy with MabThera. MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections). Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. **Hepatitis B Virus Reactivation related to fulminant hepatitis** Cases of hepatitis B reactivation have been reported in patients receiving the MabThera intravenous formulation including reports of fatal fulminant hepatitis, liver failure, and death. The majority of these patients were also exposed to cytotoxic chemotherapy and diagnosis was made from 4 months after beginning of MabThera administration to 1 month after last administration. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg status and HBcAb status. Those can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. **Progressive multifocal leukoencephalopathy** Very rare cases of PML have been reported during post-marketing survey of the MabThera intravenous formulation in RA and GPA. The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. **Immunization** The safety of immunization with viral vaccines, especially live vaccines following MabThera therapy has not been studied for NHL CLL patients. The primary or secondary humoral immune reactions has not been studied. **Skin reactions** Severe mucocutaneous reactions have been reported from specific group of patients who had administrated MabThera, which had fatal outcome. Fatal reactions occurred after 1 to 13 weeks after beginning of treatment. Patients with these reactions should discontinue MabThera and examined immediately. Skin biopsy is useful to distinguish with other skin reactions and make decision be the sequential treatment. Adverse events reported as mucocutaneous reactions include pemphigoid, psoriasis, Stevens-Johnson syndrome, Lyell's dermatitis, Sweet dermatitis, and toxic epidermal necrolysis syndrome. Among these, Safety with MabThera re-administration has not been studied. Severe skin reactions such as toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens - Johnson syndrome, some with fatal outcome, have been reported in case of such as events, with suspected relationship to MabThera treatment should be permanently discontinued. **Precautions for use** Patients with infections. Patients with history of cardiac disease. Patients with lung infiltrates. Pulmonary insufficiency or history of pulmonary insufficiency. Patients with Severe myelosuppression or marrow infiltration in cancer cell. Patients administering anti-hypertensive medicines. Patients with history of drug hypersensitivity. Patients who has lymphocyte count $< 1.5 \times 10^9$ and/or platelet count $< 0.5 \times 10^9$.

MabThera SC 2018.03.01.01

Overseas detailed product information and/or inquiries, product related adverse events, Please contact Roche Korea (02-3451-3600)
For the latest product information, please refer to the for Korea website (www.rochekorea.kr)
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TFR, treatment-free remission; **EMR**, early molecular response; **DMR**, deep molecular response

Reference 1. Tasigna Product Information **2.** Hughes et al. Blood 2014 123: 1353-1360 Feb 2014 **3.** Hochhaus A et al. Leukemia 2017;31(7):1525-1531 Epub 2017 Feb 20

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전문의약품

원료의약품 및 분량 1시린지0.6일리레이0중 (주성분: 페그필그라스딤6mg) (첨가제: 빙초산,글리시딘,아세트에이트, 수산화 나트륨, 소르비톨(30mg), 폴리오르베이트20(0.02mg)) 주사용수 성상 무색의 용액이 충전 된 주사장이 달린 투명한 유리프리필드시린지 주사제 효능효과 악성종양에 대한 세포독성 화학요법을 투여 받는 환자의 발열성 호중구 감소증의 발생과 호중구 감소증의 기간 감소(발생률과 골수이형성증후군은 제외함) **용법용량** 이 약 6mg을 항암화학요법 이후 약 24시간 후에 피하주사 *소아에 대한 사용 제한 *말기 신장에 환자를 포함한 신장에 환자에게 유량 변경은 추천되지 않음 **사용상 주의사항 1. 경고** 1) 치명적 비장 파열이 발생할 수 있음. 이 약 투여후 좌측 상복부, 어깨 통증이 있는 환자는 비장비대, 비장파열 검사 2) 급성 호흡곤란 증후군(ARDS)가 발생할 수 있음. 열, 폐 침윤, 호흡곤란이 있는 환자는 ARDS 검사. ARDS가 발생한 환자에는 투여 중지 3) 아나필락시스를 포함한 심각한 알러지 반응이 발생할 수 있음. 심각한 알러지 반응이 발생한 환자에는 투여를 영구 중지 4) 경상적혈구질환 환자가 필그라스팀, 페그필그라스팀을 투여 받는 경우 증증, 폐태루 치명적인 폐상적혈구붕증이 발생할 수 있음 5) 페그필그라스팀과 필그라스팀이 작용하는 G-CSF수용체가 암세포에서 발견됨. 페그필그라스팀이 골수성 암과 골수이형성증을 포함한 암 종류를 증가시키는 요소로 작용할 수 있음 **2. 다음 환자에는 투여하지 말 것** 대집군으로부터 유래된 단백질, 페그필그라스팀, 필그라스팀 등에 과민증이 알려진 환자 **3. 다음 환자에는 신중히 투여할 것** 1) 약물 과민증의 병력이 있는 환자 2) 알레르기 소인이 있는 환자 **포장기한** 시린지/박스 **저장방법** 빙장보관(2-8℃), 동결금지, 흔들금지, 차광보관, 밀봉됨기 **사용기한** 외부포장에 표시된 사용기한 내에 사용 *세품에 대한 자세한 정보는 제품설명서를 참조해주시기를 바라며, 홈페이지(www.kyowa-kirin-korea.com)에서 확인하실 수 있습니다. (수입판매원) 한국교와하코기린(주)

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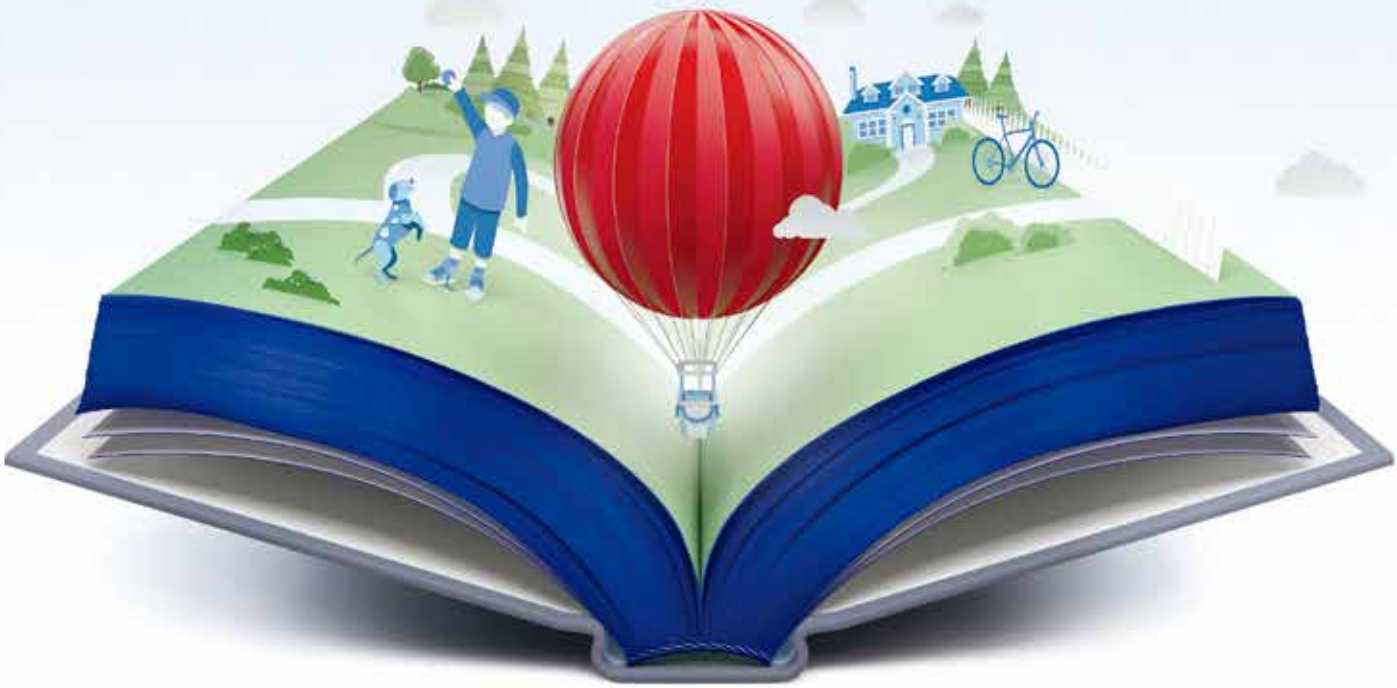

스프라이셀 제품 요약정보

[효능 효과] 1)새로이 진단받은 만성기 필라델피아 염색체 양성 만성골수성백혈병(Ph+CML) 성인환자의 치료. 이 약의 효과는 세포학적 반응률과 주요분자학적 반응률에 근거한다. 2) 이매티닙을 포함한 선행요법에 저항성 또는 불내성을 보이는 만성기, 가속기, 또는 급수성아사 림프구성 모구성발증기의 만성골수성백혈병(Ph+CML) 성인환자의 치료. 3)선행요법에 저항성 또는 불내성을 보이는 필라델피아 염색체 양성 급성 림프구성 백혈병(Ph+ALL) 성인환자의 치료. 4)만성기 필라델피아 염색체 양성 만성골수성백혈병(Ph+CML) 소아환자의 치료 **[용법용량]** 제품설명서의 용법용량 참조 **[사용상 주의사항]** 1. 경고: 이 약은 임신부에게 투여되었을 때, 태아에게 상해를 일으킬 수도 있다. 2. 다음 환자에는 투여하지 말 것: 1) 이 약의 주성분 또는 다른 성분들에 과민증 환자 2) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose malabsorption), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게 투여하면 안된다. 3. 다음 환자에게 신중히 투여할 것: 1) 이 약을 투여 받고 있는 환자들이 혈소판 기능을 억제하는 약물 또는 항응고제를 처방받아야 한다면 주의를 기울여야 한다. 2) 이 약은 QTc 연장경험이 있거나 가능성이 있는 환자에게 주의하여 투여되어야 한다. 여기에는 저칼륨혈증 또는 저마그네슘혈증 환자, 선천성 연장 QT 증후군을 가진 환자, 항부정맥약을 복용중인 환자, 또는 QT 연장을 유도할 수 있는 다른 약물을 복용하고 있는 환자, 그리고 축적성 고용량 안트라사이클린 요법을 하고 있는 환자가 포함된다. 저칼륨혈증 또는 저마그네슘증은 이 약 투여 전에 교정되어야 한다. 3) 간장애: 간기능 손상환자에서 용량조절은 필요치 않았으나, 다사티닙의 대사는 주로 간에서 이루어지므로, 간기능 손상 환자에게 이 약 투여 시 주의가 요구된다. 4) 폐동맥 고혈압: 기저 심폐 질환의 징후의 증상이 있는 환자는 이 약으로 치료 전과 치료 중에 평가하도록 한다. 만약 폐동맥 고혈압이 확진되면, 이 약은 영구 중단되어야 한다. 5) B형 간염바이러스 재활성화: 이 약의 치료가 요구되는 HBV 보균자는 치료 기간 및 치료 종료 후 수개월 동안 HBV 감염 활성화의 징후 및 증상에 대해 면밀하게 모니터링 되어야 한다.

제품을 처방하시기 전 제품설명서를 참고하여 주시기 바랍니다.

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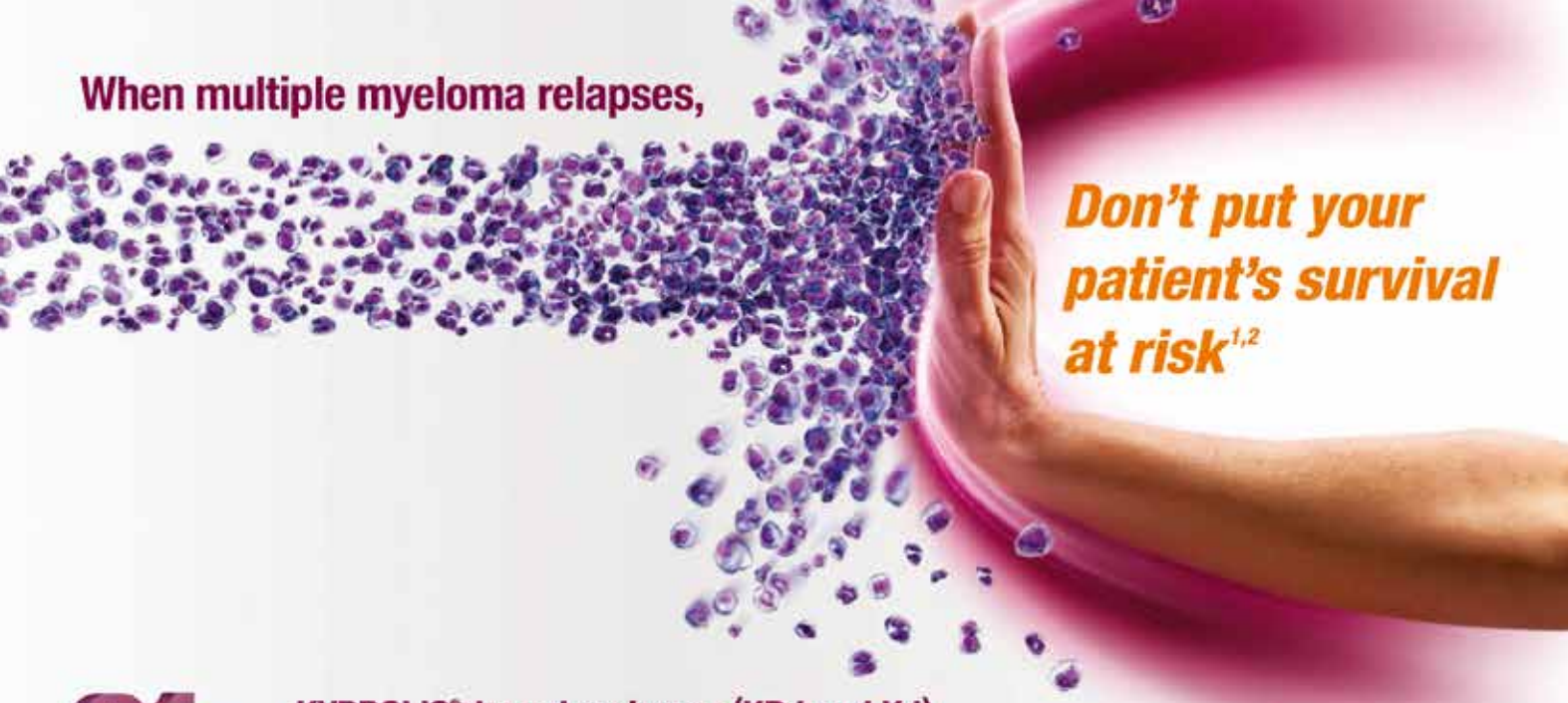

21% **KYPROLIS®-based regimens (KRd and Kd)** reduced the risk of death by **21%** vs Rd and Vd.[1,2]

KRd from ASPIRE

- **26.3 months** of median PFS with KRd vs. 17.6 with Rd[3]
  HR 0.69 (0.57-0.83), P = 0.0001
- **48.3 months** of median OS with KRd vs. 40.4 with Rd[2]
  HR 0.79 (0.67-0.95), P = 0.0045
- **3x** patients achieved ≥ CR with KRd vs. Rd[3]
  P < 0.001 in CR+sCR

Kd from ENDEAVOR

- **18.7 months** of median PFS with Kd vs. 9.4 with Vd[4]
  HR 0.53 (0.44-0.65); P < 0.0001
- **47.6 months** of median OS with Kd vs 40.0 with Vd[1]
  HR 0.79 (0.65-0.96), P = 0.010
- **2x** patients achieved ≥ CR with Kd vs. Vd[4]
  P = 0.0010 in CR+sCR

PFS, progression-free survival; **CR**, complete response; **HRQoL**, Health-Related Quality of Life; **OS**, overall survival; **PN**, peripheral neuropathy; **sCR**, stringent complete response

ASPIRE was a randomized, phase 3, open-label, multicenter study evaluating KYPROLIS® in patients with relapsed multiple myeloma who had 1 to 3 prior lines of therapy. 792 patients were randomized in a 1:1 ratio (396 patients to KRd; 396 to Rd). The primary endpoint was progression-free survival. Secondary endpoints included overall survival, overall response rate (partial response or better), duration of response, health-related quality of life, and safety.[3]

ENDEAVOR was a randomized, phase 3, open-label, multicenter study evaluating KYPROLIS® in patients with relapsed or refractory multiple myeloma who had 1 to 3 previous treatments. 929 patients were randomly assigned (1:1) to receive carfilzomib with dexamethasone (Kd) or bortezomib with dexamethasone (Vd). The primary endpoint was progression-free survival in the intention-to-treat population. Secondary endpoints included overall survival, overall response (partial response or better), duration of response, incidence of ≥ grade 2 peripheral neuropathy events, and safety.[4]

References 1. Dimopoulos MA, et al. Lancet Oncol 2017;18:1327-37 2. Siegel DS, et al. J Clin Oncol. 2018 Jan 17. doi: 10.1200/JCO.2017.76.5032 [Epub ahead of print] 3. Stewart AK, et al. N Engl J Med. 2015;372:142-52. 4. Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38.

키프롤리스®주 제품요약정보

처방명: 키프롤리스주60mg/vial 그외, 30mg/vial 고형제제(분말주입), 흡입흡과 이전에 한 가지 이상의 치료를 받은 다발성골수종 환자의 치료의 세분리이어야는 및 택시에보는 또는 택시에보는 이외 병용요법 **용법용량:** 3주 동안 매주 2일 연속으로 투여 후 1주일간 휴약하여 총 28일을 1 치료주기로 한다. 첫 번째 주기의 1일, 2일에 20mg/m²의 시작용량으로 투여한다. **[병용요법시 및 택시에보는과의 병용요법]** 10분 동안 정맥내 주입으로 투여. 시작 용량 투여 후, 첫 번째 주기의 8일째 투여 용량 27mg/m²로 증량한다. 15주 기준으로 8일과 9일에 투여하지 않으며 15 주기 이후에는 투여를 중단한다. 레날리도마이드는 1-21일에 25mg을 경구 투여하고, 택시에보는은 3회의 주기의 1일, 8일, 15일, 22일에 40mg을 경구 또는 정맥투여한다. **[택시에보는과의 병용요법]** 30분동안 정맥내 주입으로 투여. 시작용량 투여 후, 첫 번째 주기의 8일째 목표용량 56mg/m²로 증량한다. 매 28일 주기의 1, 2, 8, 9, 15, 16, 22, 23일에 택시에보는은 20mg을 경구 또는 정맥투여 한다. **다음 환자에게는 투여해서는 안 됩니다:** 주성분 또는 다른 성분에 과민반응이 있는 환자. **허가현황:** 3제날리도마이드 및 택시에보는과의 병용요법 임상시험에서 10% 이상 보고된 이상반응은 빈혈, 호중구감소증, 혈소판감소증, 설사, 변비, 구역, 피로, 발열, 말초부종, 두통증, 기침, 호흡곤란, 발진, 근육통증, 기타, 호흡곤란, 기타, 고열반응없고, 10% 이상 보고된 3-4등급 임상검사시 이상은 림프구, 혈색호중구수, 인, 혈소판, 흰 비혈구수, 헤모글로빈, 칼륨 감소이었다. 한택시에보는과의 병용요법 임상시험에서 10% 이상 보고된 이상반응은 빈혈, 혈소판감소증, 설사, 구역, 변비, 구토, 피로, 발열, 말초부종, 두통증, 상기도감염, 기관지염, 비인두염, 근육경련, 요통, 두통, 피로, 말초신경병증, 말초감, 호흡곤란, 기침, 고열반응없고, 10% 이상 보고된 3-4등급 임상검사시 이상은 림프구감소, 혈색호중구수, 인, 혈소판 감소, 칼륨 감소 및 감소, 칼륨증가이었다. 사전 후 혈혈심폐속투군 (HUS), 위치한 환자, 심근경이 저항보고 되었다. 일반적 주의: 임신독성, 급성소부전, 조심심혈관계주군: 폐독성, 폐폐색기혈압, 호흡곤란, 고혈압, 정맥혈전증, 주입관련 출혈, 혈소판감소증, 간독성 및 간부전, 혈전성 미세혈관병증, 가역성 후두부 뇌병증 증후군(PRES), 폐폐지독성이 발생할 수 있으므로 모니터링, 응용감염, 투여중지, 환난 등의 필요한 의료적 조치를 취하여야 한다. **임부 및 수유부:** 위험이 있다고 동물시험 결과로 볼 때, 태아독성을 야기할수 있으므로 적절한 피임 조치를 해야 한다. 임신 중 사용하거나 투약기 투약 중에 임신하게 되면, 위치에게 태아에 위험이 있음을 알려야 한다. **보관 및 취급상의 주의사항:** 자유 낱장 (2-8℃) 보관. **정맥 투여을 위한 제구성 및 조제방법:** 과량투여을 막기위해 투여한 개산에 주의해야 하며, 제구성하기 전 조제방법을 숙지하여야 한다. **수입판매원:** 암젠코리아유한회사 서울특별시 강남구 테헤란로 203 서울인터내셔널타워 14층. **제품을 처방하시기 전 상세 처품설명서를 참고하여주시기 바랍니다.**

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