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Vol. 53, Suppl. 1, March 2018

BLOOD RESEARCH

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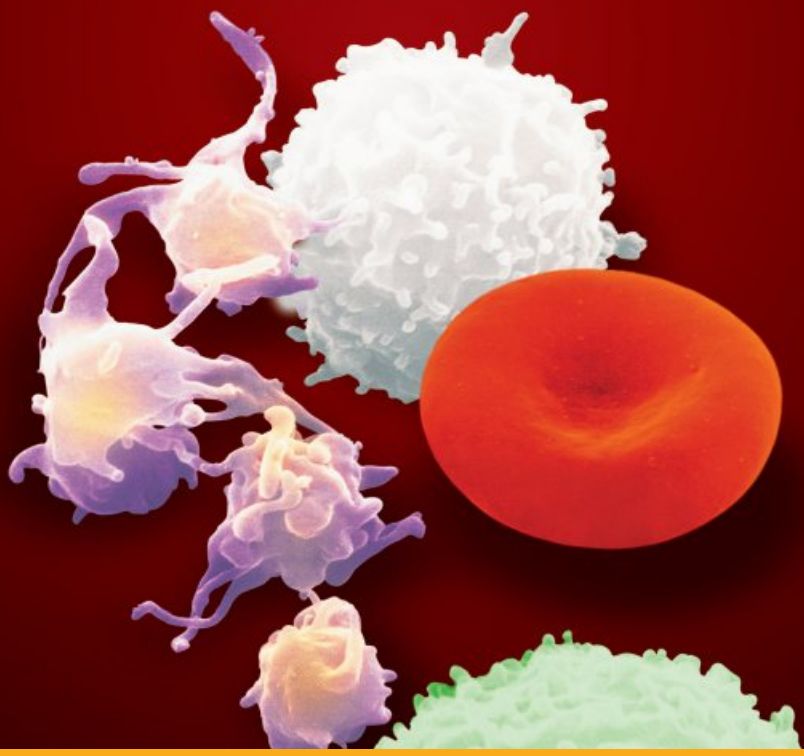
2018 Korean Society of Hematology
International Conference &
59th Annual Meeting
in conjunction with BTG 2018

Date : March 29(Thu) - 31(Sat), 2018
Venue : Grand Walkerhill Seoul, Korea



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Step Further Inside the Real World of Precision Hematology

ICKSH 2018

2018 KOREAN SOCIETY OF HEMATOLOGY INTERNATIONAL CONFERENCE & 59th ANNUAL MEETING

In conjunction with BTG 2018 by AP Hematology Consortium

MARCH 29 - 31, 2018

Grand Walkerhill Seoul, Korea

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

Editorial Office

King's Garden Officetel 2-220,
24, Sajik-ro 8-gil, Jongno-gu, Seoul 03174, Korea
Tel: +82-2-516-6581, Fax: +82-2-516-6582,
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ICKSH 2018
& 59th ANNUAL MEETING

CONTENTS

WELCOME MESSAGE

Dear Colleagues,

It is a great honor and privilege to invite you to attend the 2018 KSH International Conference & 59th Annual Meeting, hosted by the Korean Society of Hematology (KSH), to be held March 29-31, 2018, at the Grand Walkerhill Seoul, Korea.

Founded in 1958, the Korean Society of Hematology has steadily grown over the years and will soon celebrate its 60th anniversary. As the explosion in the 21st century of science and industry has brought revolutionary advancement, the expansion of knowledge and development of new technologies goes beyond imagination. The ICKSH 2018 will provide a unique opportunity to learn about the most recent findings and research from renowned experts and offer an occasion to exchange experiences and information with colleagues for the continued success and progress of our field.

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. We are also planning to open several satellite symposiums with specialists on numerous hematology-related topics.

We very much look forward to sharing this memorable and fantastic meeting together.

Hwi-Joong Yoon, M.D., Ph.D.
Congress Chairman
The Korean Society of Hematology

Hyeoung-Joon Kim, M.D., Ph.D.
President
The Korean Society of Hematology

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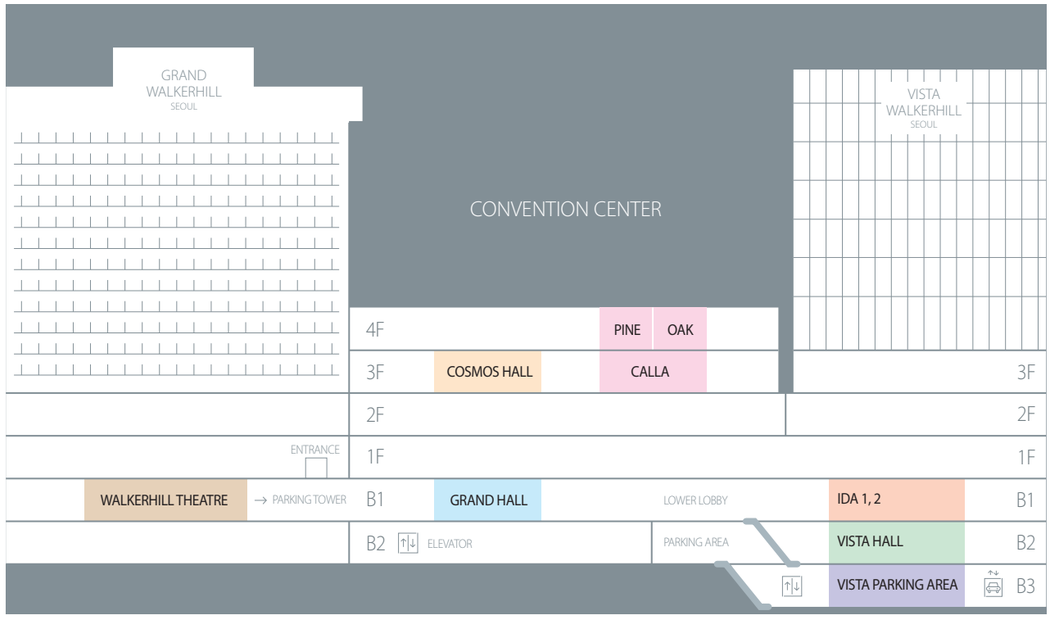
FLOOR PLAN Side View



PINE, OAK (4F)
Meeting Room

CALLA (3F)
Meeting Room

IDA 1, 2 (B1)
Organizing Committee
VIP Room
Preview Room
Registration (Lobby)

GRAND HALL (B1)
BTG2018 Scientific Session
Meeting Room
Exhibition (Lobby)

COSMOS (3F)
Exhibitor's Lunch
Business Meeting

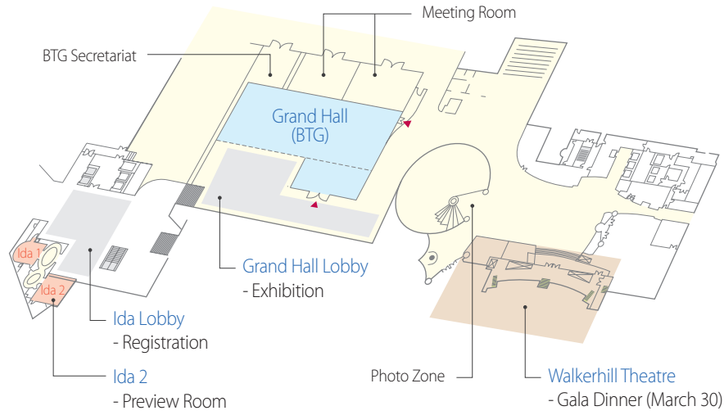
WALKERHILL THEATRE (B1)
Gala Dinner

VISTA HALL (B2)
ICKSH 2018 Scientific Session
Opening / Closing Ceremony
Plenary Session
Welcome Reception (Lobby)
Exhibition (Lobby)

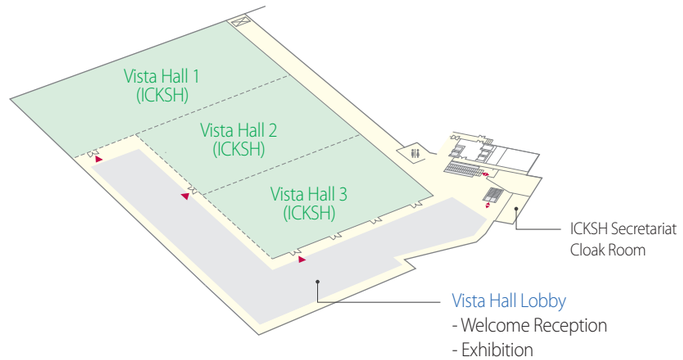
EXHIBITION HALL (B3)
Exhibition
Posters
Coffee Break
Internet Lounge

FLOOR PLAN

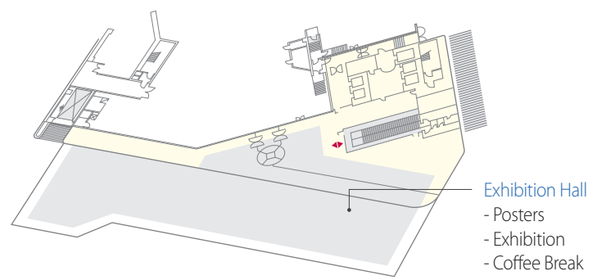
B1



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	IDA Lobby (B1)
OPERATION HOURS	March 29 (Thu.) 07:00 - 19:00 March 30 (Fri.) 07:00 - 19:00 March 31 (Sat.) 07:00 - 13:00

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 registration desk. 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, Vista Hall 2, Vista Hall 3 (B2)
OPERATION HOURS	March 29 (Thu.) 13:00 - 14:00 March 30 (Fri.) 12:00 - 13:00 March 31 (Sat.) 13:00 - 13:30

Coffee Break

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

Internet

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

Certificate of Attendance

Participants may receive the certificate of attendance. Please contact the ICKSH2018 Secretariat after the conference via icksh@icksh.org

Useful Phone Numbers

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

ICKSH2018 Secretariat Office

+ Onsite: Beside the Cloak Room, Vista Hall Lobby (B2) T. +82-2-450-2201 E. icksh@icksh.org
+ After conference: 1F, Haeoreum Bldg., 16 Yeoksam-ro 17 Gil, 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 29 (Thu.) 07:00 - 19:00 March 30 (Fri.) 07:00 - 18:00 March 31 (Sat.) 07:00 - 17:00

Preparatory Meeting

To ensure the smooth communication between chairpersons and presenters, session chairs and speakers are requested to attend our Preparatory Meeting. The meeting will take place at each session room as assigned, 30 minutes prior to your session.

CODE	SESSIONS		LOCATION / TIME	
SS01	Single Cell Genomics	March 29 (Thu.) 10:20 - 11:40	Oak	March 29 (Thu.) 09:50
SS04	Recent Advances in Natural Killer T-cell Lymphoma	March 30 (Fri.) 09:00 - 10:20	Oak	March 30 (Fri.) 08:30
SS08	Current Progress in Pediatric Acute Leukemia	March 31 (Sat.) 09:30 - 10:50	Oak	March 31 (Sat.) 09:00
SS09	Detection of Minimal Residual Disease in Hematologic Malignancy	March 31 (Sat.) 09:30 - 10:50	Pine	March 31 (Sat.) 09:00

Poster Presentation

Pre-selected posters are required to have a presentation time following the schedule below.
After onsite reviews, the scientific committee will select the Best Posters. Winners should attend the Closing Ceremony on March 31 (Sat.) to receive the award.

LOCATION	Exhibition Hall (B3)
DATE & TIME	March 29 (Thu.) 18:10 - 18:40 March 30 (Fri.) 17:50 - 18:20

SOCIAL PROGRAM

Opening

With the opening address by Congress Chairman Hwi-Joong Yoon, ICKSH2018 will begin.

LOCATION	Vista 1 Hall (B2)
DATE & TIME	March 29 (Thu.) 08:00

Welcome Reception

Welcome to ICKSH2018! The Organizing Committee has prepared a marvelous welcome reception.

LOCATION	Vista Hall Lobby (B2)
DATE & TIME	March 29 (Thu.) 18:40 - 20:00

Gala Dinner

Please join us to share an unforgettable evening. Enjoy the climax of ICKSH2018 with an excellent dinner and exciting performance.

LOCATION	Walkerhill Theatre (B1)
DATE & TIME	March 30 (Fri.) 18:20 - 20:00

PLENARY LECTURES

MARCH 29 (Thu.)

PL01-01 14:00-14:40 | VISTA Hall (B2F)

Precision Medicine in CLL

Constantine Tam
Peter MacCallum Cancer Centre, St Vincent's Hospital and University of Melbourne, Australia

PL01-02 14:40-15:20 | VISTA Hall (B2F)

The Clinical Management of FLT3-Mutated AML

Mark Levis
Johns Hopkins School of Medicine, USA

MARCH 30 (Fri.)

PL02-01 10:30-11:10 | VISTA Hall (B2F)

Human Myeloid Leukemia Stem Cells

Koichi Akashi
Kyushu University Graduate School of Medical Sciences, Japan

PL02-02 11:10-11:50 | VISTA Hall (B2F)

Pre-Cancerous Stem Cells in MDS and AML: Significance, Mechanisms, and Therapeutic Targeting

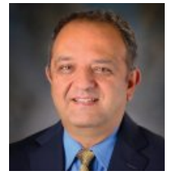
Ulrich Steidl
Albert Einstein College of Medicine, USA

MARCH 31 (Sat.)

PL03-01 11:10-11:50 | VISTA Hall (B2F)

Development of Precision Medicine Trials for ALL

Stephen Hunger
Children's Hospital of Philadelphia, USA



PL03-02 11:50-12:30 | VISTA Hall (B2F)

Progress in Therapy of Philadelphia Positive ALL

Farhad Ravandi
MD Anderson Cancer Center, USA

PROGRAM AT A GLANCE March 29 (Thu), 2018

Time	VISTA 1	VISTA 2	VISTA 3
07:30	Registration		
08:00	**OPENING REMARKS** (Place: Vista 1)		
08:00-09:00	ORAL PRESENTATION 01	ORAL PRESENTATION 02	ORAL PRESENTATION 03 (KOR)
09:00-10:00	EDUCATIONAL SESSION 01 Multiple Myeloma (KOR)	EDUCATIONAL SESSION 02 Typical and atypical Chronic Myelogenous Leukemia (KOR)	EDUCATIONAL SESSION 03 Thrombotic Microangiopathy (KOR)
	Monoclonal Gammopathy of Renal Significance (Jung Eun Lee, Korea)	Optimal First-Line Treatment of Chronic Phase CML (Kyoung Ha Kim, Korea)	Childhood aHUS (Hae Il Cheong, Korea)
	Smoldering Multiple Myeloma (Byung-Su Kim, Korea)	Update on the Treatment of CML in Children (Jae Wook Lee, Korea)	Adult aHUS (Youngil Koh, Korea)
	Next Generation Sequencing in Multiple Myeloma (Miyoung Kim, Korea)	BCR-ABL1 Negative Hematologic Neoplasms; Diseases that are Similar to but Different from CML (Hawk Kim, Korea)	Management of TTP (Doyeun Oh, Korea)
10:00-10:20	Coffee Break		
10:20-11:40	SCIENTIFIC SESSION 01 Single Cell Genomics	SCIENTIFIC SESSION 02 (KAI-KSH JOINT) Cancer Immunology	
	Single Cell Analysis of Multiple Myeloma (Woong-Yang Park, Korea)	Immune Checkpoint Inhibition in Hematologic Malignancy - Focusing on Multiple Myeloma (Yoon Seok Choi, Korea)	
	Characteristics of Tumor Infiltrating Lymphocytes Revealed by Single Cell RNA Sequencing (Zemin Zhang, China)	A New Antigen Presenting Cell based Therapeutic Cancer Vaccine (Chang-yuil Kang, Korea)	
	Dissecting the Cellular and Genetic Composition of Pediatric Leukemias by Single-Cell Genomics (Charles Gawad, USA)	Chimeric Antigen Receptor-engineered Natural Killer Cell Immunotherapy for Cancer (Kyung-Nam Koh, Korea)	
		Post-transplant Immunotherapy with WT1-speci c CTLs for High-risk Acute Myelogenous Leukemia (Tai-Gyu Kim, Korea)	
11:40-11:50	Break		
11:50-12:50	ORAL PRESENTATION 04	ORAL PRESENTATION 05	ORAL PRESENTATION 06

PROGRAM AT A GLANCE March 29 (Thu), 2018

Time	VISTA 1	VISTA 2	VISTA 3
12:50-13:00	Break		
13:00-14:00	[Luncheon] SATELLITE SYMPOSIUM 01 KYOWA KIRIN	[Luncheon] SATELLITE SYMPOSIUM 02 NOVARTIS	[Luncheon] SATELLITE SYMPOSIUM 03 HANDOK
	Updated Febrile Neutropenia Management (Won Seog Kim, Korea)	It's Time We Go Deeper (Pierre Laneuville, Canada)	Complement Mediated Glomerular Disease (Focusing on aHUS): Everything Has Changed in the Last 10 Years but Still a Lot to Do (Giuseppe Remuzzi, Italy)
14:00-15:20	PLENARY LECTURE 01 Precision Hematology in Genomics Era		
	Precision Medicine in CLL (Constantine Tam, Australia)		
	The Clinical Management of FLT3-Mutated AML (Mark Levis, USA)		
15:20-15:40	Coffee Break		
15:40-17:00	EHA-KSH JOINT SYMPOSIUM 01 Myelodysplastic Syndromes		SPECIAL REPORT 01 Updates on Cellular Therapies
	The Best Prediction of Prognosis for MDS: How to Integrate Clinical and Molecular Data (Valeria Santini, Italy)		CAR T Treatment for ALL (Jae Park, USA)
	Clinical Effects of Somatic Mutations in MDS (Je-Hwan Lee, Korea)		CAR Expressing Effector Cells in Stem Cell Transplantation (Ulrike Kohl, Germany)
	Pathogenesis and Management of Chronic Myelomonocytic Leukemias (Raphael Itzykson, France)		Ex Vivo T cell-depleted Haploidentical Hematopoietic Cell Transplantation and Cellular Therapy Post-transplantation (Ho Joon Im, Korea)
	Hypomethylating Therapy in Stem Cell Transplantation for MDS (Yoo-Jin Kim, Korea)		
17:00-17:10	Break		
17:10-18:10	ORAL PRESENTATION 07	ORAL PRESENTATION 08	ORAL PRESENTATION 09
18:10-18:40	**POSTER PRESENTATION 01** (Place: Exhibition Hall, B3)		
18:40-20:00	**WELCOME RECEPTION** (Place: Vista Hall Lobby, B2)		

* Sessions will be presented in English. Only [KOR] marked sessions will be presented in Korean.

PROGRAM AT A GLANCE March 30 (Fri), 2018

Time	VISTA 1	VISTA 2	VISTA 3
08:00-09:00	ORAL PRESENTATION 10	ORAL PRESENTATION 11	ORAL PRESENTATION 12 (KOR)
09:00-10:20	SCIENTIFIC SESSION 03 Recent Advances in Acute Promyelocytic Leukemia	SCIENTIFIC SESSION 04 Recent Advances in Natural Killer T-cell Lymphoma	ORAL PRESENTATION 13
	JALSG Prospective Study for APL (Akihiro Takeshita, Japan)	Molecular Pathogenesis of NKTL (Wee Joo Chng, Singapore)	
	Therapy of APL (Lionel Ades, France)	Recent Advances in NK/T-Cell Lymphoma (Yok Lam Kwong, Hong Kong)	
	Strategies to Define High-risk Patients in APL (Byung-Sik Cho, Korea)	Beyond Current Standard Care of ENKTL (Won Seog Kim, Korea)	
10:20-10:30	Break		
10:30-11:50	PLENARY LECTURE 02 Targeting Leukemic Stem Cells		
	Human Myeloid Leukemia Stem Cells (Koichi Akashi, Japan)		
	Pre-Cancerous Stem Cells in MDS and AML: Significance, Mechanisms, and Therapeutic Targeting (Ulrich Steidl, USA)		
11:50-12:00	Break		
12:00-13:00	[Luncheon] SATELLITE SYMPOSIUM 04 AMGEN	[Luncheon] SATELLITE SYMPOSIUM 05 Bristol-Myers Squibb	[Luncheon] SATELLITE SYMPOSIUM 06 HANDOK
	Treatment of Multiple Myeloma in Relapse (Keith Stewart, USA)	Emerging Trends in CML Management (Elias Jabbour, USA)	HSCT Early Complications: Focus on Severe Hepatic Veno-occlusive Disease; - The Revised EBMT Diagnostic and Severity Criteria for Adults and an Update on Defibrotide. (Mohamad Mohty, France)
13:00-14:20	SCIENTIFIC SESSION 05 Cell Death Mechanism	SCIENTIFIC SESSION 06 Bone Marrow Failure syndrome	SCIENTIFIC SESSION 07 (KOGO-KSH JOINT) Cancer Genomics
	Apoptotic Cell Death (Soo Youl Kim, Korea)	Non-Transplant Therapy for Bone Marrow Failure (Danielle Townsley, USA)	Variability in Chromatin Architecture and Associated DNA Repair at Genomic Positions Containing Somatic Mutations (Seon-Young Kim, Korea)
	CHIP Controls Necroptosis Through Ubiquitylation- and Lysosome-dependent Degradation of RIPK3 (Jaewhan Song, Korea)	Role of Microenvironment and Genetics in BM Failure (Myungshin Kim, Korea)	Deciphering the Cell-of-Origin Harboring Driver Mutations in Brain Tumors (Jeong-Ho Lee, Korea)

PROGRAM AT A GLANCE March 30 (Fri), 2018

Time	VISTA 1	VISTA 2	VISTA 3
	Functional Isolation of New Modulators in Apoptosis and Necroptosis (Yong-Keun Jung, Korea)	Inherited BM Failure Syndrome (Hoon Kook, Korea)	Contribution of Germline Variants in Pan-Cancer Development (Youngil Koh, Korea)
			Developing a Genetic Data based Prognostic Model for Hematologic Cancer (SeungHyun Jung, Korea)
14:20-14:40	Coffee Break		
14:40-15:40	Asian Hematology Network: JSH-KSH Joint Symposium Explore Deep Inside the Asian Hematology Network		SATELLITE SYMPOSIUM 07 Roche
	AML Prognosis based on Clinical and Genomic Data (Hyeoung-Joon Kim, Korea)		Advancing Value-Based Approaches in the Treatment of Non-Hodgkin Lymphoma (NHL): Contemporary Strategies and Innovations (Hyeon-Seok Eom, Korea)
	A Novel Mechanism of Cancer Immune Evasion Via the Disruption of PD-L1 3'-UTR (Seishi Ogawa, Japan)		
15:40-17:00	EHA-KSH Joint Symposium 02 Aplastic Anemia Paroxysmal Nocturnal Hemoglobinuria		SPECIAL REPORT 02 Multiple Myeloma Niche
	Diagnosis and Management of AA and Refractory Cytopenia of Childhood (Ayami Yoshimi, Germany)		Clinical Implications of MRD in Multiple Myeloma (Wee Joo Chng, Singapore)
	Frontline Alternative Donor SCT Versus Immunosuppressive Treatment for Children with Severe AA Who Lack Matched Related Donor (Hyoung Jin Kang, Korea)		The Ubiquitin-Proteasome Pathway : Friend and Foe in Multiple Myeloma (Robert Orlowski, USA)
	An Update on the Management of PNH (Anita Hill, UK)		Cellular Immunotherapy in Multiple Myeloma (Je-Jung Lee, Korea)
	Clinical Implications of Renal Dysfunction in Patients with PNH (Jin Seok Kim, Korea)		
17:00-17:10	Break		
17:10-17:50	BEST ABSTRACT PRESENTATION		SATELLITE SYMPOSIUM 08 Takeda ONCOLOGY
			Novel Treatment Strategies for Multiple Myeloma: A Focus on Oral Proteasome Inhibitors (Antonio Palumbo, Italy)
17:50-18:20	POSTER PRESENTATION 02 (Place: Exhibition Hall, B3)		
18:40-20:00	GALA DINNER (Place: Walkerhill Theatre B1)		

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PROGRAM AT A GLANCE March 31 (Sat), 2018

Time	VISTA 1	VISTA 2	VISTA 3
08:30-09:30	ORAL PRESENTATION 14	ORAL PRESENTATION 15	ORAL PRESENTATION 16 (KOR)
09:30-10:50	SCIENTIFIC SESSION 08 Current Progress in Pediatric Acute Leukemia	SCIENTIFIC SESSION 09 Detection of Minimal Residual Disease in Hematologic Malignancy	ORAL PRESENTATION 17
	New Developments in the Treatment of Newly Diagnosed and Relapsed ALL (Stephen Hunger, USA)	MRD Detection in Acute Leukemia, CLL and Multiple Myeloma (Alberto Orfao, Spain)	
	Therapy Optimization in Infant ALL (Daisuke Tomizawa, Japan)	NGS-based Assessment of Clonality & MRD Determination in ALL (In-Suk Kim, Korea)	
	Genomic Landscape and Therapy Optimization of Pediatric Mixed Phenotype Acute Leukemia (Hiroto Inaba, USA)	Selected Short Talk I Development and Preliminary Evaluation of Customized pan-Blood Cancer NGS Panel (Jun Hyung Lee, Korea)	
		Selected Short Talk II Evaluation of Two Commercial Kits for Flow Cytometric MRD Detection in B-ALL (Ari Ahn, Korea)	
10:50-11:10	Coffee Break		
11:10-12:30	PLENARY LECTURE 03 Development of Precision Medicine Trials		
	Development of Precision Medicine Trials for ALL (Stephen Hunger, USA)		
	Progress in Therapy of Philadelphia Positive ALL (Farhad Ravandi, USA)		
12:30-13:00	WORKING PARTY REPORTS		
13:00-13:30	AWARD CEREMONY & CLOSING MEETING		

* Sessions will be presented in English. Only [KOR] marked sessions will be presented in Korean.

ICKSH 2018
& 59th ANNUAL MEETING

DAILY PROGRAM

March 29 (Thurday)

March 30 (Friday)

March 31 (Saturday)

DAILY PROGRAM March 29 (Thursday)

07:30 - **Registration** — Lobby

08:00 - **Opening Remarks** — Vista 1

08:00-09:00 **Oral Presentation 01** (Eng.) — Vista 1

Chairs Chan-Jeoung Park (University of Ulsan College of Medicine, Korea)
In Ho Kim (Seoul National University College of Medicine, Korea)

OP01-1 Immature Platelet Fraction (IPF): A Useful Marker for Evaluating the Cause of Thrombocytopenia and Predicting Platelet Recovery
Kibum Jeon (Departments of Laboratory Medicine, Hallym University Sacred Heart Hospital, Korea)

OP01-2 Acacia Senegal Supplementation Improve Dyslipidemia in Sickle Cell Anemia Novel Effect of Gum Arabic
Lamis Kaddam (Department of Physiology, Alneelain University Faculty of Medicine, Sudan)

OP01-3 Proof of Concept - Leukodepleted Red Blood Cells by Double Filtration Can Replace Irradiated Blood
Se Jong Chun (Department of Laboratory Medicine, Chonnam National University Medical School, Korea)

OP01-4 Establishing of Reference Intervals for 16 Complete Blood Count Parameters in Healthy Elderly People
Eun Jin Lee (Department of Laboratory Medicine, Hallym University College of Medicine, Korea)

08:00-09:00 **Oral Presentation 02** (Eng.) — Vista 2

Chairs Ki Young Kwon (Keimyung University School of Medicine, Korea)
Hye Lim Jung (Sungkyunkwan University School of Medicine, Korea)

OP02-1 The Spectrum of Anemia in Therapy Naive Patients with Lymphoma and Myeloma from North India
Gaurav Prakash (Department of Internal Medicine, Clinical Hematology Unit, India)

OP02-2 Successful Treatment of Refractory Pure Red Cell Aplasia with Sirolimus
Zhangbiao Long (Department of Hematology, Peking Union Medical College Hospital, China)

OP02-3 Dynamics of CMV and EBV Loads after Rabbit ATG and Cyclosporine : A Prospective Observational Study
Sung Soo Park (Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea)

OP02-4 Helicobacter Pylori Testing in Patients with Pernicious Anemia
Ik Chan Song (Department of Internal Medicine, College of Medicine, Chungnam National University, Korea)

08:00-09:00 **Oral Presentation 03** (Kor.) — Vista 3

Chairs Chul-Won Choi (Korea Universty College of Medicine, Korea)
Won-Sik Lee (Inje University College of Medicine, Korea)

OP03-1 Treatment Outcome and Prognostic Factors of Precursor T-Acute Lymphoblastic Leukemia in Children
Hyery Kim (Department of Pediatric, University of Ulsan College of Medicine, Asan Medical Center, Korea)

DAILY PROGRAM March 29 (Thursday)

OP03-2 Allogeneic Hematopoietic Stem Cell Transplantation for Childhood Myelodysplastic Syndrome
Jae Won Yoo (Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center Children's Hospital, Korea)

OP03-3 Cell Therapy to Control Relapsed AML following Allogeneic Stem Cell Transplantation
Woo Chan Park (Department of Internal Medicine, Seoul National University Hospital, Korea)

OP03-4 Discrepancy in Efficacy of Disulfiram between NUP98-PHF23 Fusion Acute Myelogenous Leukemia
Eun Sil Park (Department of Pediatrics, Institute of Health Science, College of Medicine Gyeongsang National University, Genetics Branch, Center for Cancer Research , National Cancer Institute/National Institute of Health, Korea)

OP03-5 Arsenic Trioxide-Based Initial Treatment for Acute Promyelocytic Leukemia with High-Risk Features
Gi June Min (Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, Korea)

OP03-6 Feasibility of Blinatumomab Salvage for Adult Patients with Relapsed or Refractory Ph-Negative ALL
Jae-Ho Yoon (Department of Hematology, Catholic Blood and Marrow Transplantation Center, Leukemia Research Institute, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea)

09:00-10:00 **[ES01] Multiple Myeloma** (Kor.) — Vista 1

Chairs Ki Hyun Kim (Sungkyunkwan University School of Medicine, Korea)
Jin Seok Kim (Yonsei University College of Medicine, Korea)

ES01-1 Monoclonal Gammopathy of Renal Significance
Jung Eun Lee (Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea)

ES01-2 Smoldering Multiple Myeloma
Byung-Su Kim (Department of Hemato-Oncology, Hallym University College of Medicine, Korea)

ES01-3 Next Generation Sequencing in Multiple Myeloma
Miyoung Kim (Department of Laboratory Medicine, Hallym University College of Medicine, Korea)

09:00-10:00 **[ES02] Typical and Atypical Chronic Myelogenous Leukemia** (Kor.) — Vista 2

Chairs Chul Won Jung (Sungkyunkwan University School of Medicine, Korea)
Suk Joong Oh (Sungkyunkwan University School of Medicine, Korea)

ES02-1 Optimal First-line Treatment of Chronic Phase CML
Kyoung Ha Kim (Division of Hematology-Oncology, Department of Internal Medicine, Soonchunhyang University College of Medicine, Korea)

ES02-2 Update on the Treatment of CML in Children
Jae Wook Lee (Department of Pediatrics, College of Medicine, The Catholic University of Korea, Korea)

ES02-3 BCR-ABL1 Negative Hematologic Neoplasms; Diseases that are Similar to but Different from CML
Hawk Kim (Division of Hematology, Gachon University College of Medicine, Korea)

DAILY PROGRAM March 29 (Thursday)

09:00-10:00 **[ES03] Thrombotic Microangiopathy** (Kor.) — Vista 3

Chairs Kyung Duk Park (Chonbuk National University Medical School, Korea)
Soo Mee Bang (Seoul National University College of Medicine, Korea)

ES03-1 Childhood aHUS
Hae Il Cheong (Department of Pediatrics, Seoul National University College of Medicine, Korea)

ES03-2 Adult aHUS
Youngil Koh (Hematology & Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine, Korea)

ES03-3 Management of TTP
Doyeun Oh (Department of Internal Medicine, CHA University School of Medicine, Korea)

10:00-10:20 Coffee Break — Lobby

10:20-11:40 **[SS01] Single Cell Genomics** (Eng.) — Vista 1

Chairs Woong Yang Park (Sungkyunkwan University School of Medicine, Korea)
Dong Soon Lee (Seoul National University College of Medicine, Korea)

SS01-1 Single Cell Analysis of Multiple Myeloma
Woong-Yang Park (Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Korea)

SS01-2 Characteristics of Tumor Infiltrating Lymphocytes Revealed by Single Cell RNA Sequencing
Zemin Zhang (BIOPIC and School of Life Sciences, Peking University, China)

SS01-3 Dissecting the Cellular and Genetic Composition of Pediatric Leukemias by Single-Cell Genomics
Charles Gawad (Department of Oncology, Department of Computational Biology, St. Jude Children's Research Hospital, USA)

10:20-11:40 **[SS02] (KAI-KSH JOINT) Cancer Immunology** (Eng.) — Vista 2

Chairs Jae Hoon Lee (Gachon University College of Medicine, Korea)
Chung Gyu Park (Seoul National University College of Medicine, Korea)

SS02-1 Immune Checkpoint Inhibition in Hematologic Malignancy - Focusing on Multiple Myeloma
Yoon Seok Choi (Department of Internal Medicine, Chungnam National University College of Medicine, Korea)

SS02-2 A New Antigen Presenting Cell based Therapeutic Cancer Vaccine
Chang-yuil Kang (Laboratory of Immunology, College of Pharmacy, Seoul National University, Korea)

SS02-3 Chimeric Antigen Receptor-Engineered Natural Killer Cell Immunotherapy for Cancer
Kyung-Nam Koh (Division of Pediatric Hematology/Oncology, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea)

SS02-4 Post-transplant Immunotherapy with WT1-speci c CTLs for High-risk Acute Myelogenous Leukemia
Tai-Gyu Kim (Department of Microbiology, Catholic Hematopoietic Stem Cell Bank, College of Medicine, The Catholic University of Korea, Korea)

DAILY PROGRAM March 29 (Thursday)

11:40-11:50 Break — Lobby

11:50-12:50 **Oral Presentation 04** (Eng.) — Vista 1

Chairs Byung-Su Kim (Hallym University College of Medicine, Korea)
Won Seog Kim (Sungkyunkwan University School of Medicine, Korea)

OP04-1 Inflammatory Factor-Based Scoring System in DLBCL in the Rituximab Era
Ji Hyun Lee (Department of Internal Medicine, Dong-A University College of Medicine, Korea)

OP04-2 Clinical Features and Treatment Outcomes of Limited State Mantle Cell Lymphoma (CISL1606)
Jae-Cheol Jo (Department of Hematology and Oncology, Ulsan University Hospital, Korea)

OP04-3 Poor Clinical Outcome of Epstein-Barr Virus Associated Secondary Hemophagocytic Lymphohistiocytosis
Jae-Ho Yoon (Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, Korea)

OP04-4 3.5-Yr Follow-Up of Ibrutinib-Treated Relapsed/Refractory Mantle Cell Lymphoma Patients: Pooled Analysis
Seok-Goo Cho (Department of Hematology, Seoul St. Mary's Hospital, Korea)

11:50-12:50 **Oral Presentation 05** (Eng.) — Vista 2

Chairs Jae Yong Kwak (Chonbuk National University Medical School, Korea)
Seok Lee (College of Medicine, The Catholic University of Korea, Korea)

OP05-1 Clinical Significance of Secondary-Type Mutations in MDS and AML
Joon-Ho Moon (Department of Hematology and Oncology, Kyungpook National University Hospital, Korea)

OP05-2 Comparable Outcomes of RIC to MAC-HCT by MRD Kinetics in Adults with Ph-Positive ALL in CR1
Jae-Ho Yoon (Department of Hematology Catholic BMT Center, Leukemia Research Institute , Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea)

OP05-3 Comprehensive Analysis of Genetic Variations in Patients with Acute Lymphoblastic Leukemia
Borahm Kim (Department of Laboratory Medicine, Yonsei University College of Medicine, Korea)

OP05-4 Molecular Scoring System integrated with IPSS-R in Korean Myelodysplastic syndrome
Hee Sue Park (Department of Laboratory Medicine, Seoul National University College of Medicine, Korea)

11:50-12:50 **Oral Presentation 06** (Eng.) — Vista 3

Chairs Joon Seong Park (Ajou University School of Medicine, Korea)
Keon Hee Yoo (Sungkyunkwan University School of Medicine, Korea)

OP06-1 Decitabine Versus Intensive Chemotherapy for Induction Treatment of Elderly Patients with Acute Myeloid Leukemia
Eun-Ji Choi (Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea)

OP06-2 The Role of WT-1 as a Potential Marker to Predict Prognosis and Monitor Minimal Residual Disease
Seung-Hwan Shin (Department of Hematology, Yeouido St. Mary's Hospital, The Catholic University of Korea, Korea)

DAILY PROGRAM March 29 (Thursday)

OP06-3 Prognostic Factors in Children with Core Binding Factor Acute Myeloid Leukemia
Jae Wook Lee (Department of Pediatrics, The Catholic University of Korea, Korea)

OP06-4 Registry-Based Study of Hematopoietic Stem Cell Transplantation in Korean Children
Hee Young Ju (Department of Center for Pediatric Cancer, National Cancer Center, National Cancer Control Institute, Korea)

12:50-13:00 Break — Lobby

13:00-14:00 **Luncheon Satellite Symposium 1** (Eng.) KYOWA KIRIN — Vista 1

Chair Cheol Won Suh (University of Ulsan College of Medicine, Korea)

Updated Febrile Neutropenia Management
Won Seog Kim (Sungkyunkwan University School of Medicine, Korea)

13:00-14:00 **Luncheon Satellite Symposium 2** (Eng.) NOVARTIS — Vista 2

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

It's Time We Go Deeper
Pierre Laneuville (McGill University Health Centre Montreal, Canada)

13:00-14:00 **Luncheon Satellite Symposium 3** (Eng.) HANDOK — Vista 3

Chair Doyeun Oh (College of Medicine, CHA University, Korea)

Complement Mediated Glomerular Disease(Focusing on aHUS): Everything has Changed in the Last 10 Years but Still a Lot to Do
Giuseppe Remuzzi (Mario Negri Institute for Pharmacological Research, Italy)

14:00-15:20 **[PL01] Precision Hematology in Genomics Era** (Eng.) — Vista 1-3

Chairs Yoo-Hong Min (Yonsei University College of Medicine, Korea)
Sun Hee Kim (Sungkyunkwan University School of Medicine, Korea)

PL01-1 Precision Medicine in CLL
Constantine Tam (Peter MacCallum Cancer Centre, St Vincent's Hospital and University of Melbourne, Australia)

PL01-2 The Clinical Management of FLT3-Mutated AML
Mark Levis (Johns Hopkins School of Medicine, USA)

15:20-15:40 Coffee Break — Lobby

DAILY PROGRAM March 29 (Thursday)

15:40-17:00 **[EHA-KSH Joint Symposium 01] Myelodysplastic Syndrome** (Eng.) — Vista 1-2

Chairs Je-Hwan Lee (University of Ulsan College of Medicine, Korea)
Valeria Santini (University of Florence, Italy)

EHA-KSH-01 The Best Prediction of Prognosis for MDS: How to Integrate Clinical and Molecular Data
Valeria Santini (University of Florence, Italy)

EHA-KSH-02 Clinical Effects of Somatic Mutations in MDS
Je-Hwan Lee (Department of Hematology, University of Ulsan College of Medicine, Korea)

EHA-KSH-03 Pathogenesis and Management of Chronic Myelomonocytic Leukemias
Raphael Itzykson (Department of Hematology, Paris Diderot University, France)

EHA-KSH-04 Hypomethylating Therapy in Stem Cell Transplantation for MDS
Yoo-Jin Kim (Department of Hematology, College of Medicine, The Catholic University of Korea, Korea)

15:40-17:00 **[SP01] Updates on Cellular Therapies** (Eng.) — Vista 3

Chairs Ulrike Koehl(University Hospital Leipzig and Hannover Medical School, Germany)
Tai-Gyu Kim (College of Medicine, The Catholic University of Korea, Korea)

SP01-1 CAR T Treatment for ALL
Jae Park (Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, USA)

SP01-2 CAR Expressing Effector Cells in Stem Cell Transplantation
Ulrike Koehl(University Hospital Leipzig and Hannover Medical School, Germany)

SP01-3 Ex Vivo T cell-depleted Haploidentical Hematopoietic Cell Transplantation and Cellular Therapy Post-transplantation
Ho Joon Im (Department of Pediatrics, University of Ulsan College of Medicine, Korea)

17:00-17:10 Coffee Break — Lobby

17:10-18:10 **Oral Presentation 07** (Eng.) — Vista 1

Chairs Jong Ho Won (Soon Chun Hyang University College of Medicine, Korea)
Joo Seop Chung (Pusan National University College of Medicine, Korea)

OP07-1 The Clinical Outcomes of Lenalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma
Ho Sup Lee (Department of Internal Medicine, Kosin University College of Medicine, Korea)

OP07-2 Prognostic Significance of Clonal Evolution by Bone Marrow Cytogenetic Analysis in Multiple Myeloma
Chang Ahn Seol (Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea)

OP07-3 3-Methyladenine Potentiates Apoptosis of Myeloma Cells via Mitochondrial Reactive Oxygen Species
Yeung-Chul Mun (Department of Hematology, Ewha Womans University, Korea)

DAILY PROGRAM March 29 (Thursday)

OP07-4 The Safety and Efficacy of Pomalidomide in Combination with Cyclophosphamide and Dexamethasone (PCD)
Ho Sup Lee (Department of Internal Medicine, Kosin University College of Medicine, Korea)

17:10-18:10 **Oral Presentation 08** (Eng.) Vista 2

Chairs Seong Kyu Park (Soon Chun Hyang University College of Medicine, Korea)
Yoo-Jin Kim (College of Medicine, The Catholic University of Korea, Korea)

OP08-1 Targeted NGS Identifies a Novel Nonsense Mutation in SPTB for Hereditary Spherocytosis
Joon Hong Park (Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea)

OP08-2 Mitochondrial Genomic Analysis in Patients with Myelodysplastic Syndromes and Other Myeloid Malignancies
Seon Young Kim (Department of Laboratory Medicine, Chungnam National University School of Medicine, Chungnam National University Hospital, Cancer Research Institute, Korea)

OP08-3 Comprehensive Genomic Analyses of Core-Binding Factor AML from Serial Samples
Taehyung Kim (Department of Computer Science, University of Toronto, The Donnelly Centre for Cellular and Biomolecular Research, Canada)

OP08-4 TET2 and MicroRNA-22 in Myelodysplastic Syndrome Patients who Received Hypomethylating Agents
Se Hyung Kim (Department of Internal Medicine, Division of Hemato-Oncology, Soonchunhyang University Bucheon Hospital, Korea)

17:10-18:10 **Oral Presentation 09** (Eng.) Vista 3

Chairs June-Won Cheong (Yonsei University College of Medicine, Koreal)
Sung-Hyun Kim (Dong-A University College of Medicine, Korea

OP09-1 Evaluate the Effect of Imatinib in Treatment Chronic Myeloid Leukemia in Children
Quoc Thanh Nguyen (Department of Hematology, University of Medicine and Pharmacy in Ho Chi Minh city , 2nd Pediatric, Blood Transfusion and Hematology in Ho Chi Minh city, Ha Noi Medical University, Vietnam)

OP09-2 Evaluation of 10-Year Imatinib's Treatment E ects on Chronic Myeloid Leukemia in Chronic Phase
Nguyen Phuong Dung Co (Department of Hematology, Pham Ngoc Thach Medical University, Ha Noi Medical University, Blood Transfusion and Hematology in Ho Chi Minh city, Vietnam)

OP09-3 The Significance of Very Early Molecular Response with Frontline Dasatinib Treatment in CML Patients
Won-Sik Lee (Department of Internal Medicine, Inje University Busan Paik Hospital, Korea)

OP09-4 Deeper Molecular Response in Newly Diagnosed CML-CP Patients Receiving Radotinib: RERISE 3 Years FU
Youngrok Do (Department of Hematology and Oncology, Department of Medicine, Dongsan Medical Center, Keimyung University, Korea)

18:10-18:40 **Poster Presentation 01** Exhibition Hall, B3

18:40-20:00 **Welcome Reception** Vista Hall Lobby, B2

DAILY PROGRAM March 30 (Friday)

08:00-09:00 **Oral Presentation 10** (Eng.) Vista 1

Chairs Young-Ho Lee (Hanyang University College of Medicine, Korea)
Ki-Seong Eom (College of Medicine, The Catholic University of Korea, Korea)

OP10-1 Gene Spectrum Analysis of Thalassemia Carriers Residing in Northern China
Wenzhe Zhou (Department of Hematology, Peking Union Medical Collage, Chinese Academe of Medical Science, China)

OP10-2 Comparison of Gene Spectrum of Thalassemia in Northern, Southern China and Southeast Asia
Quexuan Cui (Department of Hematology, Peking Union Medical Collage Hospital, Chinese Academe of Medical Science, China)

OP10-3 ThalPred: A Web-Based Decision Making Tool for Discriminating Thalassemia Trait and Iron Deficiency
Pornlada Nuchnoi (Department of Clinical Microscopy, Faculty of Medical Technology, Mahidol University, Thailand)

OP10-4 Epidemiology of Hereditary Hemolytic Anemia for 10 Years (2007-2016): RBC Disorder WP Study
Ye Jee Shim (Department of Pediatrics, Keimyung University School of Medicine and Dongsan Medical Center, Korea)

08:00-09:00 **Oral Presentation 11** (Eng.) Vista 2

Chairs Seok-Lae Chae (College of Medicine, Dongguk University, Korea)
Dae-Chul Jeong (College of Medicine, The Catholic University of Korea, Korea)

OP11-1 Nutritional Iron Deficiency Anemia: Magnitude and Its Predictors among School Age Children, Southwest, Ethiopia
Amare Desalegn Wolide (Department of Biomedical Sciences, Jimma University, Ethiopia)

OP11-2 Prevalence of Inherited Hemoglobin Disorders and Relationships with Anemia and Micronutrient Status
Yannick Oyono (Department of Medical Labortory Sciences, University of Buea, Centre Pasteur, Cameroon)

OP11-3 Impact of Thrombocytopenia on In-Hospital Outcome in Patients with Acute STEMI
Ru Liu (Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, China)

OP11-4 Important Factors to Increase the Survival in Hemophilia Patient with Life-Threatening Hemorrhage
Kun Soo Lee (Department of Pediatrics, Kyungpook National University School of Medicine, Korea)

08:00-09:00 **Oral Presentation 12** (Kor.) Vista 3

Chairs Ho Jin Shin (Pusan National University College of Medicine, Korea)
Seonyang Park (Inje University College of Medicine, Korea)

OP12-1 Comparison of Outcomes between Unrelated Donor and Haploidentical Transplantation in Aplastic Anemia
Sung Soo Park (Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea)

OP12-2 Role of FDG PET for Evaluation of Bone Marrow Status and Prognosis Prediction in T-Cell Lymphomas
Go-Un Woo (Department of Internal Medicine, Seoul National University Hospital, Korea)

OP12-3 Nutritional Status and Cardiovascular Risk Factors Affect Survival of DLBCL
Ji Hyun Lee (Department of Internal Medicine, Dong-A University College of Medicine, Korea)

DAILY PROGRAM March 30 (Friday)

OP12-4 Experience of Levetiracetam for Prevention of Busulfan-Induced Seizures in Adult HSCT Patients
Soo-Jeong Kim (Department of Internal Medicine, Yonsei University College of Medicine, Korea)

OP12-5 Clinical Factors to Predict the Engraftment in Low CD34 Count Autologous Stem Cell Transplantation
Sang-A Kim (Department of Internal Medicine, Seoul National University Hospital, Korea)

OP12-6 Efficacy and Safety of Bendamustine Plus Rituximab as Early Salvage Treatment in Relapsed/Refractory NHL
Young-Woo Jeon (Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, Korea)

09:00-10:20 **[SS03] Recent Advances in Acute Promyelocytic Leukemia** (Eng.) Vista 1

Chairs Hee-Je Kim (College of Medicine, The Catholic University of Korea, Korea)
Lionel Ades (Hôpital Saint-Louis, Paris Diderot University, France)

SS03-1 JALSG Prospective Study for APL
Akihiro Takeshita (Department of Transfusion and Cell Therapy, Hamamatasu University School of Medicine, Japan)

SS03-2 Therapy of APL
Lionel Ades (Hematology, Hôpital Saint-Louis, Paris Diderot University, France)

SS03-3 Strategies to Define High-risk Patients in APL
Byung-Sik Cho (Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea)

09:00-10:20 **[SS04] Recent Advances in Natural Killer T-cell Lymphoma** (Eng.) Vista 2

Chairs Seok-Goo Cho (College of Medicine, The Catholic University of Korea, Korea)
Wee Joo Chng (National University Cancer Institute, Singapore)

SS04-1 Molecular Pathogenesis of NKTL
Wee Joo Chng (National University Cancer Institute, Singapore)

SS04-2 Recent Advances in NK/T-Cell Lymphoma
Yok Lam Kwong (Department of Medicine, University of Hong Kong, Hong Kong)

SS04-3 Beyond Current Standard Care of ENKTL
Won Seog Kim (Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea)

09:00-10:00 **Oral Presentation 13** (Eng.) Vista 3

Chairs Myungshin Kim (College of Medicine, The Catholic University of Korea, Korea)
Jin Yeong Han (Dong-A University College of Medicine, Korea)

OP13-1 Quality of Life in Patients with Type I Gaucher Disease after Long Term Enzyme Replacement Therapy
Hongmin Li (Department of Hematology, Peking Union Medical College Hospital, China)

OP13-2 Hematological Finding and Clinical Profile in Pulmonary Tuberculosis among HIV Patients
Petrus Kanisius Yogi Hariyanto (Department of Medicine, Faculty of Medicine, Udayana University, Indonesia)

DAILY PROGRAM March 30 (Friday)

OP13-3 Cefepime Versus Cefepime Plus Amikacin For Febrile Neutropenia In Pediatric Cancer Patients
Na Hee Lee (Department of Pediatrics, Cha Bundang Medical Center, Cha University, Korea)

OP13-4 Detection of Bacteremia MRSA Using a Novel Isothermal Amplification with SPR Biosensor Methodology
Zhenbo Xu (Department of Microbial Pathogenesis, School of Food Sciences and Engineering, South China University of Technology, Guangdong Province Key Laboratory for Green Processing of Natural Products and Product Safety, School of Dentistry, University of Maryland, China)

10:20-10:30 Coffee Break Lobby

10:30-11:50 **[PL02] Targeting Leukemic Stem Cells** (Eng.) Vista 1-3

Chairs Hyeoung-Joon Kim (Chonnam National University Medical School, Korea)
Dong-Wook Kim (College of Medicine, The Catholic University of Korea, Korea)

PL02-1 Human Myeloid Leukemia Stem Cells
Koichi Akashi (Department of Medicine and Biosystemic Science, Graduate School of Medical Science, Kyushu University, Japan)

PL02-2 Pre-Cancerous Stem Cells in MDS and AML: Significance, Mechanisms, and Therapeutic Targeting
Ulrich Steidl (Department of Cell Biology, and Department of Medicine, Albert Einstein College of Medicine, USA)

11:50-12:00 Break Lobby

12:00-13:00 **Luncheon Satellite Symposium 4** (Eng.) AMGEN Vista 1

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

Treatment of Multiple Myeloma in Relapse
Keith Stewart (Mayo Clinic, USA)

12:00-13:00 **Luncheon Satellite Symposium 5** (Eng.) Bristol-Myers Squibb Vista 2

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

Emerging Trends in CML Management
Elias Jabbour (Leukemia Department, MD Anderson Cancer Center, USA)

12:00-13:00 **Luncheon Satellite Symposium 6** (Eng.) HANDOK Vista 3

Chair Jong Wook Lee (College of Medicine, The Catholic University of Korea, Korea)

HSCT Early Complications: Focus on Severe Hepatic Veno-occlusive Disease;
- The Revised EBMT Diagnostic and Severity Criteria for Adults and an Update on Defibrotide
Mohamad Mohty (Clinical Hematology and Cellular Therapy Dpt., Sorbonne University, Hôpital Saint-Antoine, France)

DAILY PROGRAM March 30 (Friday)

13:00-14:20 **[SS05] Cell Death Mechanism** (Eng.) — Vista 1

Chairs Myung-Geun Shin (Chonnam National University Medical School, Korea)
Yong Goo Kim (College of Medicine, The Catholic University of Korea, Korea)

SS05-1 Apoptotic Cell Death
Soo Youl Kim (Cancer Microenvironment Branch, Division of Cancer Biology, National Cancer Center, Korea)

SS05-2 CHIP Controls Necroptosis through Ubiquitylation- and Lysosome-Dependent Degradation of RIPK3
Jaewhan Song (Department of Biochemistry, Yonsei University, Korea)

SS05-3 Functional Isolation of New Modulators in Apoptosis and Necroptosis
Yong-Keun Jung (School of Biological Science, Seoul National University, Korea)

13:00-14:20 **[SS06] Bone Marrow Failure Syndrome** (Eng.) — Vista 2

Chairs Ki Woong Sung (Sungkyunkwan University School of Medicine, Korea)
Danielle Townsley (Clinical Development – Oncology, Medimmune LLC, USA)

SS06-1 Non-Transplant Therapy for Bone Marrow Failure
Danielle Townsley (Clinical Development – Oncology, Medimmune LLC, USA)

SS06-2 Role of Microenvironment and Genetics in BM Failure
Myungshin Kim (Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea)

SS06-3 Inherited BM Failure Syndrome
Hoon Kook (Department of Pediatrics, Chonnam National University Medical School, Korea)

13:00-14:20 **[SS07] (KOGO-KSH Joint) Cancer Genomics** (Eng.) — Vista 3

Chairs Sung-Soo Yoon (Seoul National University College of Medicine, Korea)
Hyoung-Pyo Kim (Yonsei University College of Medicine, Korea)

SS07-1 Variability in Chromatin Architecture and Associated DNA Repair at Genomic Positions Containing Somatic Mutations
Seon-Young Kim (Gene Editing Research Center, Korea Research Institute of Bioscience & Biotechnology (KRIBB), Korea)

SS07-2 Deciphering the Cell-of-Origin Harboring Driver Mutations in Brain Tumors
Jeong-Ho Lee (Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Korea)

SS07-3 Contribution of Germline Variants in Pan-Cancer Development
Youngil Koh (Hematology & Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine, Korea)

SS07-4 Developing a Genetic Data based Prognostic Model for Hematologic Cancer
SeungHyun Jung (Cancer Evolution Research Center, College of Medicine, The Catholic University of Korea, Korea)

14:20-14:40 Coffee Break — Lobby

DAILY PROGRAM March 30 (Friday)

14:40-15:40 **[Asian Hematology Network: JSH-KSH Joint Symposium] Explore Deep Inside the Asian Hematology Network** (Eng.) — Vista 1-2

Chairs Seishi Ogawa (Graduate School of Medicine, Kyoto University, Japan)
Hwi-Joong Yoon (Kyung Hee University College of Medicine, Korea)

JSH-KSH-01 AML Prognosis based on Clinical and Genomic Data
Hyeoung-Joon Kim (Department of Internal Medicine, Chonnam National University Medical School, Korea)

JSH-KSH-02 A Novel Mechanism of Cancer Immune Evasion Via the Disruption of PD-L1 3'-UTR
Seishi Ogawa (Department of Pathology and Tumor Biology, Graduate School of Medicine, Kyoto University, Japan)

14:40-15:40 **Satellite Symposium 7** (Eng.) Roche — Vista 3

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

Advancing Value-Based Approaches in the Treatment of Non-Hodgkin Lymphoma (NHL): Contemporary Strategies and Innovations
Hyeon-seok Eom (National Cancer Center, Korea)

15:40-17:00 **[EHA-KSH Joint Symposium 02] Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria** (Eng.) — Vista 1-2

Chairs Hoon Kook (Chonnam National University Medical School, Korea)
Anita Hill (St. James' University Hospital, UK)

EHA-KSH 02-01 Diagnosis and Management of AA and Refractory Cytopenia of Childhood
Ayami Yoshimi (Department of Paediatrics and Adolescent Medicine, University Children's Hospital, Freiburg, Germany)

EHA-KSH 02-02 Frontline Alternative Donor SCT versus Immunosuppressive Treatment for Children with Severe AA who Lack Matched Related Donor
Hyoung Jin Kang (Department of Pediatrics, Seoul National University College of Medicine, Korea)

EHA-KSH 02-03 An Update on the Management of PNH
Anita Hill (St. James' University Hospital, UK)

EHA-KSH 02-04 Clinical Implications of Renal Dysfunction in Patients with PNH
Jin Seok Kim (Department of Internal Medicine, Yonsei University College of Medicine, Korea)

15:40-17:00 **[SP02] Multiple Myeloma Niche** (Eng.) — Vista 3

Chairs Robert Orlowski (The University of Texas MD Anderson Cancer Center (MDACC), USA)
Je-Jung Lee (Chonnam National University Medical School, Korea)

SP02-1 Clinical Implications of MRD in Multiple Myeloma
Wee Joo Chng (National University Cancer Institute, Singapore)

DAILY PROGRAM March 30 (Friday)

SP02-2 The Ubiquitin-Proteasome Pathway : Friend and Foe in Multiple Myeloma
Robert Orlowski (Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, USA)

SP02-3 Cellular Immunotherapy in Multiple Myeloma
Je-Jung Lee (Department of Hematology-Oncology, Chonnam National University Medical School, Korea)

17:00-17:10 Break — Lobby

17:10-17:50 **Best Abstract Presentation** (Eng.) — Vista 1-2
Chairs Hwi-Joong Yoon (Kyung Hee University College of Medicine, Korea)

BP-01 RAG1 High Expression Associated with IKZF1 Dysfunction in B-cell Acute Lymphoblastic Leukemia
Zheng Ge (Zhongda Hospital, Medical School of Southeast University, China)

BP-02 Decision Supporting Tool for Thrombotic Microangiopathy Based on Machine Learning Technique
Youngil Koh (Hematology & Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine, Korea)

BP-03 Aberrant ARID5B Expression and IKAROS Regulation in ALL
Chunhua Song (Pennsylvania State University Medical College, USA)

17:10-17:50 **Satellite Symposium 8** (Eng.) Takeda ONCOLOGY — Vista 3
Chair Jae Hoon Lee (Gachon University College of Medicine, Korea)

Novel Treatment Strategies for Multiple Myeloma: A Focus on Oral Proteasome Inhibitors
Antonio Palumbo (Distinguished Research Fellow Oncology, Takeda Pharmaceuticals International AG, Italy)

17:50-18:20 **Poster Presentation 02** — Exhibition Hall, B3

18:20-20:00 **Gala Dinner** — Walkerhill Theatre, B1

DAILY PROGRAM March 31 (Saturday)

08:30-09:30 **Oral Presentation 14** (Eng.) — Vista 1
Chairs Deog Yeon Jo (Chungnam National University College of Medicine , Korea)
Chuhl Joo Lyu (Yonsei University College of Medicine, Korea)

OP14-1 Comparative Study of Porcine ALG and Rabbit ATG as a First-Line Treatment of Severe Aplastic Anemia
Miao Chen (Department of Hematology, Peking Union Medical College Hospital, China)

OP14-2 PIGA Mutations as a Predictors of Treatment Response in PNH
Dajeong Jeong (Department of Laboratory Medicine, Seoul National University College of Medicine, Korea)

OP14-3 Prognostic Implications of Renal Dysfunction in Korean Patients with PNH
Jin Seok Kim (Department of Internal Medicine, Division of Hematology, Severance Hospital, Yonsei University College of Medicine, Korea)

OP14-4 Dynamics of PNH Clone in Adult Patients with PNH/aplastic Anemia Following Immunosuppressive Therapy
Sung-Soo Park (Catholic Blood and Marrow Transplantation Center, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea)

08:30-09:30 **Oral Presentation 15** (Eng.) — Vista 2
Chairs Hong Ghi Lee (Konkuk University School of Medicine, Korea)
Deok Hwan Yang (Chonnam National University Medical School, Korea)

OP15-1 Analysis of Genetic Variants Related to the Hepatic Veno-Occlusive Disease in Pediatric Patients Receiving HSCT with Targeted Dose Busulfan Based Conditioning
Jung Yoon Choi (Department of Pediatrics, Cancer Research Institute, Seoul National University College of Medicine, Korea)

OP15-2 Enhanced Immunosuppressive Properties of Human Mesenchymal Stem Cells Primed by Inflammatory Stimuli
Dae Seong Kim (Department of Pediatrics, Stem Cell and Regenerative Medicine Institute for Future Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea)

OP15-3 Ruxolitinib Treatment for Steroid-Refractory Graft-Versus-Host Disease
Han-Seung Park (Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea)

OP15-4 Change of Gut Bacterial Diversity by Antibiotics Correlates with the Occurrence of Intestinal GVHD
Chang-Ki Min (Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, College of Medicine, Korea)

08:30-09:30 **Oral Presentation 16** (Kor.) — Vista 3
Chairs Hyeon Jin Park (National Cancer Center, Korea)
Seongsoo Jang (University of Ulsan College of Medicine, Korea)

OP16-1 Mean Platelet Volume and Platelet Distribution Width Reflect the Pathophysiology of ITP and ET
Eunyup Lee (Department of Laboratory Medicine, Hallym University Sacred Heart Hospital, Korea)

OP16-2 Clinical Features and Outcomes of Borderline Thrombocytopenia: A Single Center Experience
Ik Chan Song (Department of Internal Medicine, College of Medicine, Chungnam National University, Korea)

OP16-3 Genetic Confirmation of Platelet Function Disorders by Diagnostic Exome Sequencing (K-PHOG Study)
Ye Jee Shim (Department of Pediatrics, Keimyung University School of Medicine and Dongsan Medical Center, Korea)

DAILY PROGRAM March 31 (Saturday)

OP16-4 Hot-Line to Increase the Survival in Hemophilia Patient with Life-Threatening Hemorrhage
Kun Soo Lee (Department of Pediatrics, Kyungpook National University School of Medicine, Korea)

OP16-5 Effect of Peramivir on Platelet Counts in Patients with Suspected or Confirmed Influenza Infection
Young-Gon Kim (Department of Laboratory Medicine, Korea University Medical Center, Korea)

OP16-6 Immature Platelet Fraction as a Predictor of Bone Marrow Cellularity in Thrombocytopenic Patients
Ha Jin Lim (Department of Laboratory Medicine, Chonnam National University Medical School and Chonnam National University Hwasun Hospital, Korea)

09:30-10:50 **[SS08] Current Progress in Pediatric Acute Leukemia** (Eng.) Vista 1

Chairs Stephen Hunger (Children's Hospital of Philadelphia, USA)
Ho Joon Im (University of Ulsan College of Medicine, Korea)

SS08-01 New Developments in the Treatment of Newly Diagnosed and Relapsed ALL
Stephen Hunger (Division of Pediatric Oncology, Center for Childhood Cancer Research, Children's Hospital of Philadelphia, USA)

SS08-02 Therapy Optimization in Infant ALL
Daisuke Tomizawa (Division of Leukemia and Lymphoma, Children's Cancer Center, National Center for Child Health and Development, Japan)

SS08-03 Genomic Landscape and Therapy Optimization of Pediatric Mixed Phenotype Acute Leukemia
Hiroto Inaba (Leukemia/Lymphoma Division, Department of Oncology, St. Jude Children's Research Hospital, USA)

09:30-10:50 **[SS09] Detection of Minimal Residual Disease in Hematologic Malignancy** (Eng.) Vista 2

Chairs Hee Young Shin (Seoul National University College of Medicine, Korea
Alberto Orfao (University of Salamanca (USAL), Spain)

SS09-01 MRD Detection in Acute Leukemia, CLL and Multiple Myeloma
Alberto Orfao (University of Salamanca (USAL), Spain)

SS09-02 NGS-based Assessment of Clonality & MRD Determination in ALL
In-Suk Kim (Department of Laboratory Medicine, Pusan National University School of Medicine, Korea)

SS09-03 [Selected Short Talk I] Development and Preliminary Evaluation of Customized Pan-Blood Cancer NGS Panel
Jun Hyung Lee (Department of Laboratory Medicine, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Korea)

SS09-04 [Selected Short Talk II] Evaluation of Two Commercial Kits for Flow Cytometric MRD Detection in B-ALL
Ari Ahn (Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea)

09:30-10:30 **Oral Presentation 17** (Eng.) Vista 3

Chairs Sang Kyun Sohn (Kyungpook National University School of Medicine, Korea)
Nak Gyun Chung (College of Medicine, The Catholic University of Korea, Korea)

DAILY PROGRAM March 31 (Saturday)

OP17-1 Expression of Inhibitory Receptors on T cells and Inhibitory Ligands on Leukemic Blasts in Childhood acute Leukemia
Kyung-Nam Koh (Department of Pediatrics, Division of Pediatric Hematology and Oncology, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea)

OP17-2 Reversal of Cytarabine Resistance in AML-OCI2 Cell Line after Na/H Exchanger 1 Modulation
June-Won Cheong (Department of Internal Medicine, Division of Hematology, Yonsei University College of Medicine, Korea)

OP17-3 The Role of Myeloid-Derived Suppressor Cell-Like Blasts in Acute Myeloid Leukemia
Shin Young Hyun (Department of Internal Medicine, Division of Hematology and Oncology, Yonsei University Wonju College of Medicine, Korea)

OP17-4 The Clinical Implication of Cytogenetic Clonal Evolution Pattern in Relapsed Adult ALL Patients
Ji Hyun Lee (Department of Internal Medicine, Dong-A University College of Medicine, Korea)

10:50-11:10 Coffee Break Lobby

11:10-12:30 **[PL03] Development of Precision Medicine Trials** (Eng.) Vista 1-3

Chairs Hong Hoe Koo (Sungkyunkwan University School of Medicine, Korea)
Kyoo Hyung Lee (University of Ulsan College of Medicine, Korea)

PL03-01 Development of Precision Medicine Trials for ALL
Stephen Hunger (Division of Pediatric Oncology, Center for Childhood Cancer Research, Children's Hospital of Philadelphia, USA)

PL03-02 Progress in Therapy of Philadelphia Positive ALL
Farhad Ravandi (Department of Leukemia, University of Texas – MD Anderson Cancer Center, USA)

12:30-13:00 **Working Party Reports** Vista 1-3

13:00-13:30 **Award Ceremony & Closing Meeting** Vista 1-3

ICKSH 2018
& 59th ANNUAL MEETING

POSTER PRESENTATIONS

POSTER PRESENTATIONS

PP-01 ~ PP-22 : Poster Presentation 01

March 29 (Thursday) 18:10-18:40

PP-01 Statin Promotes Apoptosis by Activating JNK Signaling in FLT3-ITD Acute Myeloid Leukemia Cells

Ji Eun Jang[1], So-Young Seol[2], Dohyu Hwang[3], Ju-In Eom[2], Hoi-Kyung Jeung[2], Soo-Jeong Kim[1], Jin Seok 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
[3] Department of Internal medicine, Catholic Kwndong University, Korea

PP-02 The Synergistic Effect of DMNT Inhibitors and Nutlin-3 on Apoptosis of of TP53 Wild Type AML in Vitro

Ji Eun Jang[1], Ju-In Eom[2], Hoi-Kyung Jeung[2], Haerim Chung[1], So-Young Seol[2], Soo-Jeong Kim[1], Jin Seok 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-03 Calcium Blocker-Induced Interference Effects on Steroid Resistance in Acute Lymphoblastic Leukemia

Hyun Joo Jung[1], Eunhee Han[2], Jun Eun Park*[3]
[1] Department of Pediatrics, Ajou University Hospital, Ajou University School of Medicine, Korea
[2] Department of Pediatrics, Ajou University School of Medicine, Korea
[3] Department of Pediatrics, Ajou University Hospital, Ajou University School of Medicine, Korea

PP-04 Role of High-Dose Cytarabine as Consolidation Therapy before Allogeneic HCT for AML without CBF

Yoojin Lee[1], Sangkyun Sohn*[1], Joonho Moon[1], Dongwon Back[1], Hyeoung-Joon Kim[2], Jae-Sook Ahn[2], Seo-Yeon Ahn[2], Sung-Hoon Jung[2]
[1] Hematology, Kyungpook National University Hospital, Korea
[2] Hematology, Chonnam National University Hwasun Hospital, Korea

PP-05 The Efficacy of Daily ATRA Monotherapy as Maintenance Therapy for Newly Diagnosed APL

Yoojin Lee, Sangkyun Sohn, Joonho Moon, Dongwon Back
Hematology, Kyungpook National University Hospital, Korea

PP-06 MiR-424/-503 Regulates Expression of Cobll1 in Chronic Myeloid Leukemia

Seung Hun Han[1], Soo-Hyun Kim[2], Hyoung-June Kim[1], Yoonsung Lee[3], Soo-Young Choi[2], Do-Hyun Kim[4], Aram Lee[5], Kibeom Park[1], Jongmin Kim[5], Je-Min Choi[4], Yonghwan Kim[5], Kyungjae Myung[3], Hongtae Kim[1], Dong-Wook Kim*[2,6]
[1] Department of Biological Sciences, Sungkyunkwan University, Korea
[2] Leukemia Research Institute, The Catholic University of Korea, Korea
[3] Center for Genomic Integrity Institute for Basic Science (IBS), Ulsan National Institute of Science and Technology, Korea
[4] Department of Life Science, Hanyang University, Korea
[5] Department of Life Systems, Sookmyung Women's University, Korea
[6] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

PP-07 Comparison of Treatment Strategies in CML Patients with Suboptimal Molecular Response to Imatinib

Sung-Eun Lee[1,9], Soo-Young Choi[1], Soo-Hyun Kim[1], Saengsuree Jootar[2], Hyeoung-Joon Kim[3], Sang-Kyun Sohn[4], Joon Seong Park[5], Sung-Hyun Kim[6], Dae-Young Zang[7], Suk-Joong Oh[8], Dong-Wook Kim*[1,9]
[1] Leukemia Research Institute, The Catholic University of Korea, Korea
[2] BMT Program, Ramathibodi Hospital, Mahidol University, Thailand
[3] Department of Hematology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Korea
[4] Department of Oncology/Hematology, Kyungpook National University Hospital, Korea
[5] Department of Hematology/Oncology, Ajou University School of Medicine, Korea
[6] Department of Internal Medicine, Dong-A University, College of Medicine, Korea
[7] Department of Internal Medicine, Hallym University College of Medicine, Korea
[8] Department of Internal Medicine, Kangbuk Samsung Hospital, Korea
[9] Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

PP-08 Compound Mutations are the Major Components of Multiple Mutations Detected in TKI Resistant CML

Ki-Hoon Kang[1], Soo-Hyun Kim[1], Soo-Young Choi[1], Sung-Eun Lee[1,2], Hae-Lyun Yoo[1], Mi-Young Lee[1], Hye-Young Song[1], Kyung-Mi Kee[1], Ji-Hyung Suh[1], Seon-Young Yang[1], Eun-Jung Jang[1], Dong-Wook Kim*[1,2]
[1] Leukemia Research Institute, The Catholic University of Korea, Korea
[2] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

POSTER PRESENTATIONS

PP-09 Optimal Time Point for BCR-ABL1 KD Mutation Analysis in CML Patients; Based on 2013 ELN Guideline

Hea-Lyun Yoo[1], Soo-Hyun Kim[1], Soo-Young Choi[1], Mi-Young Lee[1], Hye-Young Song[1], Ki-Hoon Kang[1], Kyoung-Mi Ki[1], Sun-Young Yang[1], Dong-Wook Kim*[1,2]
[1] Leukemia Research Institute, The Catholic University of Korea, Korea
[2] Department of Hematology, The Catholic University of Korea Seoul St. Mary's Hospital, Korea

PP-10 The Impact of Early Molecular Response on Long-Term Survival in CML Patients following TKIs Therapy

Sung-Eun Lee[1,2], Soo-Young Choi[2], Soo-Hyun Kim[2], Hye-Young Song[2], Kyung-Mi Kee[2], Hea-Lyun Yoo[2], Mi-Young Lee[2], Ki-Hoon Kang[2], Ji-Hyung Suh[2], Seon-Young Yang[2], Eun-Jung Jang[2], Dong-Wook Kim*[1,2]
[1] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea
[2] Leukemia Research Institute, The Catholic University of Korea, Korea

PP-11 Outcomes of CML Patients who Have Achieved CCyR but Not MMR after 24 Months on Frontline Imatinib

Sung-Eun Lee[1,9], Won-Sik Lee[2], Young Rok Do[3], Jae-Yong Kwak[4], Sukjoong Oh[5], Sung Hyun Kim[6], Jeong-A Kim[7], Dae Young Zang[8], Soo-Young Choi[9], Dong-Wook Kim*[1,9]
[1] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea
[2] Department of Internal Medicine, Inje University College of Medicine, Inje University Busan Paik Hospital, Korea
[3] Division of Hematology-Oncology, Keimyung University, School of Medicine, Keimyung University Hospital, Korea
[4] Division of Hematology-Oncology, Chonbuk National University Medical School, Chonbuk National University Hospital, Korea
[5] Department of Internal Medicine, School of Medicine, Sungkyunkwan University, Kangbuk Samsung Hospital, Korea
[6] Department of Internal Medicine, Dong-A University College of Medicine, Dong-A University Hospital, Korea
[7] Department of Hematology, The Catholic University of Korea, St. Vincent's Hospital, Korea
[8] Department of Internal Medicine, Hallym University College of Medicine, Hallym University Hospital, Korea
[9] Leukemia Research Institute, The Catholic University of Korea, Korea

PP-12 Pegylated L-Asparaginase Induced Cholestatic Jaundice and Treated with Oral L- Carnitine: A Case Report

Asma Nasir Mahmud[1], Huma Asif[1], Ayisha Imran[1], Tasneem Farzana*[2]
[1] Department of hematology, Chughtai Lab lahore, Pakistan
[2] National centre for blood diseases, National hospital and medical centre , Lahore, Pakistan

PP-13 Molecular Docking to Identify a Novel Inhibitors for Tyrosine Kinase in CML from Alkaloids

Shah Md Shahik[1,2]
[1] Genetic Engineering and Biotechnology, University of Chittagong, Bangladesh
[2] Chronic Disease, Biomedical Research Foundation Bangladesh, Bangladesh

PP-14 Erdheim–Chester Disease (ECD) is an Uncommon Aggressive, Multisystem Immunological Disease among Arab Males

Abdalla Bowirrat, Abdalla Bowirrat
Neuroscience and Genetic, Emms Hospital, Palestine

PP-15 Adverse Drug Reactions to Anti-TB Drugs: Pharmacogenomics Perspective for Identification of Host Genes

Kamal Kishor
Analytical , Institute of Pesticide Formulation Technology, India
Survey of Titanium Dioxide Nanoparaticles Exposure during Pregnancy on Hematological Parameters

PP-16 Survey of Titanium Dioxide Nanoparaticles Exposure during Pregnancy on Hematological Parameters

Cyrus Jalili[1], Faramarz Jalili[2], Mahdi Taghadosi[3], Mohammad Reza Salahshoor[4]
[1] Department of Anatomy and Cell Biology, Medical Biology Research Center, Kermanshah University of Medical Sciences, Iran
[2] Students Research Committee, Students Research Committee, Kermanshah University of medical Sciences, Iran
[3] Department of Immunology, Department of Immunology, Kermanshah University of Medical Sciences, Iran
[4] Department of Anatomy and Cell Biology, Medical Biology Research Center, Kermanshah University of Medical Sciences, Iran

PP-17 Apoptotic Genes Expression Changes of Mice Tissues Exposed to Nicotine

Faramarz Jalili[1], Cyrus Jalili[2]
[1] Students Research Committee, Students Research Committee, Kermanshah University of Medical Sciences, Iran
[2] Department of Anatomy and Cell Biology, Medical Biology Research Center, Kermanshah University of Medical Sciences, Iran

POSTER PRESENTATIONS

PP-18 Prevalence of Glucose-6-Phosphate Dehydrogenase Deficiency among Lao Theung Ethnic Group

Amkha Sanephonasa[1,2], Kamonlak Leecharoenkiat*[1], Chalisa Louicharoen Cheesunthorn[3], Issarang Nuchprayoon[4], Naly Khaminsou[2], Onkham Savongsy[2]

[1] Department of clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, Thailand
[2] Deparment of Laboratory , Faculty of Medical Technology, University of Health Sciences, Laos
[3] Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Thailand
[4] Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Thailand

PP-19 Prognostic Factors and Response to the Hypomethylating Agents in Hypocellular Myelodysplastic Syndromes: A Retrospective Study from the Korean Society of Hematology AML/MDS Working Party

Jungmin Jo[1], Sung Hwa Bae[1], Jinny Park[2], Hong-Ghi Lee[3], Chul Won Choi[4], Yong Park[5], Ho Sup Lee[6], Sung-Hyun Kim[7], Won-Sik Lee[8], Soo-Mee Bang[9], Jun-Ho Jang[10], Inho Kim[11], Je-Hwan Lee[12], June-Won Cheong[13], Seongkyu Park[14], Jong-Ho Won[15], Min Kyoung Kim[16], Hyeok Shim[17], Yeung-Chul Mun[18], Jae-Sook Ahn[19], Deog-Yeon Jo[20], Dae Young Zang[21]

[1] Daegu Catholic Univ. Medical Center, Daegu, Korea
[2] Gil Medical Center Gachon University, Inchon, Korea
[3] Konkuk University School of Medicine, Seoul, Korea
[4] Korea University, Guro Hospital, Seoul, Korea
[5] Korea University, Anam Hospital, Seoul, Korea
[6] Kosin University Gospel Hospital, Busan, Korea
[7] Department of Internal Medicine, Dong-A University College of Medicine, Dong-A University Hospital, Busan, Korea
[8] Inje Univ. Busan Baik-Hospital, Busan, Korea
[9] Seoul national university, Bundang hospital, Seongnam-si, Gyeonggi-do, Korea
[10] Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[11] Seoul national university hospital, Seoul, Korea
[12] Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[13] Yonsei University College of Medicine, Severance Hospital, Seoul, Korea
[14] Hematology/Oncology, SoonchunhyangUniveristyBucheon Hospital, Bucheon, Korea
[15] Soonchunhyang University Hospital, Seoul, Korea
[16] Department of Internal Medicine, Yeungnam University Medical Center, Daegu, Korea
[17] Wonkwang University Hospital, Iksan, Korea
[18] Department of Internal Medicine, EwhaWomans University School of Medicine, Seoul, Korea
[19] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun-Gun, Korea
[20] Department of Internal Medicine, Chungnam National University College of Medicine, Daejeon, Korea
[21] Department of Internal Medicine, Hallym University College of Medicine, Hallym University Hospital, Anyang, Korea, Korean Society of Hematology AML/MDS Working Party

PP-20 Increased Proportion of Th17/Treg T Cells for Early Prediction of Chronic Immune Thrombocytopenia in Children

Hao Gu, Zhenping Chen, Jingyao Ma, Lingling Fu, Jie Ma, Runhui Wu*

Beijing Children Hospital, Capital Medical University, China

PP-21 Torque Teno Virus/Torque Teno-Like Minivirus in Kikuchi-Fujimoto Disease

Yosep Chong[1], Seung Bum Hong[2], Ji Young Lee[1], Eun Jung Lee*[1]

[1] Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Korea
[2] Department of Genetic Analysis, Crimininal Investigation Command, Ministry of National Defense, Korea

PP-22 Genotype-Phenotype Study on Familial Hlh in Korea: A Study from Korea Histiocytosis Working Party

Hyery Kim[1], Kyung Nam Koh[1], Ho Joon Im[1], Hyung Jin Kang[2], Hee Young Shin[2], Jae Wook Lee[3], Nak Gyun Chung[3], Bin Cho[3], Ji Won Lee[4], Kun Hee Yoo[4], Ki Woong Sung[4], Hong Hoe Koo[4], Hee Jo Baek[5], Hoon Kook[5], Kyung Mi Park[6], Eu Jeen Yang[6], Young Tak Lim[6], Eun Sun Yoo[7], Kyung-Ha Ryu[7], Jong Jin Seo*[1]

[1] Pediatrics, University of Ulsan College of Medicine, Asan Medical Center, Korea
[2] Pediatrics, Seoul National University College of Medicine, Korea
[3] Pediatrics, The Catholic University of Korea College of Medicine, Korea
[4] Pediatrics, Sungkyunkwan University School of Medicine, Korea
[5] Pediatrics, Chonnam National University Hwasun Hospital, Korea
[6] Pediatrics, Pusan National University College of Medicine, Korea
[7] Pediatrics, Ewha Womans University College of Medicine, Korea
[8] Pediatrics, Yonsei University College of Medicine, Korea
[9] Pediatrics, Ajou University School of Medicine, Korea
[10] Pediatrics, Yeungnam University College of Medicine, Korea

POSTER PRESENTATIONS

PP-23 ~ PP-46 : Poster Presentation 02

March 30 (Friday) 17:50-18:20

PP-23 Prevalence of Anemia among Chronic Kidney Disease Patients in India: Evidence from a Meta-Analysis

Md Salman Hussain[1], Abul Kalam Najmi[2]

[1] Department of Pharmaceutical Medicine, Jamia Hamdard (Hamdard University), India
[2] Department of Pharmacology, Jamia Hamdard (Hamdard University), India

PP-24 Cell Bead: Affordable Counting Bead by Flow Cytometry

Duangdao Palasuwan, Attakorn Palasuwan

Clinical Microscopy, Faculty of Allied Health Sciences, Department of Clinical Microscopy, Chualongkorn University, Thailand

PP-25 Red Blood Cell Deformability in Patients with Hematologic Neoplasms

Yu Kyung Kim[1], Jae Min Lee[2], Ji Yeon Ham[1], Jang Soo Suh*[1]

[1] Clinical Pathology, Kyungpook National University School of Medicine, Korea
[2] Pediatrics, College of Medicine, Yeungnam University, Korea

PP-26 Bone Marrow and Laboratory Findings in Light Chain Amyloidosis in a Single Center Study

Taegeun Lee, Min Young Lee, Eunkyoung You, Young-Uk Cho, Seongsoo Jang, Chan-Jeoung Park*

Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea

PP-27 Synergistic Effect but Acquisition of Resistance for Danusertib and BKM120 in BL Cell Lines

Jun Liu[1], Junshik Hong*[1,2], Kwang-Sung Ahn[3], Sung-Soo Yoon[1,2]

[1] Cancer Research Institute, Seoul National University College of Medicine, Korea
[2] Department of Internal Medicine, Seoul National University Hospital Seoul National University College of Medicine, Korea
[3] PDXen Biosystems Co., Korea

PP-28 Development and Validation of Mobile Application of Machine Learning Expert Supporting System "ImmunoGenius" for Diagnosis Presumption of Lymphoid Neoplasms Using 1000 Immunohistochemistry Dataset

Yosep Chong, Gyeongsin Park*, Ji Young Lee, Myungjin Choi, Eun Jung Lee

Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Koreaa

PP-29 Seasonal Variation in PE but Not DVT Incidence: A Korean Nationwide Epidemiology Study

Junshik Hong[1], Ju Hyun Lee[2], Ji Yun Lee[2], Won-Il Choi[3], Soyeon Ahn[4], Yun Hee Lee[5], Soo-Mee Bang*[2], Doyeun Oh[6]

[1] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[2] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Korea
[3] Department of Internal Medicine, Keimyung University School of Medicine, Keimyung University Dongsan Medical Center, Korea
[4] Medical Research Collaborating Center, Seoul National University Bundang Hospital, Korea
[5] Environmental Health Center, Seoul National University College of Medicine, Korea
[6] Department of Internal Medicine, CHA university School of Medicine, CHA Bundang Medical Center, Korea

PP-30 Reevaluation of Initial Antiphospholipid Antibody Positivities

Jin-Yeong Han, In-Wha Jeong, Gyu-Dae An, Hyeon-Ho Lim, Kwang-Sook Woo

Laboratory Medicine, Dong-A University College of Medicine, Korea

PP-31 Platelet Proteome and Hypercoagulable State of Non-Splenectomized β-Thalassmia/HbE Patients

Puangpaka Chanpeng[1], Kamonlak Leecharoenkiat*[1], Saowaros Svasti[2], Duncan R. Smith[3], Kittiphong Paiboonsukwong[2], Wannapa Sornjai[3], Wasinee Kheansaard[2]

[1] Department of Clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, Thailand
[2] Thalassemia Research Center, Institute of Molecular Biosciences, Mahidol University, Thailand
[3] Molecular Pathology Laboratory, Institute of Molecular Biosciences, Mahidol University, Thailand

POSTER PRESENTATIONS

PP-32 Von Willebrand Antigen Levels in Blood Group 'O' and Non-O Individuals
Asma Nasir Mahmud, Huma Asif*, Ayisha Imran, Nauman A. Malik
Department of hematology, Chughtai lab lahore, Pakistan

PP-33 Nonstroke Arterial Thromboembolism in Pediatric Patients: A Single Institution Experience in Korea
Hyoung Soo Choi, Chang Won Choi, Heon Min Kim, Young Hwan Song
Pediatrics, Seoul National University Bundang Hospital, Korea

PP-34 Screening of HIV, HBsAg, HCV and VDRL among Voluntary Blood Donors of Western Region of Nepal
Mukunda Raj Kaloun[1], Arnav Ghosh*[2]
[1] Clinical Pathology, Manipal Teaching Hospital, Nepal
[2] Clinical Pathology, Manipal Teaching Hospital, Nepal

PP-35 Prevalence of Anemia among Type 2 Diabetes Mellitus Patients: A Pilot Study
Abul Kalam Najmi[1], Salman Hussain[2]
[1] Department of Pharmacology, Jamia Hamdard, India
[2] Department of Pharmaceutical Medicine, Jamia Hamdard, India

PP-36 Prospsective Phase II Pilot Study to Evaluate the Use of Intravenous Iron in the Treatment of Anemia
Youjin Kim, Jun Ho Jang*, Silvia Park, Chul Won Jung
Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

PP-37 SFKs Inhibitor Bosutinib and Dasatinib Enhances ATRA or ATO Induced NB4 Cell Differentiation
Hee-Jeong Cheong[1], Min Young Lee[2], Kyoung Ha Kim[2], Namsu Lee[2], Sung Hee Lim[2], Jina Yoon[2], Se Hyoung Kim[2], Chan-Kyu Kim[2], Sung Kyu Park[2], Dae Sik Hong[2], Han Jo Kim[2], Sang-Cheol Lee[2], Sang Byung Bae[2], Kyu Taeg Lee[2], Jong-Ho Won*[2]
[1] Institute for Clinical Molecular Biology Research, Soonchunhyang University Hospital, Korea
[2] Division of Hematology-Oncology, Department of Internal Medicine, Soonchunhyang University Hospital, Korea

PP-38 Advanced Serological Evaluation of a Case of Evans Syndrome with Anti D Autoantibody Induced AIHA
Nitin Agarwal, Prashant Pandey
Transfusion Medicine and Transplant immunology, Jaypee Hospital, India

PP-39 Serum NLR and PLR as a Systemic Inflammatory Marker among HIV-TB before Antiretroviral Therapy
Muhammad Faisal Putro Utomo[1], Anindia Reina Yolanda[1], Nur Rizky Amaliah[1], Petrus Kanisius Yogi Hariyanto[1], Ni Made Dewi Dian Sukmawati[2], I Made Susila Utama[2]
[1] Faculty of Medicine, Udayana University, Indonesia
[2] Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Udayana University, Sanglah General Hospital, Indonesia

PP-40 Association between Immunological Status with Hematological Findings among TB-HIV Patients
Anindia Reina Yolanda, Muhammad Faisal Utomo, Yogi Haryanto, Nurrizky Amaliah
Medical Student, Udayana University, Indonesia

PP-41 Clinical Characteristics, Treatment Patterns, and Outcome of Lymphoplasmacytic Lymphoma
Jang Ho Cho[1], Silvia Park[1], Young Hyeh Ko[2], Hee-Jin Kim[3], Sun-Hee Kim[3], Kihyun Kim[1], Won Seog Kim[1], Seok Jin Kim*[1]
[1] Medicine, Samsung Medical Center, Korea
[2] Pathology, Samsung Medical Center, Korea
[3] Laboratory Medicine, Samsung Medical Center, Korea

PP-42 Thrombocytopenia due to Dengue and Vitamin D
Narendra Gemawat
Pediatrics-School health, Hindustan Chamber Chikitsalaya, India

POSTER PRESENTATIONS

PP-43 Clinical Characteristics of Young-Age Venous Thromboembolism: A Nationwide Study in Korea
Chang-Hun Park[1], Inho Kim[2], Soo-Mee Bang[3], Ho-Young Yhim[4], Yeo-Kyeoung Kim[5], Yang-Ki Kim[6], Won-Il Choi[7], Chul Won Jung[8], Doyeun Oh[9], Sun-Hee Kim[1], Hee-Jin Kim*[1]
[1] Department of Laboratory Medicine & Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[2] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[3] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Korea
[4] Department of Internal Medicine, Chonbuk National University Medical School, Korea
[5] Department of Internal Medicine, Chonnam National University College of Medicine, Korea
[6] Department of Internal Medicine, Soonchunhyang University School of Medicine, Korea
[7] Department of Internal Medicine, Keymyung University College of Medicine, Korea
[8] Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[9] Department of Internal Medicine, School of Medicine, CHA University, Korea

PP-44 Effect of the Hydro-Alcoholic Extract of Falcaria Vulgaris on Liver Parameters of Diabetic Rats
Faramarz Jalili[1], Cyrus Jalili[2]
[1] Department of Anatomy and Cell Biology, Students Research Committee, Kermanshah University of Medical Sciences, Iran
[2] Department of Anatomy and Cell Biology, Department of Anatomy and Cell Biology, Kermanshah University of Medical Sciences, Iran

PP-45 Expression of PD-1 in Pediatric Patients with Haploidentical SCT not Correlates with GVHD
Eunkyoung You[1], Seongsoo Jang*[1], Ari Ahn[1], Min Young Lee[1], Young-Uk Cho[1], Chan-Jeoung Park[1], Yu Jin Lee[2], Nu-Ree Park[2], Eun Seok Choi[3], Hery Kim[3], Kyung Nam Koh[3], Ho Joon Im[3], Jong Jin Seo[3]
[1] Department of Laboratory Medicine, Asan Medical Center and University of Ulsan College of Medicine, Korea
[2] Asan Clinical Research Center, Asan Medical Center and University of Ulsan College of Medicine, Korea
[3] Department of Pediatrics, Asan Medical Center and University of Ulsan College of Medicine, Korea

PP-46 Successful Renal Re-Transplant after Desensitization with Plasmapheresis & IVIG in High Risk Patient
Nitin Agarwal, Prashant Pandey
Transfusion Medicine and Transplant Immunology, Jaypee Hospital, India

PP-47 ~ PP-85 : Poster Only

PP-47 Patients with Therapy-Related Myleoid Neoplasm Harboring Normal Karyotype Showed Better Outcomes
Sang-A Kim[1], Junshik Hong*[1], Go-Un Woo[1], Youngil Koh[1], Dong-Yeop Shin[1], Inho Kim[1], Dong Soon Lee[2], Sung-Soo Yoon[1]
[1] Department of Internal Medicine, Seoul National University Hospital, Korea
[2] Department of Laboratory Medicine, Seoul National University Hospital, Korea

PP-48 Micafungin Prophylaxis for Acute Myeloid Leukemia Patients Undergoing Induction Chemotherapy
Hyunkyung Park[1], Jiwon Jeong[1], Jeonghwan Youk[2], Wan Beom Park[1], Dong-Yeop Shin[1,3], Junshik Hong[1,3], Inho Kim[1,3], Nam Joong Kim[1], Sung-Soo Yoon[1,3], Youngil Koh*[4]
[1] Internal Medicine, Seoul National University Hospital, Korea
[2] Korea Advanced Institute of Science and Technology, , Korea
[3] Cancer Research Institute, Seoul National University College of Medicine, Korea
[4] Biomedical Research Institute, Seoul National University Hospital, Korea

PP-49 SET-NUP214 Fusion in Acute Myeloid Leukemia with Massive Hyperdiploidy
Gyu-Dae An[1], In-Hwa Jeong[1], Hyeon-Ho Lim[1], Kwang-Sook Woo[1], Kyeong-Hee Kim[1], Jeong-Man Kim[1], Ji-Hyun Lee[2], Jin-Yeong Han*[1]
[1] Department of Laboratory Medicine, Dong-A University College of Medicine, Korea
[2] Division of Hematology-Oncology, Department of Internal Medicine, Dong-A University College of Medicine, Korea

POSTER PRESENTATIONS

PP-50 Evaluation and Application of RNA Fusion Gene Panel for the Patients with Acute Leukemia
Borahm Kim[1], Saeam Shin[4], Jieun Jang[3], Soo Jeong Kim[3], Seung-Tae Lee[1], June-Won Cheong[2], Chuhl Joo Lyu[3], Yoo Hong Min[2], Jong Rak Choi*[1]
[1] Department of Laboratory Medicine, Yonsei University College of Medicine, Korea
[2] Department of Pediatrics, Yonsei University College of Medicine, Korea
[3] Department of Internal Medicine, Yonsei University College of Medicine, Korea
[4] Department of Laboratory Medicine, Hallym University College of Medicine, Kangnam Sacred Heart Hospital, Korea

PP-51 A Case of Lineage Conversion with Clonal Evolution from Acute Lymphoblastic Leukemia to Acute Myeloid Leukemia
Heerah Lee[1], Chan-Jeoung Park*[1], Eunkyoung You[1], Hyery Kim[2], Jong Jin Seo[2]
[1] Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea
[2] Pediatrics, University of Ulsan College of Medicine and Asan Medical Center, Korea

PP-52 Inhibition of Mitochondrial Respiration by Treatment of PDTA Entails Depletion of ATP Content in AML
Ilhwan Ryu[1,2,3], Jeongsu Han[1,3], Yunseon Jang[1,2]3, Soo Jeong Kim[1,2,3], Min Joung Lee[1,2,3], Xianshu Ju[2,3], Byeong Hyeon Yoo[1,2,3], Yu Lim Lee[1,2,3], Min Jeong Ryu[1,4], Woosuk Chung[6], Gi Ryang Kweon[1,2,4], Jun Young Heo*[1,2,3]
[1] Department of Biochemistry, Chungnam National University School of Medicine, Korea
[2] Department of Medical Science, Chungnam National University School of Medicine, Korea
[3] Infection Control Convergence Research Center, College of Medicine, Chungnam National University, Korea
[4] Research Institute for Medical Science, Chungnam National University School of Medicine, Korea
[5] Brain research Institute, Chungnam National University School of Medicine, Korea
[6] Department of Anesthesiology and Pain Medicine, Chungnam National University Hospital, Korea

PP-53 Single Center Experience of Blinatumomab for Relapsed/Refractory B Cell Acute Lymphoblastic Leukemia
Soo-Jeong Kim[1], Ji Eun Jang[1], Hae Rim Chung[1], Chul-Joo Yoo[2], Jin Seok Kim[1], June-Won Cheong*[1], Yoo Hong Min[1]
[1] Department of Internal Medicine, Yonsei University College of Medicine, Korea
[2] Department of Pediatrics, Yonsei University College of Medicine, Korea

PP-54 Acute Myeloid Leukemia Classification in an Era of the WHO 2016 Diagnostic Criteria
Jung Jin, Eunhee Han, Myungshin Kim*, Yonggoo Kim, Kyungja Han
Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea

PP-55 Clinical Dissection of Infectious Event following ATG Treatment for Aplastic Anemia and Hypoplastic Myelodysplastic Syndrome
Hee Ryeong Jang[1], Youngil Koh*[1], Sung-Soo Yoon[1], Inho Kim[1], Soo-Mee Bang[2], Jeong-Ok Lee[2]
[1] Internal Medicine , Seoul National University Hospital, Korea
[2] Internal Medicine, Seoul National University Bundang Hospital , Korea

PP-56 Diagnostic Considerations for the Recently Described Entity, MDS/MPN-RS-T: A Review of 6 Cases
Min Young Lee, Seongsoo Jang*, Chan-Jeoung Park, Young-Uk Cho, Eunkyoung You, Ari Ahn
Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea

PP-57 A Rare Case of MPN with a Coexistence of JAK2 V617F Mutation and BCR/ABL1 Translocation
Sang Hyuk Park[1], Ji-Hun Lim*[1], Joseph Jeong[1], Sun-Ho Lee[1], Yunsuk Choi[2], Jae-Cheol Cho[2], Young-Uk Cho[3], Sang-Hyun Hwang[3], Seongsoo Jang[3], Chan-Jeoung Park[3]
[1] Department of Laboratory Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Korea
[2] Department of Hematology and Cellular Therapy, University of Ulsan College of Medicine, Ulsan University Hospital, Korea
[3] Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea

PP-58 Very Early Molecular Response at 1 Month is a Predictor of the Outcome of CP-CML Treated with TKIs
Hye-Young Song[1], Soo-Young Choi[1], Sung-Eun Lee[2], Soo-Hyun Kim[1], Hea-Lyun Yoo[1], Mi-Young Lee[1], Ki-Hoon Kang[1], Kyung-Mi Kee[1], Ji-Hyung Suh[1], Seon-Young Yang[1], Dong-Wook Kim*[1,2]
[1] Leukemia Research Institute, The Catholic University of Korea, Korea
[2] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

POSTER PRESENTATIONS

PP-59 Dasatinib-Induced Pulmonary Arterial Hypertension Diagnosed by Echocardiography in CML
Jee Hyun Kong[1], Sung-Eun Lee[2], Young-Woo Jeon[2], Soo Young Choi[3], Soo-Hyun Kim[3], Eun-Jung Jang[3], Hae-Eok Jung[4], Dong-Wook Kim*[2,3]
[1] Hematology-Oncology, Wonju Christian Hospital, Yonsei University College of Medicine, Korea
[2] Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea
[3] Leukemia Research Institute, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea
[4] Cardiology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

PP-60 Therapeutic Targeting of BCR-ABL in Chronic Myelogenous Leukemia by Modulating NAD Levels
Jeongsu Han[1,2,3,4], Soo Jeong Kim[1,2,4], Min Joung Lee[1,2,4], Ilhwan Ryu[1,2,4], Xianshu Ju[1,2,4], Byeong Hyeon Yoo[1,2,4], Yu Lim Lee[1,2,4], Yunseon Jang[1,2,4], Min Jeong Ryu[1,2,3], Junyoung Heo[1,2,4,5], Gi Ryang Kweon*[1,2,3]
[1] Department of Biochemistry, Chungnam National University School of Medicine, Korea
[2] Department of Medical Science, Chungnam National University School of Medicine, Korea
[3] Research Institute for Medical Science, Chungnam National University School of Medicine, Korea
[4] Infection Control Convergence Research Cente, Chungnam National University School of Medicine, Korea
[5] Brain Research Institute, Chungnam National University School of Medicine, Korea

PP-61 Quantification of BCR-ABL1 Using Digital PCR in CML Patients for TKI Discontinuation
Hee-Jung Chung[1], Hye-Won Lee[2], Mi-Kyoung Han[2,3], Hyun-Seok Um*[2]
[1] Laboratory Medicine, Konkuk Medical Center, Korea
[2] Internal Medicine, Center for Hematologic Malignancy, National Cancer Center Hospital, Korea
[3] Division of Convergence Technology, Immunotherapeutics Branch, National Cancer Center Research institute, Korea

PP-62 Performance of Automated Imaging Cell Analyzer Vision Hema for White Blood Cell Differentials
Sumi Yoon, Mikyoung Park, Hanah Kim*, Mina Hur
Department of Laboratory Medicine, Konkuk University School of Medicine, Korea

PP-63 Performance Evaluation of the Automated Digital Cell Morphology Analyzer Di-60 in Pediatric Patients
Gyu-Dae An[1], In-Hwa Jeong[1], Hyeon-Ho Lim[1], Sung-Suk Cho[2], Kwang-Sook Woo[1], Kyeong-Hee Kim[1], Jeong-Man Kim[1], Hee-Won Chueh[3], Jin-Yeong Han*[1]
[1] Department of Laboratory Medicine, Dong-A University College of Medicine, Korea
[2] Department of Laboratory Medicine, Dong-A University Hospital, Korea
[3] Department of Pediatrics Medicine, Dong-A University College of Medicine, Korea

PP-64 A Case of Iron-Refractory Iron Deficiency Anemia with Autoimmune Chronic Gastritis
Hyunjung Kim[1], Der Sheng Sun*[2], Joonhong Park[1], Myungshin Kim[1]
[1] Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea
[2] Internal Medicine, College of Medicine, The Catholic University of Korea, Korea

PP-65 Performance Evaluation of Automatic Image Analyzer for Differential Count of Bone Marrow Cells
Yong Jun Kwon, Jun Hyung Lee, Ha Jin Lim, Hyun Jung Choi, Soo Hyun Kim, Myung Geun Shin*
Departments of Laboratory Medicine, Chonnam National University Medical School and Chonnam National University Hwasun Hospital, Korea

PP-66 Relapsed Acute Myeloid Leukemia Preceded by Discrepant Morphologic and Molecular Evaluations
Sumi Yoon, Hanah Kim, Mina Hur*
Department of Laboratory Medicine, Konkuk University School of Medicine, Korea

PP-67 Visionhema is Useful for Nucleated Cell Differentials in Bone Marrow Aspirates without Abnormalities
Eunkyoung You, Chan-Jeoung Park*, Min Young Lee, Young-Uk Cho, Seongsoo Jang
Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea

PP-68 Clonal TCR Rearrangements in Patients with Hemophagocytic Lymphohistiocytosis without Malignancy
Heyjin Kim[1], Keon Hee Yoo[2], Silvia Park[3], Seok Jin Kim[3], Duck Cho[1], Sun-Hee Kim[1], Hee-Jin Kim*[1]
[1] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[2] Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[3] Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

POSTER PRESENTATIONS

PP-69 Myc and Bcl2 Coexpression is Not Related with Inferior Outcome in the Diffuse Large B-Cell Lymphoma

Yu Ri Kim[1], Sun Och Yoon[2], Soo-Jeong Kim[3], June-Won Cheong[3], Haerim Chung[3], Jung Yeom Lee[4], Ji Eun Jang[3], Yundeok Kim[1], Woo-Ick Yang[2], Yoo Hong Min[3], Jin Seok Kim*[3]

[1] Division of Hematology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Korea
[2] Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Korea
[3] Dicision of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Korea
[4] Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University, Wonju College of Medicine, Korea

PP-70 Different Role of Surveillance 18FDG-PET/CT according to Histologic Subtypes in Patients with NHL

Yu Ri Kim[1], Soo-Jeong Kim[2], June-Won Cheong[2], Yundeok Kim[1], Ji Eun Jang[2], Huynsoo Cho[2], Haerim Chung[2], Yoo Hong Min[2], Woo Ick Yang[3], Arthur Cho[4], Jin Seok Kim*[2]

[1] Division of Hematology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Korea
[2] Division of Hematology, Department of Internal Medicine, , Severance Hospital, Yonsei University College of Medicine, Korea
[3] Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Korea
[4] Department of Nuclear Medicine, Severance Hospital, Yonsei University College of Medicine, Korea

PP-71 Efficacy and Safety of Once-Weekly Bortezomib in Relapsed/Refractory Multiple Myeloma Patients

Sang Eun Yoon, Yeung-Chul Mun*, Chu-Myong Seong, Eun-Mi Nam, Kyoung-Eun Lee, Soon-Nam Lee
Department of Internal Medicine, Ewha Womans University, Hemoto-Oncology, Korea

PP-72 Thalidomide/Dexamethasone Maintenance after Autologous Stem Cell Transplantation in Multiple Myeloma

Sang-A Kim[1], Youngil Koh*[2], Dong-Yeop Shin[2], Jin Seok Kim[3], Kihyun Kim[4], Chang-Ki Min[5], Hyeon-Seok Eom[6], Je Jung Lee[7], Jeong-Ok Lee[8], Soo-Mee Bang[8], Sung-Soo Yoon[2]

[1] Department of Internal Medicine, Seoul National University Hospital, Korea
[2] Division of Hematology, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Korea
[3] Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Korea
[4] Division of Hematology, Department of Internal Medicine, Samsung Medical Centre, Sungkyunkwan University School of Medicine, Korea
[5] Division of Hematology, Department of Internal Medicine, Seoul St Mary's Hospital, The Catholic University of Korea, College of Medicine, Korea
[6] Hematology-Oncology Clinic, Department of Internal Medicine, National Cancer Center, Korea
[7] Division of Hematology, Department of Internal Medicine, Chonnam National University Hwasun Hospital, Korea
[8] Division of Hematology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Korea

PP-73 Prognostic Role of Myeloid-Derived Suppressor Cells in Transplant-Eligible Multiple Myeloma

Sung-Soo Park[1,2], Gi June Min[1,2], Young-Woo Jeon[1,2], Jae-Ho Yoon[1,2], Seung-Ah Yahng[3], Seung-Hwan Shin[4], Sung-Eun Lee[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], Jong Wook Lee[1], Chang-Ki Min*[1,2]

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

PP-74 Prognostic Impact of 18F-FDG PET/CT at Diagnosis in Newly Diagnosed Multiple Myeloma

Sung-Hoon Jung, Seo-Yeon Ahn, Seung-Shin Lee, Deok-Hwan Yang, Jae-Sook Ahn, Yeo-Kyeoung Kim, Hyeoung-Joon Kim, Je-Jung Lee*
Department of Hematology-Oncology, Chonnam National University Hwasun Hospital , Korea

PP-75 Single Center Experience of Pomalidomide Plus Low-Dose Dexamethasone in Patients with Refractory and Relpased Multiple Myeloma

Sung Won Lim[1], Silvia Park[1], Seok Jin Kim[1], Jun Ho Jang[1], Won Seog Kim[1], Chul Won Jung[1], Hyo Jung Kim[2], Kihyun Kim[1]

[1] Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[2] Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Korea

PP-76 The Use of mTOR Inhibitor in Patients with Activated PI3K δ Syndrome 1; A Case Series in Korea

Ji-Man Kang [1,2], Su Kyung Kim [1], Hyeon-Jin Park [3], Sae Rom Choi [1], Yeon Jung Lim [4], Soon Ki Kim [5], Meerim Park [6], Youn-Soo Hahn [6], Byung-Kiu Park [2], Weon Seo Park [8], Young Hye Ko [7], Sung Yoon Cho[1], Dong-Kyu Jin[1], Yon Ho Choe[1], Ji Won Lee[1], Keon Hee Yoo[1], Yae-Jean Kim*[1]

[1] Pediatrics, Sungkyunkwan University School of Medicine, Samsung Medical Center, Korea
[2] Center for Pediatric Cancer, National Cancer Center, Korea
[3] Pediatrics, Seoul National University College of Medicine, Korea

POSTER PRESENTATIONS

[4] Pediatrics, College of Medicine, Chungnam National University, Korea
[5] Pediatrics, Inha University Medical Center, Korea
[6] Pediatrics, College of Medicine, Chungbuk National University, Korea
[7] Pathology, Sungkyunkwan University School of Medicine, Samsung Medical Center, Korea
[8] Pathology, National Cancer Center, Korea

PP-77 Efficacy Of Darbepoetin Alfa for Chemotherapy-Induced Anemia in Solid Cancer Patients

Jang Ho Cho, Jun Ho Jang, Silvia Park, Jong-Mu Sun, Jeeyun Lee, Yeon Hee Park, Jin Seok Ahn, Chul Won Jung*
Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

PP-78 The Implementation of Next Generation Sequencing in Myeloid Neoplasm Clinical Diagnostics

Smbat Daghbashyan[1], Aline Aywaz[1,2]

[1] Hematology, Hematology Center after Prof. Yeolyan, USA
[2] Molecular genetics and immunophenotyping laboratory, Hematology Center after Prof. Yeolyan, USA

PP-79 Evaluation of the Immature Platelet Fraction in the Diagnosis of ITP and Other Various Diseases

Dong Jin Park[1], Sooyoung Kim[1], Yeongsic Kim[1], Jeong-A Kim[2], Young Hoon Park[2], Dong Jin Park*[1]

[1] Laboratory Medicine, The Catholic University of Korea, St. Vincent's Hospital, Korea
[2] Division of Hematology, Department of Internal Medicine, The Catholic University of Korea, St. Vincent's Hospital, Korea

PP-80 Association of HSV to Chemotherapy-Induced Oral Mucositis in Patients with Hematologic Malignancies

Junshik Hong[1], Youngnim Choi[2], Ji-Yeob Choi[4], Dong-Yeop Shin[1], Youngil Koh[1], Hee Kyung Park[3], Inho Kim*[1], Sung-Soo Yoon[1]

[1] Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Korea
[2] Department of Oromaxillofacial Infection & Immunity, School of Dentistry and Dental Research Institute, Seoul National University, Korea
[3] Department of Oral Medicine and Oral Diagnosis, School of Dentistry and Dental Research Institute, Seoul National University, Korea
[4] Department of Biomedical Sciences, Seoul National University College of Medicine, Korea

PP-81 Efficacy of Olanzapine-Containing Antiemetic Regimen in ASCT Patients with TBC Conditioning

Bobae Kim[1], Youree Jung[1], Eunjeong Shin[1], Sungyun Suh[1], Yoonsook Cho[1], Ju-Yeun Lee[2], Youngil Koh*[3]

[1] Pharmacy, Seoul National University Hospital, Korea
[2] College of Pharmacy, Hanyang University, Korea
[3] Hematology , Seoul National University Hospital, Korea

PP-82 Prevention of PTLD in Children Using Preemptive Rituximab Therapy

Bo Kyung Kim, Hyoung Jin Kang*, Kyung Taek Hong, Jung Yoon Choi, Hong Yul An, Che Ry Hong, Hee Young Shin
Department of Pediatrics, Cancer Research Institute, Seoul National University College of Medicine, Korea

PP-83 A Comparative Analysis of Efficiency Among the Different Donor Groups in Stem Cell Collection Result According to Injected with GCSF on Unrelated Peripheral Blood Stem Cell Donors

Ok-Ja Hyoung[1], Min-Jung Kawk[1], Tai-Gyu Kim[1], Young-Shin Lee[2], Min-Jin Choi[3]

[1] Catholic Hematopoietic Stem Cell Bank, Department of Coordination, Catholic University of Korea, Korea
[2] Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Korea
[3] Department of Internal Medicine, Samsung Medical Center, Korea

PP-84 Granulocyte Transfusions in Pediatric Patients with Neutropenic Fever: A Single Center Experience

Eu Jeen Yang[1], Kyung Mi Park[1], Hyun-Ji Lee[2], Young Tak Lim*[1]

[1] Pediatrics, Pusan National University Children's Hospital, Korea
[2] Laboratory Medicine, Pusan National University Yangsan Hospital, Korea

PP-85 Low Rate of Rh Alloimmunization after Rh-Incompatible Solid Organ Transplantations

Ari Ahn[1], Duck Cho[2], Sang-Hyun Hwang*[1]

[1] Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea
[2] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunwan University School of Medicine, Korea

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PLENARY LECTURE

PL01-01

Precision Medicine in Chronic Lymphocytic Leukemia

Contantine Tam
Peter MacCallum Cancer Centre, St Vincent's Hospital and University of Melbourne, Australia

Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in the Western World. Although CLL typically responds well to chemoimmunotherapy, most patients relapse, and eventually develop chemorefractory disease. Improved understanding of CLL genetics have led to the identification of TP53 deletions and/or mutations as a vital determinant of chemo-sensitivity. Further advances have led to the development of drugs which inhibit elements of the B-cell receptor pathway (eg BTK, PI3K, SYK) and the apoptotic pathway mediated by BCL2 (eg navitoclax, venetoclax) as highly effective therapies in CLL. These targeted molecules are orally administered, are better tolerated especially in older patients, have activity against TP53 aberrant CLL, and in the case of the BTK inhibitor ibrutinib, has migrated into the frontline therapy of patients not suitable for treatment with chemoimmunotherapy. However, new problems emerge with new treatments. Side-effects including platelet-related bleeding and atrial fibrillation with BTK inhibitors, immune hepatitis and colitis with PI3K inhibitors, and tumor lysis syndrome and neutropenia with BCL2 inhibitors pose therapeutic challenges. In addition, the requirement for indefinite therapy with the oral molecules impose a burden on health systems, and emergence of resistant CLL (eg those with BTK mutations) has been observed across all classes of novel therapeutics.

Combinations of B-cell receptor antagonist and BCL2 inhibitor are now being tested in clinical studies of CLL and related diseases, with high activity and clearance of minimal residual disease. Such combinations hold the promise of improved efficacy and the potential for deep responses allowing drug holidays, and thus may reduce the overall cost of treatment by shortening the duration of therapy.

PL01-02

The Clinical Management of FLT3-mutated AML

Mark Levis
Adult Leukemia Service, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, USA

Activating mutations of the receptor tyrosine kinase FLT3 are one of the most common mutations found in AML. Although they most commonly occur in the setting of a normal karyotype and often with an NPM1c mutation, they can be found across multiple genetic subtypes of the disease, and thus have resisted classification by the World Health Organization as defining a distinct category of AML. While these mutations can confer an aggressive phenotype and an adverse prognosis, allogeneic transplant has proven to be an effective treatment. Furthermore, the judicious use of targeted kinase inhibitors may well move patients with these mutations into a relatively favorable subset of AML in the near future. In this talk I will discuss the biology of these mutations and how they impact the clinical features of the disease, review current data on standard-of-care approaches, and provide an overview of the ongoing development of FLT3 inhibitors.

PL02-01

Human Myeloid Leukemia Stem Cells

Koichi Akashi
Department of Medicine and Biosystemic Science, Graduate School of Medical Science, Kyushu University, Japan

Acute myeloid leukemia (AML) originates from self-renewing leukemic stem cells (LSCs), an ultimate therapeutic target. We have previously reported that the T-cell immunoglobulin mucin-3 (TIM-3) is expressed on the surface of LSCs in most patients with AML of various FAB types, and that targeting TIM-3 by anti-TIM-3 monoclonal antibodies could eradicate human AML LSCs in vivo by utilizing xenograft models (1). We then tested the role of TIM-3 signaling evoked by its ligand, galectin-9 (Gal-9) in the development and maintenance of human AML LSCs. We found that TIM-3+ AML cells secreted Gal-9 into sera, and the ligation of TIM-3 by serum galectin-9 positively regulate the self-renewal capacity of TIM-3+ LSCs via co-activation of NF-kB and β-catenin pathways. We found that this TIM-3/Gal-9 "autocrine stimulatory loop" is involved also in other types of myeloid leukemias developed from preleukemic malignancies, including myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN) and chronic myelogeneous leukemia (CML). Strikingly, in all cases, frequencies of CD34+CD38-TIM-3+ cells progressively increased along with disease progression from early/chronic phase to overt leukemia. These data collectively suggest that TIM-3 and Gal-9 constitutes a pan-myeloid autocrine loop to develop malignant stem cells in the vast majority of human myeloid malignancies (2). Thus, signaling molecules downstream of TIM-3 and galectin-9 ligation, as well as surface TIM-3 itself might be good candidates for cancer stem cell-target therapy common to most types of myeloid malignancies.

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PL02-02

Pre-Cancerous Stem Cells in MDS and AML: Significance, Mechanisms, and Therapeutic Targeting

Ulrich Steidl
Department of Cell Biology, and Department of Medicine, Albert Einstein College of Medicine, U.S.A.

Relapse continues to be the most common cause of death in acute myeloid leukemia (AML) and many other cancers. Recent evidence has shown that the accumulation of stepwise genetic and epigenetic changes in tissue-specific stem cells lead to the formation of pre-cancerous/pre-leukemic stem cells (pre-LSC) that play a pivotal role not only in disease origination but also in relapse. While the existence and essentiality of such pre-cancerous cell states has been demonstrated in mice and humans, still very little is known about the molecular mechanisms driving pre-LSC formation and progression. We have recently performed molecular studies of pre-leukemic cell states in mouse genetic models as well as primary cells from patients, and discovered new transcription factors and regulatory mechanisms in pre-LSC in myelodysplastic syndromes (MDS) and AML. We uncovered critical roles for several non-clustered homeobox transcription factors in pre-LSC, and identified functionally critical and pharmacologically targetable downstream effectors. We also found that enhancer haplodeficiency and resulting minimal reduction of key transcription factors is sufficient to induce pre-LSC formation and subsequent progression to MDS and AML. Such models provide novel tools for mechanistic study of pre-LSC and their progression to overt MDS and AML, and for the development and testing of pharmacological approaches to therapeutically interfere with these processes.
In summary, recent studies have started to shed light on pre-cancerous stem cell states as the earliest origin of various malignancies including MDS and AML, as well as molecular mechanisms driving their formation and progression. These advances provide a basis for the specific therapeutic targeting of pre-cancerous stem cells for the causative treatment of MDS and AML and other cancers.

PL03-01

Development of Precision Medicine Trials for Acute Lymphoblastic Leukemia

Stephen Hunger
Division of Pediatric Oncology, Center for Childhood Cancer Research, Children's Hospital of Philadelphia, USA

Acute lymphoblastic leukemia (ALL) is the most common cancer occurring in children and adolescents. The first long-term cures for ALL occurred in the mid 1960s. Since then, cure rates have improved steadily with overall survival rates now exceeding 85% in high income countries throughout the world. The survival improvements of the past 50 years were achieved largely by optimizing multiagent chemotherapy regimens that employed drugs widely available since the late 1970s. Following development of ABL-directed tyrosine kinase inhibitors (TKIs) for chronic myeloid leukemia, it was shown that addition of imatinib or dasatinib to intensive chemotherapy regimens dramatically improved survival for Philadelphia chromosome positive (Ph+ or BCR-ABL1+) ALL, but this very high risk subset accounts for less than 5% of pediatric ALL cases. Over the past decade, targeted gene sequencing, RNA sequencing, and whole genome or whole exome sequencing have identified previously unrecognized subsets of childhood ALL including Philadelphia chromosome-like (Ph-like) ALL, DUX4-rearranged ALL, and cases with fusion genes involving MEF2D or ZNF384. Ph-like ALL has a gene expression profile highly similar to that of Ph+ ALL, but lacks BCR-ABL1 fusion, and is characterized by a diverse variety of genetic alterations that activate a limited number of signaling pathways, all of which may be amenable to inhibition with approved TKIs. Precision medicine trials have now been implemented to test addition of imatinib or dasatinib to chemotherapy in Ph-like pediatric ALL cases with gene fusions involving ABL1, ABL2, CSF1R, and PDGFRB (ABL-class fusions). Parallel trials have been developed to test the JAK1/JAK2 inhibitor ruxolitinib in Ph-like ALL cases with CRLF2 alterations with or without JAK1 or JAK2 point mutations, JAK2 fusions, and truncating rearrangements of the erythropoietin receptor.

PL03-02

Progress in Therapy of Philadelphia Positive ALL

Farhad Ravandi
Department of Leukemia, University of Texas – MD Anderson Cancer Center, USA

Treatment of Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) exemplifies how the addition of potent targeted agents, directed at the molecular aberrations responsible for leukemic transformation, can overcome resistance mechanisms to traditional regimens and lead to improved outcomes. The introduction of tyrosine kinase inhibitors (TKIs) has significantly improved the outcomes not only by allowing more patients to undergo allogeneic hematopoietic cell transplantation (alloHCT) but also by diminishing our reliance on this potentially toxic strategy particularly in the older population. Long-term data using chemotherapy and TKI combinations suggest that a proportion of patients treated can achieve durable relapse-free survival without undergoing alloHCT. Furthermore, the availability of sensitive minimal residual monitoring assays may allow early detection of the patients who are more likely to relapse and who are likely candidates for early alloHCT. The emergence of more potent TKIs with significant activity against resistant mutations has allowed de-intensification of chemotherapy regimens, particularly in the older and infirm population. If long term cure is the goal, the complexities of leukemogenic mechanisms in acute leukemias is unlikely to allow complete independence from more intensive chemotherapy and/or alloHCT, using TKIs alone or with minimal additional therapy. However, introduction of other highly effective agents that can be combined with TKIs may allow further minimization of chemotherapy and alloHCT in the future, as we have witnessed in acute promyelocytic leukemia.

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ASIAN HEMATOLOGY NETWORK: JSH-KSH JOINT SYMPOSIUM

AML Prognosis Based on Clinical and Genomic Data

Hyeoung Joon Kim
Department of Internal Medicine, Chonnam National University Hwasun Hospital, Korea

Acute myeloid leukemia (AML) is a genetically heterogeneous disease. In the past two decades, clonal chromosomal aberrations have been recognized as the most important marker for prognostication in AML patients. Then a revised WHO classification system in 2016 incorporated emerging data into the system and classified the group with mutations in NPM1 and biallelic mutations of CEBPA as a separate AML subtype. In addition, the provisional category of AML with mutated RUNX1 was added to the de novo AML classification.
Several studies have attempted to adopt the molecular genetic classification to correlate clinical outcome in AML patients in a group with a specific cytogenetic subgroup. More recently, Papaemmanuil et al. reported that genomic classification in AML can improve the classification of AML subtype according to prognosis, and can distinguish each subtype of AML based on their driver mutation and underlying pathway to induce leukemogenesis.
A subset of common somatic mutations alone or combination of two or more have shown to be prognostic and been incorporated into the recent risk stratification systems.
A recent study by Klco et al demonstrated that persistent allelic burden at morphologic complete remission (CR) is common and is associated with an increased risk of relapse.
Thus, in this study, we evaluated whether the recommended genomic classification of AML is relevant to patients with AML, particularly in the subgroup with a normal karyotype, including elderly AML patients. Mutation profiling on sequential samples showed that some mutations persist after therapy, leading to clonal expansion during remission, and eventually lead to relapse of leukemia. As some mutations persist at morphologic CR, a subset of mutations may still persist after allogeneic HCT and could elevate risk of relapse and reduce OS. As such, post-HCT mutation dynamics and their clinical relevance using NGS is a topic of interest.
As of now, only few studies attempted to explore clonal changes and allogeneic HCT outcome on sequential samples. We hypothesized that allelic burden of pre- and post-HCT using NGS could be prognostically relevant, particularly in terms of HCT outcome. Current study aims to investigate feasibility of post-transplant monitoring of NGS and its prognositc implications on HCT outcomes in AML patients.

ASIAN HEMATOLOGY NETWORK: JSH-KSH JOINT SYMPOSIUM

A Novel Mechanism of Cancer Immune Evasion Via the Disruption of PD-L1 3'-UTR

Seishi Ogawa
Department of Pathology and Tumor Biology, Graduate School of Medicine, Kyoto University, Japan

Successful treatment of many advanced cancer patients using antibodies against programmed cell death 1 (PD-1) and its ligand (PD-L1) has highlighted the critical importance of PD-1/PD-L1-mediated immune escape in cancer development. However, the genetic basis for the immune escape has not been fully elucidated, with the exception of elevated PD-L1 expression by gene amplification and utilization of an ectopic promoter by translocation, as reported in Hodgkin and other B-cell lymphomas, as well as stomach adenocarcinoma. Here we show a unique genetic mechanism of immune escape caused by structural variations (SVs) commonly disrupting the 3' region of the PD-L1 gene. Widely affecting multiple common human cancer types, including adult T-cell leukemia/lymphoma (27%), diffuse large B-cell lymphoma (8%), and stomach adenocarcinoma (2%), these SVs invariably lead to a marked elevation of aberrant PD-L1 transcripts that are stabilized by truncation of the 3' -untranslated region (UTR). PD-L1-involving SVs are especially frequent in virally induced cancers. Disruption of Pd-l1 3' -UTR in mice enables immune evasion of EG7-OVA tumorcells with elevated Pd-l1 expression in vivo, which is effectively inhibited by Pd-1/Pd-l1 blockade, supporting the role of relevant SVs in clonal selection through immune evasion. Our findings not only unmask a novel regulatory mechanism of PD-L1 expression, but also suggest that PD-L1 3' -UTR disruption could serve as a genetic marker to identify cancers that actively evade anti-tumorimmunity through PD-L1 overexpression.The critical role of the 3'-UTRdisruption in cancer immune evasion will be discussed, particularly with regard to viral infection.

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EHA-KSH JOINT SYMPOSIUM 01

The Best Prediction of Prognosis for MDS: How to Integrate Clinical and Molecular Data

Valeria Santini
Hematology, MDS Unit, University of Florence, Italy

Myelodysplastic syndromes (MDS) are a heterogeneous group of diseases that can be prognostically stratified into lower risk (LR MDS) and higher risk, according to the International prognostic scoring systems (both IPSS and IPSS-R)(1,2). IPSS-R prognostic evaluation is based on clinical data: depth of cytopenias, percentage of bone marrow blasts, but also cytogenetic abnormalities, and the risk is defined as the overall survival and propensity to develop acute leukemia. The great majority of MDS patients belong to IPSS-R lower risk categories; nevertheless, within the two broad definitions of higher and lower risk there are very different forms of MDS, with quite divergent outcomes. While careful clinical and geriatric evaluation is fundamental, additional variables can refine prognosis: presence of comorbidities, DNA methylation status, and somatic mutations, the latter recently demonstrated to have the most important prognostic significance (3). Their analysis has not yet been routinely integrated into diagnosis of MDS, but will be soon, given the increased accessibility of NGS methods. And more precise prognostication ensures more adapted and personalized therapy (4).
Around 90% of MDS cases carry one or more recurrent somatic mutations. The number of mutations present correlates with survival (3). On the other hand, gene mutations in MDS are independent prognostic
indicators and different mutations may have different impact on outcome. Mutations of TP53, CBL, EZH2, RUNX1, U2AF1, ASXL1 confer dismal outcome (3), while SF3B1 mutations are correlated with prolonged survival (5).
Mutated TET2 and DNMT3A are predictive of response to hypomethylating agents (6), while ASXL1 is a negative predictor of response both to hypomethylating agents (7) and to lenalidomide in non del5q MDS (8).
Evaluation of presence of somatic mutations and their variant allele frequency that defines the importance of the various clones present in MDS as well as the burden of disease has become of paramount importance (9). This is especially true in younger/fit patients for whom a more sophisticated prognosis may support therapeutic decision of early stem cell transplant or more aggressive therapy.

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EHA-KSH JOINT SYMPOSIUM 01

Clinical Effects of Somatic Mutations in Myelodysplastic Syndrome

Je-Hwan Lee
Department of Hematology, University of Ulsan College of Medicine, Korea

Somatic mutations, which are involved in the pathogenesis of myelodysplastic syndrome (MDS), have become relevant in MDS prognostication in addition to clinical variables. Several large scale studies demonstrated the prognostic impact of somatic mutations. A study for 439 MDS patients showed that 5 genetic mutations (TP53, EZH2, ETV6, RUNX1, and ASXL1) were independently associated with poor survival. In a study for 288 lower-risk MDS patients, combining EZH2 mutation and the Lower-Risk Prognostic Scoring System could identify a subgroup with a worse-than-expected prognosis. An extensive analysis of oncogenic mutations in large cohorts (111 genes across 738 patients) illustrated a complex structure of gene-gene interactions and the total number of oncogenic mutations was significantly associated with overall survival. A novel prognostic model, which combined the status of 14 genes with clinical factors, was proposed from the analysis of 104 genes in 944 MDS patients. Hypomethylating therapy (HMT) with azacitidine or decitabine is one of main treatment modalities in MDS. Around half of the patients respond to HMT and majority of the patients with HMT responses eventually progress within two years. It is important, but still unresolved issues to predict outcomes (response, survival) after HMT. Among genetic predictors of response to HMT, the most commonly mentioned one is TET2 mutation. Several studies showed a higher response rate in patients with TET2 mutation, but the other studies did not find the association. Allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment modality for patients for MDS. Clinical outcomes after HCT are quite variable and it is crucial to select patients who will be benefited from allogeneic HCT. Mutations in TP53, RAS pathway genes, JAK2, CBL, ASXL1, RUNX1, TET2, IDH2, and U2AF1 have each been reported to influence on overall survival in the setting of HCT, but only mutations in the TP53 gene were consistently reported as poor prognostic factors in most studies. We investigated the prognostic effects of somatic mutations of 26 genes in 107 patients who received HMT for MDS and 202 patients who underwent allogeneic HCT for de novo MDS in two consecutive studies. Mutations in DNMT3A, RAS, and TP53 were independently associated with overall and acute myeloid leukemia-free survival after HMT. TP53 mutation was significantly associated with poor outcomes after HCT for patients with de novo MDS, mainly due to higher incidence of disease relapse. In the near future, somatic mutations are anticipated to be incorporated into current prognostic scoring systems for MDS.

EHA-KSH JOINT SYMPOSIUM 01

Pathogenesis and Management of Chronic Myelomonocytic Leukemias

Raphael Itzykson
Department of Hematology, Paris Diderot University, France

Chronic Myelomonocytic Leukemia (CMML) is the most frequent form of overlap Myelodysplastic/myeloproliferative neoplasm (MDS/MPN) in adults. It is a disease of the elderly, caused by the mostly linear accumulation of somatic mutations in genes encoding epigenetic and splice regulators, leading to biased granulomonocytic differentiation at the expanse of erythroid differentiation, leading to monocytosis, anemia and dysplasia, followed in half of patients with secondary mutations affecting GM-CSF signaling, leading to GM-CSF hypersensitivity and more proliferative features, including high white blood cell count (WBC) and splenomegaly. The mutational signature of CMML is in keeping with natural aging of the HSC compartment.
Contrasting with a relatively homogeneous molecular landscape, the clinical presentation and prognosis of CMML patients is very heterogeneous. Patients can be broadly categorized on the basis of clinical presentation into myelodysplastic (MD-CMML) with predominant cytopenias, and myeloproliferative (MP-CMML). An orthogonal prognostic stratification, using a variety of second-generation validated CMML-specific scores, further stratifies MD-CMML and MP-CMML into lower-risk and higher-risk patients.
The treatment strategy of CMML is not well established, because of the limited number of CMML-specific trials. Most treatments approved in CMML rely on the inclusion of a minority of CMML patients into MDS trials. After portraying the clinical, molecular and prognostic landscape of CMML, I will discuss the management of cytopenias, with a focus on thrombocytopenia and the management of myeloproliferative disease. I will specifically debate the role of hypomethylating agents and allogeneic stem cell transplantation in the disease, then will envisage how pre-clinical data can inform future therapeutic trials in CMML.

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EHA-KSH JOINT SYMPOSIUM 01

Hypomethylating Therapy in Stem Cell Transplantation for MDS

Yoo-Jin Kim
Department of Hematology, College of Medicine, The Catholic University of Korea, Korea

Myelodysplastic syndromes (MDS) are a group of myeloid diseases defined by clonal stem cell disorders and characterized by progressive peripheral blood cytopenias associated with bone marrow dysplasia. These disorders show variable clinical courses from an indolent condition to life-threatening conditions related to severe cytopenia or progression to acute myeloid leukemia. Recent advances have been made in MDS treatment due to the introduction of hypomethylating agents (HMA) and lenalidomide as well as improvements in allogeneic hematopoietic stem cell transplantation (HSCT). Among these treatment options, HMA or HSCT are the first considered treatment option for patients with lower risk MDS and significant cytopenia or higher-risk MDS.
HSCT is one of the most important curative options for hematological malignancies and significantly improved survival rates over time is observed. Survival improvement appears to result from reductions in treatment related mortality due to organ damage, infection, and severe acute GVHD, but relapse still remains the major cause of transplantation failure. As one of strategies to lower post-transplant relapse, incorporation of novel agents, such as hypomethylating agents (HMA), into pre- or post-HSCT settings has been tried. Regarding HMA, in addition to pre-transplant debulking effects, HMA, such as 5-azacitidine or 5-aza-2'-deoxycytidine, has potential to induce indirect antitumor effects due to its influences on gene expression and key cellular regulatory pathways and on various immune cells. Actually, human studies showed that HMA induced T cell response against tumor antigen and post-transplant 5-azacitidine separated graft-versus-leukemia effects from graft-versus-host disease via induction of regulatory T cells and immunomodulatory cytokines. These data suggest that pre- and post-transplant HMA could be a feasible option for relapse control and also be adopted in various form of cellular immunotherapy including donor leukocyte infusion.
In this discussion, roles of HMA as a pre-transplant bridging treatment, post-transplant maintenance treatment, and a primer of donor lymphocyte infusion will be presented.

EHA-KSH JOINT SYMPOSIUM 02

Diagnosis and Management of Aplastic Anemia and Refractory Cytopenia of Childhood

Ayami Yoshimi-Nöllke
Department of Paediatrics and Adolescent Medicine, University Children's Hospital, Freiburg, Germany

Aplastic anemia (AA) and refractory cytopenia of childhood (RCC) are two major acquired bone marrow failures (BMFs) in children. Immune-mediated destruction of hematopoietic stem cells is associated with pathophysiology of SAA as well as at least partially of RCC. RCC is a provisional entity of the WHO classification since 2008 and is the most common subtype of pediatric MDS. About 80% of children with RCC have hypocellular bone marrow and cytogenetic abnormalities are found in 25% of cases. Therefore, careful histological diagnosis with a bone marrow biopsy is mandatory to distinct RCC from SAA. Classical inherited BMF syndromes such as Fanconi anemia and dyskeratosis congenital need to be excluded in children with a suspected diagnosis of SAA and RCC. Moreover, recent advance in molecular diagnostics revealed novel predisposition syndromes, such as GATA2 deficiency and germline SAMD9/SAMD9L mutations, in some children with histological diagnosis of RCC.

Hematopoietic stem cell transplantation (HSCT) is the first choice of treatment for children with SAA and a HLA-identical family donor (MFD). Immunosuppressive therapy (IST) with anti-thymocyte globulin and cyclosporine A is given as first-line therapy in children without such a donor. The long-term survival is around 90% in children with SAA after both IST and MFD-HSCT. The major problems after IST are non-response, relapse and clonal evolution, although the incidence of clonal disease is decreasing in children due to improved histological diagnosis and early indication of second-line HSCT in case of treatment failure. Some recent studies show excellent overall survival after HSCT from an alternative donor in children with SAA.

Therapy approaches in patients with RCC cover a wide range of options from a watch and wait strategy, IST and HSCT, which are chosen based on blood counts, karyotypes and bone marrow cellularity. Currently, overall survival of patients with RCC is around 80 to 90% with no differences according to primary therapy. Identification of underlying predisposition syndromes in some children with RCC has major influences on the therapy decision, donor selection as well as long-term management of patients.

Accurate diagnosis, exclusion of underlying diseases, early treatment and long-term monitoring are important for the successful management of children with SAA and RCC.

EHA-KSH JOINT SYMPOSIUM 02

Frontline Alternative Donor Stem Cell Transplantation versus Immunosuppressive Treatment for Children with Severe Aplastic Anemia who Lack Matched Related Donor

Hyoung Jin Kang
Department of Pediatrics, Seoul National University College of Medicine, Korea

Hematopoietic stem cell transplantation (HSCT) with a matched related donor (MRD) is a curative therapy for severe aplastic anemia (SAA), and cyclophosphamide based conditioning with anti-thymocyte globulin (ATG) is generally known to be optimal for HSCT with a matched related donor.Patients without a suitable MRD are candidates for IST consisting of ATG and cyclosporine (CSA). However, 25-35% of responders experienced relapse. Another problem ofpatients treated with IST is risk for clonal evolution and development of MDS, AML, and PNH.

Although IST has remained first-line therapy for patients without a MRD, IST has achieved limited improvement in survival.With the development of transplantation techniquesuch as the introduction of fludarabine and/or low dose total body radiation in the conditioning regimen to avoid graft failure,promising results of transplantation with matched unrelated donor (MUD) that were comparable to those of transplantation from a MRD were reported in SAAespecially for children.

As early intervention was recommended for better outcomes whatever the first-line therapyand as IST and MUD transplant have each pro and cons, prospective randomized study is necessary to solve the controversy about the choice of optimal treatment for SAA patients without MRD.

EHA-KSH JOINT SYMPOSIUM 02

An Update in the Management of Paroxysmal Nocturnal Haemoglobinuria

Anita Hill
Department of Haematology, St. James' University Hospital, UK

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal haematopoietic stem cell (HSC) disease that may present with haemolytic anaemia, thrombosis and/ or smooth muscle dystonias, and can also be associated with bone marrow failure. PNH is caused by somatic mutations in PIGA (phosphatidylinositol glycan anchor biosynthesis class A), occurring in one or more HSC clones. The natural history of PNH is highly variable, ranging from quiescent to life-threatening. Complications may be silent and monitoring of patients is paramount in the management of this rare disease. Therapeutic strategies include terminal complement blockade and bone marrow transplantation. Eculizumab, a monoclonal antibody complement inhibitor, is highly effective and the only licensed therapy for PNH. There are however further novel drugs in development creating another exciting era for patients with PNH.

EHA-KSH JOINT SYMPOSIUM 02

Clinical Implications of Renal Dysfunction in Patients with PNH

Jin Seok Kim
Department of Internal Medicine, Yonsei University College of Medicine, Korea

Paroxysmal nocturnal hemoglobinuria (PNH) is arare, life-threatening blood disease.At the time of diagnosis of PNH, impaired renal function (IRF)defined as history of acute renal failure or reported glomerular filtration rate [GFR] < 60 ml/min/1.73m^2 was reported in 16.6% of Korean PNH patients and 21% of PNH patients from theinternational eculizumab trials showed a later stage chronic kidney disease (CKD) (GFR ≤60 ml/min/1.73 m^2; stage 3, 4, or 5). The IRF in patients with PNH at the time of diagnosis of PNH was considered as a risk factor related to mortality. The PNH patients with IRF at the time of diagnosis had a higher incidence of thromboembolic events and had a mortality rate 7.8-fold greater than the age- and gender-matched general population.It has been known that IRFcontributes to 8-18% of PNH-related deaths. Renal damage in PNH is caused by increased cell-free plasma hemoglobin and nitric oxide (NO) depletion during intravascular hemolysis. Increased cell-free hemoglobin and NO depletioninduce vasoconstrictionand intravascular thrombosis which is considered as the one of the pathogenesis of IRFin PNH. Hemosiderin deposition in the renal proximal tubular cells is the most consistent finding in all patients with PNH and is another cause of IRFin PNH.Typical MRI findings of renal cortical hemosiderosissuch as loss of cortical signal intensity on both T1-and T2-weighted images can be observed in the patients with PNH. Considering thispathogenesis of IRFin PNH, the clinical characteristics and dynamics of renal dysfunction during PNH natural disease course should be intensively evaluated.

According to the recently published Spanish data, 45.0% of patients experienced acute (ARF) or chronic (CRF) renalfailure. The median time to the firstARF episode was 6.5 (CI 95%; 2.2, 14.9) years, whereas themedian to the diagnosis of CRF was 14.5 (CI 95%; 3.8, 19.2)years after the diagnosis of PNH.From the Korean multicenter, retrospective study (n=101), the renal events were observed in 55 patients (55/101; 54.5%)during themedian follow upof 94.2 months.Eleven patients (10.9%) experienced both acute kidney disease (AKD) and CKD. Median time to first renal event from diagnosis of PNH was 79.3 months. The elevated levels of LDH at the time of first renal event were observed compared to the level of LDH at the time of diagnosis.The rate of TE was a higher trend in the patients with renal events ≥ 2 (10/32, 31.3%) compared to those with renal events ≤ 1 (15/69, 21.7%; P = 0.303). The rate of recurrent TE was significantly higher in patients with renal events ≥ 2 (6/32, 18.8%) compared to those with renal events ≤ 1 (2/69, 2.9%; P = 0.012). The patients with renal events ≥ 2 showed a trend toward inferior overall survival (OS) compared to those with renal events ≤ 1 (86.4% vs. 96.0% at 10 years OS; P = 0.124). The rate of TE was a higher trend in the patients with the patients with CKD+AKD compared to the other patients (5/11, 45.5% vs. 20/90, 22.2%; P = 0.134). The rate of recurrent TE was significantly higher in patients with CKD+AKD (3/11, 27.3%) compared to the other patients (5/90, 5.6%; P = 0.040). Of note, the OS was significantly inferior in the patients with CKD+AKD compared to the other patients (75.0% vs. 95.8% at 10 years OS; P = 0.011).

Eculizumab, a humanized monoclonal antibodyagainst terminal complement protein C5 that inhibits terminal complement activation,in patients with PNH.Treatment of PNH patients with eculizumab resulted in a reduction in hemolysis, cell-free plasma hemoglobin, and NO depletion. Improvement in renal function was more commonly seen in patients with baseline CKD stages 1-2 although the improvement was also observed in patients with CKD stages 3-4.

Therefore, paying attention to the renal events during follow-up period is essential for taking care of PNH patients. In addition, eculizumab therapy should be considered in the PNH patients with renal dysfunction during the disease course. Moreover, the PNH patients who experienced repeated renal events, especially CKD+AKD, must be treated with eculizumab as soon as possible.

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SS01-01

Single Cell Analysis of Multiple Myeloma

Daeun Ryu[1], Seok Jin Kim[2], Hee Jin Kim[3], Hae-Ock Lee[1], Kihyun Kim[2], Woong-Yang Park[1]

[1] Samsung Genome Institute, Korea
[2] Division of Hematology-Oncology, Department of Medicine, Korea
[3] Department of Laboratory Medicine, Samsung Medical Center, Seoul, Korea

Extramedullary progression of multiple myeloma leads to treatment resistance and high rate of mortality. To understand molecular mechanism of extramedullary progression of multiple myeloma, we isolated myeloma single cells from the bone marrow and extramedullary sites and analyzed transcriptome together with bulk tumor tissues. Transcripts for cell proliferation, immune responses, and metabolic alterations were enriched in transcriptome of extramedullary myeloma cells. IL-6, integrins, chemokines and their receptors related to autocrine and paracrine stimulation of myeloma cell growth were overexpressed in the extramedullary myeloma cells. MHC class I and NK inhibitory receptor genes were also up-regulated in extramedullary myeloma cells. We will discuss about the genomic features of extramedullary progression of multiple myeloma at single cell level, which will provide a clue for therapeutic targets for refractory multiple myeloma.

SS01-02

Characteristics of Tumor Infiltrating Lymphocytes Revealed by Single Cell RNA Sequencing

Zemin Zhang

BIOPIC and School of Life Sciences, Peking University, China

Detailed single cell characterization of infiltrating leukocytes coupled with genomic analysis of tumor cells enables a wide array of research directions concerning the leukocytes classification, activation, suppression, T-cell receptor (TCR) repertoire, and immune therapy responses. We performed deep single-cell RNA sequencing on thousands of single T cells isolated from peripheral blood, tumor and adjacent normal tissues from multiple hepatocellular carcinoma patients. The transcriptional profiles of these individual cells, coupled with assembled TCR sequences, enabled us to identify T cell subsets based on their molecular and functional properties, and delineate their developmental trajectory. Specific subsets such as exhausted CD8+ T cells and Tregs were preferentially enriched and potentially clonally expanded in HCC, and we identified signature genes for each subset. One of the genes, Layilin, is upregulated on activated CD8+ T cells and Tregs, and represses the CD8+ T cell functions in vitro. We have now expanded this study to include additional types of tumor and leukocytes, and found distinct patterns of clonal expansion, functional states and transition processes. Such compendium of transcriptome data provides valuable insights and a rich resource for understanding the immune landscape in cancers.

SS01-03

Dissecting the Clonal Selection Pressures Exerted by ALL Induction Therapy with Single-Cell Genomics

Charles Gawad
Department of Oncology, Department of Computational Biology, St. Jude Children's Research Hospital, USA

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and remains a leading cause of pediatric cancer-associated morbidity and mortality. Previous studies have shown that there can be significant changes in the frequencies of clonal leukemic populations as the disease evolves from the time of initial diagnosis to the time of disease recurrence. These findings suggest that clones that are resistant to treatment can undergo positive selection to cause relapse. However, aside from measuring clonal evolution between those two distant time points, we have a limited understanding of the depth of clonal diversity and extent of clonal evolution present during treatment. Moreover, we do not know if and to what extent the phenotype of residual diseased cells that harbor leukemia-associated mutations changes during treatment. In this talk, I will present recent work demonstrating how we have begun to use single-cell and other sensitive sequencing methods to provide high-resolution views of ALL clonal evolution as patients undergo induction therapy. These initial studies have revealed much greater population genetic and phenotypic diversity than can be detected with standard sequencing methods with important implications for disease persistence and monitoring, as well as treatment resistance.

SS02-01

Immune Checkpoint Inhibition in Hematologic Malignancy - Focusing on Multiple Myeloma

Yoon Seok Choi
Department of Internal Medicine, Chungnam National University College of Medicine, Korea

Various immune checkpoint inhibitory molecules expressed on tumor-recognizing T cells are a critical component of the immunosuppressive tumor microenvironment. Trials of monoclonal antibody drugs targeting immune checkpoint have achieved noteworthy clinical benefit in many types of solid tumors, including melanoma and non-small cell lung carcinoma, by blocking inhibitory signals and restoring anti-tumor immune response. In contrast, recent clinical trials of immune checkpoint blockade performed in patients with multiple myeloma failed to demonstrate significant single-agent anti-tumor efficacy. To predict and improve the clinical responsiveness to immune checkpoint blocking treatment in multiple myeloma, explicit functional characterization of tumor antigen-specific T cells is an essential prerequisite. Therefore, we investigated the immunologic characteristics of marrow-infiltrating myeloma antigen-specific T cells, focusing on the expression of T cell inhibitory molecules, in our newly-diagnosed myeloma patients.
Malignant plasma cells, defined as CD14-CD19-CD138+CS1+CD56hi, expressed PD-L1 abundantly and the level of PD-L1 correlated positively with tumor burden. Marrow-infiltrating T cells contained significantly more CD8 T cells than circulating T cells. Marrow-infiltrating CD8 T cells showed higher PD-1 expression in multiple myeloma patients than in control group. PD-1+ marrow-infiltrating T cells co-express other types of T cell inhibitory receptors including Tim-3, LAG3 and TIGIT. Likewise, myeloma antigen-specific CD8 T cells, defined by MHC multimer technique, were enriched in effector-memory T cell population and expressed high level of PD-1 and Eomes, indicating that they were profoundly exhausted functionally.
Collectively, although PD-1/PD-L1 axis acts as a major component of immunosuppressive microenvironment in multiple myeloma, the clinical efficacy of PD-1 blockades in multiple myeloma might be hampered by (1) heterogeneity and multiplicity in expression patterns of T cell inhibitor receptors and (2) molecular depth of T cell exhaustion. Therefore, for successful rejuvenation of anti-myeloma T cell responses, combination immunotherapeutic approaches are required. These results provide a basis for utilizing multiple immune checkpoint inhibitors targeting different molecules and incorporating immunomodulatory agents into the immune checkpoint inhibitor in treatment of multiple myeloma.

SS02-02

A New APC Based Therapeutic Cancer Vaccine

Chang-Yuil Kang
Laboratory of Immunology, College of Pharmacy, Seoul National University, Korea

During cancer immunoediting, tumor cells with spontaneous loss of Major Histocompatibility Complex (MHC) class I expression tend to gradually increase in the tumor microenvironment by preferentially escaping from immune surveillance of cytotoxic T cells even though MHC class I-deficient tumors have been historically considered to be susceptible to NK cell-dependent cytotoxicity. Recent studies demonstrated that most NK cells found in the tumor microenvironment of advanced cancers are defective, releasing the malignant MHC class I-deficient tumors from NK cell-dependent immune control.
We have previously reported that an invariant natural killer T (NKT) cell ligand, alpha-galactosylceramide (αGC), loaded on a tumour antigen (tAg)-expressing B cell- and monocyte-based vaccine (B/Mo/tAg/αGC) elicited diverse antitumour immune responses such as NKT cell, NK cell, CD4, CD8 T cell and antibody responses. Here, we showed that B/Mo/tAg/αGC effectively eradicated these advanced tumors that are not curable with a single immunotherapy. In this process, we found that the co-expression of Tim-3 and PD-1 marks functionally exhausted NK cells in advanced tumors and that MHC class I downregulation in tumors was closely associated with the induction of NK cell exhaustion in tumor-bearing mice as well as in cancer patients. Furthermore, the recovery of NK cell function by IL-21 by NKT cell derived was critical for the anti-tumor effect of the vaccine against these advanced tumors. These results reveal the process involved in the induction of NK-cell dysfunction in advanced cancers and provide a guidance for the development of strategies for cancer immunotherapy.

SS02-03

Chimeric Antigen Receptor-Engineered Natural Killer Cell Immunotherapy for Cancer

Kyung-Nam Koh
Division of Pediatric Hematology/Oncology, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea

For decades, cancers have been treated with standard treatments, including surgery, radiation, and chemotherapy. However, patients with refractory or recurrent cancers require other therapeutic modalities. Immunotherapy, an emerging therapeutic option, can harness the components of immune system to fight the disease. It represents the future of cancer treatment and its efficacy has been shown even in aggressive types of cancer.
Immune surveillance eliminates molecules which are identified as non-self. Cancer cells can obtain antigenicity and hence immunogenicity through the expression of neo-antigens that can be recognized as non-self. However, cancer cells employ several strategies to evade host immune response, including down-regulation or weak immunogenicity of target antigens and generation of an immunosuppressive tumor environment.
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 rapidly growing. 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, it is unclear whether huge success of CAR T-cell therapy for patients with ALL and lymphoma can be translated into success in other malignant tumors. Also, CAR ¬T-cell therapy has several limitations such as severe cytokine release syndrome, prolonged in-vivo persistence, and a hassle in production of patient-specific products.
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.
However, there are also barriers such as difficulty of ex-vivo expansion of CAR-modified primary NK cells, low transduction efficiency of NK cells, presumed inferiority over CAR T cells, and limited in-vivo persistence. In contrast to the abundance of clinical trials in CAR-T cell therapy, studies on CAR NK cells are mostly in preclinical stage.
This lecture will review the current status of research of CAR NK-cell therapy and ongoing trials, and future prospects of CAR NK-cell immunotherapy in oncology.

SS02-04

Post-transplant Immunotherapy with WT1-specific CTLs for High-risk Acute Myelogenous Leukemia

Hee-Je Kim[1,2], Hyun-Jung Sohn[3], Jung-A Hong[3], Hyun-Joo Lee[3], Dae-Hee Sohn[3], Chang-Ae Shin[3], Hyun-Il Cho[3], Woo-Sung Min[1,2], Tai-Gyu Kim[3,4]

[1] Leukemia Research Institute, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2] Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[3] Catholic Hematopoietic Stem Cell Bank, College of Medicine, The Catholic University of Korea, Seoul, Korea
[4] Department of Microbiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

High-level WT1 expression in leukemic cells is correlated with clinical outcome in patients with acute myelogenous leukemia (AML); therefore, WT1 has been also used as an immunotherapeutic target. In this prospective phase I/II clinical trial of WT1-specific cytotoxic T cell (WT1-CTL) immunotherapy following allogeneic hematopoietic stem cell transplantation (HSCT) in 10 adult patients with high-risk AML, WT1-CTLs, including CD4+ and CD8+ cells, were infused four times beginning on day +35 post-transplantation. All patients were engrafted successfully, and five were alive at a median follow-up of 127 months (range, 102–130 months). The 8-year event-free survival rate was 50% among all patients and 71.4% among seven patients with first complete remission pre-HSCT. Three patients were initially resistant to standard induction chemotherapies and died of relapse after transplant. Two patients died without evidence of relapse, one of human cytomegalovirus (HCMV) disease and one of bacterial septicemia. The frequencies of WT1-specific CD8+ and CD4+ T cells increased in response to fluctuating WT1 antigen levels. In this study, we demonstrated that adoptive transfer of WT1-CTLs is a feasible therapeutic tool with acceptable safety that induces a long-term clinical response in patients with high-risk AML after allogeneic HSCT.

SS03-01

The Japan Adult Leukemia Study Group (JALSG) Studies For Acute Promyelocytic Leukemia (APL)

Akihiro Takeshita

Department of Transfusion and Cell Therapy, Hamamatasu University School of Medicine, Japan

The JALSG study for acute promyelocytic leukemia (APL) has started independently from the AML study on 1992. We conducted a multicenter study of differentiation therapy with ATRA alone or in combination with chemotherapy followed by intensive post-remission chemotherapy in newly diagnosed adult patients with APL (the JALSG APL92 trial). It demonstrated that ATRA with or without chemotherapy gives a statistical improvement in CR rate and early mortality rate, as well as superior survival in newly diagnosed APL.
In the JALSG APL97 trial, we conducted in newly diagnosed patients with APL achieving molecular remission after treatment with ATRA and chemotherapy to examine the efficacy of intensified maintenance chemotherapies. It showed that the intensified maintenance chemotherapy did not improve DFS, but resulted in poorer survival in APL in molecular remission at the end of the consolidation chemotherapy.
In the JALSG APL204 trial, patients with newly diagnosed APL achieving the molecular remission at the end of consolidation therapy were randomly assigned to receive ATRA or tamibarotene (Am80) to evaluate the efficacy of maintenance therapy with tamibarotene in APL. Maintenance therapy with tamibarotene was effective at decreasing the relapse rate in APL patients by comparison to ATRA at the 7-year observation point. In particular, tamibarotene was significantly more effective than ATRA for high risk patients.
In our on-going protocol, patients with newly diagnosed APL after achieving hematological CR, were sequentially received some molecular specific agents including ATO, gemtuzumab ozogamicin (GO) and Am80. (the JALSG APL212 study) This study is in observation period and will be evaluated after comparing with the prognostic outcomes from the APL97 and APL204 studies.
ATO has been applied the Japanese Pharmaceuticals and Medical Devices Agency for the first line agent in the treatment of newly diagnosed APL, and we are planning new trial including concomitant use of retinoid and ATO will organize. Another trial, composed of combination treatment composed of Am80 and ATO for the patients with relapsed APL (the JALSG APL218R), will provide the efficacy and safety of them with the pharmacologic data.

SS03-02

Therapy of Acute Promyelocytic Leukemia

Lionel Adès
Hematology, Hôpital Saint-Louis, Paris Diderot University, France

1. background

Acute Promyelocytic Leukemia (APL) is a specific type of acute myeloid leukemia (AML) characterized by its morphology (M3 or M3v in the FAB classification), t(15;17) translocation leading to PML-RARa fusion gene, and by a specific coagulopathy combining D.I.C., fibrinolysis and non specific proteolysis. In the SEER database, the overall annual incidence rate of APL was 0.23 per 100 000. The median age at diagnosis was 44 years and the incidence rate was lower in older patients. Before the advent of all trans retinoic acid (ATRA), APL was treated exclusively by conventional anthracycline-AraC leading to a complete remission (CR) rates of 70 to 80%, with optimal treatment of coagulopathy by massive platelet transfusion, and about 40% of the patients who achieved CR were cured with consolidation chemotherapy.

ATRA can differentiate APL blasts both in vitro and in vivo. With ATRA treatment as a single agent, about 90% of newly diagnosed or relapsed APL can obtain CR, through differentiation of APL blasts. However, in some cases, ATRA also leads to major blood hyperleukocytosis and potentially fatal "ATRA syndrome" also called “differentiation syndrome” (DS). Furthermore, almost all patients relapsed unless they received consolidation chemotherapy. This lead clinical groups to combine ATRA and classical anthracycline-AraC chemotherapy in the treatment of newly diagnosed APL, resulting in reduction in the incidence and severity of ATRA syndrome, and the incidence of relapse.

In recent years, the advent of a new specific and “targeted” drug in APL, ie Arsenic, has even allowed APL patients to be cured by the combination of ATRA and arsenic, without chemotherapy .

2. Prognostic factors in APL

Pretreatment factors still associated with a higher risk of early death include older age and high WBC count, whereas pretreatment factors associated with a higher risk of relapse include high WBC counts (>10 G/L), FAB M3v morphology, presence of the short bcr3 transcript, CD2, CD56 and CD34 expression, FLT3 internal tandem duplication and slow and incomplete in vitro differentiation of blasts with ATRA. Except for slow and incomplete differentiation these parameters are generally correlated to high WBC counts. The Sanz’s score individualized a high risk group characterized by WBC > 10G/L that carries a greater risk of relapse.

Finally, the major prognostic factor of relapse is response to treatment defined by the achievement of molecular complete remission, determined by RT-PCR in bone marrow cells, after consolidation treatment.

3. Early death (ED)

Some recent studies have suggested that the dramatic improvement in the ED rate observed in APL clinical trials may, to some extent, reflect a patient selection. They reported ED rates as high as 15 to 17% in newly diagnosed APL, when patients not included in clinical trials were analyzed together with protocol patients. In addition when analyzed in the SEER database ED , did not seem to have much improved between 1977 and 2007, in spite of the advent of ATRA treatment, although in many cases delay of ATRA onset had increased the risk of ED. All together, those data suggest that a delay in ATRA administration might lead to an increase in early death rate. Morover, as earlier mentioned, rigorous transfusion support to maintain adequate platelet and fibrinogen levels is mandatory to avoid any fatal bleeding early during induction.

4. Optimal treatment of coagulopathy

Bleeding, mainly Intracerebral and pulmonary, are the first causes of early death before and during induction therapy in APL, To prevent them, supportive measures should be instituted as soon as the diagnosis of APL is suspected, even before the confirmation by marrow aspirate and cytogenetics: ATRA should be started immediately to decrease the risk of severe bleeding.

Supportive care consists of massive transfusion of platelets, in order to maintain a platelet count above 50 G/L whenever possible. Fresh frozen plasma and fibrinogen are advocated in case of fibrinogen level below 150 mg/dL. During the coagulopathy period, central venous catheterization, lumbar puncture, and other invasive procedures should be avoided.

5. First-line treatment of APL based on Chemotherapy and ATRA

With ATRA treatment alone, 85 to 90% of newly diagnosed APL cases can obtain CR, through differentiation of APL blasts. but almost all patients relapse when ATRA was used a a single agent. Thus, several groups combined ATRA with classical anthracycline-based chemotherapy in the treatment of newly diagnosed APL, to reduce the incidence of ATRA syndrome and of relapse.

The combination of ATRA and anthracycline based chemotherapy has been the mainstay of newly diagnosed APL treatment over the last 2 decades. Published results have shown in particular that immediate onset of ATRA was mandatory (before diagnosis certainty if necessary) to reduce the risk of early death, that AraC could be omitted from chemotherapy in standard risk APL (ie with baseline WBC <10 G/l) but appeared useful in high risk APL (with WBC > 10G/l), possibly at high dose, to reduce the incidence of relapsef5. A beneficial role for prolonged maintenance treatment with continuous low dose CT (6MP and MTX) and intermittent ATRA was also strongly suggested especially in high risk APL following in particular randomized results from our group and of from a recent metanalysis7 of several trials. Regarding anthracyclines, at least one study suggested that Idarubicin gave better results than daunorubicin, while non randomized studies suggested a potential interest of adding ATRA during consolidation cycles, at least if AraC was omitted.

6. Role of arsenic derivatives

Arsenic trioxide is the treatment of choice for relapsing APL. It is not associated with toxicities commonly observed with anthracycline-based chemotherapy, especially myelosuppression. Those results lead investigators from China, Iran, Indian and from the Western world countries to evaluate the role of ATO in newly diagnosed APL, either in addition to ATRA and anthracycline-based chemotherapy, or in order to reduce the amount of chemotherapy administered, and even avoiding any concomitant chemotherapy.

7. ATO During consolidation courses

A Chinese trial randomized newly diagnosed APL patients for induction between ATRA alone, ATO alone and the combination of both. Patients who achieved CR then received anthracycline-based consolidation chemotherapy. The CR rate was the same in each of the 3 treatment arms, but decrease of the fusion transcript was faster and, more importantly, the incidence of relapse significantly lower in patients treated with the ATRA-ATO combination upfront. A U.S. Intergroup trial evaluated the benefit of two additional courses of ATO as first post-remission therapy in a standard treatment based on ATRA and anthracycline–AraC chemotherapy. Three-year EFS was 77% in the ATO arm compared to 59% in the standard arm, and three-year OS was 86% in the ATO arm compared to 77% in the standard arm. The benefit of the addition of two courses of ATO consolidation following remission induction was particularly important in patients presenting with high WBC counts.

8. ATO During Induction

In this approach, ATO was used as a single agent or with limited ATRA and/or chemotherapy. In the Indian experience, patients received ATO alone for induction and one consolidation course, followed by maintenance 6 monthly consolidation courses (10 days/month). The complete remission rate was 86% and the three year DFS and OS were 87% and 86% respectively.

Similar results, but with a higher relapse rate (40% vs. 15%), were observed in an Iranian trial that used the same approach of induction and 1 consolidation course of ATO alone, but without maintenance treatment. The M.D. Anderson group also reported on 44 patients who received ATO and ATRA for induction (associated with gemtuzumab ozogamycin [GO] in high-risk patients) with 89% CR (all with molecular CR). In low- and intermediate-risk patients, the CR rate was 96%. Very few relapses (exclusively in high-risk patients) were seen with ATRA-ATO maintenance.

Finally, results of a phase III, randomised, prospective trial was recently reported by the Italian GIMEMA group and the German SAL and AMLSG groups. In this study, younger patients with low WBC were randomized to receive ATO+ATRA combination or the Italian AIDA2000 risk-adapted (based on Idarubicin and Anthracyclin) protocol for non high-risk disease (arm B). After a median follow-up of 31 months the 2 year EFS was 97% and 86.7% in the ATO+ATRA and ATRA+chemo arms, respectively (P=0.03). Similarly, OS, DFS, and CIR rates were 98.7% vs. 91.1% (P=0.03), 97% vs. 91.6% (P=0.19) and 1.6% vs. 4.3% (P=0.41) in ATO+ATRA and ATRA+chemo arms, respectively. Those results strongly suggested that for patients with low WBC, th etreatement without chemotherapy based on ATO+ATRA is at least as effective as the classicial ATRA+chemotherapy regimen.

Those reports were very impressive, as constituted the first demonstration that a leukemia could be cured without any chemotherapy.

SS03-03

Strategies to Define High-Risk Patients in Acute Promyelocytic Leukemia

Byung -Sik Cho
Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

In spite of outstanding progress in management of acute promyelocytic leukemia (APL) due to introduction of all trans retinoic acid (ATRA) and arsenic trioxide (ATO), APL still remains associated with a high incidence of early death due to the frequent occurrence of an abrupt bleeding diathesis. While most APL experts are aware of the high rate of early death, such awareness is not typically present among general hematologists and oncologists. Thus, the risk assessment for APL management requires significant prognostic factors associated with early death as well as increased probability of relapse.
While there have been several evidences suggesting prognostic impacts of immunophenotypic and molecular features of APL blasts, the analysis of the available data indicates that the stratification of APL risk according to Sanz stratification based on WBC and platelet counts remains the most reliable and validated way to rapidly identify high-risk APL patients. However, new treatment modalities including ATO may impact on the value of current prognostic factors which were mainly established in the context of ATRA and chemotherapy.
This talk will introduce the current evidences of various prognostic factors to define high-risk APL patient in terms of early death and relapse, which may help to minimize early mortality and better design risk-adapted treatment in APL.

SS04-01

Molecular Pathogenesis of Natural Killer T-cell Lymphoma

Wee Joo Chng
National University Cancer Institute, Singapore

Natural Killer / T-cell lymphoma is a rare type of non-Hodgkin's lymphoma that is more prevalent in some Asian countries such as Korea, Japan, southern China and Hong Kong. It is associated with EBV infection. Current treatment consisted mainly of combination chemotherapy which are quite toxic and radiation. Outcomes of patients with advance disease is poor. A better understanding of the underlying molecular biology and critical molecular events / pathways in NK/T-cell lymphoma is therefore critical to advance treatment. In the recent years, a number of studies utilising genomic tools such as microarray and next generation sequencing has identified some recurrent genetic abnormalities and perturbed pathways that may be important for the survival of NK/T-cell lymphoma cells and may herald the emergence of target therapy.

SS04-02

Recent advances in NK/T-cell lymphoma

Yok-Lam Kwong
Department of Medicine, Queen Mary Hospital, Hong Kong

Significant advances have been made in the management of NK/T-cell lymphomas in the past decade.

Advent of L-asparaginase containing regimens. NK/T-cell lymphomas express high levels of P-glycoprotein, and conventional anthracycline-containing regimens are ineffective. L-asparaginase works as a single agent in relapsed/refractory cases, and regimens containing L-asparginase, with SMILE the most popular, are now considered the standard treatment of NK/T-cell lymphoma of any stage.

Plasma EBV DNA quantification in monitoring of response. NK/T-cell lymphomas are universally infected by Epstein Barr virus (EBV). Quantification of plasma EBV DNA, released as a result of apoptosis of lymphoma cells, is an accurate surrogate biomarker of lymphoma load. Whole blood is unsuitable as a starting material, as it contains circulating EBV-infected memory B-cells, which introduce errors in assays.

PET/CT as an integral part of management. NK/T-cell lymphomas are FDG-avid, and PET/CT is considered the standard imaging. Interim and end-of-treatment PET/CT has been shown to be of prognostic significance.

Prognostication of NK/T-cell lymphoma. In the era of non-anthracycline-containing reigmens, two prognostic indices, Prognostic Index for NK/T-cell lymphoma (PINK) and PINK-EBV DNA (PINK-E), have been devised, which can be used to predict treatment outcome of patients.

Optimal sequencing of chemotherapy and radiotherapy. With the use of effective non-anthracycline-containing regimens, it has recently been shown that sequential chemotherapy and radiotherapy results in outcome that is comparable with concurrent chemotherapy and radiotherapy.

Immunotherapy of NK/T-cell lymphoma. Antibodies against programmed death protein 1 (PD1) on effector T-cells have been shown recently to be highly effective in relapsed/refractory NK/T-cell lymphomas.

SS04-03

Beyond Current Standard Care of ENKTL

Won-Seog Kim
Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

There was a big progress in treatment of extranodal/NK-T cell lymphoma (ENKTL) during last decade. Based on the literatures, more than 70% of stage I/II disease can survive more than 2 years. But still the long term survival of stage III/IV patients was around 30%. Also, most patients with relapsed or refractory(R/R) ENKTL have poor prognosis with short survival. In this presentation, we will discuss with novel therapeutic approaches including targeted molecules, monoclonal antibodies, and immunotherapy.

SS05-01

Apoptosis in Cancer

Soo-Youl Kim
Cancer Microenvironment Branch, Division of Cancer Biology, National Cancer Center, Korea

Apoptosis is considered a vital component of various processes including normal cell turnover. There are two main apoptotic pathways: the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway. There is an additional pathway that involves T-cell mediated cytotoxicity and perforin-granzyme dependent killing of the cell. The extrinsic, intrinsic, and granzyme pathways converge on the same terminal, or execution pathway. This pathway is initiated by the cleavage of caspase-3 and results in DNA fragmentation, degradation of cytoskeletal and nuclear proteins, crosslinking of proteins, formation of apoptotic bodies, expression of ligands for phagocytic cell receptors and finally uptake by phagocytic cells. Inappropriate cell death is a key factor in many human diseases including neurodegenerative diseases, ischemic damage, autoimmune disorders and cancer. In cancer, defective or inefficient apoptosis is an acquired hallmark of cancer physiology. Therefore it is important to understand how cancer cell can evade apoptosis and manage proliferation for developing anti-cancer drug. The process of programmed cell death, apoptosis, is generally characterized by distinct morphological characteristics and energy-dependent biochemical mechanisms. An alternative understanding of cell death mechanism by negatively regulated energy metabolism is a new opportunity to discover novel drug targets for designing cancer specific therapeutic strategies.

SS05-02

CHIP Controls Necroptosis through Ubiquitylation- and Lysosome-Dependent Degradation of RIPK3

Jaewhan Song
Department of Biochemistry, Yonsei University, Korea

Receptor-interacting protein kinase 3 (RIPK3) functions as a key regulator of necroptosis. Here, we report that the RIPK3 expression level is negatively regulated by CHIP (carboxyl terminus of Hsp70-interacting protein; also known as STUB1) E3 ligase-mediated ubiquitylation. Chip-/- mouse embryonic fibroblasts and CHIP-depleted L929 and HT-29 cells exhibited higher levels of RIPK3 expression, resulting in increased sensitivity to necroptosis induced by TNF (also known as TNF). These phenomena are due to the CHIP-mediated ubiquitylation of RIPK3, which leads to its lysosomal degradation. Interestingly, RIPK1 expression is also negatively regulated by CHIP-mediated ubiquitylation, validating the major role of CHIP in necrosome formation and sensitivity to TNF-mediated necroptosis. Chip-/- mice (C57BL/6) exhibit inflammation in the thymus and massive cell death and disintegration in the small intestinal tract, and die within a few weeks after birth. These phenotypes are rescued by crossing with Ripk3-/- mice. These results imply that CHIP is a bona fide negative regulator of the RIPK1–RIPK3 necrosome formation leading to desensitization of TNF-mediated necroptosis.

SS05-03

Functional Isolation of New Modulators in Apoptosis and Necroptosis

Yong-Keun Jung
School of Biological Science, Seoul National University, Korea

Despite its ability to selectively kill cancer cells, tumor necrosis factor (TNF)-related apoptosis-inducing ligand, or TRAIL, clinical trials of TRAIL or TRAIL-receptor agonists have failed to achieve beneficial anticancer activity because many primary cancers are resistant to TRAIL. Among two cognitiveTRAIL receptors, DR4 and DR5, we isolated a mutant form of DR4 as a suppressor of TRAIL-induced cell death from cell-based functional screen using cancer patient-derived cDNA expression library. Here, we show that DR4 Ser424 within death domain (DD)is O-GlcNAcylated, to triggernot only apoptosis but also necrosis upon TRAIL ligation. Replacement of DR4 Ser424 with either proline (S424P) or alanine (S424A) lost their cytotoxic activity due tolack of O-GlcNAcylation.Compared to wild-type DR4,O-GlcNAcylation-defective DR4 mutantdid not translocate to the aggregated compartmentsfor receptor clustering andwas not able to formdeath-induced signaling complex or necroptosome.Unlike DR4, DR5 was not O-GlcNAcylated by TRAIL and like DR4, its activity was blocked by DR4-S424P mutant. Interestingly, most of TRAIL-resistant cancer cells we tested were resistantto DR4 O-GlcNAcylation and promoting DR4O-GlcNAcylation intentionally by combinational treatment ofTRAILand either high glucose or 2-DG remarkably sensitized TRAIL-resistantcancer cells to TRAIL,illustrating significant association between O-GlcNAcylation and cells' sensitivity to TRAIL.In addition, we also isolated necroptosis regulators using cell-based functional screen and characterized its role in necroptosis.

SS06-01

Nontransplant Therapy for Bone Marrow Failure

Danielle M. Townsley
Clinical Development – Oncology, Medimmune LLC, USA

Nontransplant therapeutic options for acquired and constitutional aplastic anemia have significantly expanded during the last 5 years. In the future, transplant may be required less frequently. That trilineage hematologic responses could be achieved with the single agent eltrombopag in refractory aplastic anemia promotes new interest in growth factors in bone marrow failure. In newly diagnosed severe aplastic anemia, eltrombopag enhances responses to standard immunosuppressive therapy when administered in combination, but long-term follow-up data evaluating clonal evolution is required before promoting its standard use in treatment-naive disease. Danazol, which is traditionally less preferred for treating cytopenias, is capable of preventing telomere attrition associated with hematologic responses in constitutional bone marrow failure resulting from telomere disease.

SS06-02

Role of Microenvironment and Genetics in BM Failure

Myungshin Kim
Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea

BBone marrow (BM) is the site of hematopoiesis and is composed of hematopoietic cells (HCs) and their niche, which includes BM stromal cells (BMSCs), osteoblastic cells, osteoclasts, skeletal stem cells, endothelial cells, endosteal monocytes/macrophages, and sympathetic nervous system neurons. The hematopoietic niche is the physical locale of the microenvironment that regulates self-renewal, proliferation and differentiation of HCs and protects HCs from oncogenic, physical and chemical damage. BMSCs have been reported to control hematopoiesis through the production of cytokines that are active in effective hematopoiesis and to support T cell and B cell survival by preventing apoptosis.

Recent evidence suggests that the hematopoietic stem cell microenvironment contributes to the pathogenesis of hematologic disorders. A number of factors including environmental, genetic and prior exposure to chemotherapy or radiation therapies are associated with the development of several BM failure syndromes, including myelodysplastic syndrome (MDS). The BM microenvironment plays a critical role in the fate of HCs and contributes to the pathogenesis of MDS. There is much research needed among aging, BM stroma and MDS development. BMSCs from patients with MDS and acute myeloid leukemia are genetically and epigenetically altered. In addition, there are a number of inherited BM failure syndromes including Fanconi anemia, Shwachman–Diamond syndrome, and dyskeratosis congenital that often develop during childhood and predispose patients to the development of MDS at an early age. Despite the advances in this field, little is known regarding the molecular basis of interaction between HCs and BMSCs in humans that could lead to development of hematologic disorders in BM. In this talk, I would like to review the clinical and molecular features of BM failure, the BM microenvironment, and specific pathways that lead to abnormal blood cell development in BM failure. This information will be crucial for the development of novel therapies to treat the BM failure syndromes.

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SS06-03

Inherited Bone Marrow Failure Syndrome

Hoon Kook
Department of Pediatrics, Chonnam National University Medical School, Korea

Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in the Western World. Although CLL typically responds well to chemoimmunotherapy, most patients relapse, and eventually develop chemorefractory disease. Improved understanding of CLL genetics have led to the identification of TP53 deletions and/or mutations as a vital determinant of chemo-sensitivity. Further advances have led to the development of drugs which inhibit elements of the B-cell receptor pathway (eg BTK, PI3K, SYK) and the apoptotic pathway mediated by BCL2 (eg navitoclax, venetoclax) as highly effective therapies in CLL. These targeted molecules are orally administered, are better tolerated especially in older patients, have activity against TP53 aberrant CLL, and in the case of the BTK inhibitor ibrutinib, has migrated into the frontline therapy of patients not suitable for treatment with chemoimmunotherapy. However, new problems emerge with new treatments. Side-effects including platelet-related bleeding and atrial fibrillation with BTK inhibitors, immune hepatitis and colitis with PI3K inhibitors, and tumor lysis syndrome and neutropenia with BCL2 inhibitors pose therapeutic challenges. In addition, the requirement for indefinite therapy with the oral molecules impose a burden on health systems, and emergence of resistant CLL (eg those with BTK mutations) has been observed across all classes of novel therapeutics.

Combinations of B-cell receptor antagonist and BCL2 inhibitor are now being tested in clinical studies of CLL and related diseases, with high activity and clearance of minimal residual disease. Such combinations hold the promise of improved efficacy and the potential for deep responses allowing drug holidays, and thus may reduce the overall cost of treatment by shortening the duration of therapy.

SS07-01

Variability in Chromatin Architecture and Associated DNA Repair at Genomic Positions Containing Somatic Mutations

Seon-Young Kim
Gene Editing Research Center, Korea Research Institute of Bioscience & Biotechnology (KRIBB), Korea

Dynamic chromatin structures result in differential chemical reactivity to mutational processes throughout the genome. To identify chromatin features responsible for mutagenesis, we compared chromatin architecture around single-nucleotide variants (SNV), insertion/deletions (indels) and their context-matched, non-mutated positions. We found epigenetic differences between genomic regions containing missense SNV and those containing frameshift indels across multiple cancer types. Levels active histone marks were higher around frameshift indels than around missense SNV, whereas repressive histone marks exhibited the reverse trend. Accumulation of repressive histone marks and nucleosomes distinguished mutated positions (both SNV and indels) from the context-matched, non-mutated positions, whereas active marks were associated with substitution- and cancer type-specific mutagenesis. We also explained mutagenesis based on genome maintenance mechanisms, including nucleotide excision repair (NER), mismatch repair (MMR), and DNA polymerase epsilon (POLE). Regional NER variation correlated strongly with chromatin features; NER machineries exhibited shifted or depleted binding around SNV, resulting in decreased NER at mutation positions, especially at sites of recurrent mutations. MMR-deficient tumors selectively acquired SNV in regions with high active histone marks, especially H3K36me3, whereas POLE-deficient tumors selectively acquired indels and SNV in regions with low active histone marks. These findings demonstrate the importance of fine-scaled chromatin structures and associated DNA repair mechanisms in mutagenesis.

SS07-02

Deciphering the Cell-of-Origin Harboring Driver Mutations in Brain Tumors

Jeong-Ho Lee
Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Korea

Glioblastoma (GBM) is a devastating and incurable brain tumor, with a median overall survival of 15 months from time of diagnosis. Identifying the cell of origin that harbors mutations driving GBM could provide a fundamental basis for understanding disease progression and developing novel treatments. Given that the accumulation of somatic mutations is implicated in gliomagenesis, studies have suggested that neural stem cells (NSCs), with their self-renewal and proliferative capacities, in the subventricular zone (SVZ) of the adult human brain may be the cells from which GBM originates. However, there is a lack of direct genetic evidence thereof in human GBM patients. Here, we describe direct molecular genetic evidence from patient brain tissue and genome-edited mouse models that show astrocyte-like NSCs in the SVZ to be the cell of origin that harbors the driver mutations of human GBM. First, we performed deep sequencing of triple-matched tissues, consisting of i) radiologically and pathologically normal SVZ tissue away from the tumor mass, ii) tumor tissue, and iii) normal cortical tissue (or blood), from 23 patients with primary GBM (isocitrate dehydrogenase-wild type) or other types of brain tumors. In doing so, we found that normal SVZ tissue away from the tumor in 46.2% of primary GBM patients contained low-level GBM driver mutations (down to ~1% of the mutational burden) that were observed at high levels in their matching tumors. Moreover, via single cell sequencing and laser microdissection analysis of patient brain tissue and genome editing of a mouse model, we discovered that astrocyte-like NSCs carrying driver mutations migrate from the SVZ and lead to the development of high- grade malignant gliomas in distant brain regions through aberrant growth of oligodendrocyte precursor lineage. Altogether, our results highlight NSCs in human SVZ tissue as the cell of origin that harbors the driver mutations of GBM.

SS07-03

Contribution of Germline Variants in Pan-Cancer Development

Youngil Koh
Hematology & Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine, Korea

Germline contribution of cancer development has been an important research interest for researchers studying carcinogenesis. In addition to well known hereditary cancer syndromes such as Li-Fraumeni syndrome, Lynch syndrome, and Multiple Endocrine Neoplasias, familial clustering of cancer without evident genetic background has been frequently reported. For this matter, the advance of large public database such as 1000 Genome Projects and International Cancer Genome Consortium (ICGC) Pan-Cancer Analysis of Working Group (PCAWG) enables further research regarding association between germline variants and cancer development.
Using those whole genome sequencing (WGS) databases, we revealed germline contribution of lysosomal storage diseases (LSDs) and immune disorders for cancer development. Our assumption is that putative pathogenic variants with subclinical manifestation in LSD and immune disorder genes would facilitate cancer development. Using whole genome sequence data from ICGC-PCAWG and 1000 Genome projects, we successfully analyzed association between putative pathogenic variants (PPVs) in LSD/Immune genes and cancer. We could observe increased PPV prevalence in the ICGC-PCAWG cohort compared to the 1000 Genomes cohort. PPV carriers in these genes had earlier cancer development,validating germline predisposition of these variants. We could further confirm by analysis of transcriptome data which revealed differentially expressed genes according to PPV status, which were highly relevant for cancer-related signaling pathways.
Germline PPV carriers of LSD/Immune gene have increased incidence of cancer. Our finding suggests a potential promise of personalized cancer prevention in these patients. We expect further studies may reveal more precise germline contribution in cancer development.

SS07-04

Developing a Genetic Data based Prognostic Model for Hematologic Cancer

Seung-Hyun Jung[1], Sung-Eun Lee[2], Chang-Ki Min[2] and Yeun-Jun Chung[3]
Departments of [1]Cancer Evolution Research Center, [2]Hematology, Seoul St. Mary's Hospital, [3]Integrated Research Center for Genome Polymorphism, The Catholic University of Korea

Serum of multiple myeloma patient contains sufficiently stable microRNAs (miRNAs), which can be valuable markers for patient management. However, little is known about the expression profiles of miRNAs and their biological implications in relapsed/refractory multiple myeloma (RRMM) patients receiving lenalidomide plus low dose dexamethasone (Len-dex) treatment. To develop a miRNA-based prediction model for treatment response, we explored the associations of miRNAs with treatment outcome of Len-dex treatment and prognosis in 100 RRMMs (45 good responders and 55 poor responders) and identified six microRNAs associated with treatment outcome. Of note, lower expression of the six miRNAs was also significantly associated with shorter time to progression or poorer overall survival. For reliable prediction of treatment outcome, we developed a Len-dex treatment response prediction (LdTRP) model by combining miRNA markers and clinical factors. The LdTRP model showed more robust prediction power than other models based on either miRNAs or clinical variables only. Our results suggest the potential of circulating miRNAs as minimally invasive markers for treatment response and prognosis in RRMM patients, which may replace traditional invasive tumor cell examination by bone marrow biopsy. In addition, since our LdTRP model suggests a specific score threshold for predicting treatment response, it can be easily applied in the clinical setting to select treatment regimens.

SS08-01

New Developments in the Treatment of Newly Diagnosed and Relapsed Acute Lymphoblastic Leukemia

Stephen Hunger
Division of Pediatric Oncology, Center for Childhood Cancer Research, Children's Hospital of Philadelphia, USA

Cure rates for pediatric acute lymphoblastic leukemia (ALL) have improved steadily since the mid 1960s. Over the past decade the death rate for T-cell ALL has been cut by 50% through clinical trials that have optimized chemotherapy regimens. However, recent trials in B-ALL have showed that further intensification of standard chemotherapy regimens may have reached the limits of effectiveness. In parallel new immunotherapy drugs and strategies have been developed and shown remarkable response rates and short-term efficacy in adults and children with relapsed and refractory ALL. These include the bi-specific T-cell engager antibody blinatumomab, the CD22-targeted antibody-drug conjugate inotuzumab and several different chimeric antigen receptor modified T-cell products directed at CD19. These new agents have changed the landscape of treatment for relapsed and refractory B-ALL and will soon be tested in cohorts of children and adolescents with newly diagnosed B-ALL.

SS08-02

Therapy Optimization in Infant ALL

Daisuke Tomizawa
Division of Leukemia and Lymphoma, Children's Cancer Center, National Center for Child Health and Development, Japan

Acute lymphoblastic leukemia (ALL) in infants less than one year old, particularly those with KMT2A (previously known as MLL) gene rearrangement, which account for approximately 80% of cases, is still a challenging disease for pediatric oncologists worldwide. Continuing efforts by the major study groups in Europe, North America, and Japan, mostly by intensifying conventional chemotherapy with or without allogeneic hematopoietic stem cell transplantation have enabled us to cure nearly half of the cases. However, its progress is lagging far behind compared with that in older children with ALL, which now achieves 90% or higher survival rate. Thus, development of novel targeted therapy based on leukemia biology is urgently needed to overcome the dismal outcome of infants with KMT2A-rearranged ALL. Recent progress in basic researches has revealed that the aberrant methylation and histone modifications via DOT1L and other related molecules by KMT2A fusion proteins are key mechanisms of leukemogenesis. Based on these data, clinical trials to introduce epigenetic modifiers are currently underway. In addition, novel immunotherapies such as bispecific T-cell engager (BiTE) antibody constructs or chimeric antigen receptor (CAR) T-cell therapy have emerged as an attractive treatment option especially for refractory/relapsed cases. Lastly, due to the extreme rarity of the disease, international collaboration would be a key solution to establish a future standard of care for infants with ALL.

SS08-03

Genomic Landscape and Therapy Optimization of Pediatric Mixed Phenotype Acute Leukemia

Hiroto Inaba
Leukemia/Lymphoma Division, Department of Oncology, St. Jude Children's Research Hospital, USA

Despite our great advances in curing acute lymphoblastic leukemia (ALL), pediatric mixed phenotype acute leukemia (MPAL) still has a poor prognosis. MPAL is uncommon, representing only 2% to 5% of all acute leukemias. The 2008/2016 World Health Organization (WHO) classification defines MPAL as acute leukemia expressing a combination of antigens not restricted to a single lineage. Aside from 2 genetic abnormalities, BCR-ABL1/t(9;22)(q34;q11.2) and KMT2A (MLL)/11q23 rearrangement, the genetic basis of MPAL has not been well characterized, and cases are categorized by blast-cell lineage as B/myeloid not otherwise specified, T/myeloid not otherwise specified, or MPAL not otherwise specified—rare types. The common subtypes in children are B/myeloid, T/myeloid, and MPAL with KMT2A (MLL)/11q23 rearrangement. The prognosis for pediatric patients with MPAL is similar to that for those with acute myeloid leukemia (AML) (i.e., 60%–70% survival), and no effective treatment is known. Historically, therapy has consisted of an ALL- or AML-directed regimen or one combining elements of both. Although ALL-directed therapy appears to be more effective than AML-directed therapy in inducing complete remission, the treatment regimen is selected mainly at the discretion of the treating physician. The genetic characterization of MPAL will lead to better classification and appropriate treatment. Here, the results of a recent international collaborative pediatric MPAL genomic study, the possible pathophysiology of MPAL, and treatment/management options will be discussed.

SS09-01

MRD Detection in Acute Leukemia, Chronic Lymphocytic Leukemia and Multiple Myeloma

Alberto Orfao[1] and Jacques J.M. van Dongen[2] on behalf of the Euro Flow Consortium and the International Myeloma Foundation
[1] Cancer Research Center (IBMCC-CSIC/USAL-IBSAL); General Cytometry Service (NUCLEUS) and Department of Medicine, University de Salamanca, IBASAL and CIBERONC, Salamanca, Spain (USAL)
[2] Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands.

In recent years the treatment of haematological malignancies has undergone significant changes that have led to greater response rates and prolonged patient survival. Because of such improvements, conventional criteria used to assess complete response (CR) have progressively become insufficient to evaluate the quality of response in a significant fraction of the patients, highlighting the need for more sensitive minimal residual disease (MRD) techniques.
In the past, both conventional (4-10 color) flow cytometry and ASOqPCR have shown to be relatively sensitive approaches to monitor the effect of therapy in virtually all patients with acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM) and, to a less extent also, in a significant fraction of acute myeloid leukemia (AML) cases, via MRD detection. Thus, both groups of methods have shown to add clinically relevant and useful information to conventional CR criteria, because of their greater sensitivity, and the adverse prognostic impact of MRD-positivity on both progression-free survival (PFS) and overall survival (OS), particularly among patients who are in CR. Because of this MRD has progressively become more and more used in clinical trials for making decisions about subsequent therapies to be administered, particularly in childhood ALL. Despite this, a significant fraction of all ASOqPCR and conventional flow MRD-negative adult ALL, CLL, MM and AML patients will still relapse, and the identification of these high-risk cases vs patients who are potentially cured, still remains a challenge, highlighting the need for even more sensitive MRD approaches.
In recent years, Next-Generation Sequencing (NGS) has been proposed as an alternative PCR-based molecular MRD approach with greater sensitivity than conventional ASOq PCR. In parallel, the EuroFlow Consortium has generated also highly-sensitive, standardized and innovative semi-automated Next Generation Flow (NGF) approaches for MRD monitoring in ALL, MM and CLL, which overcomes the limitations of conventional >4-10 color flow cytometry approaches. The novel NGF approaches rely on innovative procedures and tools developed by EuroFlow for sample preparation (e.g. bulk lysis) and automated data analysis, as well as in new, optimized and validated antibody paneld for fast, sensitive, efficient and automated detection of MRD. Of note, the new NGF approaches can be applied for virtually all ALL, CLL and MM patients that reach conventional CR, independently of the specific immunophenotypic profile of tumor cells at diagnosis and the therapy that had been administered. In contrast to NGS, it also provides an overall assessment of the quality of the bone marrow (BM) sample (e.g. assessment of extensive hemodilution) and the BM B-cell regeneration profiles. Overall, it has proven to be more sensitive than conventional flow and molecular-MRD approaches, reaching levels similar to those achieved also by NGS (2 x 10-6), whenever enough cells (e.g. >106 cells) are evaluated per sample. This has translated in e.g. MM, into a more robust prediction of patient outcome. However, successful adaptation of the novel NGF and NGS MRD assays to AML still remains to be achieved.
In this presentation, we summarize the critical features of the new EuroFlow NGF vs. NGS assays and other conventional molecular and flow-MRD approaches, particularly focusing on the sample preparation procedures, the optimized antibody panel and the innovative automated gating tools as well as their clinical impact.

SS09-02

NGS-based Assessment of Clonality & MRD Determination in Acute Lymphoblastic Leukemia

In-Suk Kim
Department of Laboratory Medicine, Pusan National University School of Medicine, Korea

Minimal residual disease (MRD) monitoring has proven to be one of the strongest independent prognostic factors in patients with acute lymphoblastic leukemia (ALL). Sequential monitoring of MRD using sensitive and specific methods, such as real-time quantitative polymerase chain reaction (RQ-PCR) or flow cytometry (FCM), has improved the assessment of treatment response and is currently used for therapeutic stratification and the early detection.

Although both FCM and RQ-PCR yield highly consistent results with sensitivities of 10-4, each method has several limitations. For example, RQ-PCR is time consuming and laborious: the immunoglobulin (IG) and T-cell receptor (TCR) gene rearrangements at diagnosis and the design of corresponding primers can take 3–4 weeks. In addition, the evolution of additional clones beyond the first or index clone during therapy cannot be detected, which might cause false-negative results. FCM requires experienced technicians and sometimes does not achieve a sensitivity of 10-4. Accordingly, a next generation sequencing (NGS)-based method has been developed in an attempt to overcome these limitations. With the advent of high-throughput, NGS technologies, a deeper analysis of IG and/or TCR gene rearrangements is now within reach, which impacts on all main applications of IG/TR analysis. However, standardization, quality control and validation of this new technology are warranted prior to its incorporation into routine practice.

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ES01-01

Monoclonal Gammopathy of Renal Significance (MGRS)

Jung Eun Lee
Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

The clinical spectrum of diseases associated with monoclonal gammopathies is wide including premalignant monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma, amyloidosis, and multiple myeloma. The kidney is often affected in the setting of a monoclonal gammopathy. The term 'monoclonal gammopathy of renal significance (MGRS)' was recently introduced to distinguish the nephropathic nature of these diseases from the truly benign MGUS. Thus, patients with MGRS do not meet the criteria for overt multiple myeloma, by definition.

Renal disease can be caused by deposition of the monoclonal immunoglobulin (MIg) (direct mechanism) or by activation of the alternative pathway of complement by the MIg (indirect mechanism). The deposition of MIg can affect the glomeruli, tubules, and the interstitium and vessels. The glomerular diseases include proliferative glomerulonephritis with MIg deposits, immunotactoid glomerulopathy, and, less commonly, fibrillary glomerulonephritis. Tubular lesions include cast nephropathy and light-chain proximal tubulopathy. Lesions involving the glomeruli, tubules, interstitium or vessels include amyloidosis and MIg deposition diseases (MIDD). Rarely, MIg may also cause C3 glomerulopathy or atypical hemolytic uremic syndrome by interfering with the regulation of the alternative pathway of complement.

Kidney biopsy is indicated in most cases to determine the exact lesion associated with MGRS and evaluate its severity. Diagnosis requires integration of morphologic alterations by light microscopy, immunofluorescence (IF), electron microscopy. The identification of MIg in serum or urine is critical as suppression of MIg secretion by chemotherapy often improves outcomes. Complete hematologic workup with serum and urine protein electrophoresis, immunofixation, and serum-free light-chain assay is required.

The lack of experience in dealing with these diseases can delay treatment. Hence, there is a need to increase clinicians' awareness of MGRS not to delay efficient chemotherapy for patients with MGRS, who by definition do not fulfill the criteria for MM. A multidisciplinary team consisting of nephrologists and hematologists should take responsibility for an individualized therapeutic approach as no standardized treatments based on prospective studies exist.

ES01-02

Smoldering Multiple Myeloma

Byung-Su Kim
Department of Hemato-Oncology, Hallym University College of Medicine, Korea

The term of 'smoldering myeloma' was first coined by Robert Kyle, MD in 1980 when he reported six patients who met the diagnosis criteria of multiple myeloma but did not show a progressive course (1). The International Myeloma Working Group (IMWG) criteria, which were published in 2003 and updated in 2009, defined that asymptomatic or smoldering myeloma should have >3 g/dL of serum M protein and/or >10% of bone marrow plasma cells (BMPC) without related organ damage (2,3). Evidences of end organ damage that can be attributed to the underlying plasma cell proliferation are acronymized as "CRAB" (Hypercalcemia, Renal insufficiency, Anemia, Bone lesions). They are the key features to distinguish smoldering myeloma from active myeloma (3). The exact prevalence of smoldering myeloma is not known, but studies in the US and Sweden suggested that as many as 14% of newly diagnosed myeloma patients are asymptomatic (4,5). Smoldering myeloma may progress to the active myeloma at a rate of 10%/year for the first 5 years, 3%/year for the next 5 years, and 1% per year thereafter (6). This reflects the fact that smoldering myeloma is a biologically heterogeneous disease and patients are at varying risks of progression. Therefore, a lot of efforts have been put to select high risk patients and to initiate therapy before the target organ damages take place (7).

Risk factors such as serum M protein ≥3 g/dL, M protein of IgA isotype, immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes, serum involved/uninvolved free light chain (FLC) ratio ≥8, evolving pattern (increase in serum M protein by 25% on 2 successive evaluations within a 6-month period), clonal BMPC 50%-60%, cytogenetic abnormalities i.e. t(4;14) or del(17p) or 1q gain, diffuse marrow infiltration pattern or 1 focal lesion on MRI, and PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction were suggested to define high-risk smoldering myeloma (8-13). Among them, some features (BMPC >60%, serum FLC ratio >100, ≥2 focal lesions with size of >5 mm on MRI) are associated with very high risk of progression (80% within 2 years). The current IMWG criteria revised in 2014 recommend that patients with these factors should be diagnosed as active myeloma, not smoldering myeloma any more, and relevant treatments be initiated (14). This change upstaged 20% of patients who had been previously diagnosed as smoldering myeloma to the active myeloma.

Since the late 1980s, researchers have been trying to apply chemotherapy toward smoldering myeloma (15). Variations of alkylating regimens containing melphalan did not bring the significant benefit to the response rate or overall survival (16,17). A prospective study of thalidomide in 76 patients with smoldering myeloma demonstrated significant reduction of tumor burden (18). However, clinically meaningful response rate was low (PR or better in 42%) and did not improve survival. (18). In addition, long-term thalidomide therapy was not tolerable and required dose reduction (86%) or discontinuation (50%). The traditional concept of watch-and-wait for smoldering myeloma was founded on these outcomes and considered as standard before the advent of novel agents. The Spanish group (GEM/PETHEMA) reported the first study that demonstrated survival benefit in smoldering myeloma in 2013 (19). They prospectively randomized 119 patients with high-risk smoldering myeloma to the early treatment (lenalidomide plus dexamethasone) or the observation arm, yielding significant survival benefit for early treatment (3-year overall survival 93% vs. 76%). Recently, outcomes of the phase 2 study that evaluated the efficacy of elotuzumab in addition the lenalidomide and dexamethasone backbone were reported. Fifty-one patients with high-risk smoldering myeloma were enrolled. Overall response rate was 82.6% (CR 8.7%, VGPR 26.1%, PR 47.8%) and no patients had progressed until 24 months (20).

In the 2017 Annual Meeting of ASH, results of two important studies were presented. The GEM/PETHEMA group designed a phase 2 trial for high-risk smoldering myeloma patients (CESAR trial). The experimental treatment consisted of 6 cycles of induction chemotherapy

(carfilzomib, lenalidomide, dexamethasone), autologous hematopoietic cell transplantation with melphalan 200 mg/m2 conditioning (HDT-ASCT), 2 cycles of consolidation (carfilzomib, lenalidomide, dexamethasone), and maintenance (lenalidomide, dexamethasone). Response rates were unprecedented: CR+sCR were achieved in 43% of patients at the end of induction, 54% after HDT-ASCT, and 75% after consolidation. Progression-free survival (PFS) at 28 months was 94% (21). Results of daratumumab monotherapy for patients with intermediate or high-risk smoldering myeloma were also encouraging (CENTAURUS trial). Patients were randomized to 3 different dosing schedules (long, intermediate, and short) of daratumumab monotherapy. PFS at 12 months was 95%, 88%, and 81% for the long, intermediate, and short dosing schedule, respectively (22).

Last but not least, a few analyses had been reported about smoldering myeloma in Korea. The Korean Myeloma Registry (KMR) enrolled 3,209 multiple myeloma patients from 1999 to 2009 and found that only 193 patients (6.0%) were asymptomatic, which is considerably lower from that of western population (23). Currently, the Korean Multiple Myeloma Working Party (KMMWP) is conducting the retrospective study about smoldering myeloma (KMM 172) and calls for active participation.

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ES01-03

Next Generation Sequencing in Multiple Myeloma

Miyoung Kim
Department of Laboratory Medicine, Hallym University College of Medicine, Korea

Recent advances in next generation sequencing (NGS) have confirmed that multiple myeloma (MM) is genetically heterogenous, and show many gene mutations but no certain unifying mutation. In terms of the number of mutations, MM is in the middle of the landscape: more mutations than other hematologic malignancies, such as leukemias, but fewer than carcinogen-induced tumors, such as lung cancers.
The most frequently mutated genes are KRAS and NRAS (~20%) followed by TP53, DIS3, FAM46C, and BRAF (~10%). Other mutations were observed in less than 5% of patients. Some patients present two or more mutations in genes involved in the same pathway (eg, KRAS, NRAS or BRAF in the MAPK pathway) and it has not been reported in other tumors.
Investigation of V(D)J rearrangement could be a potential tool as a highly patient-specific detection marker in the monitoring of MM.

ES02-01

Optimal First-Line Treatment of Chronic Phase CML

Kyoung Ha Kim
Division of Hematology-Oncology, Department of Internal Medicine, Soonchunhyang University College of Medicine, Korea

A dramatic improvement in the survival of patients with chronic myeloid leukemia (CML) occurred after the introduction of imatinib mesylate, the first tyrosine kinase inhibitor (TKI). Currently, three TKIs (imatinig, dasatinib and nilotinib) are approved for the first-line treatment of CML in chronic phase (CP). And additional BCR-ABL1 TKIs approved for the treatment of patients with CML resistant/intolerant to first line treatment. Consequentially, TKIs have increased life expectancy in patients with CML to almost the same as that of the general population today. However, there remains a need to determine the primary treatment in consideration of the characteristics of each TKI and the characteristics of the patient. Patient characteristics include comorbidities, concomitant medications, lifestyle, risk factors, BCR-ABL1 transcript type and additional chromosomal abnormalities. In addition, the importance of treatment free remission (TFR) is emphasized as the operational cure gradually becomes the goal of treatment. In this presentation, I will discuss efficacy and safety of each TKI, the future of treating CML and TFR.

ES02-02

Update on the Treatment of Chronic Myeloid Leukemia in Children

Jae Wook Lee
Department of Pediatrics, College of Medicine, The Catholic University of Korea, Korea

Chronic myeloid leukemia (CML) is rare in children and adolescents, accounting for less than 3~5% of pediatric leukemia. Allogeneic hematopoietic cell transplantation (HCT) remains the only curative method of treatment, and plays a key role in patients who present in advanced disease phase. Past studies on HCT for pediatric CML showed superior outcomes for a matched sibling donor (MSD) HCT compared to transplant from an unrelated donor (UD). For UD-HCT, disease phase at transplant, infused cell dose and cytogenetic response to pre-transplant imatinib were found to significantly affect post-transplant survival. Results of pediatric CML patients who received allogeneic HCT at our institution also indicate higher overall survival of MSD-HCT recipients compared with those who received alternative donor transplants.

Successful treatment of adult CML patients with the tyrosine kinase inhibitor (TKI) imatinib has also altered therapy for pediatric CML. Despite key studies on the effectiveness of imatinib in adult CML patients, studies on the role of imatinib in pediatric CML are few. Important trials, however, showed that more than 70% of treated patients achieved complete cytogenetic response (CCyR), indicating efficacy in the pediatric setting. At our institution, we also treat newly diagnosed CML patients with imatinib, and only consider allogeneic HCT if the patient shows suboptimal response or is intolerant of TKI therapy, or if the patient presents in blast phase (BP).

Second generation TKIs, including dasatinib and nilotinib, are indicated for patients who show resistance to imatinib therapy. The initial phase I study of dasatinib in pediatric CML patients previously treated with imatinib found that 60mg/m2 and 80mg/m2 once daily dosing were optimal for children. We recently participated in a multi-national phase II study of dasatinib both for imatinib resistant or intolerant patients, as well as newly diagnosed chronic phase (CP) patients. Among 29 patients with imatinib resistance, more than half achieved major cytogenetic response (MCyR) after three months of treatment, whereas greater than 55% of newly diagnosed CML CP patients (N=84) achieved CCyR after six months of treatment.

In my talk, I will give an update on the treatment of pediatric CML, specifically allogeneic HCT for CML, and treatment with first and second generation TKIs.

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ES02-03

BCR-ABL1 Negative Hematologic Neoplasms; Diseases that are Similar to but Different from CML

Hawk Kim
Division of Hematology, Gachon University College of Medicine, Korea

"Atypical chronic myeloid leukemia, BCR-ABL1 negative" (aCML) is a leukemic disorder with myelodysplastic as well as myeloproliferative features present at the time of initial diagnosis. It is characterized by principal involvement of the neutrophil lineage, with leukocytosis resulting from an increase of morphologically dysplastic neutrophils and their precursors. aCML exhibits morphologic similarity to chronic myeloid leukemia (CML) but lacked both the Ph chromosome by standard cytogenetics and BCR-ABL1 rearrangement by polymerase chain reaction according to current World Health Organization (WHO) diagnostic criteria. The differential diagnosis of these BCR-ABL1 negative hematologic neoplasms not only includes aCML, but also chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia (CNL), and myelodysplastic syndrome/myeloproliferative neoplasm, unclassifiable (MDS/MPN, U).
The rare MDS/MPN subtype atypical CML (aCML) is now better characterized molecularly and can be more easily separated from CNL, a rare subtype of MPN similarly characterized by neutrophilia. Although CNL is strongly associated with the presence of CSF3R mutations, these appear to be very rare in aCML (,10%). Conversely, aCML is associated with SETBP1 and/or ETNK1 mutations in up to a third of cases. The so-called MPN-associated driver mutations (JAK2, CALR, MPL) are typically absent in aCML.
We'd like to discuss the diagnostic and therapeutic approaches to these rare and unfamiliar disease entities.

ES03-01

Childhood Atypical Hemolytic Uremic Syndrome

Hae Il Cheong
Department of Pediatrics, Seoul National University College of Medicine, Korea

Hemolytic uremic syndrome (HUS) is one of the disease processes that belong to thrombotic microangiopathy (TMA) and is clinically characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury (AKI). The most frequently encountered TMAs clinically are HUS associated with Shiga toxin–producing Escherichia coli infection (STEC-HUS or typical HUS) and thrombotic thrombocytopenic purpura (TTP), followed by atypical HUS (aHUS) and HUS with a coexisting disease (called secondary HUS). Currently, aHUS is known to be caused by the uncontrolled activation of the alternative complement pathway.
A link between complement and aHUS was first reported in 1981 in two brothers who had a deficiency of complement factor H (CFH) and loss-of-function mutations in the CFH gene were recognized to be associated with aHUS in 1998. Thereafter, loss-of-function mutations in several other complement regulator genes, including CFI (complement factor I) and CD46/MCP (membrane cofactor protein), and gain-of-function mutations in other complement activating proteins, including C3 and CFB (complement factor B), have been identified. The overall detection rate of theses mutations in patients with aHUS is over 50%. In addition, anti-CFH autoantibodies have been detected in approximately 10 % of patients with aHUS, i.e., acquired aHUS. Alternative complement pathway activation is based on continuous, low-level covalent deposition of C3b molecules onto practically all surfaces in contact with plasma. If the C3b molecule is allowed to form the C3 convertase (C3bBb), new C3b deposits will be formed around the enzyme leading to rapid amplification of the activation and subsequent generation of the final membrane attack complex (C5b-9). If the regulator CFH binds to C3b, the convertase enzyme is inactivated and no complement activation follows. The simultaneous interaction of CFI with both C3b is essential for proper regulation on self red cells, platelets, and endothelial cells. In patients with loss-of-function mutations in complement regulatory genes (CFH, CFI, and MCP), C3b is not degraded efficiently and forms the C3 and C5 convertases of the alternative pathway. A similar situation applies to patients with gain-of-function mutations in CFB and C3. Mutant CFB forms a superconvertase that is resistant to dissociation by CFH. Mutant C3b does not bind CFH and MCP and is resistant to degradation by CFI. Therefore, disbalance between activation and regulation in the alternative pathway can lead to development of aHUS. In addition to mutations or autoantibodies in complement proteins, some patients with aHUS have mutations also in or only in molecules linked to the coagulation pathway, such as plasminogen (PLG) and thrombomodulin (THBD), which has a role in both coagulation and complement regulation. Furthermore, mutations in diacylglycerol kinase ε (DGKE) have also been found to cause complement-independent forms of aHUS.
Recently, we performed a study to describe the clinical and genotypic findings of a Korean pediatric aHUS cohort. A total of 51 unrelated Korean children with aHUS were enrolled in this study. Clinical data were retrospectively collected by reviewing the patients' medical records. Complement profiles and plasma anti-CFH titers were measured. Mutational analyses were performed for genetic diagnosis, and the CFHR1 and CFHR3 genes were genotyped. Fifteen (29.4%) patients were confirmed to have anti-CFH-HUS, and genetic mutations were identified in an additional six (11.8%) patients. The patients with anti-CFH-HUS exhibited more severe symptoms at the onset of the disease but had better outcomes than the patients with other forms of aHUS. Eleven (77.5%) of the 15 patients with anti-CFH-HUS had homozygous deletions of CFHR1 with or without the deletion of CFHR3. The prevalence of anti-CFH-HUS differed by ethnic group for unknown reasons, and it did not correlate with the CFHR1 deletion frequency of the geographic population norms.
Molecular genetic diagnosis of aHUS is essential to establish a therapeutic strategy and determine prognosis for individual patients. Because most of the mutations causing aHUS are autosomal dominant inheritance, family member screening is also important.

ES03-02

Adult aHUS

Youngil Koh
Hematology & Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine, Korea

Atypical hemolytic uremic syndrome (aHUS) in adults is one of thrombotic microangiopathy (TMA). Controversies exist in the field of optimal diagnosis and treatment of aHUS. Key pathogenesis of aHUS include complement activation and dysregulated complement system stimulates and injures endothelial cells, red blood cells and platelets. These cascades eventually damage target organs including kidney. Although enormous researches have been performed regarding genomic bases of complement dysregulation, genetics of adult aHUS has not been clearly defined. This may be attributable to weak penetrance of genetic variants and role of environmental factors in adult aHUS.

TMA includes aHUS, Thrombotic Thromboctopenic Purpura (TTP), and TMA's due to secondary causes (mostly due to drugs and autoimmune disorders). Due to similarities in clinical manifestations, differential diagnosis among TMA subtypes is not evident based on symptoms and signs. Although differential diagnosis between aHUS and TTP is critical, mainly due to different treatment strategy, ADAMTS13 activity is not easily measurable in practice and takes time. Hence, there are vigorous efforts to adequately differentiate aHUS from TTP based on easily accessible parameters using machine learning technique.

From therapeutic viewpoint, development of complement inhibitors improved prognosis of aHUS. As of Jan 2018, while eculizumab is the only commercially available drug for aHUS, many complement inhibitors are under clinical investigation for aHUS. Duration of complement inhibitor treatment is one of issue in adult aHUS. Unlike pediatric aHUS, where genetics play a major role in the pathogenesis of aHUS and disease activity is relatively stable, activity of adult aHUS show fluctuation. Hence, there is a doubt regarding continuous use of complement inhibitor in the treatment of adult aHUS.

In this session, aforementioned issues regarding adult aHUS would be discussed.

ES03-03

Management of Thrombotic Thrombocytopenic Purpura (TTP)

Doyeun Oh
Department of Internal Medicine, CHA University School of Medicine, Korea

Thrombotic thrombocytopenic purpura (TTP) is a rare, potentially fatal syndrome characterized by microangiopathic hemolytic anemia (MAHA) and non-immune thrombocytopenia. It is characterized by severe deficiency of ADAMTS13 activity caused by acquired antibody formation or genetic abnormality. Diagnosis of TTP is obtained by two essential clinical features of MAHA, thrombocytopenia and severe deficiency of ADAMTS13 activity in the blood. Genetic analysis can be required to diagnose hereditary TTP. The management principles of TTP are the replacement of deficient ADAMTS13 and the removal of autoantibody. Most of patients with acquired or hereditary TTP are controlled by plasma exchange (PEX) or plasma infusion with or without corticosteroid. However about 20% of patients are refractory or recurred with initial management with PEX and steroid. Recurrent TTP can be managed by rituximab, bortezomib or splenectomy. Clinical trials of new drugs including recombinant ADAMTS13, anti-VWF nanobody and anti-VWF aptamer are undergoing to find out their role in the management of TTP. Caplacizumab, anti-VWF nanobody, induced a faster recovery of TTP with paying a cost of more bleeding tendency in phase II study. BAX930, recombinant ADAMTS13, demonstrated a dose- and time- dependent efficacy with neglect able side effect in phase I trial.

Keywords
Thrombotic thrombocytopenic purpura (TTP), Diagnosis, Management

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SPECIAL REPORT

SP01-01

CAR T Treatment for ALL

Jae Park
Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, USA

In the last several years, we have observed emergence of several promising immunotherapeutic approaches in solid and hematologic malignancies. One of this approach involves a genetic modification of patient's own T cells to express a chimeric antigen receptor (CAR) targeting a tumor-specific antigen. A CAR is a recombinant receptor construct composed of an antibody-derived single-chain variable fragment (scFv), linked to intracellular T-cell signaling domains of the T-cell receptor, thereby redirecting T-cell specificity to the tumor in an HLA-independent manner. We have created a second-generation CAR targeting a B-cell specific antigen, CD19, with CD28 costimulatory domain (19-28z) in the laboratory and translated this adoptive T cell therapy to clinic. Subsequently, we and others have demonstrated that treatment of patients with CD19 targeted CAR T cells induce 80-90% complete response rates in patients with relapsed or refractory B cell acute lymphoblastic leukemia. While treatment with CD19-CAR T cells has been shown to be highly effective and potent in eradicating tumor cells, it is associated with unique set of side effects, mainly cytokine release syndrome (CRS) and various neurological symptoms. These side effects are mostly reversible, and can be effectively managed with IL-6R inhibitors or steroid. In the presentation, we will discuss the current clinical data of CD19 CAR T cells in ALL from various clinical trials as well as approaches to potentially minimize the predictable CRS and neurological toxicities. Furthermore, we will discuss next generation of CAR T cells, termed "armored CARs", further genetically modified to constitutively express 4-1BBL to overcome an immune suppressive tumor microenvironment and further improve clinical outcome in patients with ALL.

SP01-02

CAR Expressing Effector Cells in Stem Cell Transplantation

Ulrike Koehl
University Hospital Leipzig and Hannover Medical School, Germany

Adaptive immunotherapy using redirected chimeric antigen receptor (CAR) T cells against leukemia has led to promising results with improved patient survival. The continuously increasing interest in those advanced gene therapy medicinal products leads to a manufacturing challenge regarding automation, process robustness, and cell storage. In this respect our results from a study for relapsed Melanoma regarding manufacturing of CAR T cells in a closed and automated system will be presented, which gives rise to improve harmonized manufacturing protocols for engineered T cells in future gene therapy studies.

In contrast to T cells, natural killer (NK) cells are known to mediate anti-cancer effects without the risk of inducing graft-versus-host disease, which makes them a promising source for third-party-donor immunotherapy. However, tumor cells can escape NK cell immunosurveillance by tumor immune escape mechanisms (TIEMs). In order to overcome TIEMs and to make NK cell-based therapies more specific, we engineered primary human NK cells to express a CAR designed to recognize CD19 or CD123, which are highly expressed on the surface of primary acute lymphoblastic or myeloid leukemia, respectively. NK cells were transduced with state-of-the-art alpharetroviral self-inactivating (SIN) vectors encoding EGFP alone as control or a second or third generation CAR engineered with an anti-CD19 or anti-CD123 single chain variable fragment (scFv) and containing the CD28 transmembrane domain, the 4-1BB costimulatory domain, the CD3ζ signaling domain and an internal ribosomal entry site (IRES) element for EGFP expression. CAR-modified NK cells showed a strongly improved cytotoxicity against leukemic cells compared to activated NK cells with a nearly complete elimination of leukemic cells after 48 h. Moreover, our side-effect studies demonstrated minimal or no cytotoxicity of CAR NK cells against PBMNCs and lung epithelia cells, respectively.

Since autologous T cells cannot consistently be expanded ex vivo for all patients, third-party allogeneic CAR NK cells as an "off the shelf product" may serve as an alternative strategy. Since NK cells have a significantly shorter lifespan than T cells, off-tumor toxicity might be reduced. However, for durable anti-tumor effects immature CAR NK cells or repeated cell infusions of mature CAR NK cells might be necessary.

SP01-03

Ex vivo αβ T Cell-Depleted Haploidentical Hematopoietic Cell Transplantation and Cellular Therapy Post-Transplantation

Ho Joon Im
Department of Pediatrics, University of Ulsan College of Medicine, Korea

Recent advances in effective ex vivo depletion of T cells or unmanipulated in vivo regulation of T cells, along with better supportive care, and optimal conditioning regimens, have significantly improved the outcome of haploidentical hematopoietic cell transplantation (HCT). The ex vivo techniques for removal of T cells have evolved from the selection of $CD34^+$ hematopoietic stem cell progenitors towards the depletion of $CD3^+$ cells and to the depletion of $\alpha\beta^+$ T cells more recently. The depletion of $\alpha\beta^+$ T cells produces grafts containing many $\gamma\delta^+$ lymphocytes and other effector cells including NK cells. While αβ+ T cells are known to be associated with the initiation of GVHD, $\gamma\delta^+$ T cells can enhance immune reconstitution and are not implicated in GVHD. The $\alpha\beta^+$ T cell depletion is the current approach applying in haploidentical HCT at our center and more than 100 cases of haploidentical HCT using $\alpha\beta^+$ T cell-depleted grafts have been performed so far.

The $\gamma\delta^+$ T cells share characteristics of both the innate and adaptive immune system, displaying both innate cytotoxicity and antigen-presenting potential. These functional properties of γδ T cells make them a promising candidate for cancer immunotherapy. Unlike αβ T cells, γδ T cells are not MHC-dependent for antigen recognition leading to mediate GVL without GVHD. Cellular immunotherapy utilizing γδ T cells has been developed over the past decades. Phosphoantigens such as isopentenyl pyrophosphate (IPP) are potent stimulator of γδ T cell receptor (TCR) and activates γδ T cells in a TCR-dependent manner. Besides, synthetic nitrogen-containing bisphosphonate (N-bis) such as pamidronate and zoledronate can also enhance intracellular levels of IPP, contributing to activation and expansion of γδ T cells. The γδ T cell-based immunotherapy include in vivo stimulation by systemic administration of synthetic phoaphoantigens or N-bis and ex vivo expansion followed by administration of expanded γδ T cells.

Most recently, a new depletion technique to remove $CD45RA^+$ naïve T cells has been developed to enhance immune function as well as to prevent GVHD after haploidentical HCT. The selective depletion of $CD45RA^+$ cells can effectively remove alloreactive naïve T cells responsible for GVHD while preserving pathogen-specific $CD45RO^+$ memory lymphocytes. The CD45RA-depleted graft with abundant memory T cells can be used for therapeutic or preemptive antiviral boost after ex vivo T cell-depleted haploidentical HCT.

In this presentation, I will to talk about the recent progress in ex vivo αβ T cell-depleted haploidentical HCT and cellular therapy following transplantation using γδ T cells and CD45RO memory lymphocytes with introducing our experience in this field.

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SP02-01

Clinical Implications of Minimal Residual Disease (MRD) in Multiple Myeloma

Wee Joo Chng
National University Cancer Institute, Singapore

There has been great advances in the treatment of multiple myeloma in the last decade. Treatment today are achieving high degree of complete remission rate. However, many patients who achieve completed remission relapse within a short time. This suggest that the current methods of defining complete remission is not very sensitive. With the advent of flow cytometry and next generation sequencing, we now have sensitive methods that can detect 1 tumor cell in 1000000 cells. In recent years several important progress has been made that has brought MRD assessment to the fore in myeloma management. Firstly, there is better standardisation of techniques to ensure reproducibility and comparability of results. Second, the incorporation of MRD assessment into different clinical trials have clearly shown that patients who achieve MRD negative remission have a significantly longer overall survival. This has led to the inclusion of a new category of MRD negative remission by the International Myeloma Working Group. There is future discussion with FDA and other regulatory agencies to allow the use of this endpoint for drug approval. This may greatly speed up the trial approval timelines. Third, data is also emerging that achieving MRD negative remission may be particularly important for patients with high-risk disease (especially those with high risk genetic abnormalities), and this may only be achieve by certain potent drug combinations. Lastly, patients who achieve MRD negative remission and is able to maintain this for a period of time, may be those who can stop treatment rather than have continuous treatment. This concept is currently being tested in a number of cooperative group trials. In the coming years, we will surely see the use of MRD testing more and more entrench in clinical practice as their utility become clearer.

SP02-02

The Ubiquitin-Proteasome Pathway : Friend and Foe in Multiple Myeloma

Robert Z. Orlowski
Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, USA

Inhibition of the function of the ubiquitin-proteasome pathway (UPP) with regimens based on the proteasome inhibitors(PIs) bortezomib, carfilzomib, or ixazomib is an acceptedstandard of care for the treatment of newly diagnosed, and either relapsed or refractorymultiple myeloma.Protein turnover capacity through the UPP is reduced during plasma cell differentiation, which may in part explain whymyeloma is especially sensitive to PIs, and why the UPP can be a friend in our battle against myeloma. This reduced capacity increases the proteasome load, thereby triggering cellular stress and enhancing relianceon the unfolded protein response (UPR) for survival, which iseasily overwhelmed by PIs through theirrapid induction of ubiquitin-protein conjugates.Indeed, theratio of proteasome load to capacity may determine apoptoticsensitivity to PIs, with plasma cells having a high loadand/or low capacity showing the greatest sensitivity. However, even inpatients whose disease initially responds very well to PIs,resistance eventually develops in the majority, and recent studies have identified a number of mechanisms that contribute to this phenotype. Most of these in some way impact upon the UPP and the UPR, including by either down-regulating proteasome load through reduced immunoglobulin production, or by enhancing proteasome subunit production and assembly, thereby increasing capacity. Examples of the former include emergence of X-box binding protein 1s-negative plasma cell precursors, while examples of the latter include decreased expression of Tight junction protein 1 with increased expression of Proteasome maturation proteinand, in this way, the UPP can also be a foe in our fight against myeloma. Significantly, such findings provide a rationale for the potential use of these mechanisms as both biomarkers of patient sensitivity to PIs, and for targeting of these pathways to restore sensitivity to this key drug class. Moreover, they indicate that exploiting other targets in the UPP could be of interest, and special focus has been aimed at Deubiquitinating enzymes and E3 ubiquitin ligases since each of the many proteins with these functions serve a more restricted set of clients, and their inhibition could therefore be more targeted. Initial studies also suggest that inhibition of the E1 ubiquitin activating enzyme has activity against myeloma models, and can overcome prior PI resistance. Finally, the activity of the UPP can now be exploited using Protein targeting chimeric molecules that have the capacity to induce degradation of specific proteins by inducing their poly-ubiquitination by E3 ligases such asCereblon. Taken together, these facts indicate that our ability to exploit the UPP for the therapy of multiple myeloma will only grow moving forward, and that novel agents targeting the UPP will continue to contribute to our goal of curing this disease.

SP02-03

Cellular Immunotherapy in Multiple Myeloma

Je-Jung Lee
Department of Hematology-Oncology, Chonnam National University Medical School, Korea

Multiple myeloma (MM) is characterized by generalized immune dysregulation, such as functional hypogammaglobulinemia and defects in T cell immunity, natural killer (NK) cell function, and antigen-presenting capacities of dendritic cells (DCs), resulting in susceptibility to infection as well as tumor progression. Additionally, there is a rise in immune suppressor cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), in the bone marrow microenvironment. The impairment in the function of several immune cells favors the tumor escape from immune surveillance and contributes to induce myeloma cell growth and survival. Recently, immunotherapy has emerged as a promising treatment for MM, and monoclonal antibodies, vaccines, and genetically engineered T cells may represent a new era for the treatment of myeloma. DC vaccination and NK cell therapy are very safe strategies that have shown some efficacy in a subset of MM patients and may become a crucial part of MM treatment when combined with immunomodulatory drugs, immune check-point blockades, or proteasome inhibitors. Genetically engineered T cells, such as chimeric antigen receptor (CAR) T cells or T cell receptor (TCR)-engineered T cells, have also shown encouraging results, despite of worries in terms of toxicities, in recent clinical studies of patients with MM. In this presentation, I will discuss the recent progresses of cellular immunotherapeutic approaches with vaccine using DCs, NK cells, and genetically engineered T cells in management of MM.

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SATELLITE SYMPOSIUM

ST01-01 KYOWA KIRIN

Updated Febrile Neutropenia Management

Won Seog Kim
Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard chemotherapy in diffuse large B-cell lymphoma (DLBCL) patients. Although Event-Free-Survival was improved significantly in RCHOP treated group, we have still a concern to overcome the infections including Febrile Neutropenia (FN) and NNF (Non-neutropenic fever) and HBV reactivation.
FN is defined as an oral temperature >38.5℃ or two consecutive readings of >38.0℃ for 2h and an absolute neutrophil count <0.5 × 109/l, or expected to fall below 0.5 × 109/l. NCCN guideline recommends the prophylactic use of G-CSF from 1st cycle for regimens with an overall risk of FN≥20% including CHOP-like regimens. A prospective cohort study was conducted at Samsung Medical Center and enrolled patients from 2008 to 2011 which was to evaluate the FN incidence during R-CHOP without FN prophylaxis for newly diagnosed DLBCL. 262 patients were enrolled in total. FN developed in 104 patients(39.7%) with the overall incidence of 11.2% (168/1,501) in the cycles. Overall survival was reduced significantly in FN experienced group (p=0.006). Treatment delay was more significant in FN experienced group (P < 0.05). After an introduction of Pegfilgrastim as a prophylactic use from 2014 in Korea, CISL (Consortium for Improving Survival of Lymphoma) conducted a prospective registry study to evaluate FN incidence in DLBCL patients treated by R-CHOP and Pegylated G-CSF, which was given 24 hours subcutaneously after R-CHOP. According to the interim-analysis, FN developed in 74 (10.7%) patients with the overall incidence of 4.2% (124/2,957) in the cycles. The FN incidence was lower than the previous result from SMC, which were without FN prophylaxis. Age, ECOG performance status and LDH level were related with the development of FN.
In the previous cohort study report from SMC, approximately 10% of DLBCL patients experienced non-neutropenic fever (NNF)during R-CHOP, and interstitial pneumonitis comprised approximately 55% of NNF cases. Pneumocystis jirovecii is one of the most common pathogens causing interstitial pneumonia, and increasing evidences suggest that R-CHOP may increase the risk of PJP (Pneumocystis jirovecii pneumonia) with reported incidence of 5%. From 2012 to 2016, SMC conducted a new prospective cohort study to evaluate R-CHOP chemotherapy. From 2014, the prophylaxis for PJP using oral Bactrim was added from 4th cycle of R-CHOP. Of 404 patients in the cohort, 220 (54.5%) patients were the candidates for routine prophylaxis with Bactrim. The incidence of definite and probable PJP before prophylaxis was 5.5% (10 out of 184 patients), which was decreased to 1.4% (3 out of 220 patients) after routine prophylaxis with bactrim (p=0.038).
There are two prophylactic strategies for R-CHOP chemotherapy in DLBCL. One is to prevent FN using Pegylated G-CSF and the other is to prevent NNF using oral Bactrim. Although we need further studies to warrant the related results, these two strategies would be additional options to be considered in terms of the infection management during R-CHOP in DLBCL patients.

ST02-01 NOVARTIS

It's Time We Go Deeper

Pierre Laneuville
Department of Medicine and Oncology, McGill University, Canada

Identifying the treatment goal and patient co-morbidities is important for choosing TKI.Treatment-Free Remission is moving into mainstream clinical practice as an emerging treatment goal in CML. Several studies have demonstrated the feasibility of treatment discontinuation for patients achieving sustained deep molecular responses with regular and frequent molecular monitoring. 2GTKI improves chances of reaching a DMR and trial of TFR. In this session, Dr. Laneuville will provide recent updated guidelines in CML and strategies to maximize deep molecular response and treatment free remission through his experiences and patient cases.

ST03-01 HANDOK

Complement Mediated Glomerular Disease(Focusing on aHUS): Everything has Changed in the Last 10 years but Still a Lot to Do

Giuseppe Remuzzi
Mario Negri Institute for Pharmacological Research, Italy

Hemolytic uremic syndrome (HUS) is a rare disorder (incidence, about 2 cases/year/100,000 people) of microangiopathic hemolysis, thrombocytopenia and renal failure. About 90% of childhood cases are caused by E.coli strains producing Shiga-like toxins (STEC-HUS) and have a good prognosis. Less than 10% of cases are not caused by STEC. This atypical form (aHUS) has a worse outcome with a 10-15% mortality during the first clinical manifestation and up to 50% of cases progressing to end-stage renal disease (ESRD). In the last 15 years, a clear link has been established between aHUS and defects in regulation of the alternative complement pathway, which has paved the way for complement-tailored treatments.

The complement system is part of innate immunity and consists of several plasma and membrane-bound proteins protecting against invading organisms. Three activation pathways -classical, lectin and alternative pathways- produce protease complexes, termed C3 and C5 convertases that cleave C3 and C5, respectively, eventually leading to the membrane attack complex (C5b-9) that causes cell lysis. The alternative pathway is initiated spontaneously in plasma by C3 hydrolysis responsible for covalent deposition of a low amount of C3b onto practically all plasma-exposed surfaces. On bacterial surface, C3b leads to opsonization for phagocytosis by neutrophils and macrophages. Without regulation, a small initiating stimulus is quickly amplified to a self-harming response till consumption of complement components. On host cells, such dangerous cascade is controlled by membrane-anchored and fluid-phase regulators. Foreign targets and injured cells that either lack membrane-bound regulators or cannot bind soluble regulators are attacked by complement.

Approximately half of aHUS patients have mutations in CFH, CFI and MCP, encoding the complement regulatory proteins complement factor H, factor I and membrane-cofactor protein. In 3-5% of patients, hybrid genes deriving from uneven cross-over between CFH and CFHR1 have been found. These genetic defects result in gene products with decreased complement regulatory activity on cell surfaces.

Inhibitory anti-CFH antibodies are reported in 5-10% of aHUS patients. They predominantly target the C-terminus of CFH, thereby impairing complement regulation on host cell surfaces. The development of CFH autoantibodies in aHUS has a genetic predisposition, being strongly associated with deletion of CFHR1 gene.

About 3% of patients carry mutations in the gene encoding thrombomodulin (THBD), a membrane-bound anticoagulant protein that modulates complement.

Gain-of-function mutations in key proteins of the alternative pathway, C3 and complement factor B (CFB) have been reported in 10% and 1-2% of patients, respectively. Mutant proteins are resistant to inactivation by complement regulators.

The above defects lead to unrestricted complement activation, which eventually results in platelet, leukocyte and endothelial cell activation and microvascular thrombosis.

Incomplete penetrance of aHUS has been reported in mutation carriers, indicating that additional genetic and/or environmental hits are necessary for disease manifestation. In an European survey including 795 patients from 4 cohorts, 3% of patients carried mutations in two or three complement genes. Within families, the concomitant presence of CFH and MCP risk haplotypes increased aHUS penetrance in combined mutation carriers, further underlying the oligogenic feature of aHUS.

The advent of eculizumab, a monoclonal antibody that blocks terminal complement activation, has markedly improved outcome and quality of life in patients with aHUS as documented by published case reports and clinical trials. Advances have also been achieved in tools to monitor eculizumab effectiveness and to tailor drug dose and timing of administration.

Recently, DGKE mutations were reported in nine kindreds with autosomal recessive inheritance and early aHUS onset. DGKE encodes diacylglycerol kinase- that is apparently unrelated to complement. The mechanism by which DGKE mutations cause aHUS remains to be elucidated.

ST04-01 AMGEN

Treatment of Multiple Myeloma in Relapse

Keith Stewart
Mayo Clinic, USA

Overall survival (OS) is improving as a result of the introduction of numerous new therapeutics over the past decade. Indeed, a plethora of choice can be confusing to non expert clinicians and as such we seek here to provide some general guidance. The first general rule is that no patient is the same; age, frailty, co-morbidity, prior treatment history and tolerance, duration of remission, tempo of relapse, genetic risk, geography and drug access all have to be considered when selecting the most appropriate therapy. A second general rule is that when possible three drugs tend to outperform two. This principle has been demonstrated numerous times with bortezomib, carfilzomib, ixazomib, lenalidomide, panobinostat, elotuzumab and daratumumab triplets when compared to standard of care doublets. That said, doublets can be successfully used when access to three drug combinations or patient specific factors make a two drug combination more acceptable.

Indeed the two drug combination of carfilzomib and dexamethasone has been compared to bortezomib and dexamethasone in the ENDEAVOUR trial. In this phase 3 head-to-head comparison of two proteasome inhibitors (PIs) in patients with relapsed or refractory multiple myeloma (RRMM), progression-free survival (PFS) was shown to be significantly longer with carfilzomib and dexamethasone (Kd) than with bortezomib and dexamethasone (Vd) (median 18.7 months vs 9.4 months, hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.44–0.65; P < 0.0001; Dimopoulos MA et al. Lancet Oncol. 2016;17:27–38).

Patients who had RRMM and had received 1–3 prior lines of therapy were randomized in a 1:1 ratio to receive Kd or Vd. In the Kd arm, carfilzomib was given on days 1, 2, 8, 9, 15, and 16 (20 mg/m2 on days 1, 2 of cycle 1; 56 mg/m2 thereafter) and dexamethasone 20 mg was given on days 1, 2, 8, 9, 15, 16, 22, and 23 of 28-day cycles. In the Vd arm, bortezomib (1.3 mg/m2) was given intravenously or subcutaneously on days 1, 4, 8, and 11 and dexamethasone 20 mg was given on days 1, 2, 4, 5, 8, 9, 11, and 12 of 21-day cycles. Patients were treated until progression or withdrawal of consent. OS was compared between treatment arms using a stratified log-rank test.

The median treatment duration was 48 weeks for carfilzomib (N=464) and 27 weeks for bortezomib (N=465), with a median follow up of 38 months for Kd and 37 months for Vd. The median OS (95% CI) was 47.6 (42.5-NE) months in the Kd arm and 40.0 (32.6-42.3) months in the Vd arm, and all-cause mortality was significantly reduced with Kd vs Vd (HR, 0.791; 95% CI, 0.648-0.964; 1-sided p = 0.0100). The overall survival benefit was consistent regardless of prior bortezomib therapy (HR 0.75 for Kd vs Vd, no prior bortezomib; HR 0.84 for Kd vs Vd, prior bortezomib) and across all age groups (HR, 0.85 <65 yo; 0.71, 65-74 yo; 0.84, >75 yo), baseline ECOG performance status groups (HR, 0.81, ECOG 0; 0.80, ECOG 1; 0.50, ECOG 2), cytogenetic risk groups (HR, 0.83, high risk; 0.85, standard risk), and number of prior lines of therapy (HR, 0.83, 1 prior line; 0.76, 2-3 prior lines). The most frequent any-grade adverse events in the Kd arm were (Kd vs Vd) anemia (42.5% vs 28.3%), diarrhea (36.3% vs 40.6%), pyrexia (32.4% vs 15.4%), dyspnea (32.2% vs 13.6%), fatigue (32.2% vs 30.7%), and hypertension (32.2% vs 9.9%). Grade 3 or higher adverse events were experienced by 81.4% of patients in the Kd arm and 71.1% of patients in the Vd arm.

In conclusion the ENDEAVOR trial was the first randomized phase 3 trial to directly compare two different PIs in RRMM. Patients who received Kd had significantly longer OS compared with patients who received Vd despite a small increase in serious adverse events.

With respect to triplet therapies, regimens which contain either carfilzomib or daratumumab stand out. The first such regimen is from the ASPIRE study of carfilzomib, lenalidomide, and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma. Adults with relapsed multiple myeloma (1-3 prior lines of therapy) were eligible and randomized (1:1) to receive KRd or Rd in 28-day cycles until withdrawal of consent, disease progression, or occurrence of unacceptable toxicity. After

18 cycles, all patients received Rd only. PFS was the primary endpoint; OS was a key secondary endpoint. Progression-free survival (PFS) was significantly improved in the carfilzomib group (HR, 0.69; two-sided P=0.0001).
Median OS (95% CI) was 48.3 (42.4–52.8) months for KRd vs 40.4 (33.6–44.4) months for Rd (HR, 0.79; 95% CI, 0.67–0.95; 1-sided P=0.0045). In patients receiving 1 prior line of therapy, median OS was 11.4 months longer for KRd versus Rd and 6.5 months longer for KRd versus Rd among patients receiving ≥2 prior lines of therapy. Treatment discontinuation due to an adverse event (AE) occurred in 19.9% (KRd) and 21.5% (Rd) of patients. Grade ≥3 AE rates were 87.0% (KRd) and 83.0% (Rd). Selected grade ≥3 AEs of interest (grouped terms; KRd vs Rd) included acute renal failure (3.8% vs 3.3%), cardiac failure (4.3% vs 2.1%), ischemic heart disease (3.8% vs 2.3%), hypertension (6.4% vs 2.3%), and hematopoietic thrombocytopenia (20.2% vs 14.9%).

In conclusion, KRd demonstrated a statistically significant and clinically meaningful 21% reduction in the risk of death vs Rd. The KRd efficacy advantage is most pronounced at first relapse.

These two carfilzomib containing regimes are the first to demonstrate both higher and deeper response rates as well as PFS and an OS advantage in phase 3 studies. In the ASPIRE clinical trial, health related quality of life was also improved.

In a second series of very positive clinical trials of triplet therapy the monoclonal antibody daratumumab has been shown to significantly improve PFS when combined with either bortezomib or with lenalidomide. Current studies are examining the combination of daratumumab with carfilzomib both in relapse and in newly diagnosed disease.

One of the drawbacks of carfilzomib therapy relates to the delivery schedule twice weekly. Consequently the ARROW clinical trial has examines weekly versus twice weekly dosing.

Twice-weekly Carfilzomib at the 20/27 mg/m2 dose received accelerated approval for the treatment of RRMM patients who had received at least two prior therapies based on favorable responses and tolerability achieved in the phase 2 single-arm 003-A1 study (Siegel et al. Blood 2012;120:2817-2825). To improve convenience of the approved twice-weekly dosing regimen, the safety and efficacy of once-weekly Carfilzomib (K) K with dexamethasone (d) was explored in the phase 1/2 CHAMPION-1 study, establishing a well-tolerated and highly active maximum tolerated dose (MTD) of K 20/70 mg/m2 in patients with RRMM (Berenson et al. Blood 2016;127:3360-3368). A.R.R.O.W. is the open-label, multi-center, phase 3 study comparing Kd once-weekly at the 20/70 mg/m2 K dose (once-weekly group) vs twice-weekly at the 20/27 mg/m2 K dose (twice-weekly group).

Adult patients with RRMM who had ECOG status of 0 or 1, had received 2-3 prior therapies, and had previous exposure to a proteasome inhibitor and an immunomodulatory agent were eligible. The planned enrollment was 460 patients (230 patients per treatment group). Patients were randomized in a 1:1 ratio to receive either once-weekly or twice-weekly K plus d. Randomization was stratified by ISS stage (1 vs 2 or 3), refractory to BTZ treatment (yes vs no), and age (< 65 vs ≥ 65 age). The once-weekly group received K (30-minute IV infusion) on days (D) 1, 8 and 15 of all cycles (20 mg/m2 on D1 [cycle 1]; 70 mg/m2 thereafter). The twice-weekly group received K (2 to 10-min IV infusion) on D1, 2, 8, 9, 15, and 16 (20 mg/m2 on D1 and 2 [cycle 1] and 27 mg/m2 thereafter. Patients received (40 mg) d on D1, 8, 15 (all cycles) and 22 (cycle 1-9 only) in the once- and twice-weekly groups. Study treatment was administered in 28-day cycles and cycles were repeated until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was PFS. Data have only been released to date for the primary endpoint. Median PFS (once- vs twice-weekly) was 11.2 mo vs 7.6 mo (HR = 0.693; 1-sided P=0.0014). No new safety risks were found in the once-weekly group. Overall, once-weekly Kd showed a superior efficacy vs twice-weekly Kd.

ST05-01 BMS

Emerging Trends in CML Management

Elias Jabbour
Leukemia Department, MD Anderson Cancer Center, USA

The landscape of chronic myeloid leukemia (CML) management has changed with the advent of tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 oncoprotein. Imatinibmesylate, followed by second generation TKIs, have been approved for newly diagnosed patients. Clinical trials with second generation TKIs reported significantly deeper and faster responses; their impact on long-term survival remains to be determined. The efficacy and safety of generic imatinib are well established and are comparable to branded imatinib, at a significantly lower price. Physicians will have to assess the "treatment value" of second generation TKI in the frontline setting against the generic imatinib in relation to benefits versus cost. Second generation TKIs may be offered for patients with high-risk disease, while imatinib and/or its generic formulation will be offered for patients with low-risk disease. Whatever TKI is chosen as frontline, non-compliance or treatment failure should be recognized early as a prompt intervention increases the chance of achieving best possible response. Patients should be monitored carefully for response, and treatment failure should prompt a timely switch to another TKI. For patients who fail frontline therapy, second-line options include second and third generation TKIs. Although second and third generation TKIs are potent and selective TKIs, they exhibit unique pharmacological profiles and response patterns relative to different patient and disease characteristics, such as patients' comorbidities, disease stage, and BCR-ABL1 mutational status. Patients who develop the T315I "gatekeeper" mutation display resistance to all currently available TKIs except ponatinib. Side effect profile and drug cost are other important considerations in therapy choice. In several clinical studies, achieving undetectable and durable disease status allowed some patients to discontinue the TKI and enjoy long-term treatment-free remission. Cure for CML may be possible with TKIs alone or TKIs in combination with other investigational therapies. Allogeneic stem cell transplantation remains an important therapeutic option for patients with CML-CP who have failed at least two TKIs, and for all patients in advanced phase disease.

ST06-01 HANDOK

HSCT Early Complications: Focus on Severe Hepatic Veno-occlusive Disease; the Revised EBMT Diagnostic and Severity Criteria for Adults and an Update on Defibrotide

Mohamad Mohty

Clinical Hematology and Cellular Therapy Dpt., Sorbonne University, Hôpital Saint-Antoine, France

Sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD) is a frequent and serious toxic complication of hematopoietic stem cell transplantation (HSCT). Although it has been described following both autologous and allogenic HSCT it seems much more frequent following the latter, with a reported incidence of 8 to 14%. This can dramatically increase in high risk populations. The pathophysiology of VOD involves activation and lesion, often multifactorial, of sinusoidal endothelial cells, permeabilization of the endothelial barrier with penetration of blood cells and cellular debris into the space of Disse leading to the narrowing of the sinusoidal lumen, and the development of a post-sinusoidal portal hypertension.

The risk factors are related to the transplant, to the patient or disease characteristics, or to liver status before HSCT. The transplant-related risk factors include unrelated donor or HLA-mismatched donor, non T-cell depleted transplant, myeloablative conditioning regimen, busulfan-based regimen, total body irradiation and second (or more) HSCT. Predisposing patient or disease characteristics include older age (in the adult population), Karnofsky score below 90%, metabolic syndrome, norethisterone treatment, advanced disease (beyond second complete response or relapsing or refractory), thalassemia and some genetic factors such as hemochromatosis C282Y allele. Hepatic status risk factors include previous history of hepatic disease such as cirrhosis or active viral hepatitis, elevation of transaminases or bilirubin, iron overload, hepatic irradiation or treatment with hepatotoxic drugs such as gentuzumab ozogamicin or inotuzumab ozogamicin.

SOS/VOD usually occurs within 3 weeks after HSCT but can develop later, and diagnosis criteria have been revised to include these late forms. Symptoms include hyperbilirubinemia, weight gain, ascites, and painful hepatomegaly. Most severe forms evolve toward multi-organ failure with a mortality rate greater than 80%.

Defibrotide is an oligonucleotide derived from porcine tissue which possesses anti-inflammatory and pro-fibrinolytic properties and has proved its effectiveness in the treatment of severe SOS/VOD.

This lecture will address the most recent available research evidence related to SOS/VOD.

This symposium has been organized and fully funded by Jazz Pharmaceuticals and Handok Pharmaceuticals.

ST07-01 ROCHE

Advancing Value-Based Approaches in the Treatment of Non-Hodgkin Lymphoma (NHL): Contemporary Strategies and Innovations

Hyeon-Seok Eom

Department of Hematology-Oncology, Center for Hematologic Malignancy, National Cancer Center, Korea

Systemic chemotherapy and immunotherapy are the main treatment stragegies for lymphoma. R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) combination chemotherapy has been the gold standard in the treatment of diffuse large B cell lymphoma (DLBCL) for more than a decade. Also, rituximab-containing regimens have been the standard of care for patients with CD20-positive other B-cell malignancies. The switching from rituximab intravenous (IV) to rituximab subcutaneous (SC) route shows the same clinical benefits such as anti-lymphoma activity of rituximab as IV but in less time. Median administration time (5 minutes for SC versus 3 hours for IV), overall hospital stay were shorter with SC compred to IV rituximab. This is confirmed in phase 3 study of rituximab SC or IV plus chemotherapy (CHOP, CVP or bendamustine) in diffuse large B-cell lymphoma or follicular lymphoma. This is one of the advancing value-based approaches in the treatment of non-Hodgkin lymphoma.

Recently the cell-of-origin (COO) classification is revealed by the molecular heterogeneity of DLBCL. Therapeutic strategies to target subtypes are investigated according to germinal center B-cell–like (GCB) and activated B-cell–like (ABC) types. Targeted agents are effective when they meet the right target. When antibodies are conjugated to drugs, they potentiate the anti-lymphoma activity of antibodies. For example, polatuzumab vedotin (pola) is an antibody–drug conjugate comprised of an anti-CD79b monoclonal antibody conjugated to the antimitotic agent monomethyl auristatin E (MMAE) by a protease-cleavable peptide linker. In randomized trial, pola + bendamustine and rituximab (BR) revealed efficacy in transplant-ineligible relapsed/refractory DLBCL patients with survival prolongation.

Another example of advancing vaue-based technique is engineered T cells. A promising approach is the genetic modification of T cells with chimeric antigen receptors (CARs). CAR T cells targeting specific antigen (Ag) such as CD19 effectively eradicate B cell lymphoid malignancies in acute and chronic lymphoblastic leukemia (ALL and CLL) and non-Hodgkin lymphoma (NHL).

Collectively, with these advancing-value based approaches and innovations, patients with NHL would have convenience in treatments and prolongation of survivals. Moreover, it could be expected that a cure might be just around the corner.

ST08-01 TAKEDA

Novel Treatment Strategies for Multiple Myeloma: a Focus on Oral Proteasome Inhibitors

Antonio Palumbo
Distinguished Research Fellow Oncology, Takeda Pharmaceuticals International AG, Italy

The Changing Treatment Landscape in MM

Although the approach to therapy remains largely the same, the treatment options at every stage have changed:
Carfilzomib, pomalidomide, panobinostat, daratumumab, elotuzumab and ixazomib have been approved. These drugs combined with older agents (such as cyclophosphamide, dexamethasone, thalidomide, bortezomib, and lenalidomide) dramatically increase the repertoire of regimens
Preclinical studies have demonstrated that multiple genetically distinct subclones are present at diagnosis of multiple myeloma and these subclones evolve over time due to selective pressures from treatment and factors in the microenvironment.
Clonal heterogeneity suggests that combination therapy may be necessary to target coexisting subclones, although clinical studies are needed to validate these findings.
The study by Morgan GJ (Blood 2013) illustrates how maintenance therapy can theoretically prevent or delay disease relapses in a MM patient who has received primary induction therapy, ASCT, and post-transplant consolidation. In the hypothetical patient, maintenance therapy helps to further decrease the reduction in tumor bulk achieved with prior therapy, and to maintain a sustained period of remission.
It is believed that maintenance treatment acts by controlling the biology of the residual clonal population and by killing myeloma stem cell populations entering the cell cycle.

Ixazomib Clinical Overview

Ixazomib is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
Treatment with ixazomib in combination with lenalidomide and dexamethasone was evaluated in TOURMALINE-MM1. This triplet regimen was studied in a large, global, phase 3 trial and administered until disease progression or unacceptable toxicity.
The primary endpoint was PFS and key secondary endpoints included OS, OS in patients with deletion 17, overall response rates, PFS in patients with high-risk cytogenetics, and safety. PFS was assessed every 4 weeks until disease progression, according to the 2011 International Myeloma Working Group criteria as assessed by a blinded independent review committee based on central lab results.
TOURMALINE-MM1 is the first clinical trial using an all-oral PI-based treatment regimen that was administered until disease progression or unacceptable toxicity in order to assess long-term therapy. The study is ongoing, continuing to assess key secondary endpoints, including OS.
This trial included a broad range of patients, including those who had received bortezomib as a prior therapy. The treatment arms were well balanced. The trial had representative proportions of patients with renal impairment, primary refractory multiple myeloma, and free light chain–measurable only disease. Many of these patients are often excluded from multiple myeloma trials.
As for the results of the primary endpoint, PFS, the Kaplan-Meier curve displayed demonstrates about a 6-month median improvement (a 40% increase) in PFS in patients receiving the ixazomib regimen compared with those receiving the placebo regimen. Overall response rates demonstrated in the TOURMALINE-MM1 trial were high in both arms. Additionally, nearly 50% of patients achieved a VGPR or better with the ixazomib regimen.
As for responses, the ixazomib regimen delivered rapid responses compared with the placebo regimen. The time to response was quick with an all-oral regimen. Responses deepened with continued ixazomib treatment. Most CRs were achieved after 6 cycles of treatment.
In general, the rates of all-grade nonhematologic adverse events (ARs) were similar between treatment arms. Ixazomib offered a safety profile amenable to treatment to progression.
Patients may require the use of concomitant medications while on treatment. Some may be taken prophylactically; others when symptoms appear; for nausea and vomiting, antiemetics may be prescribed; antidiarrheals, such as loperamide, may be used if symptoms develop. It may be helpful to tell your patients to buy an over-the-counter medicine to have at hand if needed; prophylactic antivirals should be considered to prevent herpes zoster reactivation; rash can be treated with corticosteroids or antihistamines; antibacterials may be used to treat bacterial infections.
Proactively managing certain conditions could be a key to helping patients stay on treatment.

Conclusion

This overview illustrates how maintenance therapy can theoretically prevent or delay disease relapses in a MM patient who has received primary induction therapy, ASCT, and post-transplant consolidation. In this hypothetical patient, maintenance therapy helps to further decrease the reduction in tumor bulk achieved with prior therapy, and to maintain a sustained period of remission. It is believed that maintenance treatment acts by controlling the biology of the residual clonal population and by killing myeloma stem cell populations entering the cell cycle.
Continuous therapy is more effective than fixed duration one. In terms of efficacy, triplet regimens have demonstrated more benefits than doublets. HR for PFS has been similar among different studies of the newer agents except daratumumab, while best safety profiles has been shown for ixazomib among PI/IMiD triplet. Ixazomib brings the convenience to patients enabling all oral regiments. Improvement of the clinical efficacy is expected with PI/MoAb triple in the near future.

ICKSH 2018
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BEST ABSTRACT PRESENTATION

BP-01

RAG1 High Expression Associated with IKZF1 Dysfunction in B-cell Acute Lymphoblastic Leukemia

Zheng Ge[1,2], Qi Han[1,2], Yan Gu[1,2], Chunhua Song[*2,3]

[1] Hematology, Zhongda Hospital, Medical School of Southeast University, China
[2] International Cooperative Leukemia Group and International Cooperative Laboratory of Hematology, Zhongda Hospital, Medical School of Southeast University, China
[3] Pediatrics, Pennsylvania State University Medical College, USA

Background : The recombinationactivating gene (RAG)-mediated recombination is the dominant mutational process and is the predominant driver of oncogenic genomic rearrangement in acute lymphoblastic leukemia (ALL). This then leads to further leukemic clonal evolution. IKZF1 encodes a kruppel-like zinc finger protein, IKAROS which acts as leukemia suppressor. Casein Kinase II (CK2) inhibitor-CX-4945 could restore IKAROS function. ChIP-seg data showed obvious IKAROS binding peaks on RAG1 promoter in B-ALL patients' samples, and here we explore clinical significance of RAG1 expression in B-ALL and IKAROS regulation on RAG1 expression in B-ALL cells.

Methods : The 131 subjects with newly-diagnosed B-ALL were recruited. RAG1 mRNA level was examined by qPCR and allocated into a high or low expression cohort (1-2th quartile vs. 3-4th quartiles) determined by SPSS 20.0. Median or frequency differences between the cohorts were evaluated using a Mann–Whitney U-test or uni- and multivariate Cox mode. The retroviral gene expression, shRNA knockdown and qChIP are used to observe IKAROS regulation on RAG1 transcription.

Results : We observed that RAG1 is significantly increased in subsets of B-ALL patients. High RAG1 expression correlates with higher % of white blood cell (WBC) ≥30x109/L (67.7% vs. 38.5%, P<0.001), higher blasts in peripheral blood (75.0% vs. 61.0%, P=0.026) and higher median WBC (47.9×109/L vs. 17.0×109/L, P=0.025), the markers of poorer prognosis and proliferation in B-ALL. ChIP-seq and qChIP data showed that Ikaros directly binds to the RAG1 promoter and regulates RAG1 expression in leukemic cells and patients' samples. CX-4945 significantly increases Ikaros binding in ALL cells and suppresses RAG1 expression in an Ikaros-dependent manner. RAG1 expression is significantly higher in patients with IKZF1 deletion, as compared to patients without IKZF1 deletion. Treatment with CX-4945 also results in an increase in IKZF1 binding to the RAG1 promoter and suppression of RAG1 expression in primary ALL cells.

Conclusions : High expression of RAG1 correlates with high proliferation markers in B-ALL, and this is first time to demonstrate that IKAROS directly suppresses RAG1 expression. Our data suggest RAG1 high expression works together with IKAROS dysfunction to drive oncogenesis of B-ALL, which have significance in an integrated prognostic model for adult ALL.

Keyword : RAG1, IKZF1, Acute lymphoblastic leukemia, Adult

BP-02

Decision Supporting Tool for Thrombotic Microangiopathy Based on Machine Learning Technique

Youngil Koh[1], Choong-Hyun Sun[2], Sung-Soo Yoon[1], Inho Kim[1], Hongseok Yun[4], Doyeon Oh[*3]

[1] Internal Medicine, Seoul National University Hospital, Korea
[2] Bioinformatic team, Genome Opinion, Korea
[3] Internal Medicine, CHA University College of Medicine, Korea
[4] Precision Medicine Center, Seoul National University Hospital, Korea
[12] Thrombotic thrombocytopenic purpura,

Background : Prompt differential diagnosis (DDx) of thrombotic microangiopathy (TMA) is of great concern in the era of effective treatments. We determined to develop a tool based on machine learning (ML) technique method that could support clinical decision for DDx of TMA in the absence of ADAMTS13 level. Considering cons and pros of variable various ML methods, we decided to ensemble ML methods to improve performance.

Methods : Three hundred and nineteen adult patients with TMA (TTP (N=72) or TMA other than TTP (N=247)) were classified using 9 machine learning methods using a set of easily measured 19 clinical variables. After variable elimination considering variable importance and correlation between variables, we divided patient data into training set and validation set to check performance of each ML model. Based on performance, we selected 4 models for ensemble to make a decision supporting tool in TMA and combined them in weighted average manner.

Results : Among 19 variables, we could select 5 variables (Platelet count, creatinine, AST, LDH, and prothrombin time) that could be used for ML tools using feature elimination method. When each tool performance was evaluated, Area Under the Curve (AUC) of nine ML tools ranged from 0.798 to 0.974. Using AUC value and highly correlated model filtering, we selected 4 models (RF, KNN, Naïve Bayses (NB) and Logistic Regression (LR)) for ensemble.
For ensemble of these 4 models, when simulation grid search was performed while varying the weights to 4 selected tools using training set, we could find an optimal weight vector to predict non-TTP most accurately (kappa value of 0.886 and AUC of 0.985). In validation set, this ensemble showed 4% false positive rate for the prediction of non-TTP. Performance of this ensemble was AUC of 0.981 and accuracy of 93.1% (95% CI 0.96-0.99). Overall, we could observe weight on RF is correlated with high AUC and specificity both in training and validation sets. On the other hand, weight on NB was related to high sensitivity but low specificity in validation set.

Conclusions : Using ML models and their ensemble, we could successfully develop and validate a tool that could DDx TMA's regardless of ADAMTS13 level. This is superior to other models reported so far for DDx of TMA. We expect this tool could be utilized in TMA practice for adequate use of effective but costly therapeutics.

Keyword : Thrombotic microangiopathy, Machine learning, Atypical hemolytic uremic syndrome, Thrombotic thrombocytopenic purpura

BP-03

Aberrant ARID5B Expression and IKAROS Regulation in Acute Lymphoblastic Leukemia

Chunhua Song[1], Yan Gu[2], Qi Han[2], Sinisa Dovat[1], Zheng Ge[*2]

[1] Pediatrics, Pennsylvania State University Medical College, USA
[2] Hematology, Zhongda Hospital, Medical School of Southeast University, China

Background : Background AT-rich interactive domain-containing protein 5B (ARID5B) forms a complex with PHD finger protein 2 (PHF2), which then inducesH3K9me2 demethylation leading to transcription activation. Genomic defects in ARID5B are associated with the development of acute lymphoblastic leukemia (ALL) and treatment outcome. PHF2 is down-regulated in ALL patients. But ARID5B expression and the clinical significance are not determined in ALL patients. Ikaros, the product of the IKZF1 gene, functions as a leukemia suppressor. We identified the obvious Ikaros binding peaks in promoter of ARID5B by ChIP-seq, which suggested Ikaros regulation on ARID5B expression in ALL cells.

Methods : The 164 newly-diagnosed ALL subjects were studied. ARID5B mRNA were allocated in a high or low expression (4th quartile vs. 1st-3rd quartiles) determined by SPSS 20.0. The ChIP-seq and qChIP assays were performed to determine the enrichment of Ikaros and H3K4me3 in promotor of the genes. Lentiviral Ikaros delivery or IKZF1 shRNA were used for functional analysis in the leukemia cells.

Results : ARID5B is significantly down-regulated in ALL patients and positively correlated with PHF2 expression in ALL. ARID5B particularly ARID5B+PHF2 low expression was associated with a higher % of bone marrow blasts (91.2%vs. 82.4%, P=0.000), a CR time ≥4 weeks (53% vs. 21%, P=0.003), Ik6(+) (49.3% vs. 15.8%, P=0.001), and also the higher % of stem cell marker CD34+, myeloid marker CD33+ and splenomegaly. ChIP-seq and qChIP assays identified Ikaros binding peaks in the ARID5B promoter in ALL cell and patients' samples. Expression of Ikaros promotes ARID5B expression, while efficient Ikaros knockdown decreased ARID5B expression; and ARID5B expression was significantly lower in B-ALL with Ik6(+). CX-4945, the Ikaros function activator promotes expression of ARID5B mRNA and protein in an Ikaros-dependent manner, also significantly increases binding of Ikaros and enrichment of H3K4me3 to the ARID5B promoter in ALL cells and patients' samples.

Conclusions : ARID5B especially ARID5B+PHF2 low expression is associated with leukemia proliferation and poor prognostic markers. Ikaros promotes ARID5B expression through histone modification in ALL. ARID5BlowPHF2low expression is associated with Ikaros dysfunction which may be involved in the oncogenesis of high-risk ALL.

Keyword : ARID5B, IKZF1, PHF2, Acute lymphoblastic leukemia, Epigenetics

ICKSH 2018
& 59th ANNUAL MEETING

SHORT TALK

SST-01

Development and Preliminary Evaluation of Customized Pan-Blood Cancer NGS Panel

Jun Hyung Lee[1], Hyun-Jung Choi[1], Soo-Hyun Kim[1], Myung-Geun Shin*[1,2]

[1] Department of Laboratory Medicine, Chonnam National University Medical School and Chonnam National University Hwasun Hospital, Hwasun, Korea
[2] Department of Laboratory Medicine, Brain Korea 21 Project, Center for Biomedical Human Resources, Chonnam National University, Gwangju, Korea

Background : Genetic aberrations found in hematologic malignancies provide important information for the diagnosis and treatment of disease. Hwasun Chonnam National University Hospital (Hwasun, Korea) and NGeneBio (Seoul, Korea) have jointly developed customized pan-blood cancer NGS panel (HEMEaccuTest) that can detect important genetic aberrations in hematologic malignancies as a single test. In this study, we evaluated clinical performances of this newly developed pan-blood cancer panel.

Methods : Two hybrid capture panels of HEMEaccuTest were evaluated. Acute, myeloid panel was designed for acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), Lymphoblastic leukemia (ALL). Chronic, lymphoid panel was for plasma cell myeloma (PCM), lymphoma. For the performance evaluation of this panel, 8 patient samples (2 AML, 2 MDS, 1 MPN, 1 B-ALL, 1 PCM, 1 CLL), and 1 quality control material (Tru-Q 1, Horizon Discovery, USA) was tested. The patients consisted of 3 males and 5 females at a median age of 66.5 years (range: 23–79 years). A total of 177 genes (all exons and splicing regions) were targeted in HEMEaccuTest. The combined coverage was 670 kb in sequence length. Paired-end sequencing run were performed on a MiSeqDx (Illumina, USA) genome sequencer. Sequences obtained were analyzed by NGeneAnalySys (NGeneBio).

Results : The mean count of sequencing reads obtained per sample was 407.8 million and the mean sequencing depth was 602x. Average 99.0% (range 98.2–99.5%) of the total targeted regions were covered more than 100x depth. Total 178 variants in 141 genes were detected in patients samples when the following filtering criteria were applied: Exonic or splicing region, variant allele frequency ≤ 1% in population database, non-synonymous SNV or frameshift indels. On average, 22.25 variants (range 11–30) were detected per sample. As results of accuracy test, 14 known variants of QC material were all detected in the results of HEMEaccuTest. In patient samples, all the variants detected in NPM1, FLT3, CEBPA, JAK2, CALR by conventional methods were completely detected in HEMEaccuTest.

Conclusions : HEMEaccuTest, based on NGS technology, was able to sensitively detect various variants in hematologic malignancies. It is expected to provide useful and reliable genetic information for diagnosis, risk stratification, and detection of minimal residual disease.

Keyword : Bioinformatics, Genetic Variant, HEMEaccuTest, Hematologic Malignancy, Next-Generation sequencing, Targeted sequencing

SST-02

Evaluation of Two Commercial Kits for Flow Cytometric MRD Detection in B-ALL

Ari Ahn[1], Chan-Jeoung Park*[1], Min Young Lee[1], Eunkyoung You[1], Chang Ahn Seol[1], Young-Uk Cho[1], Seongsoo Jang[1], Eul-Ju SEO[1], Hyery Kim[2], Kyung-Nam Koh[2], Ho-Joon Im[2], Jong-Jin Seo[2]

[1] Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea
[2] Department of Pediatrics, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea

Background : Minimal residual disease (MRD) is an important independent prognostic factor that can identify poor responders among patients with B-acute lymphoblastic leukemia (ALL). There are ongoing efforts to standardize MRD quantification using flow cytometry to improve accuracy and reproducibility, because hematogones that may morphologically resemble the leukemic cells of ALL are often increased in regenerating marrow.

Methods : 32 bone marrow aspirates with less than 5% leukemic cells by conventional morphology from treated 28 pediatric patients with B-ALL were obtained. MRD was measured using two commercial kits for flow cytometeric MRD detection; DuraClone (Beckman Coulter, Miami, USA) and BCP-ALL-MRD (Cytognos SL, Salamanca, Spain). The main methodological approach for detecting MRD is antigen over/underexpression of DuraClone (CD58/CD34/CD10/CD19/CD38/CD20/CD45) and aberrant expression of BCP-ALL-MRD (CD20/CD45/CD81/CD66c+CD123/CD73+CD304/CD34/CD19/CD10/CD38).

Results : The median patient age was 7 years (range, 3-20) and the ratio of boy to girl was 1:1. The median time of sample collection was 120 days (14-3930) after starting induction chemotherapy or hematopoietic stem cell transplantation. The immunophenotype of leukemic cells at diagnosis in all patients except one were positive (cutoff ≥20%) for CD34 and CD58, and variable expression of CD20 and CD38. Aberrant expression at diagnosis was CD66c (11/20, 55%), CD123 (8/20, 40%), CD73 (7/20, 35%), CD304 (1/20, 5%), CD13 (6/25, 24%), CD33 (4/25, 16%) and CD56 (1/25, 4%). The leukemic cell % were 1.4±1.3% by conventional morphology, 0.152±0.278% by DuraClone and 0.055±0.188% by BCP-ALL-MRD (Fig.1, P=0.001 in difference). MRD % by DuraClone and BCP-ALL-MRD were well correlated (P≤0.001); however, MRD % by BCP-ALL-MRD was lower than that of DuraClone (P=0.003).

Conclusions : Detection of MRD in patients with B-ALL is limited by conventional morphology. For the flow cytometric detection of MRD in B-ALL, the kit detecting antigen over or under expression was adequate, but the kit detecting aberrant expression showed significantly lower level of MRD, and it is very helpful for analysis of MRD to know the immunophenotype of leukemic cells at diagnosis.

Keyword : Flow Cytometry, Minimal Residual Disease , B-Acute Lymphoblastic Leukemia

ICKSH 2018
& 59th ANNUAL MEETING

ORAL PRESENTAION

OP01-1

Immature Platelet Fraction (IPF): A Useful Marker for Evaluating the Cause of Thrombocytopenia and Predicting Platelet Recovery

Kibum Jeon, Miyoung Kim, Han-Sung Kim, Hee Jung Kang, Young Kyung Lee*
Departments of Laboratory Medicine, Hallym University Sacred Heart Hospital, Korea

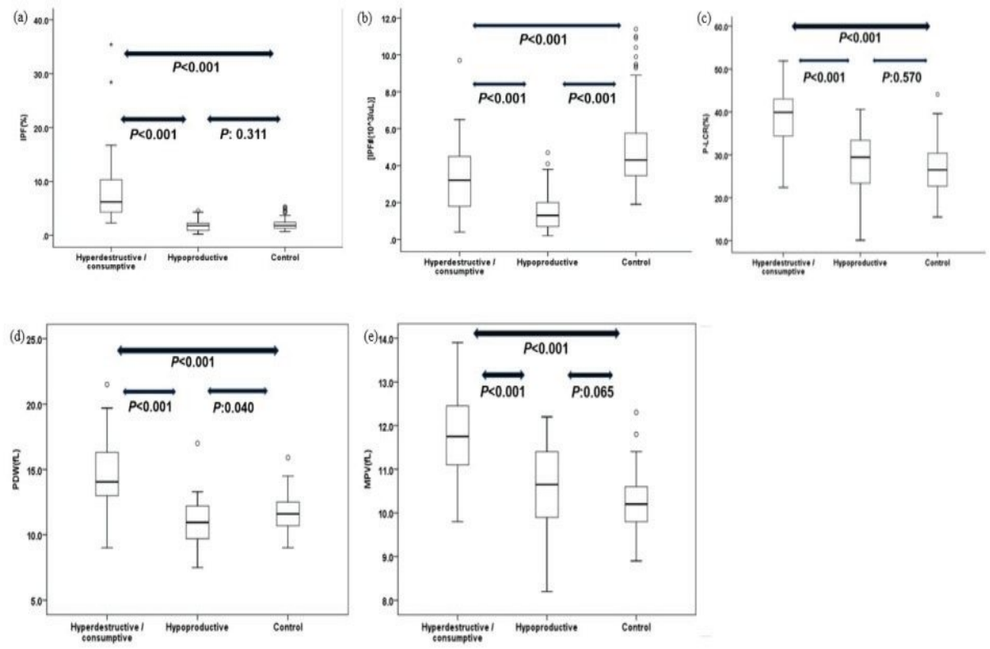
Background : The assessment of thrombopoietic activity in the bone marrow is necessary in thrombocytopenia in terms of both correct diagnosis and efficient treatment. We evaluated the discriminatory power of immature platelet fraction (IPF) for hyperdestructive / consumptive thrombocytopenia and hypoproductive thrombocytopenia, and its potential use as a predictive marker for platelet recovery.

Methods : Platelet indices including IPF (%) was measured in 105 healthy individuals as the control group, 31 patients (14 ITP and 17 LC) as the hyperdestructive / consumptive thrombocytopenia group and 34 patients (4 AA and 30 cancer patients under chemotherapy) as the hypoproductive thrombocytopenia group by using Sysmex XN-3000 hematology analyzer.

Results : PDW, MPV, P-LCR, IPF (%) and IPF# were significantly elevated in the hyperdestructive / consumptive thrombocytopenia group compared with the hypoproductive thrombocytopenia group ($p < 0.001$), and among them, IPF (%) showed the highest value difference between the two groups (200%) when the mean value of control group was considered as the baseline (Figure 1). The discriminatory power of IPF (%) was also demonstrated in ROC analysis, showing the largest AUC among all the platelet indices analyzed with the cut-off value of 2.5%. In the hyperdestructive / consumptive group, the IPF (%) significantly increased as the number of platelet decreases especially in severe thrombocytopenia with the platelet count under 40.0 × 103/uL ($p = 0.010$) (Figure 2). However, this phenomenon was not observed in the hypoproductive thrombocytopenia group ($p = 0.912$). IPF (%) decreased 3-4 days in advance to the platelet count elevation in ITP and increased in 5.5 days before platelet count increases up to 13.0 × 103/uL in cancer patients under chemotherapy.

Conclusions : Using XN-3000, we demonstrated that IPF (%) is an excellent marker to evaluate the cause of thrombocytopenia for the first time. By reflecting the BM thrombopoietic activity, IPF (%) reported by XN-300 is a robust and reliable marker for the prediction of platelet recovery in ITP and cancer patients under chemotherapy, providing future therapy guide and preventing unnecessary transfusion.

Keyword : Immature platelet fraction, Thrombocytopenia, XN-3000



OP01-2

Acacia Senegal Supplementation Improve Dyslipidemia in Sickle Cell Anemia Novel Effect of Gum Arabic

Lamis Kaddam[1], Imad Fdle Almula[2], Omer Eisawi[3], Hyadar Awad[4], Amal Saeed[5]

[1] Physiology , Alneelain University Faculty of Medicine , Sudan
[2] Clinical Genetics , Alneelain University Faculty of Medicine , Sudan
[3] Hematology , Military Hospital , Sudan
[4] Pediatrics , Military Hospital , Sudan
[5] Physiology , University of Khartoum Faculty of Medicine , Sudan

Background : Sickle cell disease (SCD) is an inherited hemolytic anemia with a variable course and severity. The knowledge of prognosis biomarkers may help in the establishment of therapeutic intervention, management, and follow-up of patients. There have been scattered reports of low HDL-C and increased triglyceride in SCD patients. Additionally, triglyceride levels have also been suggested to be elevated in patients with increased endothelial activation. Increased triglyceride levels were associated with hemolysis, vascular dysfunction, and increased prevalence of pulmonary hypertension.
Gum Arabic (GA), is edible, dried, gummy exudates from Acacia Senegal tree. Several studies GA ingestion reduced plasma cholesterol and LDL concentrations in humans.
We investigated GA therapeutic potential to modulate serum lipids in patients with sickle cell anemia.

Methods : 47 patients (5-42 years) carrying hemoglobin SS were recruited. Patients received 30g/day GA for 12 weeks. Total cholesterol, triglycerides, LDL and HDL were measured before and after GA intake. Cobas C311 (Roche,Germany) automated chemistry analyzer directly determined the values of lipid profile. hydrogen peroxide (H2O2) level was measured by spectrophotometric methods

Results : Gum Arabic significantly decreased triglyceride level and LDL (P= 0.04 and 0.02 respectively). GA showed no effect on total cholesterol and HDL level.
Baseline serum triglycerides and LDL correlated significantly with Hydrogen Peroxide (H2O2) level which is known as oxidative stress marker P.V=0.003 and 0.04 respectively

Conclusions : Our results reveled that dyslipidemia in Sickle cell patients is associated with oxidative stress. GA significantly decreased LDL and triglycrides levels, findings reveal a novel effect of GA, which may be used as natural dietary fiber to modulate lipid profile in patients with SCA.

Trial registration: ClinicalTrials.gov Identifier: NCT02467257.

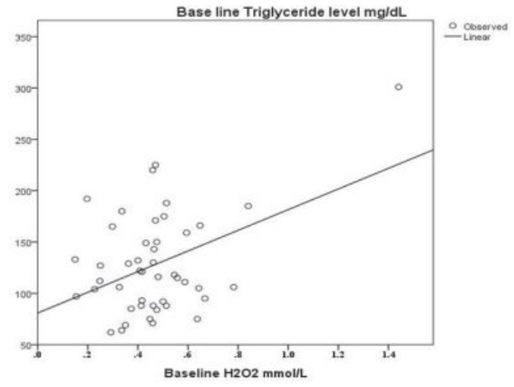


Fig 1:
Linear regression between H2O2 and Triglycerides level
(r2=185, P=0.04)

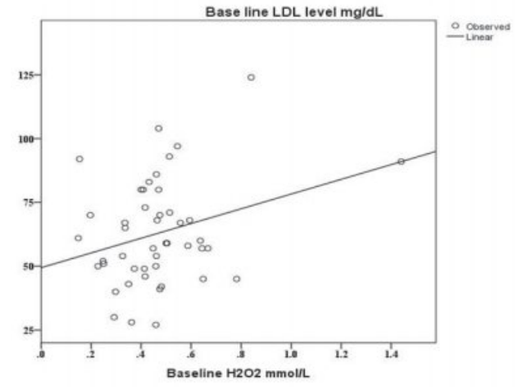


Fig 2:
Linear regression between H2O2 and LDL level
(r2=86 , P=0.04)

OP01-3

Proof of Concept – Leukodepleted Red Blood Cells by Double Filtration Can Replace Irradiated Blood

Sejong Chun[1], Saet-Byul Hong[2], Minh-Trang Phan[3], Jehoon Yang[2], Jungwon Kang[4], Jaehyun Kim[4], Duck Cho*[3]

[1] Laboratory Medicine, Chonnam National University Medical School, Korea
[2] Animal Research and Molecular Imaging Center, Samsung Medical Center, Korea
[3] Laboratory Medicine and Genetics, Samsung Medical Center, Korea
[4] Blood Transfusion Research Institute, Korean Red Cross, Korea

Background : Transfusion associated graft versus host disease (TA-GVHD) can be caused by residual leukocytes in blood products. Irradiation to blood components is necessary for its prevention. However, irradiated blood is not always available, and irradiation itself can be the cause of other transfusion related adverse effects. Under the hypothesis that complete leukocyte depletion doesn't induce TA-GVHD, we have previously evaluated that double filtration can accomplish near-zero residual leukocytes in RBC products. Herein, we have further evaluated in vitro expandability of residual T cells in controlled quantities of PBMCs, and experimented the amount of cell burden required for induction of GVHD in an in vivo model.

Methods : In vitro expandability of T cells was evaluated with peripheral blood mononuclear cells (PBMC) prepared in quantities of 6x10^3,1x10^3, 1x10^2 and 10 cells. These were cultured with anti-CD3/CD28 coated Dynabeads in complete RPMI 1640 medium. Evaluation of expanded T cells were done by cell counting using trypan blue exclusion and the percentage of CD3+C56- cells determined by flow cytometry. In vivo evaluation of GVHD potency was done with 18 male NSG mice, prepared at 8 weeks of age. Mice were prepared with total body irradiation was delivered at a dose of 2 Gy/min on the day prior to PBMC injection. PBMC injection was done in quantities of 1x10^7, 1x10^6,1x10^5 cells, 1x10^4 cells and 1x10^3 cells. Histologic evaluation was done on the liver, lung, kidney, skin and bone marrow of mice, and the presence of human leukocytes were evaluated by CD45, CD3 and CD8 counts with flow cytometry analysis on the drained blood.

Results : In vitro expansion rate of T cells showed that 6x10^3 and 1x10^3 cell-seeded specimens showed 60.8 and 10.2 fold expansion, respectively. Cell expansion was not observed in 1x10^2 or 10 cells. In vivo experiments showed that mice injected with 1x10^5 or more cells cause fatal GVHD. GVHD induced inflammation was observed in mice injected with 1x10^4 or more cells. No evidence of GVHD was found in mice injected with 10^3 cells.

Conclusions : We have established proof of concept that residual leukocytes in double filtrated blood products cannot cause TA-GVHD. Our results suggest that RBC products with near-zero residual leukocytes by double filtration can replace irradiated blood.

Keyword : GVHD, Transfusion, Leukodepletion, Leukoreduction, Filtration, RBC

OP01-4

Establishing of Reference Intervals for 16 Complete Blood Count Parameters in Healthy Elderly People

Eun Jin Lee, Miyoung Kim*, Eunyup Lee, Kibum Jeon, Jiwon Lee Han-Sung Kim, Hee Jung Kang, Young Kyung Lee

Laboratory Medicine, Hallym University College of Medicine, Korea

Background : Different age groups may have different reference intervals. However, the currently used reference interval for complete blood count (CBC) in clinical laboratories is established based on results from healthy adults between 20 and 50 years of age. In this study, we aimed to establish reference intervals for 16 CBC parameters in Korean healthy elderly individuals.

Methods : A total of 8,151 healthy adults were selected from 64,532 adults (aged ≥20 years) who underwent regular health check-ups based on the medical examination by interview. In two age groups (aged <60 and ≥60 years), the reference intervals for CBC measured by ADVIA 2120i (Siemens, Munich, Germany) were established according to nonparametric method suggested in Clinical and Laboratory Standards Institute EP28-A3. According to Student T-test and Harris and Boyd method, the statistical significance in partitioning of reference intervals between the two age groups was also evaluated.

Results : In results of Student T-test, statistical significances between the two age groups were observed in most parameters: hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW) in both male and female; red blood cells (RBC), platelet, platelet distribution width (PDW), and monocyte % in male; mean corpuscular hemoglobin concentration (MCHC), neutrophil %, lymphocyte %, and basophil % in female. However, according to Harris and Boyd method, there were not required a separate reference interval between the two age groups except for MCH and RDW in women. Among the men, every 16 CBC parameters were not required a separate reference interval between the two age groups.

Conclusions : The reference intervals for most CBC parameters were not significantly different between the two age groups. Except for MCH and RDW in women, reference intervals for CBC parameters based on results from individuals younger than 60 years of age could also be applied in those that are 60 years of age or older.

Keyword : Complete Blood Count, Elderlies, Reference Interval

Table 1. The reference intervals in healthy geriatric population (≥ 60 years old).

	Male				Female			
	RI lower limit	RI upper limit	Lower 90% CI	Higher 90% CI	RI lower limit	RI upper limit	Lower 90% CI	Higher 90% CI
WBC (×109/L)	3.9	10.9	3.79-4.01	10.79-11.01	3.4	9.6	3.29-3.51	9.49-9.71
RBC (×1012/L)	4.00	5.50	3.98-4.02	5.48-5.52	3.70	5.00	3.68-3.72	4.98-5.02
Hb (g/dL)	12.9	17.1	12.83-12.97	17.03-17.17	11.4	15.2	11.33-11.47	15.13-15.27
Hct (%)	38.0	50.1	37.81-38.19	49.91-50.29	33.4	44.8	33.20-33.60	44.60-45.00
RDW (%)†	12.0	14.0	11.96-12.04	13.96-14.04	11.9	14.2	11.86-11.94	14.16-14.24
Platelet (×109/L)	160.0	389.0	156.39-163.61	385.39-392.61	158.0	401.0	153.64-162.36	396.64-405.36
MCV (fL)	83.7	99.4	83.45-83.95	99.15-99.65	83.5	99.4	83.21-83.79	99.11-99.69
MCH (pg)†	28.6	34.1	28.51-28.69	34.01-34.19	27.90	33.5	27.80-28.00	33.40-33.60
MCHC (g/dL)	31.9	36.9	31.82-31.98	36.82-36.98	31.8	36.1	31.72-31.88	36.02-36.18
PDW (fL)	7.2	11	7.14-7.26	10.94-11.06	7.0	10.9	6.93-7.07	10.83-10.97
MPV (fL)	36.3	63.2	35.85-36.75	62.75-63.65	35.5	62.6	34.94-36.06	62.04-63.16
Neutrophil (%)	37.4	70.2	36.86-37.94	69.66-70.74	35.4	71.6	34.74-36.06	70.94-72.26
Eosinophil (%)	0.6	10.5	0.40-0.80	10.30-10.70	0.5	7.6	0.37-0.63	7.47-7.73
Basophil (%)	0.1	1.1	0.08-0.12	1.08-1.12	0.1	1.1	0.08-0.12	1.08-1.12
Lymphocyte (%)	18.9	50.0	18.41-19.39	49.51-50.49	20.0	53.2	19.41-20.59	52.61-53.79
Monocyte (%)	3.6	9.4	3.51-3.69	9.31-9.49	3.2	8.3	3.11-3.29	8.21-8.39

*All reference ranges were established according to CLSI guideline EP28-A3c and 2.5th-97.5th percentile. The 90% CI was calculated according to the flowing formula: mean ±

1.645xSD÷√number.
†If the calculated standard normal deviation (z) exceeds z*(3[naverage / 120]1/2), or the larger standard deviation (s2) exceeds 1.5 smaller standard deviation (s1), or s2/(s2 – s1) is less than 3, it is recommended partitioning the reference intervals for age groups.
Abbreviations: RI, reference interval; CI, confidence interval; WBC, white blood cells; RBC, red blood cells; Hb, Hemoglobin; Hct, hematocrit; RDW, red cell distribution width; PDW, Platelet distribution width; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MPV, Mean platelet volume.

OP02-1

The Spectrum of Anemia in Therapy Naive Patients with Lymphoma and Myeloma from North India

Gaurav PRAKASH[1], Durlabhesh RAWAT[1], Prashant SHARMA[2], Savita VERMA[3], Alka KHADWAL[1], Deepesh LAD[1], Vikas SURI[1], Pankaj MALHOTRA[1], Savita KUMARI[1], Neelam VARMA[2], Subhash VARMA[4]

[1] Clinical Hematology Unit, Department of Internal Medicine, PGIMER, India
[2] Department of Hematology, PGIMER, India
[3] Department of Pediatrcis, PGIMER, India
[4] Hematology and Internal Medicine, Fortis Hospital, India

Background : Profound anemia is a serious and common complication in patients with hematolymphoid malignancies even before receiving chemotherapy and significantly contributes to reduced quality of life and clinical symptomatology including fatigue. In developing countries, coexisting nutritional deficiencies are likely to play a major part in the pathogenesis of anemia. This prospective study evaluated the etiological profile of anemia in lymphoma and multiple myeloma (MM).

Methods : We prospectively enrolled 109 patients with newly-diagnosed lymphoma and MM who were anemic (as per WHO definition) to study their etiological spectrum and clinical and laboratory profiles. Consenting patients were subjected to detailed hemogram with reticulocyte count, serum iron, transferrin saturation percentage, total iron binding capacity, ferritin, vitamin B12, and folate levels. A FACT-an (Functional Assessment of Cancer Therapy - Anemia) questionnaire was filled by all enrolled patients. The data was analysed according to the underlying malignancy and the results are presented below

Results : 109 anemic patients (64.2% male and 75.2% vegetarian) with a median age of 55 years (range 13-80 years) were included. Of these, 71 (65%) patients had various Hodgkin and non-Hodgkin lymphomas while 38 (35%) had MM. Sixty-two (87%) lymphoma patients had Ann Arbor stage III or IV disease. The mean±SD hemoglobin values of the entire cohort, lymphoma, and myeloma groups were 9.1±2.0, 9.6±1.9, and 8.0±1.9 respectively ($p<0.01$). Anemia of chronic disease (ACD) was the commonest subtype of anemia seen in 34/109 (31.2%) patients whereas ACD with concomitant iron deficiency was present in 33/109 (30.3%). Total 8 (7.3%) patients had only IDA. Mean (SD) FACT-An scores in the total patients, lymphoma and MM patients were 105.2(23.7), 102.2(15.9) and 101.4(12.5) respectively.

Conclusions : Our study demonstrates a high prevalence of anemia among Indian patients of lymphoma and MM. The etiology of anemia was multi-factorial in majority of the patients and anemia of chronic disease was the commonest factor.
In our part of the world, 75% patients were taking vegetarian diet and 57 % patients were found to have an associated nutritional deficiency as one of the etiology of anemia.

Keyword : Anemia, Lymphoma, Multiple Myeloma

OP02-2

Successful Treatment of Refractory Pure Red Cell Aplasia with Sirolimus

Zhangbiao Long, Yali Du, Hongmin Li, Miao Chen, Junling Zhuang, Bing Han
Department of hematology, Peking union medical college hospital, China

Background : Pure red cell aplasia (PRCA) is a kind of anemia characterized by severe reticulocytopenia and obvious bone marrow erythroblastic cells decreased. Cyclosporine with /without steroids is the first line therapy, but some patients are refractory or intolerant to the treatment. The effects of the second line therapy like cyclophosphamide, anti-CD20, anti thymocyte globin are not satisfactory and sometimes not available. In this study, we analyzed the efficacy and side-effect of sirolimus on refractory PRCA and investigate the possible mechanism of sirolimus.

Methods : Twenty-one patients with refractory PRCA from March, 2014 to September, 2017 in Peking Union Medical College Hospital were enrolled in this study, and were administered with sirolimus at the dose of 1- 3mg/d for at least six months.Clinical data and side effects were collected before and after sirolimus at different time points. Patients were followed at the medium time of 17-month. CD4+CD25+foxP3+ Treg cells from normal controls and PRCA patients before and after effective sirolimus treatment were tested by flow cytometry.

Results : Totally 76.2% of patients responded to the sirolimus with 42.9% complete response during the experimental period. The median time for reaction was 4 months. Side effects were tolerable including infections, mild oral mucositis, sinus tachycardia, increase of creatinine, transaminase, triglyceride or cholesterol and thrombocytopenia. Most patients stayed in remission or remained stable during the follow-up period. Early drug withdrawal may lead to quick relapse. Compared with normal control, Treg levels in patients with PRCA reduced significantly before sirolimus but recovered after successful treatment. Level of Treg cells correlated with hemoglobin level after effective sirolimus treatment.

Conclusions : Sirolimus was effective and tolerable for refractory PRCA. Effective sirolimus treatment may lead to the upregulation of Treg cells which may partly explain the underlying mechanism.

Keyword : Pure red cell aplasia, Refractory, Cyclosporine, Sirolimus, Regulatory T cells

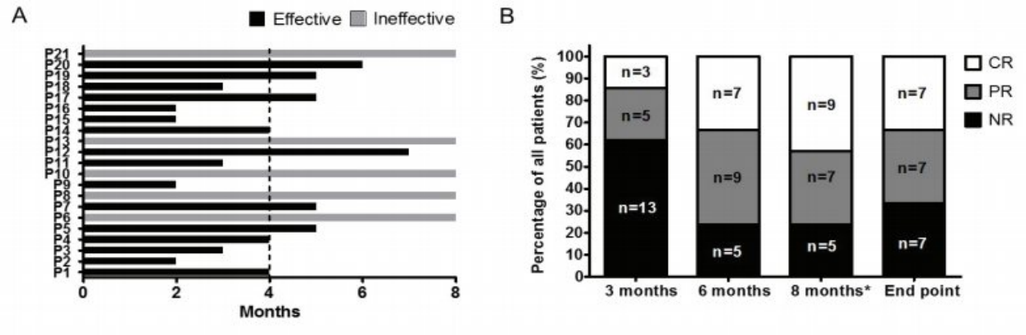


Figure1. Response of patients to sirolimus. A. Time to response with sirolimus. Black bar represented patients who responded to sirolimus, and grey bar represented those who did not respond during follow-up period, dash line represented the median time of response. B. Response to sirolimus at different time point. * Patients reached the best efficacy to sirolimus at 8 months in this study.

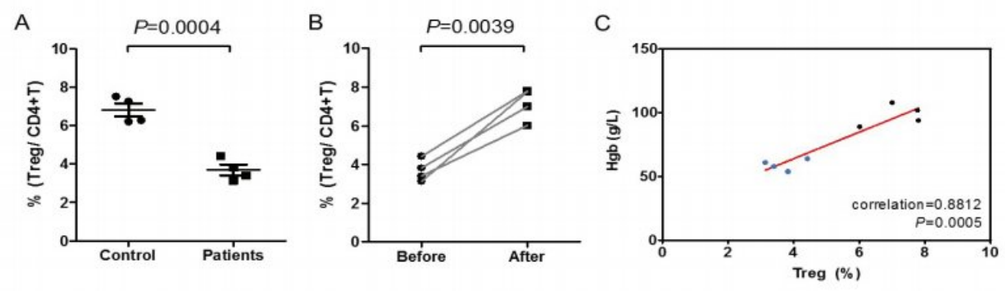


Figure 2. Regulatory T cells (T_{reg}) level in PRCA patients and healthy controls.

The whole blood samples of patients pre and post sirolimus, age and gender matched healthy controls were collected, and regulatory T cells level were detected by flow cytometer. A. The level of T_{reg} in healthy controls and patients before treatment. B. The level of T_{reg} in patients before and after treatment with sirolimus. C. The correlation between the level of Treg and the level of hemoglobin (Hb) in PRCA patients. Blue dots represented the level of Treg and Hb before sirolimus, black dots represented the level of Treg and Hb after sirolimus.

OP02-3

Dynamics of CMV and EBV Loads after Rabbit ATG and Cyclosporine : A Prospective Observational Study

Sung-Soo Park, Gi June Min, Young-Woo Jeon, Jae-Ho Yoon, Sung-Eun Lee, Byung-Sik Cho, Ki-Seong Eom, Seok Lee, Hee-Je Kim, Chang-Ki Min, Seok-Goo Cho, Woo-Sung Min, Jong Wook Lee*
Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Background : The natural courses of Cytomegalovirus (CMV) and Ebstein-Barr virus (EBV) after immunosuppressive treatment (IST) with rabbit antithymocyte globulin and cyclosporine A (ATG/CsA) for aplastic anemia (AA) has not been well described.

Methods : In this prospective study, CMV and EBV viral load of 99 with acquired adult AA who received ATG/CsA were analyzed. Each viral cohort was classified into two groups by the presence of viral load at the time of IST as follows: no CMV viral load at baseline (CMV-G1, n=98) and the presence of CMV at baseline (CMV-G2, n=1); No EBV viral load at baseline (EBV-G1, n=88) and the presence of EBV load at baseline (EBV-G2, n=11). Each viral data were collected at baseline, 1, 3, 6, and 12 months from IST.

Results : Median age and follow-up periods of cohort were 41 (18-75) years and 17.9 (1.1-71.2) months, respectively. In CMV-G1, CMV reactivation and disease occurred in 41 (42.2%) and 4 (4.1%), respectively. Dynamics of CMV-load tended to increase until 3 months, but were completely resolved at 6 and 12 months. Four (4.1%) patients developed CMV diseases after median 79 (45-138) days from IST. One of CMV-G2 who presented 4.08 log of load at the time of IST had resolved state at 1 and 3 months without CMV treatment. Median CMV-load at the time of CMV disease was 5.61 (negative - 5.87) log. However, highest CMV load of 95 patients without CMV disease were not reached to 5.0 (negative-4.87) log.
In EBV-G1, EBV reactivation and disease occurred in 54 (61.4%) and 1 (4.1%), respectively. EBV load peaked at 1 month and gradually decreased throughout 12 months, but remained until 12 months. Dynamics of EBV-G2 revealed fluctuated EBV-load without time point of a specific peak. None of EBV-G2 presented EBV disease during the follow-up periods. Individual median peak EBV-load was 4.48 (2.76-6.00) log. One of EBV associated lymphoproliferative disease (EBV-LD) showed EBV-loads of 7.06 and 5.52 log at 1 and 3 months, respectively. Median highest of EBV-load in 98 patients without EBV-LD was 2.99 (negative-6.72) log.

Conclusions : Reactivation of CMV and EBV was common after ATG/CsA and showed different dynamics. To predict the onset of viral disease, it should be recommended to monitor CMV load for at least 3 months and EBV load for at least 1 month after IST, respectively. Cut-off for preemptive therapy might suggest 5 log of CMV-load and 7 log of EBV-load, respectively.

Keyword : Aplastic anemia, Anti-Thymocyte globulin, ATG, Cytomegalovirus, Ebstein-Barr virus

OP02-4

Helicobacter Pylori Testing in Patients with Pernicious Anemia

Ik Chan Song[1], Hyewon Ryu[1], Yoon Seok Choi[1], Hyo-Jin Lee[1], Hwan Jung Yun[1], Yong Moon Lee[2], Kyu Sang Song[2], Seung Woo Baek[1], Deog Yeon Jo*[1]
[1] Department of Internal medicine, College of Medicine, Chungnam National University, Korea
[2] Department of Pathology, College of Medicine, Chungnam National University, Korea

Background : The causative role of Helicobacter pylori infection in pernicious anemia is not clearly understood. This study reviewed H. pylori infection status and its clinical implications in patients with pernicious anemia.

Methods : Medical records were obtained for all patients diagnosed with pernicious anemia between 2002 and 2017 at the Chungnam National University Hospital, Daejeon, Korea. We performed Giemsa staining of gastric body and antrum tissue prepared from paraffin blocks, reviewed the results of H. pylori testing, and analyzed clinical data.

Results : Of the 70 patients who were diagnosed with pernicious anemia during the study period, 40 were included the analysis. The median age was 64 years (range: 33–81), and the male/female ratio was 1.2. Autoimmune disorders were found in eight patients (20.0%). Antibody to intrinsic factor was detected in 24 of 37 patients (64.9%), and antibody to parietal cells in 18 of 39 patients (46.2%). Of the 38 patients who underwent gastroscopic examination, 22 (59.5%) revealed intestinal metaplasia in addition to chronic gastritis in the body. Positive results for various H. pylori tests included: one of four patients (25.0%) for immunoglobulin G (IgG) antibodies to H. pylori, four of eight patients (50.0%) in the urea breath test, and one of seven patients (14.3%) in the CLO test. Additionally, three of 38 patients (7.9%) showed positive Giemsa staining. In total, nine of 40 patients (22.5%) tested positive for at least one H. pylori test. Compared to the H. pylori-negative patients, H. pylori-positive patients showed higher mean corpuscular volume (119.3 ± 9.5 vs. 102.3 ± 7.9 fL, P<0.001) and less frequent autoimmune disorders (0% vs. 25.8%, P<0.001). No other differences were observed between the two groups in terms of symptoms, laboratory and histologic findings, and responses to treatment.

Conclusions : H. pylori infection was not found to play a pivotal role in the development or progression of pernicious anemia.

Keyword : Pernicious anemia, Vitamin B12, Helicobacter pylori

OP03-1

Treatment Outcome and Prognostic Factors of Precursor T-Acute Lymphoblastic Leukemia in Children

Hyery Kim, Sung-Han Kang, Yoo Jae Won, Kyung-Nam Koh, Ho Joon Im, Jong Jin Seo*
Pediatric, University of Ulsan College of Medicine, Asan Medical Center, Korea

Background : Precursor T cell acute lymphoblastic leukemia (ALL) has been associated with a worse prognosis than other forms of childhood ALL. Our study aimed to determine the important prognostic variables of pediatric T-ALL in our treatment setting.

Methods : We reviewed the medical records of 36 precursor T-ALL patients who had been diagnosed and treated at Asan Medical Center from March 2001 to March 2017. Six patients (16.7%) were Early T-cell precursor ALL (ETP-ALL). Most of the patients received COG-1882 based chemotherapy with intensified post-induction treatment and prophylactic cranial irradiation. Clinical features at presentation, response to therapy and treatment outcome were analyzed.

Results : There were 27 males/9 females, and median age at diagnosis was 10.6 years. The median white blood cell (WBC) count at diagnosis was 24,150/uL (range, 1,100-530,500/uL). Complete remission after induction was not achieved in 3 patients including 2 ETP patients. Twenty patients showed rapid early response during induction. The 5-year overall survival (OS) rate was 77.2%, and event free survival (EFS) rate was 69.1%. ETP leukemia and slow early response during induction was the significant adverse prognostic factors. In addition, patients with extensive extramedullary involvement at diagnosis showed poorer survival than others. Hyperleukocytosis at diagnosis (WBC≥100,000/uL) was not the adverse prognostic factor in our cohort. CCG-1882 base chemotherapy (OS 87.5%, EFS 78.9%) gave survival benefit over CCG-1901 chemotherapy (OS 50.0%, EFS 64.3%), and patients with prophylactic cranial irradiation shower better EFS than non-radiated patients.

Conclusions : Our study showed that high risk ALL protocol with intensified post-remission therapy including prophylactic cranial irradiation conferred a comparable survival outcome in T-cell ALL with Western studies. Further treatment intensification should be considered for patients with ETP-ALL and slow induction response.

Keyword : Acute lymphoblastic leukemia, Pediatric , T-Cell ALL, ETP-ALL

OP03-2

Allogeneic Hematopoietic Stem Cell Transplantation for Childhood Myelodysplastic Syndrome

Jae Won Yoo, Sung Han Kang, Hyery Kim, Kyung Nam Koh, Eun Seok Choi, Ho Joon Im*, Jong Jin Seo
Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center Children's Hospital, Korea

Background : Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curable approach for myelodysplastic syndromes (MDS). In this study, we evaluated the outcome of HSCT in childhood MDS at a single center

Methods : Thirty-six patients with MDS underwent allogeneic HSCT at Asan Medical Center Children's Hospital between December 1997 and September 2017. At the time of transplantation, 24 were low grade MDS (Refractory anemia, refractory cytopenia with multilineage dysplasia and refractory cytopenia of childhood) and 12 were advanced MDS (refractory anemia with excess blasts-1 and 2). Cytogenetic risk group was stratified according to revised IPSS (23 Good, 8 Intermediate, 4 Poor, 1 Very poor). The endpoint analysis was conducted on January 20, 2018

Results : Median age at transplantation of the 36 patients (22 male and 14 female) was 12 years (range, 2-24). Median time from diagnosis to transplantation was 5.9 months (range, 1-139). Ten (28%) transplants were performed between 1997 and 2007, and 26 (72%) between 2008 and 2018. Thirty-two (89%) patients achieved engraftment and the median time to engraftment of absolute neutrophil count and platelet were 11 and 18 days, respectively. Grade II to III acute GVHD occurred in 13 patients (36%) and no patient developed grade IV acute GVHD. Extensive chronic GVHD occurred in 4 patients (11%). With a median follow-up of 55 months (range, 2-240), 5-year EFS and OS were 71% and 79%, respectively. Four patients died of transplant-related causes, leading to TRM of 8.7% at 1 year and 12.3% at 2 years. Patients with low grade MDS represented significantly higher OS compared to advanced MDS (90% vs. 58%, p=0.02). In the multivariate analysis, patients who transplanted between 1997 and 2007 were associated with lower OS (OR, 8.0; 95% CI 1.5-42). Among the patients with advanced MDS, the OS has improved in the recent cohort (33% for 1997-2007 vs. 83% for 2008-2017, p=0.07). Nine (25%) out of 36 patients underwent haploidentical HSCT with RIC regimen, all patients except one achieved sustained engraftment and were alive in remission at the time of analysis

Conclusions : Our study demonstrated that the allogeneic HSCT is a feasible treatment option for tchildhood MDS, especially in low grade MDS. The outcome of advanced MDS has improved over time. Furthermore, haploidentical HSCT with RIC regimen could be a realistic alternative for childhood MDS

Keyword : Myelodysplastic syndrome, Allogeneic stem cell transplantation, Children

OP03-3

Cell Therapy to Control Relapsed AML following Allogeneic Stem Cell Transplantation

Woochan Park[1], Inho Kim[1], Sung-Soo Yoon[1], Seonyang Park[2], Youngil Koh*[1]

[1] Internal Medicine, Seoul National University Hospital, Korea
[2] Internal Medicine, Inje University Haeundae Paik Hospital, Korea

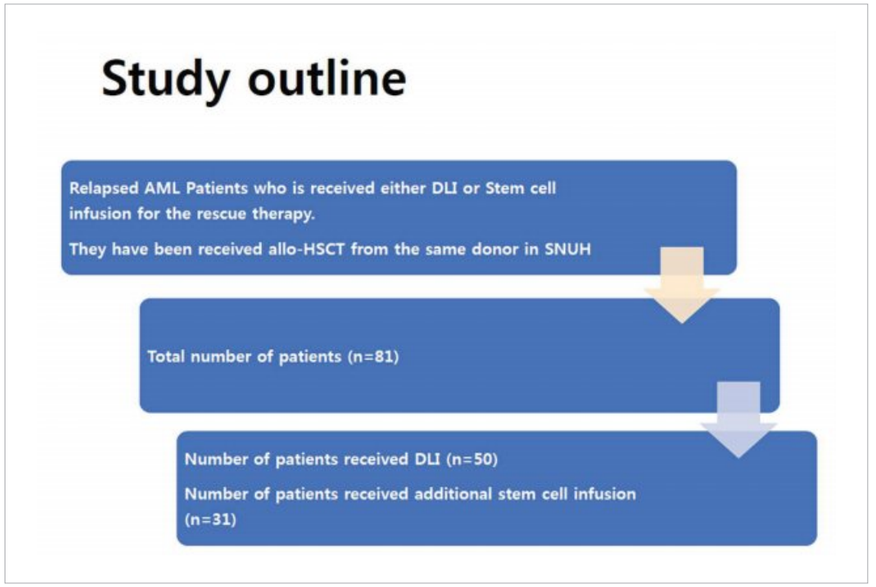
Background : Although, allogenic hematopoietic stem cell transplantation (Allo-SCT) is curative therapy for acute myeloid leukemia (AML), many patient experience relapse following allo-SCT. For this patients, it is well known that donor lymphocyte infusion (DLI) could rescue certain proportion of patients via graft versus leukemia effect. On the other hand, residual stem cell after allo-SCT is also frequently used as a rescue therapy for AML relapse. However, clinical utility of residual stem cell is not well established yet. Hence, in this study, we compare the outcome of DLI with residual stem cell infusion in relapsed AML after allo-SCT.

Methods : We retrospectively reviewed the AML patients who underwent DLI or residual stem cell infusion for relapsed disease after allo-SCT from 2001 to 2017 in Seoul National University Hospital. We analyzed factors including overall survival (OS), cell counts, disease status at cell therapy, and GVHD development. Our primary outcome was to compare OS after cell therapy between DLI group and residual stem cell group.

Results : A total of 81 patients were analyzed. There were 50 patients (25 males and 25 females) who received cell therapy using DLI, and 31 patients (11 males and 20 females) who received residual stem cell infusion. There was no difference in age, duration from allo-SCT to cell therapy between the two groups. Majority of patients received cell therapy for first relapse after allo-SCT (63% in DLI, 93% in residual stem cell group). Median CD3 cell count infused was not different between DLI and residual stem cell product (median value of 0.967 * 10 ^ 8/kg and 0.964*10^8/kg). Median CD34 cell dose was 2.34 * 10 ^ 6 / kg in residual stem cell group. There was no difference in OS between the two groups (median OS 8.5 months for DLI and 10.2 months for residual stem cell group, p-value 0.673). GVHD occurred in 44% in DLI group and 41.9% in residual stem cell group.

Conclusions : This study demonstrates that clinical utility of DLI and residual stem cell infusion is similar in relapsed AML after allo-SCT. Hence, residual stem cell could be used as an alternative source for T cell therapy following allo-SCT.

Keyword : Acute myeloid leukemia, Relapse, Donor lymphocyte infusion, Stem cell transplantation, Stem cell infusion, CD3



Baseline characteristics (n=81)

Table 1.

변수	DLI	stem cell infusion	p-value
진단 연령	41.76	47.02	0.106
키	165.8	161.4	0.05
체중	59.18	57.99	0.603
AlloSCT 후 Relapse (day)	376.1	268.1	0.459
AlloSCT 후 Cell therapy (day)	339.6	235.7	0.444

OP03-4

Discrepancy in Efficacy of Disulfiram between NUP98-PHF23 Fusion Acute Myelogenous Leukemia

Eun Sil Park[1,2], Yang Jo Chumg[2], Peter D Aplan[2]

[1] Department of pediatrics and institute of Health Science, College of Medicine Gyeongsang National University, Korea
[2] Genetics Branch, Center for Cancer Research , National Cancer Institute/National Institute of Health, United States
[3] Genetics Branch, Center for Cancer Research , National Cancer Institute/National Institute of Health, United States

Background : Background: NUP98 has numerous partner genes of which plant homeodomain (PHD) finger protein 23 (PHF23) fusion with NUP98 (NP23) can be detected by RT-PCR in patients with cytogenetically normal acute myelogenous leukemia (AML). In this fusion transcript of NP23 plant homeodomain (PHD) of PHF23 is known to specifically bind H3K4me3 residues and act as chromatic modifier. Disulfiram (DSF) which inhibit the binding of PHD to H3K4me3 residues was selectively killed NP23 myeloblasts in vitro and therefore, we planted to evaluate the efficacy of DSF in vivo.

Methods : Cultured 961C cells (CD45.2), NP23 myeloblast cell were transplanted in B57BL/6 mice (CD45.1). Using limit dilution assay the number of leukemic stem cells (LSCs) can be calculated. Certain quantity of 961C were transplanted in B57BL/6 mice and DSF was treated after 1week. The engraftment level was monitored with CD45.2. The Kaplan Meier survival curve was plotted and compared the survival between therapeutic groups and control.

Results : Results: 961C cells could be transplanted without radiation in recipient mice. Calculated LSC was estimated to be 1 out of 184 cells (95% CI range, 56 609). When treated with DSF (several dosage and several administrative route) in 961C recipient mice we could not show any survival benefit between groups even though engraftment level was consistent in both group.

Conclusions : We could not show the survival advantage of DSF in 961C transplanted immunocompetent mouse but could know that 961C cells shared niche with normal hematopoietic stem cells (HSCs). We expect that 961C cells and their transplanted mice will be used as in vivo system for the new drugs development as well as for the basic study dealing with niche for normal HSCs and LSCs.

Keyword : Acute myelogenous leukemia, NUP98, Leukemic stem cell

OP03-5

Arsenic Trioxide-Based Initial Treatment for Acute Promyelocytic Leukemia with High-Risk Features

Gi June Min, Byung Sik Cho*, Dae-Hun Kwak, Sung-Soo Park, Young-Woo Jeon, Jae-Ho Yoon, Sung-Eun Lee, Ki-Seong Eom, Yoo-Jin Kim, Seok Lee, Chang-Ki Min, Seok-Goo Cho, Dong-Wook Kim, Jong-Wook Lee, Hee-Je Kim, Woo-Sung Min

Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, Korea

Background : Acute promyelocytic leukemia (APL) has become a highly curable disease with all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy. Arsenic trioxide (ATO) with or without ATRA is also highly effective in the treatment of APL and showed even better hematologic toxicity profiles. In this study, we investigated the safety and efficacy of a chemotherapy-free ATO/ATRA regimen in APL with high-risk features for early death and/or relapse.

Methods : Since ATO became available in 2007, 18 patients have been treated with an ATO/ATRA regimen for induction due to either old age with multiple comorbidities or septic condition at the time of diagnosis. The median duration of induction was 30 days (range, 2~62 days), and 17 of 18 patients achieved either hematologic CR (64.7%) or molecular CR (29.4%). The median time to complete remission (CR) was 35 days (range, 25~86 days). One patient (5.9%) died of septic shock after only 2 days of ATO/ATRA.

Results : In terms of safety profiles with ATO/ATRA regimen, 48 patients treated with anthracycline/ATRA regimen were used as control group having similar baseline characteristics with an exception of younger age (39 years vs. 67 years, P=0.01). Grade 3 or 4 neutropenia (81.3% vs 100%, p=0.029) and thrombocytopenia (62.5% vs. 100%, p=0.01) was significantly less frequent in ATO/ATRA regimen and duration of grade 3 or 4 thrombocytopenia was shorter in ATO/ATRA regimen (4.5 days vs. 14 days, p=0.003). There were no significant differences in neutropenic fever, hepatotoxicity, the incidence of differentiation syndrome and leukocytosis between two groups. Four patients had a peak QTc above 500ms, but there was no major arrhythmia such as Torsa de pointes without any interruption of ATO. Overall survival in all 18 ATO frontline treatment group was 88.5% with a median follow up period of 29.5 months (range, 0 ~121 months) without any of relapse events.

Conclusions : This study is the first report in Korea indicating safety and efficacy of chemotherapy free ATO-based induction in APL patients with high-risk features for early death or inferior survival, such as old age and multiple comorbidities or severe infectious complications. Favorable hematologic toxicity profile with an encouraging anti-APL effect of ATO/ATRA regimen suggests that APL can be curable without conventional chemotherapy even in this high-risk group of APL.

Keyword : Acute promyelocytic leukemia, Retinoic acid, Arsenic trioxide, Frontline therapy, Postremission therapy

OP03-6

Feasibility of Blinatumomab Salvage for Adult Patients with Relapsed or Refractory Ph-Negative ALL

Jae-Ho Yoon, Gi June Min, Sung-Soo Park, Sung-Eun Lee, Byung-Sik Cho, Ki-Seong Eom, Yoo-Jin Kim, Hee-Je Kim, Chang-Ki Min, Seok-Goo Cho, Dong-Wook Kim, Jong Wook Lee, Woo-Sung Min, Seok Lee*

Department of Hematology, Catholic Blood and Marrow Transplantation Center, Leukemia Research Institute, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea,

Background : Among the patients with relapsed or refractory acute lymphoblastic leukemia (ALL), remission rates are much lower with poorer OS. For safe salvage and bridge therapy to allogeneic hematopoietic cell transplantation (allo-HCT), several immune-based treatments have been tried. Among them, blinatumomab (bispecific T-cell engaging monoclonal antibody) was approved for relapsed or refractory Ph-negative ALL (r/rALL) and phase III result was published recently.

Methods : We enrolled 20 adults for outcome analysis of blinatumomab salvage in patients with r/rALL – the present indication of blinatumomab. Patients with r/rALL due for blinatumomab received pre-phase dexamethasone 10mg bid for 4 days (total 80mg) and cytoreduction using hydroxyurea or cytarabine until leukocyte < 20,000/ . Blinatumomab was infused continuously for 4 weeks (9μg/day for 1 week, then 28μg/day at week 2–4) and cessation for 2 weeks, and then followed by one more 4 weeks cycle (28μg/day). For patients with suspicious cytokine releasing, we applied additional dexamethasone 5mg bid for 3 to 5 days. For patients with remission, urgent allo-HCT was planned.

Results : Overall, 14 (70.0%) finished planned 2 cycles of blinatumomab and all of them achieved CR, while 2 (10.0%) finished only 1 cycle due to remission failure and 4 (20.0%) stopped blinatumab during first cycle. Among the 14 (70.0%) with CR, 11 achieved CR after first cycle, and 3 achieved after second cycle. CR rate was higher in intermediate-risk karyotype (76.9% vs. 50.0%). For the timing of blinatumomab, 4 (20.0%) were treated with blinatumomab after induction failure (CR in all patients), 5 (25.0%) at first relapse after consolidation therapy (CR in 3 [60%]), 9 (45.0%) at first relapse after allo-HCT (CR in 5 [55%]), and 2 (10.0%) at second relapse after second allo-HCT (CR in 1 [50%]). Among 6 patients with extramedullary relapse (EMR) after allo-HCT, all 3 with isolated EMR achieved CR and underwent next allo-HCT, but all 3 with both hematological relapse and EMR failed to achieve CR. Finally, 14 out of 20 underwent allo-HCT after salvage therapy and 12 are alive in CR after median follow-up of 7.7 months.

Conclusions : Blinatumomab is a feasible choice for salvage for adults with r/rALL which showed an acceptable remission rate at any time of salvage. However, the role in patients with both hematological relapse and EMR should be further studied in next studies.

Keyword : Blinatumomab, Refractory, Relapsed, Acute lymphoblastic leukemia

OP04-1

Inflammatory Factor-Based Scoring System in DLBCL in the Rituximab Era

Ji Hyun Lee[1], Sung Yong Oh[1], Ho Sup Lee*[2], Won-Sik Lee[4], Ho-Jin Shin[3], Jae-Cheol Jo[5], Yunsuk Choi[5], Yoo Jin Lee[6], Kyung A Kwon[7]

[1] Department of Internal Medicine, Dong-A University College of Medicine, Korea
[2] Department of Hematology and Oncology, Kosin University Gospel Hospital, Korea
[3] Department of Hematology and Oncology, Busan National University Hospital, Korea
[4] Department of Hematology and Oncology, Busan Paik Hospital, Inje University College of Medicine, Korea
[5] Department of Hematology and Oncology, University of Ulsan College of Medicin, Korea
[6] Department of Internal Medicine, Kyungpook National University School of Medicine, Korea
[7] Department of Internal Medicine, Dongnam Institute of Radiological and Medical Sciences, Korea

Background : Prognostic scoring system has made a progress to better predict progression and survival of diffuse large B-cell lymphoma (DLBCL) patients, but there is still need for sophisticated prognostic scoring system with simply testable variables to individualize prognosis in patients treated with immunochemotherapy.

Methods : Five hundred and twenty-three patients with DLBCL treated with at least 2 or more cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as a first-line treatment were retrospectively analyzed. Each 6 factors for inflammatory scoring system were dichotomized by the reference of previously published papers and were given 1 point for each variables after the following criteria: the ALC < 1100/mm3, LDH > normal, albumin < 3.0 g/dL, CRP > 1.0 mg/dL, ferritin > 500 ng/mL, and beta 2-microglobulin ≥ 2.5 mg/L. Patients were further classified by inflammatory factor-based scoring system: score 0 (points 0-1), score 1 (points 2-3) and score 2 (points 4-6) and these scores substituted LDH in the IPI. The IPI scores plus scores by inflammatory factor-based scoring system was further classified into 4 risk groups: low (score 0-1), low-intermediate (score 2), high-intermediate (score 3), and high (score 4-6).

Results : The median follow-up duration was 37.61 months (range 0.60 – 139.03 months). In multivariate analysis, LDH > normal and CRP > 1.0 mg/dL remained statistically significant for OS and CRP > 1.0 mg/dL was marginally significant for PFS (Table 1). By inflammatory factor-scoring system, score 0, 1, and 2 showed statistically significant OS (Figure 1, P= 0.000) and PFS (Figure 2, P= 0.000), and modified IPI risk groups showed significant differences in OS (Figure 3, P= 0.000) and PFS (Figure 4, P= 0.000).

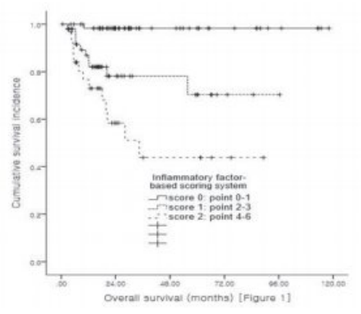
Conclusions : The risk groups stratified by inflammatory factor-based scoring system showed significant difference in both progression-free and overall survival in DLBCL patients in the Rituximab era. The inflammatory factor-based scoring system can further make delicate modification to IPI, substituting LDH. Validation of the finding in a larger cohort of patients is needed.

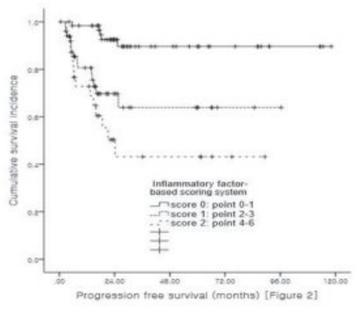
Keyword : Inflammatory factors, Prognostic scoring system

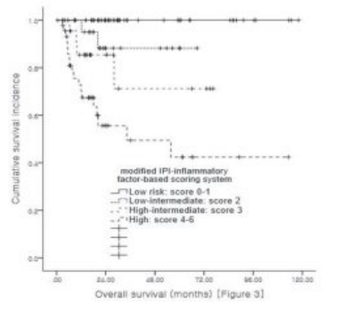
Table 1. Univariate and multivariate analysis for overall survival and progression free survival

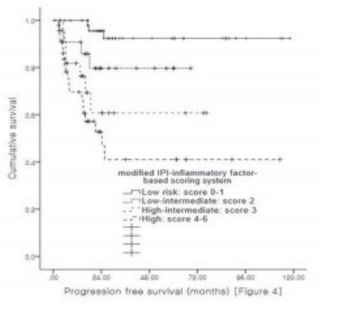
OS	Univariate analysis		Multivariate analysis	
	HR	*P*-value	HR	*P*-value
ALC				
≥ 1100				
< 1100	1.806 (1.156-2.823)	0.009	0.776 (0.318-1.894)	0.577
LDH.				
≤ normal				
> normal	3.893 (2.302-6.585)	0.000	10.501 (1.351-81.635)	0.025
Albumin				
≥ 3.0				
< 3.0	4.863 (2.795-8.459)	0.000	1.343 (0.469-3.840)	0.583
CRP				
≤ 1.0				
> 1.0	4.033 (2.487-6.540)	0.000	3.673 (1.504-12.807)	0.041
Ferritin				
≤ 500				
> 500	2.866 (1.454-5.647)	0.002	1.110 (0.452-2.727)	0.819
serum b2-microglobulin				
< 2.5				
≥ 2.5	3.595 (2.065-6.259)	0.000	1.923 (0.676-5.466)	0.220

PFS	Univariate analysis		Multivariate analysis	
	HR	*P*-value	HR	*P*-value
ALC				
≥ 1100				
< 1100	2.520 (1.436-4.421)	0.001	0.936 (0.454-2.072)	0.936
LDH.				
≤ normal				
> normal	2.220 (1.489-3.310)	0.000	2.275 (0.872-5.939)	0.093
Albumin				
≥ 3.0				
< 3.0	1.991 (1.038-3.819)	0.038	0.872 (0.303-2.508)	0.799
CRP				
≤ 1.0				
> 1.0	2.633 (1.789-3.879)	0.000	2.382 (0.943-6.014)	0.066
Ferritin				
≤ 500				
> 500	2.024 (1.046-3.914)	0.036	1.366 (0.619-3.013)	0.440
serum b2-microglobulin				
< 2.5				
≥ 2.5	2.141 1.361-3.368)	0.001	2.289 (0.983-5.332)	0.055









OP04-2

Clinical Features and Treatment Outcomes of Limited State Mantle Cell Lymphoma (CISL1606)

Jae-Cheol Jo[1], Seok Jin Kim[2], Ho Sup Lee[3], Hyeon-Seok Eom[4], Soon Il Lee[5], Yong Park[6], Jeong-Ok Lee[7], Yoojin Lee[8], Ho-Young Yhim[9], Cheolwon Suh*[10]

[1] Hematology and Oncology, Ulsan University Hospital, Korea
[2] Hematology and Oncology, Samsung Medical Center, Korea
[3] Hematology and Oncology, Kosin University College of Medicine, Korea
[4] Hematology and Oncology, National Cancer Center of Korea, Korea
[5] Hematology and Oncology, Dankook University College of Medicine, Korea
[6] Hematology and Oncology, Korea University College of Medicine, Korea
[7] Hematology and Oncology, Seoul National University Bundang Hospital, Korea
[8] Hematology and Oncology, Kyungpook National University Hospital, Korea
[9] Hematology and Oncology, Chonbuk National University Hospital, Korea
[10] Oncology, Asan Medical Center, Korea

Background : Limited stage (Ann Arbor stage 1 or 2) mantle cell lymphoma (MCL) is an extremely rare disease. Thus, there are little data about the clinical feature and treatment outcomes of patients with early stage mantle cell lymphoma.

Methods : We consecutively collected stage 1 or 2 MCL cases diagnosed between 2000 and 2016 in 16 institutions in CISL group. All patients were pathologically confirmed and received systemic evaluation for staging work-up. The clinical features were reviewed, and the treatment outcomes were analyzed.

Results : The median age of patients was 66 years (range: 18 – 85 years), male (n=31, 75.6%) was predominant compared to female. The majority of patients (n=28, 68.3%) had stage 2 disease, 29 patients (70.7%) were symptomatic. The elevation of LDH (n=2, 4.9%) was not common, thus, 39 patients (95.1%) had low risk (0 or 1 score) of the International Prognostic Index (IPI), and 28 patients (68.3%) had low risk (1-3 score) of the MIPI. As the first therapeutic strategy, most patients (n=37, 90.1%) received chemotherapy, radiotherapy (n=2), surgical resection (n=1), and no treatment (n=1). Of patients who received chemotherapy, 23 patients (56.9%) were administered with rituximab containing regimen, and R-CHOP (n=17) was most common regimen. The best response rate was 97.4% (n=38) including 34 complete response (82.9%). With the median follow-up duration of 40.6 months, the median relapse free survival was 56.1 months, and the 5-year overall survival rate was 80.4%.

Conclusions : Limited state MCL showed indolent clinical and low risk prognostic features. Chemotherapy could be effective for controlling localized MCL lesion with high complete response rate.

Keyword : Limited stage , Mantle cell lymphoma, Chemotherapy

OP04-3

Poor Clinical Outcome of Epstein-Barr Virus Associated Secondary Hemophagocytic Lymphohistiocytosis

Jae-Ho Yoon[1], Seung-Ah Yahng[2], Gi June Min[1], Sung-Soo Park[1], Young-Woo Jeon[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], Seok-Goo Cho[1], Dong-Wook Kim[1], Woo-Sung Min[1], Jong Wook Lee*[1]

[1] Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, Korea
[2] Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Background : Hemophagocytic lymphohistiocytosis (HLH) is a severe overwhelming systemic inflammatory process which is triggered by several causes.

Methods : In this single center retrospective study, we initially found 165 patients who were diagnosed as HLH from medical records. All but 12 patients satisfied the criteria of HLH2004 for diagnosis, including fever and bone marrow hemophagocytosis. After exclusion of 27 patients with malignancies, we finally focused on 126 secondary HLH with several causes such as Epstein-Barr virus (EBV), autoimmune disease, and infection other than EBV. All but 4 were treated with HLH-94 based therapy which consists of steroid and etoposide. For prognostic analysis, most severe cytopenia was checked before chemotherapy and the worst blood chemistry results were checked within 4 weeks after treatment. Treatment response was evaluated at 4 and 8 weeks and complete remission (CR) was determined when both cytopenias and blood chemistry results were normalized.

Results : Compared to autoimmune disease (n=13), infection other than EBV (n=24), and both combined cases (n=9), EBV-associated HLH showed worse 5-year OS (25.1% vs. 78.7%, 76.9%, 63.5%) and progressive course in 77.8%. We identified overall response rate at 4 weeks was similar between the causes, but decreased at 8 weeks in the EBV-HLH subgroup from 75.0% to 52.3% due to disease progression which finally decreased to 29.5% afterward. In another subgroup, the proportion was maintained. Multivariate analysis also revealed poor 8-week treatment response was the most significant factor for outcomes. Except for treatment response, EBV-association, old age > 45 years old, abnormal karyotype, high ferritin > 20,000 ng/mL, and thrombocytopenia < 35X10^9/L were associated with both poor survival and more disease progression. We used them for a risk-stratification (1 point for each except for age with 2 points); low-risk (0-1, n=49), intermediate-risk (2, n=23), and high-risk (3-6, n=54) which showed 5-year progression rate at 17.1%, 55.8%, and 87.0% respectively. In EBV-HLH, regardless of risk-stratification, progression rate was 96.0% in non-responder group and 77.8% even in stable responders, and EBV-titer > 5-Log and hyperbilirubinemia were affecting factors for outcome.

Conclusions : EBV independently showed poor clinical outcomes with old age, abnormal karyotype, thrombocytopenia, and hyperferritinemia in secondary HLH.

Keyword : Hemophagocytic lymphohistiocytosis, Epstein Barr virus, Prognosis

OP04-4

3.5-Yr Follow-Up of Ibrutinib-Treated Relapsed/Refractory Mantle Cell Lymphoma Patients: Pooled Analysis

Simon Rule[1], Seok-Goo Cho[2], Martin Dreyling[3], Andre Goy[4], Georg Hess[5], Rebecca Auer[6], Brad Kahl[7], José-Ángel Hernandez-Rivas[8], Anil Londhe[9], Fong Clow[10], Sanjay Deshpande[9], Lori Parisi[9], Michael Wang[11]

[1] Department of Haematology, Plymouth University Medical School, United Kingdom
[2] Department of Hematology, Seoul St. Mary's Hospital, Korea
[3] Department of Medicine III, Klinikum der Universität München, Germany
[4] Department of Hematology & Oncology, John Theurer Cancer Center at Hackensack University Medical Center, United States
[5] Department of Hematology, Oncology and Pneumology, University Medical School of the Johannes Gutenberg University, Germany
[6] Centre for Haemato-Oncology, Barts Cancer Institute, United Kingdom
[7] Department of Medicine, Washington University, United States
[8] Hematology Department, Hospital Universitario Infanta Leonor, Spain
[9] Research & Development, United States
[10] Biometrics and Data Management, Pharmacyclics, United States
[11] Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

Background : We previously reported results of a pooled analysis of 370 ibrutinib (IBR)-treated pts with R/R MCL in the PCYC-1104 (n=111), SPARK (MCL2001; n=120), and RAY (MCL3001; n=139) studies (median follow-up 24 mo). Here, we present median 3.5-yr follow-up, including additional follow-up of 87 pts across the 3 studies who enrolled in the open-label phase 3b long-term access study CAN3001, which provided continued access to IBR.

Methods : Pts in SPARK, RAY, and PCYC-1104 received IBR 560 mg PO QD until PD or unacceptable toxicity. This analysis was limited to pts on IBR therapy, excluding those who crossed over to IBR from the comparator arm in RAY. Investigator-assessed tumor response, PFS, and OS were evaluated. PFS and OS were analyzed by number of prior LOT and best tumor response. TEAEs of grade ≥3 were summarized.

Results : Median duration of follow-up in the pooled dataset (N=370) was 41.1 mo (95% CI, 37.3-42.5); median treatment exposure was 11.1 mo (range: 0.03-72.1) with median 2 (range: 1-9) prior lines of therapy (LOT) before IBR. 83 and 40 pts had IBR exposure ≥3 and ≥4 yrs. 54/87 (62.1%) pts in CAN3001 remain on IBR.
At 2 and 3 yrs, 36% (95% CI, 0.31-0.42) and 26% (0.20-0.32) of pts were progression free; median PFS was 13.0 mo (Table). Median PFS in pts with 1 prior LOT was 33.6 (19.4-42.1) mo (Figure) and in pts with CR, 46.2 (42.1-NE) mo (Table). Overall, 53% (95% CI, 0.47-0.58) and 45% (0.39-0.50) of pts were alive at 2 and 3 yrs. Median OS was 26.7 mo (Table). CR rate increased to 26.5% with 41 mo of follow-up. DOR was 55.7 mo in complete responders and 2 times longer with 1 vs >1 prior LOT (Table).
Grade ≥3 TEAEs occurred in 295 (79.7%) pts; events decreased over time after Yr 1. Cumulative incidence of any major hemorrhage was 7.3%; incidence of grade ≥3 atrial fibrillation was 5.9% and led to dose reductions in 2 (0.5%) pts and no discontinuations. Treatment-emergent SAEs occurred in 229 (61.9%) pts; SAEs decreased over time.

Conclusions : In this pooled analysis of IBR-treated R/R MCL pts with median 3.5 yrs of follow-up, clinical outcomes were best for pts who achieved a CR and those treated with IBR at first relapse/progression. Grade ≥3 AEs/SAEs decreased over time.

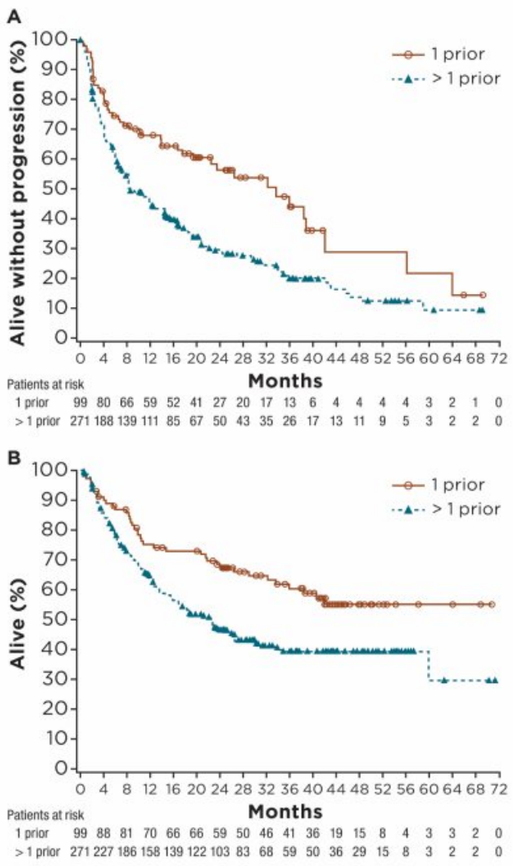
Keyword : Ibrutinib, Mantle cell lymphoma, Long-Term follow-Up

Table. PFS, OS, Clinical Responses, and DOR for Pooled Analysis Including CAN3001

End point	Overall (N = 370)	Prior lines of therapy		Best response		
		1 (n = 99)	> 1 (n = 271)	CR (n = 98)	PR (n = 160)	SD (n = 43)
PFS – months, median (95% CI)	13.0 (8.4-16.8)	33.6 (19.4-42.1)	8.4 (7.1-12.8)	46.2 (42.1-NE)	14.3 (10.4-17.5)	4.9 (3.5-6.3)
OS – months, median (95% CI)	26.7 (22.5-38.4)	NE (36.0-NE)	22.5 (16.2-26.7)	NE (59.9-NE)	26.2 (21.6-34.7)	10.0 (8.7-16.2)
ORR, n (%)	258 (69.7)	77 (77.8)	181 (66.8)			
CR	98 (26.5)	36 (36.4)	62 (22.9)	--	--	--
PR	160 (43.2)	41 (41.4)	119 (43.9)			
SD	43 (11.6)	11 (11.1)	32 (11.8)			
DOR[a] - months, median (95% CI)						
All responders	22.3[b] (16.5-28.8)	34.4[c] (23.1-NE)	16.0[g] (12.9-23.5)	--	--	--
CR	55.7[e] (55.7-NE)	55.7[f] (33.1-NE)	NE[g] (40.7-NE)			
PR	10.4[h] (7.7-14.9)	22.1[i] (10.6-34.4)	8.5[j] (6.2-12.1)			

CI, confidence interval; CR, complete response; DOR, duration of response; MCL, mantle cell lymphoma; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]Kaplan-Meier estimate; [b]n = 258; [c]n = 77; [d]n = 181; [e]n = 98; [f]n = 36; [g]n = 62; [h]n = 160; [i]n = 41; [j]n = 119.

Figure. Kaplan-Meier Plot of Progression-Free Survival (A) and Overall Survival (B) by Prior Line of Therapy



OP05-1

Clinical Significance of Secondary-Type Mutations in MDS and AML

Joon-Ho Moon[1], TaeHyung Kim[2], Jae-Sook Ahn[3], Yeo-Kyeoung Kim[3], Seung Hyun Choi[4], Ja-Yeon Lee[4], Yoo Jin Lee[1], Sang Kyun Sohn[1], Hyeoung-Joon Kim*[3], Zhaolei Zhang[2], Dennis (Dong Hwan) Kim[5]

[1] Hematology-Oncology, Kyungpook National University Hospital, Korea
[2] Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Canada
[3] Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea
[4] Genomic Research Center for Hematopoietic Diseases, Chonnam National University Hwasun Hospital, Korea
[5] Medical Oncology and Hematology, Princess Margaret Cancer Centre, Korea

Background : Secondary-type mutations (STMs; i.e. mutations in SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, or STAG2 genes) are known to be >95% specific for the diagnosis of secondary AML and predictive of clinical outcomes for patients treated with intensive chemotherapy. However, the clinical significance of secondary-type mutations in patients with AML or higher-risk myelodysplastic syndrome (MDS) treated with hypomethylating agent is largely unknown.

Methods : Sixty-four patients diagnosed with IPSS higher-risk MDS (n=28) and AML (n=36) treated with decitabine from 2010 May to 2016 Jan were included in the current study. Targeted deep sequencing was performed on the diagnostic samples using an Illumina 2000 sequencer on the 84 myeloid gene panels.

Results : Median age was 62 years (range 32-73) in MDS patients and 76 (range 68-85) in AML patients. Through targeted deep sequencing, we detected 194 were detected mutations in 60/64 (94%) patients at the time of diagnosis. DNMT3A (n=11, 17%), DDX41 (n=10, 15%), TET2 (n=9, 14%), NPM1 (n=8, 12%), and TP53 (n=8, 12%), U2AF1 (n=7, 11%), NRAS (n=7, 11%), and SETBP1 (n=7, 11%) were frequently mutated (> 10%). Secondary-type mutations were expressed in 50% (n=14/28) of MDS patients and in 36% (n=13/36) of AML patients. CR/mCR rate was 86% and 36% in MDS patients without and with secondary-type mutations, respectively (p=0.02). The presence of secondary-type mutations was found to be associated with less achievement of CR/mCR in MDS (OR 0.09, 95% CI 0.02-0.59, p=0.01), but not in AML.
The presence of secondary-type mutations affected adversely on overall survival (OS) (HR 5.70, 95% CI 1.34-24.22, p=0.02) as well as the presence of TP53 mutation (HR 7.68, 95% CI 1.73-34.07, p=0.01) and high-risk cytogenetics by IPSS (HR 8.75, 95% CI 1.10-69.86, p=0.04) in MDS patients. Non-relapse mortality was relatively higher in patients with secondary-type mutations in MDS patients (HR 3.79, 95% CI 0.84-17.2, p=0.08). However, the presence of secondary-type mutations was not significantly affected CR/CRi rates and OS in AML patients treated with decitabine.

Conclusions : The presence of secondary-type mutations affected adversely on the achievement of CR and long-term survival in MDS patients treated with decitabine. However, the presence of these mutations was not predictive factor for CR or OS in AML patients treated with decitabine.

Keyword : Myelodysplastic syndrome, Acute myeloid leukemia, Secondary type mutations, Hypomethylating agents, Decitabine

OP05-2

Comparable Outcomes of RIC to MAC-HCT by MRD Kinetics in Adults with Ph-Positive ALL in CR1

Jae-Ho Yoon, Gi June Min, Sung-Soo Park, Young-Woo Jeon, Sung-Eun Lee, Byung-Sik Cho, Ki-Seong Eom, Yoo-Jin Kim, Hee-Je Kim, Chang-Ki Min, Seok-Goo Cho, Dong-Wook Kim, Jong Wook Lee, Woo-Sung Min, Seok Lee*

Department of Hematology, Catholic BMT Center, Leukemia Research Institute, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Background : The use of tyrosine kinase inhibitor (TKI)-based chemotherapy has improved complete remission (CR) rates and increased applicability to allogeneic hematopoietic cell transplantation (HCT), thus allowing better survival in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL). However, the sensitivity of Ph-positive ALL to reduced-intensity conditioning (RIC) vs. myeloablative conditioning (MAC) by minimal residual disease (MRD) kinetics is not well established.

Methods : We analyzed195 adults (median age, 41 years [range, 16-65 years]) with Ph-positive ALL. All received allogeneic HCT (79 RIC [fludarabine and melphalan] and 116 MAC [total body irradiation and cyclophosphamide]) in CR1 following first-line TKI (161 imatinib and 34 dasatinib)-based chemotherapy and had data on prospectively determined quantitative MRD kinetics. MRD monitoring was centrally evaluated by real-time quantitative PCR (4.5 log sensitivity) through BM samples. Calcineurin inhibitors (cyclosporine for sibling donor transplants, tacrolimus for unrelated donor transplants) and methotrexate was used for GVHD prophylaxis and antithymocyte globulin (ATG) was administered to the patients who received mismatched unrelated donor grafts.

Results : After a median follow-up of 67.1 months (range, 15.0-183.5 months), RIC regimen showed comparable 5-year cumulative incidence of relapse (CIR; 30.6% vs 31.7%, P=0.848), non-relapse mortality (NRM; 17.5% vs 14.9%, P=0.472), disease-free survival (DFS; 51.9% vs 53.4%, P=0.692), and overall survival (OS; 61.1% vs 61.4%, P=0.843) compared to MAC. . Based on the MRD kinetics during the pre-HCT TKI-based chemotherapy courses, we classified patients into 5 subgroups: early-stable complete molecular responders (early CMR, n=32), early-stable major molecular responders (early MMR, n=39), late CMR (n=24), late MMR (n=52), and poor molecular responders (PMR, n=48). In all MRD-based subgroups of patients, no significant differences in CIR or DFS were observed between RIC and MAC. The presence of chronic GVHD and early molecular responders were associated with better DFS but old age and severe chronic GVHD was associated with higher NRM.

Conclusions : RIC-HCT showed comparable long-term outcomes to MAC-HCT in all MRD-based subgroups in patients with Ph-positive ALL in CR1 and is worthy of further investigation in prospective trials.

Keyword : Acute lymphoblastic leukemia, Hematopoietic cell transplantation, Reduced intensity conditioning

OP05-3

Comprehensive Analysis of Genetic Variations in Patients with Acute Lymphoblastic Leukemia

Borahm Kim[1], Saeam Shin[4], Jieun Jang[3], Soo Jeong Kim[3], Seung-Tae Lee[1], June-Won Cheong[3], Chuhl Joo Lyu[2], Yoo Hong Min[3], Jong rak Choi*[1]

[1] Department of Laboratory Medicine, Yonsei University College of Medicine, Korea
[2] Department of Pediatrics, Yonsei University College of Medicine, Korea
[3] Department of Internal Medicine, Yonsei University College of Medicine, Korea
[4] Department of Laboratory Medicine, Hallym University College of Medicine, Kangnam Sacred Heart Hospital, Korea

Background : Researches on genetic variations in patients with B-cell and T- cell acute lymphoblastic leukemia(ALL) are ongoing, but a comprehensive analysis of genetic variations including chromosomal and genic copy number variations is rarely reported.

Methods : We developed and applied next-generation sequencing (NGS)-based targeted gene panel and bioinformatics pipeline to profile the genetic changes in patients with acute lymphoblastic leukemia. We analyzed 185 genes in 87 patients with B-cell ALL(n=72) and T-cell ALL(n=15). Thirty five adults and 53 pediatric patients were included.

Results : Among 72 patients with B-ALL, 33 has chromosomal abnormality such as hyperdiploidy. A total of 197 genetic variants were detected and 149 of these were deletion or duplication of genes(75.6%). CDKN2A/B and IKZF1 genes were most frequently deleted. Among single nucleotide variants and small indels, those of TP53, RAS and PTPN11 were most frequently detected. Among 15 patients with T-cell ALL, variations in PTEN, PHF6 genes were frequently observed along with CDKN2A deletion. Deletions of genes indicating poor prognosis, such as IKZF1 and EBF1 deletion was more frequent in adult patients.

Conclusions : Using NGS-based gene panel which can assess copy number variations as well as sequence variations, genetic variations of lymphoblastic leukemia could be better understood. Further study would be needed to connect the genetic variations to the clinical outcomes.

Keyword : Acute lymphoblastic leukemia, NGs, Copy number variation

OP05-4

Molecular Scoring System Integrated with IPSS-R in Korean Myelodysplastic Syndrome

Hee Sue Park, Jeunseo Park, Kyongok Im, Sung-Min Kim, Jiwon Yun, Dajeong Jeong, Sang Mee Hwang, Dong-Yeop Sin, Sung-Soo Yoon, Lee Dong Soon*

Department of Laboratory Medicine, Seoul National University College of Medicine, Korea
Cancer Research Institute, Seoul National University College of Medicine, Korea
Department of Laboratory Medicine, Seoul National University Bundang Hospital, Korea
Department of Internal Medicine, Seoul National University College of Medicine, Korea

Background : Revised International Prognostic Scoring System (IPSS-R) is global prognostic system in myelodysplastic syndrome (MDS). Recently, multi-gene target sequencing is widely performed for the purpose of prognostic prediction and application of targeted therapy. In spite of many reports on the prognostic implication of somatic mutation, combined implication with conventional IPSS-R have not been reported yet. Here we proposed a new scoring system that encompass gene variations and IPSS-R together.

Methods : In 153 patients diagnosed with MDS in SNUH, G-banding, fluorescence in situ hybridization (FISH), targeted capture sequencing for 88 hematopoiesis-related genes, and measurement of telomere length (TL) were performed. K-M survival analysis and Cox proportional hazards regression analysis were used to develop a new prognostic system using Mathematica.

Results : We developed new model including targeted capture sequencing and telomere length addition to IPSS-R scoring. We calculated prognostic implication of genes with frequency over 5% or more (ASXL1, U2AF1, TP53, RUNX1, TET2, DNMT3A, SRSF2, BCOR, EZH2, SF3B1, STAG2, and WT1) and prognostic implication of TL. Patients with TL <5.58 showed an adverse survival. In univariate analysis, age, IPSS-R score, mutation in ASXL1, EZH2, TP53 and TL were significantly associated with OS. We developed a new scoring model incorporating the weighted coefficients of these variables: age x 0.017 + IPSS-R score x 0.220 + ASXL1mutation x 0.375 + EZH2 x 0.706 + TP53 x 0.897 + TL x 3.376. The age and IPSS-R score were used as a continuous variable. The presence of gene mutations and TL below 5.58 was scored as 1. According to this new scoring system, patients were divided into four groups: low score cutoff (≤5.44), intermediate-1 (5.44-5.98), intermediate-2 (5.98-7.30), high (>7.30). The median OS was 100.0, 49.7, 33.5, 10.6 months for low, intermediate-1, intermediate-2, and high, retrospectively (p<0.001). Meanwhile, according to conventional IPSS-R scoring system, the median OS was 97.2, 78.2, 79.1, 62.8, 33.7 months for very low, low, intermediate, high and very high, retrospectively (p <0.001).

Conclusions : The newly developed model incorporating molecular variations and TL yielded more clear separations of the survival curves. By adding the presence of gene mutation and telomere length to the existing IPSS-R, its predictive ability can be further improved in MDS.

Keyword : Myelodysplastic Syndrome, Revised International Prognostic Scoring System , Targeted Capture Sequencing, Telomere Length

OP06-1

Decitabine versus Intensive Chemotherapy for Induction Treatment of Elderly Patients with Acute Myeloid Leukemia

Eun-Ji Choi, Je-Hwan Lee*, Jung-Hee Lee, Han-Seung Park, Sun-Hye Ko, Miee Seol, Young-Shin Lee, Young-Ah Kang, Mijin Jeon, Ji Min Woo, Kyoo-Hyung Lee

Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea

Background : Elderly patients with acute myeloid leukemia (AML) has generally poor prognosis. Hypomethylating agents have shown potential in the treatment of AML as well as myelodysplastic syndrome (MDS). In this retrospective study, we compared the outcomes of elderly AML patients according to induction treatment options: decitabine versus intensive chemotherapy. We also tried to identify specific subsets of patients who are most likely to benefit from decitabine or intensive chemotherapy.

Methods : This study included elderly patients (65 years or older) who received induction treatment with decitabine or intensive chemotherapy for newly diagnosed AML between Dec 2013 and Dec 2017 at the Asan Medical Center, Seoul, Korea. Patients who had acute promyelocytic leukemia or blastic phase of chronic myeloid leukemia or those who had received hypomethylating therapy for MDS were excluded from this study. The endpoints for this study were overall survival (OS),response,and relapse-free survival (RFS). Response included complete remission (CR) and CR with incomplete hematologic recovery (CRi).

Results : A total of 101 patients, decitabine for 71 and intensive chemotherapy for 30, were analyzed. Decitabine was given as 20 mg/m2/day for 5 days every 4 weeks. Median 4 courses (range, 1-40) were delivered to the patients and 17 patients were still on decitabine treatment at the time of analysis. Intensive chemotherapy regimens included cytarabine plus daunoruribin (n=19) or idarubicin (n=10), and hyper-CVAD (n=1): 22 patientsreceived one course and 8 received two courses for induction treatment. The rate for CR + CRi (CRR) was 48.4% (46 of 95 assessable patients). With a median follow-up duration of 305 days (range, 21-1288) among surviving patients, 70 patients died and 28 relapsed. Median OS was 11.7 months and median RFS was 9.0 months. Decitabine showed lower CRR (30.8% vs. 86.7%, P<0.001), higher RFS (median 17.0 vs. 6.9 months, P=0.050), and similar OS (median 10.7 vs. 14.6 months, P=0.130) compared to intensive chemotherapy. Multivariate analysis demonstrated that induction treatment option and cytogenetic/molecular risk were independent risk factors for CRR, and presence of FLT3-ITD was for OS. Subgroup analysis for OS showed that intensive chemotherapy was superior to decitabine in patients with FLT3-ITD mutation, but decitabine was superior to intensive chemotherapy in those with monosomy 7 or del(7q).

Conclusions: Decitabine showed similar OS to intensive chemotherapydespite of lower response rate in elderly AML patients. Clinical outcomes of specific subgroups seemed to be different according to induction treatment options. Further studies are warranted for selection of optimal treatment options for elderly AML patients.

OP06-2

The Role of WT-1 as a Potential Marker to Predict Prognosis and Monitor Minimal Residual Disease

Seung-Hwan Shin[1], Sung-Soo Park[2], Young-Woo Jeon[2], Jae-Ho Yoon[2], Seung-Ah Yahng[3], Sung-Eun Lee[2], Ki-Seong Eom[2], Yoo-Jin Kim[2], Seok Lee[2], Hee-Je Kim[2], Chang-Ki Min[2], Seok-Goo Cho[2], Dong-Wook Kim[2], Jong-Wook Lee[2], Woo-Sung Min[2], Byung-Sik Cho*[2]

[1] Hematology, Yeouido St. Mary's Hospital, The Catholic University of Korea, Korea
[2] Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, Leukemia Research Institute, The Catholic University of Korea, Korea
[3] Hematology, Incheon St. Mary's Hospital, The Catholic University of Korea, Korea

Background : Although decitabine has been a standard of care for patients with elderly acute myeloid leukemia (eAML), the real-world outcomes and prognostic marker are scarcely investigated.

Methods : We analyzed the clinical outcomes of 81 eAML patients who received decitabine at our institution to explore significant prognostic factors. WT-1 and BAALC expression were measured by qRT-PCR to evaluate at diagnosis and monitor treatment response.

Results : The median age of patients was 73 (range, 64-86) years. Poor performance status (ECOG ≥ 2) and HCT-CI (≥ 3) were observed in 15 (18.5%) and 32 (39.5%) patients, respectively. In addition, 18 (22.2%) patients had adverse cytogenetic risk. Patients received median 5 cycles of decitabine (range, 1-28) and achieved best response after 4 (range, 2-26) cycles. The overall response (OR) and complete response (CR) rates were 51.4% (95% CI, 39.3-63.3) and 29.2% (95% CI, 19.0-41.1), respectively, with the median duration of response of 4.3 months (range, 0.4-24.2). The median overall survival (OS) of patients was 7.9 months (95% CI, 5.1-11.7). Patients and disease-related factors, including molecular profile, did not affect clinical outcomes, except significant effect of age for OS rate (≤ 75 vs > 75 yrs; 49.6% vs. 15.0% at 1 year; P = 0.02). The OS rates of patients achieved CR, partial + marrow response (PR + mR), and no response were significantly different (88.4%, 50.3%, and 7.4% at 1 year, respectively; P < 0.01).
Further analysis, using 49 patients who had WT-1 and BAALC qRT-PCR data at diagnosis and follow-up, showed that the high (≥ 3.5×10-1) WT-1 group showed a significantly higher OS rate compared that of the low (< 3.5×10-1) WT-1 group (48.4% vs. 22.5% at 1 year; P = 0.03), with relatively higher OR (61.5% vs. 39.1%; P = 0.20) and CR (38.5% vs. 17.4%; P = 0.19) rates. The WT-1 expression of patients who achieved CR also significantly decreased at the time of response compared to that at the diagnosis (5.1×10-1 to 0.2×10-1; P = 0.02). Whereas, there was no association between the BAALC expression and clinical outcomes, including OR, CR, and OS rates (P > 0.50).

Conclusions : Current study suggested that WT-1 could be used as a surrogate marker to predict prognosis and/or monitor minimal residual disease in eAML patients treated with decitabine. Also in the real-word setting, decitabine was also effective and tolerable in patients with eAML.

Keyword : Elderly acute myeloid leukemia, Decitabine, WT-1

OP06-3

Prognostic Factors in Children with Core Binding Factor Acute Myeloid Leukemia

Jae Wook Lee, Seongkoo Kim, Pil-Sang Jang, Nack-Gyun Chung, Bin Cho*, Kyung Eon Kim
Pediatrics, The Catholic University of Korea, Korea

Background : Core binding factor acute myeloid leukemia (CBF-AML) comprises leukemia with the AML1-ETO or CBFB-MYH11 genetic abnormalities, and has a favorable outcome. Our study aimed to determine the most important prognostic variables among an aggregate of clinical, genetic, and treatment response-based factors in pediatric CBF-AML.

Methods : The study cohort included 48 patients (17 female) who were diagnosed with and treated for CBF-AML at The Catholic University of Korea from April 2008 to December 2016. Median age at diagnosis was 9.4 years, and forty of the patients had AML1-ETO rearrangement (83%). Whole body magnetic resonance imaging (MRI) undertaken at diagnosis in all patients showed myeloid sarcoma (MS) in 15 patients (31%). KIT mutation was found in 16 patients (33%). Residual disease was checked by polymerase chain reaction (PCR)-based measurement of respective fusion transcript levels, and follow-up imaging for patients with MS.

Results : Of the 48 patients, 29 (60%) were treated with chemotherapy only while 19 (40%) received allogeneic hematopoietic cell transplantation (HCT) in first remission. MS at diagnosis, presence of KIT mutation, and less than -2.2log fusion transcript decrement after remission induction predicted lower event-free survival (EFS). However, only fusion transcript decrement proved significant in multivariate study, while the presence of MS at diagnosis showed borderline significance. Remnant MS after the first two courses of chemotherapy did not have a major impact on outcome. A separate sub-analysis according to treatment arm showed that fusion transcript decrement after remission induction was the only significant factor for EFS in the group treated with chemotherapy only. Analysis of the 40 AML1-ETO (+) patients also confirmed significance of MS at diagnosis, presence of KIT mutation, and fusion transcript decrement after remission induction. Multivariate study showed that both MS at diagnosis and lower fusion transcript decrement were significant predictors of worse outcome. The EFS of the 48 patients was 70.4±7%, and overall survival was 86.8±5.6%.

Conclusions : A comprehensive study of risk factors in pediatric CBF-AML showed that fusion transcript decrement after remission induction chemotherapy was the most important prognostic variable. The presence of MS at diagnosis resulted in worse outcome for AML1-ETO (+) patients.

Keyword : Core binding factor acute myeloid leukemia, Children, Fusion transcript, Myeloid sarcoma, KIT

OP06-4

Registry-Based Study of Hematopoietic Stem Cell Transplantation in Korean Children

Hee Young Ju[1,2], Young Ae Kim[2], Ji-Man Kang[1], Eun Jung Joo[3], Byung-Kiu Park[1], Hyeon Jin Park*[1]

[1] Center for Pediatric Cancer, National Cancer Center, Korea
[2] National Cancer Control Institute, National Cancer Center, Korea
[3] Department of Nursing, National Cancer Center, Korea

Background : Hematopoietic stem cell transplantation (HSCT) has become an established therapy for congenital and acquired disorders of the lymphoid and hematopoietic system, as well as for solid tumors, in children. To comprehend the trend and outcome of HSCT, we conducted the first national registry-based study of hematopoietic stem cell transplantation in Korean children.

Methods : Clinical data of 0-19 years old patients who underwent HSCT between 2006 and 2015 were extracted from Korean national health insurance service. Data about patients' diagnosis, gender, age at HSCT, number of HSCTs, type of HSCT donor, total body irradiation, follow-up duration, survival, and complications were collected.

Results : Total 3,602 times of HSCTs were done in 3,197 patients during the study period. Among these, 518, 9, 2 patients underwent HSCT for 2 times, 3 times, and 4 times, respectively. According to the type of HSCT donors, 1,542 of allogenetic peripheral stem cell transplantations (uPBSCT), 326 allogeneic bone marrow transplantations (uBMT), 298 cord blood transplantations (CBT), and 1,436 autologous stem cell transplantations (aHSCT) was done. Median age of HSCT was 11, 11, 5.5, 8 years for uPBSCT, uBMT, CBT, and aHSCT, respectively. When classified by disease categories, acute myeloid leukemia (AML) was the most common indication for HSCT (694, 22.68%), followed by acute lymphoblastic leukemia (ALL) (593, 19.38%), and aplastic anemia (AA) (428, 13.99%). AML was the most common indication for uPBSCTs (33.66%), ALL was the most common indication for CBT (34.06%), and AA was the most common indication for uBMT (30.79%). The trend showed increase of total HSCTs uPBSCT (11.9%/5yrs), stasis of aHSCT from 2011, decrease of uBMT (-38%/5yrs) and CBT (-17%/5yrs). Sinusoidal obstruction syndrome was detected in 249 patients (7.8%), and other transplant-related systemic endothelial diseases (including graft-versus-host disease, engraftment syndrome, post-transplant lymphoproliferative disorder) occurred in 1212 patients (37.9%).

Conclusions : Total 3,602 times of HSCTs were done in Korean children between 2006 and 2015. The trend showed increase of total HSCTs and uPBSCT, and decrease of CBT, similar with the children's data of international CIBMTR (center for international blood and marrow transplant research). In this study we could know the state and trend of HSCTs in Korean children.

Keyword : Hematopoietic stem cell transplantation, Children, Registries

OP07-1

The Clinical Outcomes of Lenalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma

Ho Sup Lee[1], Chang-Ki Min*[2], Kihyun Kim[3], Je-Jung Lee[4], Sung-Soo Yoon[5], Soo-Mee Bang[6], Jin Seok Kim[7], Hyeon-Seok Eom[8,] Dok Hyun Yoon[9], Yoojin Lee[10]

[1] Internal Medicine, Kosin University College of Medicine, Korea
[2] Internal Medicine, Seoul St. Mary's Hospital, Catholic University of Korea, Korea
[3] Internal Medicine, Samsung Medical Center, Sunkyunkwan University School of Medicine, Korea
[4] Internal Medicine, Chonnam National University Hwasun Hospital, Korea
[5] Internal Medicine, Seoul National University Hospital, Korea
[6] Internal Medicine, Seoul National University Hospital, Korea
[7] Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Korea
[8] Internal Medicine, National Cancer Center of Korea, Korea
[9] Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea
[10] Internal Medicine, Kyungpook National University Hospital, Korea

Background : Lenalidomide and dexamethasone (RD) is a standard of care for relapsed/refractory multiple myeloma (RRMM). The purpose of this study was to estimate efficacy and safety of RD chemotherapy in RRMM patients of the clinical practice.

Methods : Data from patients at 25 university hospitals in South Korea between October 2009 to December 2016 were collected retrospectively. Because this study included patients who received RD treatment in clinical situations and not in prospective clinical studies, many patients had renal impairment (ClCr < 30 ml/min; 10.4%), poor comorbidity conditions (≥2; 12.1%), and poor Eastern Cooperative Oncology Group performance status (≥2; 25.1%).

Results : The median age of the 538 patients was 65.4 years (range, 30 – 88). The male:female ratio was 1.2. 32.7% of all patients were treated with only one therapy prior to RD, and 67.3% were treated with more than one therapy prior to RD. The overall response rates (ORR; at least partial response) to treatment with RD was 64.9 % (n=349). The PFS and OS of all patients were 13.97 months (range 12.39 – 17.13) and 24.23 months (range 20.38 – 30.51), respectively. The differences in 2-year PFS and OS in patients who achieved VGPR or better versus patients who did not achieve VGPR were 58.4% versus 28.3% (p<0.001) and 68.6% versus 41.8% (p<0.001), respectively. The differences in 2-year PFS and OS in patients treated with RD for less than 10 cycles versus patients treated with 10 cycles or more were 22.8% versus 63.4% (p<0.001) and 31.6% versus 77.7% (p<0.001), respectively. In multivariate analysis, patients who achieved VGPR or better and treated with 10 cycles or more were shown significant prolonged survival (PFS; p=0.002 and p<0.001, OS; p=0.004 and p<0.001). This study presented acceptable adverse events.

Conclusions : RD is an effective and safe treatment in real clinical setting which includes patients with comorbidities. Early and continual use of RD improved survival, and achievement of rapid and good response after RD therapy may also improve survival outcomes in RRMM.

Keyword : Multiple myeloma, Lenalidomide plus dexamethasone, Efficacy, Survival, Real world evidence

OP07-2

Prognostic Significance of Clonal Evolution by Bone Marrow Cytogenetic Analysis in Multiple Myeloma

Chang Ahn Seol[1], Young-Uk Cho[1], Seongsoo Jang[1], Chan-Jeoung Park[1], Jung-Hee Lee[2], Dok Hyun Yoon[2], Jung Yong Hong[2], Cheolwon Suh[2], Eul-Ju Seo*[1]

[1] Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea
[2] Department of Internal Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea

Background : Risk stratifications for multiple myeloma (MM) patients are mainly based on primary cytogenetic analysis, which can be attenuated during long-term treatment. However, the data regarding subsequent cytogenetic abnormalities are lacking. We investigated the characteristics and prognostic significance of clonal evolution in MM patients with serial cytogenetic analysis.

Methods : A total of 107 MM patients were included in this study, who were re-evaluated with BM cytogenetic analysis during follow-up from January 2008 to March 2016. The median age at the time of diagnosis was 60 years (34-81). The median time between primary and secondary cytogenetic evaluation was 18 months (1-104). We reviewed the clinical and laboratory data and bone marrow (BM) cytogenetic findings. Cytogenetic analysis was performed by conventional karyotype and fluorescence in situ hybridization (FISH) analysis. FISH probes comprised CKS1B/CDKN2C, D13S319, 13q34, IGH/MAF (Cytocell, UK), IGH/FGFR3, IGH/CCND1 (Vysis, Abbott Molecular, USA), and TP53, CEP17 probes (MetaSystems, Germany). The patients were divided into the clonal evolution (CE) group and non-clonal evolution (non-CE) group for the analysis. Statistical analysis was performed using SPSS 19.0 (IBM, USA).

Results : Clonal evolution was present in 53 (49.5%) of 107 patients, comprising 1q gain (50.9%), 13/13q loss (30.2%), 17p loss (9.4%), 14q32 rearrangement with unknown partners (9.4%), 8q24 rearrangement (3.8%), trisomies (22.6%), and other structural aberrations (67.9%). Between the CE group and non-CE group, baseline characteristics including age, gender, International Staging System (ISS) and Revised ISS (R-ISS) stages, were not significantly different. The survival from the secondary cytogenetic evaluation was significantly shorter in the CE group compared to the non-CE group. 1q gain was significantly associated with poor prognosis.

Conclusions : Clonal evolution including 1q gain can be a key indicator for poor prognosis. When the patients were not reached to complete response or very good partial response after optimal treatment, the follow-up BM cytogenetic analysis is recommended to re-evaluate patient prognosis.

Keyword : Multiple myeloma, Cytogenetic abnormality, Clonal evolution, Prognosis

OP07-3

3-Methyladenine Potentiates Apoptosis of Myeloma Cells via Mitochondrial Reactive Oxygen Species

Yeung-Chul Mun[1], Jee-Young Ahn[1], Eun-Sun Yoo[2], Kyoung Eun Lee[1], Eunmi Nam[1], Soon Nam Lee[1], Hyun Ae Woo[3], Sue Goo Rhee[4], Chu Myong Seong*[1]

[1] Department of Hematology, Ewha Womans University, Korea
[2] Pediatrics, Ewha Womans University, Korea
[3] Graduate School of Pharmaceutical Sciences, Ewha Womans University, Korea
[4] Yonsei Biomedical Research Institute, Yonsei University, Korea

Background : Autophagy may play a pro-survival role cooperating with the ubiquitin proteasome system in maintaining myeloma cell's life by degrading misfolded proteins for energy recycling. Therefore, the inhibition of autophagy could effectively induce the death of myeloma cells, synergizing the killing of myeloma cells with proteasome inhibitors. In this study, we have investigated the mechanisms of myeloma cell death including close relationship among autophagy, mitochondrial reactive oxygen species (ROS) and redox enzymes induced by bortezomib (BTZ) treatment.

Methods : We evaluated the change of autophagy activities, apoptosis, mitochondrial ROS and cellular level of redox enzymes, especially peroxiredoxin (Prx), thioredoxin (Trx), thioredoxin reductase (Trx-R) in MM.1S and MM.1R, human myeloma cell lines with BTZ treatment. We have studied sulfinic acid (SO2) or multimeric form of Prx, Trx and Trx-R by western blot using non-reducing or reducing gel. We also treated Multiple Myeloma cells with 3-Methyladenine (3MA) autophagy inhibitor with and without BTZ.

Results : Apoptosis of MM cell after BTZ treatment was increased in concordance with mitochondrial ROS increment. 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, autophagy-related protein, 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 were reversed. Inhibition of autophagy with 3-Methyladenine (3-MA) resulted in synergistic increase in BTZ-induced apoptosis and mitochondrial ROS in MM cells.

Conclusions : Autophagy is induced during BTZ-induced MM cell apoptosis. Our experiment found the evidence of crosstalk among autophagy, mitochondrial ROS and redox enzymes 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 autophagy of myeloma cells during BTZ treatment showing the potential synergism on apoptosis with autophagy inhibitor for patients with multiple myeloma.

Keyword : Multiple Myeloma, Autophagy, ROS

OP07-4

The Safety and Efficacy of Pomalidomide in Combination with Cyclophosphamide and Dexamethasone (PCD)

Ho Sup Lee[1], Chang-Ki Min*[2], Kihyun Kim[3], Seok Jin Kim[3], Je-Jung Lee[4], Inho Kim[5], Sung-Soo Yoon[5], Jin Seok Kim[6], Hyeon-Seok Eom[7], Dok Hyun Yoon[8], Cheolwon Suh[8], Ho-Jin Shin[9], Yeung-Chul Mun[10]

[1] Internal Medicine, Kosin University College of Medicine, Korea
[2] Internal Medicine, Seoul St. Mary's Hospital, Catholic University of Korea, Korea
[3] Internal Medicine, Samsung Medical Center, Sunkyunkwan University School of Medicine, Korea
[4] Internal Medicine, Chonnam National University Hwasun Hospital, Korea
[5] Internal Medicine, Seoul National University Hospital, Korea
[6] Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Korea
[7] Internal Medicine, National Cancer Center of Korea, Korea
[8] Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea
[9] Internal Medicine, Pusan National University Hospital, Korea
[10] Internal Medicine, Ewha Womans University School of Medicine, Korea

Background : Patients who have relapsed MM after exposure to the above agents and have progressive disease have a short life expectancy. Tolerable third-line therapy is needed for retrieving elderly patients hereafter. Therefore, a clinical trial in which the efficacy and safety of the completely oral regimen, pomalidomide, cyclophosphamide and prednisone (PCD) were combined for treatment failure in both bortezomib and lenalidomide was conducted in Korea.

Methods : This clinical trials began in June 2015 and the study protocol was approved by the institutional review board of each participating fourteen hospital. The treatment scheme was pomalidomide 4mg day 1-21, dexamethasone 40mg once weekly and oral cyclophosphamide 400mg day 1, 8, 15. And then the dose of dexamethasone can be reduced when at least a minimal response is achieved after 3 months of treatment with the initial dose. Three months later (6 months after the initial treatment), the response remains in stable disease, second dose reduction (dexamethasone 10mg or prednisone 50mg) will be carried out. The first objective of the study is progression free survival (PFS), and the second is overall survival (OS), overall response rates (ORR), toxicities.

Results : This study is currently underway and 49 out of 55 target registered subjects (89%) are registered. During this time, 6 died, and 14 patients were discontinued due to progression of disease. Four patients had discontinued medication due to side effects, and three patients had withdrawal of consent and failed follow-up. Currently, 19 patients are taking clinical trial drugs. Six deaths were reported: 2 septic shocks, 1 heart failure, 1 colonic perforation, and 2 pneumonia. To date, the results of the intermediate response evaluation were confirmed as CR (10.4%), VGPR (8.3%), PR (37.5%) and MR (14.5%). The ORR including PR was 56.2% and the ORR including MR was 70.7%. The survival analysis results of this study have not yet been confirmed.

Conclusions : The phase 2 clinical trials are ongoing to confirm the efficacy and safety of PCD in relapsed and/or refractory MM. The results of the response evaluation and the survival analysis will be reported with the final analysis results after the completion of the further study.

Keyword : Multiple myeloma, Pomalidomide, Toxicity, Survival

OP08-1

Targeted NGS Identifies a Novel Nonsense Mutation in SPTB for Hereditary Spherocytosis

So Young Shin[1], Joon Hong Park*[1], Young Jun Yang[2]

[1] Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, Korea
[2] Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, Korea

Background : Hereditary spherocytosis (HS) is an inherited disorder characterized by the presence of sphericalshaped red blood cells (RBCs) on the peripheral blood (PB) smear. To date, a number of mutations in five genes have been identified and the mutations in SPTB gene account for about 20% patients.
A 65-year-old female had been diagnosed as hemolytic anemia 30 years ago, based on a history of persistent anemia and hyperbilirubinemia for several years. She received RBC transfusion several times and a cholecystectomy roughly 20 years ago before. Round, densely staining spherical-shaped erythrocytes (spherocytes) were frequently found on the PB smear, Numerous spherocytes were frequently found in the PB smears of symptomatic family members, her third son and his two descendants.

Methods : To confirm the genetic cause of HS, genetic testing using targeted NGS that consists of genes related anemia and bone marrow failure syndromes was performed in the proband. The gene panel included five HSassociated genes such as ANK1 (HS type 1, OMIM # 182900), SPTB (HS type 2, OMIM # 616649), SPTA1 (HS type 3, OMIM # 270970), SLC4A1 (HS type 4, OMIM # 612653), and EPB42 (HS type 5, OMIM #612690).

Results : One heterozygous mutation of SPTB was identified by targeted next-generation sequencing (NGS).
The nonsense mutation, c.1956G>A (p.Trp652*), in exon 13 was confirmed by Sanger sequencing and thus the proband was diagnosed with HS.

Conclusions : In summary, a novel nonsense mutation (p.Trp652*) in SPTB was identified using NGS in a Korean family affected by HS. Five known causative genes involving in RBC cytoskeleton formation are considered in HS.
Moreover, more than 20 genes are associated with hyperbilirubinemia and bilirubin metabolism. Thus, to discover the mutation causing the patient's clinical manifestations, both pedigree analysis and genetic testing are required simultaneously. We suggest that NGS of causative genes could be a useful diagnostic tool for the genetically heterogeneous RBC membrane disorders, especially in cases with a mild or atypical clinical manifestation.

Keyword : Targeted next-Generation sequencing, Nonsense mutation, SPTB gene

OP08-2

Mitochondrial Genomic Analysis in Patients with Myelodysplastic Syndromes and Other Myeloid Malignancies

Seon Young Kim[1,2], Yumi Park[1], Hyunjin Kim[1], Jinsook Lim[1], Jimyung Kim[1], Ik-Chan Song[3], Gye Cheol Kwon[1], Sun Hoe Koo[1]

[1] Department of Laboratory Medicine, Chungnam National University School of Medicine, Chungnam National University Hospital, Korea
[2] Cancer Research Institute, Chungnam National University School of Medicine, Korea
[3] Department of Internal Medicine, Chungnam National University School of Medicine, Chungnam National University Hospital, Korea

Background : Mitochondrial DNA (mtDNA) somatic mutation frequently occur in neoplasms. Because of heteroplasmy of mDNA, it is difficult to determine whether genetic variations in mtDNA occur as germline variants or truly somatic variant. Genetic abnormalities in nuclear DNA in myelodysplastic syndrome (MDS) and other myeloid malignancies are massively investigated. However, the molecular abnormalities in mtDNA in MDS and other myeloid malignancies have not been poorly revealed. In this study, we analysed full sequence of mtDNA using next generation sequencing (NGS) technique in patients with MDS or other myeloid malignancies to investigate possible variants in mtDNA in these patients.

Methods : We collected total DNA from bone marrow or peripheral blood samples with malignant cells in 36 patients with various myeloid malignancies [16 MDS, 7 acute myeloid leukemia (AML) without recurrent genetic abnormalities, 6 primrary myelofibrosis (PMF), 3 myelomomocytic leukemia (CMML), 2 atypical chronic myeloid leukemia (aCML), and 1 BCR-ABL1-positive chronic myeloid leukemia (CML)]. In addition, 43 patients with non-hematologic diseases are included as controls. Whole mitochondrial genomic sequencing was amplified, and NGS was performed by HiSeq 2000 (illumine). In addition, targeted sequencing using genomic DNA for 138 genes including well-known genes in MDS was also performed.

Results : We selected candidate mtDNA single nucleotide variants (mt-SNVs) according to the heteroplasmy levels of variants and filtering from reference database and control patients' results. We discarded small insertion or deletions from our analysis. When same selection criteria were applied in control samples, no candidate mt-SNVs were found except 1 known mutation in MELAS patients. We finally selected 62 candidate mt-SNVs in 25 patients (69.4%). The mt-SNVs were found similar frequencies in MT-CO3, MT-ND5, and MT-RNR2 (all n = 7). Among MDS patients, mt-SNVs in MT-RNR2 were most frequently found (4/10, 40%). Only 1 MDS patient had mt-SNVs in MT-CO3. Among patients having ASXL1 mutations and U2AF1 mutations, mt-SNVs in MT-ND4 were most frequent (5/13, 38.5%; and 3/6, 50.0%).

Conclusions : Our results suggested that somatic mtDNA may present different distiributions among disease subtypes of myeloid malignancies, which may give new insight on the pathogenesis of myeloid malignancies.

Keyword : Mitochondria, Myelodysplastic sydnrome, Somatic variants

OP08-3

Comprehensive Genomic Analyses of Core-Binding Factor AML from Serial Samples

Taehyung Kim[1,2], Joon Ho Moon[3], Jae-Sook Ahn[4,5], Marc S. Tyndel[2,6], Yeo-Kyeoung Kim[4,5], Seung-Shin Lee[4,5], Seo-Yeon Ahn[4,5], Sung-Hoon Jung[4,5], Deok-Hwan Yang[4,5], Je-Jung Lee[4,5], Seung Hyun Choi[5], Ja-Yeon Lee[5], Yoo Jin Lee[3], Sang Kyun Sohn[3], Yoo Hong Min[7], June-Won Cheong[7], Hyeoung-Joon Kim[4,5], Zhaolei Zhang[1,2,8], Dennis Dong Hwan Kim*[9]

[1] Department of Computer Science, University of Toronto, Canada
[2] The Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Canada
[3] Department of Hematology-Oncology, Kyungpook National University Hospital, Korea
[4] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea
[5] Genomic Research Center for Hematopoietic Diseases, Chonnam National University Hwasun Hospital, Korea
[6] The Edward S. Rogers Sr. Department of Electrical and Computer Engineering, University of Toronto, Canada
[7] Department of Internal Medicine, Yonsei University Hospital, Korea
[8] Department of Molecular Genetics, University of Toronto, Canada
[9] Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Canada

Background : Core-binding factor AML (CBF AML) is a subgroup of AML with favorable risk. Two subtypes of CBF-AML carry distinct chromosomal rearrangements, t(8;21)/RUNX1-RUNX1T1 and inv(16)/CBFB-MYH11. Although they are often grouped together, it has been shown that their morphologic and molecular features are distinct. This study aims to assess the value of longitudinal tracking using targeted sequencing in CBF-AML.

Methods : Eighty seven patients (pts) diagnosed with CBF AML were included (62 pts with RUNX1-RUNX1T1 and 25 pts with CBFB-MYH11. Using a custom gene panel targeting 84 genes, we performed targeted sequencing on in 357 samples using Illumina Hiseq 2500. Sequenced samples were taken at initial diagnosis (n=87), complete remission (CR) (n=53), and relapse (n=15). For diagnosis samples, T-cell (CD3+), CD34+/CD38- and CD34+/CD38+ fractions were sequenced as well. Average of on-target coverage was 1657.8x.

Results : We detected 166 mutations in 79 pts at time of diagnosis (90.8%). At diagnosis, KIT (40%), NRAS (34%), ASXL2 (14%), KRAS (13%), RAD21 (7%), and FLT3 (7%) were commonly mutated. When grouped by biological pathways, frequencies of mutations in RAS (KRAS or NRAS), cohesin complex and chromatin modifiers were significantly different among two sub-populations (p = 0.002, 0.01, and 0.02, respectively). Survival analyses show that KIT-D816 mutation is an adverse prognostic factor for overall survival (HR 2.31, p=0.04) and relapse (HR 2.76, p =0.04). Mutation in RAS was a favorable factor for relapse (HR 0.13, p=0.001). Multivariate analysis confirmed that only RAS mutation was a favorable factor for the incidence of relapse (HR 0.20, p=0.03).
We inferred mutation dynamics and clonal hierarchy from serial samples. Mean allelic burden at diagnosis and relapse were comparable (22.2% and 22.2%), whereas mutations were nearly cleared at CR (0.3%). Systematic analyses of serial samples revealed clonal mutations are more likely to be detected at relapse. Furthermore, integration of the RUNX1-RUNX1T1 levels and mutation dynamics showed RUNX1-RUNX1T1 is no later event than all targeted mutations, further explaining clonal hierarchies of CBF AML.

Conclusions : This study showed distinct mutation patterns between two subtypes of CBF AML. A Mutation in RAS was a favorable prognostic factor. Lastly, mutation profile combined with RUNX1-RUNX1T1 level elucidated the order of genetic mutation acquisition.

Keyword : AML, Next generation sequencing, Core binding factor

OP08-4

TET2 and MicroRNA-22 in Myelodysplastic Syndrome Patients who Received Hypomethylating Agents

Se Hyung Kim[1], Seong Kyu Park*[1], Sung Hee Kim[1], Jina Yun[1], Chan Kyu Kim[1], Kyung Ha Kim[2], Jong Ho Won[2], Dae Sik Hong[1]

[1] Division of Hemato-Oncology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Korea
[2] Division of Hemato-Oncology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Korea

Background : MicroRNAs are small RNA species that regulate gene expression post-transcriptionally and are aberrantly expressed in many cancers including hematological malignancies. Some reports suggested that aberrations in the miR-22-TET2 regulatory network are common in myelodysplastic syndrome (MDS) and leukemia, and its aberrant expression correlates with poor survival. We attempted to identify the clinical role of miR-22 and TET-2 in patients with myelodysplastic syndrome.

Methods : A total of 41 MDS patients who treated with hypomethylating agents were recruited. Real time RT-PCR was performed to assess the expression levels of miR-22 and TET-2 in bone marrow samples at the time of diagnosis. And we investigated the relationship between its results and clinical outcomes.

Results : TET2 expression in the higher risk group based the IPSS and IPSS-R was lower than that of lower risk group (higher risk: 0.024 ± 0.019 versus lower risk: 0.061 ± 0.047, $p < 0.05$). miR22 expression was also down-regulated in higher risk group. TET2 expression was significantly different according to the responsiveness to hypomethylating agents. TET2 and miR-22 expression seemed to be negatively associated with the risk of leukemic transformation without statistical significance. Lower expression of TET2 that was a value below the mean tended to be associated with poor survival outcome (survival rate at 3 years: 38.1% for lower expression versus 57.9% for higher expression, p=0.122). Other prognostic factors for survival included older age, higher risk group of IPSS or IPSS-R, leukemic transformation.

Conclusions : Down-regulation of TET2 protein was showed to be correlated with the responsiveness to hypomethylating agents and poor clinical outcomes. And TET2 and miR-22 expression might have a potential as a prognostic factor for MDS patients.

Keyword : Myelodysplastic syndrome, TET2, MicroRNA22, Hypomethylating agent

OP09-1

Evaluate the Effect of Imatinib in Treatment on Chronic Myeloid Leukemia in Children

Quoc Thanh Nguyen[1,2,3], Thi Kieu My Tran[3], Nghia Huynh[1,2]

[1] Hematology, University of Medicine and Pharmacy in Ho Chi Minh city , Vietnam
[2] 2nd Pediatric, Blood Transfusion and Hematology in Ho Chi Minh city, Vietnam
[3] Hematology, Ha Noi Medical University, Vietnam

Background : Chronic myeloid leukemia (CML) is relatively rare in children. There hasn't been any study of characteristics, treatment and prognostic of CML in children in Vietnam.

Methods : Review medical records to describe the epidemiologic, clinical and biologic features and to evaluate the effect of Imatinib therapy in 37 children with CML who were admitted to The Blood Transfusion and Hematology Hospital, Ho Chi Minh city from January 2006 to January 2011.

Results : The majority of affected children are more than 10 years old at diagnosis. A male to female ratio is approximately 1,0. About 90% of patients present in the chronic phrase. All of them have splenomegaly and other findings at presentation are anemia, leukocytosis and thrombocytosis affected in most children.
93,8% of patients have achieved a cytogenetic response and 71,8% of these have achieved a complete cytogenetic response after 36 months follow-up. The relapse straight into blast crisis and death occur in 13,5% and 8,1%, respectively. After 5 years follow-up, the event-free survival is 93% and the overall survival is 96% in the Imatinib-treated patients.
Several side effects including anemia, nausea, vomiting, rash, muscle cramps, bone pain are modest and acceptable.

Conclusions : Although CML is rare in children, its distinct features can easily lead a definite diagnosis. Response to Imatinib is extremely good, it is therefore appropriate for front-line therapy in children with CML and Ph-positive, especially in those who don't have conditions for allogeneic stem cell transplantation.

Keyword : Chronic myeloid leukemia, Children, Imatinib

OP09-2

Evaluation of 10-Year Imatinib's Treatment Effects on Chronic Myeloid Leukemia in Chronic Phase

Nguyen Phuong Dung Co[1,2], Quoc Thanh Nguyen[2,3], Thi My Hoa Nguyen[1,2], Chi Dung Phu[2]

[1] Hematology, Pham Ngoc Thach Medical University, Vietnam
[2] Hematology, Blood Transfusion and Hematology in Ho Chi Minh city, Vietnam
[3] Hematology, University of Medicine and Pharmacy in Ho Chi Minh city, Vietnam

Background : Chronic myeloid leukemia (CML) attributes 15% leukemia cases in adults. Only in 2014, there was 5,980 newly diagnosed cases in the United States, children and adults included, and 810 deaths among them.
The CML is characterized by the presence of BCR/ABL fusion gene, which results from the translocation of chromosomes 9 and 22. This mutation cause Philadelphia chromosome, encountered in 95% cases.
As a targeted therapy, IM inhibits the activity of tyrosine kinase of protein BCR-ABL, which leads to inhibition of cell proliferation and results in complete remission with regard to hematological, cytogenic and molecular response. Consequently, the disease is kept under control for a long time.
Having shown those advantages, IM has been adopted in many countries. In Vietnam, this therapy has been introduced to CML patients since 2005, primarily through the GPAP (Glivec International Patient Assistance Program).

Methods : Retrospective case series.

Results : 432 patients were included in the study.
All patients had hematological response in 3 months. After 10 years, the major cytogenetic response rate was 86.6%; the complete cytogenetic response rate was 81.1% and the complete molecular response rate was 56.5%.
The event-free-survival rate, the progression-free survival rate, and the overall survival were 78.3%, 89.6% and 89.4%, respectively. Prognostic factors for treatment results were complete cytogenetic and molecular response ($p < 0.05$).
The common side effects were thrombocytopenia, leukopenia, neutropenia, edema, weight gain, muscular pain, joint pain and aminotransferase elevation (> 10%). Side effects of Imatinib were mild to moderate.

Conclusions : Imatinib mesylate is remarkably effective for newly diagnosed patients with chronic myeloid leukemia.

Keyword : Chronic myeloid leukemia, Imatinib mesylate, Cytogenetic response

OP09-3

The Significance of Very Early Molecular Response with Frontline Dasatinib Treatment in CML Patients

Won-Sik Lee[1], Hyeong-Joon Kim[2], Dae Young Zang[3], Hawk Kim[4], Young Rok Do[5], Jae-Yong Kwak[6], Sukjoong Oh[7], Sung Hyun Kim[8], Jeong-A Kim[9], Sung-Eun Lee[10], Dong-Wook Kim*[10]

[1] Department of Internal Medicine, Inje University Busan Paik Hospital, Korea
[2] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea
[3] Department of Internal Medicine, Hallym University College of Medicine, Hallym University Hospital, Korea
[4] Department of Hematology, University of Ulsan College of Medicine, Ulsan University Hospital, Korea
[5] Division of Hematology-Oncology, Keimyung University, School of Medicine, Keimyung University Hospital, Korea
[6] Division of Hematology-Oncology, Chonbuk National University Medical School, Chonbuk National University Hospital, Korea
[7] Division of Hematology-Oncology, Department of Internal Medicine, Sungkyunkwan University, Kangbuk Samsung Hospital, Korea
[8] Department of Internal Medicine, Dong-A University College of Medicine, Dong-A University Hospital, Korea
[9] Department of Hematology, The Catholic University of Korea, St. Vincent's Hospital, Korea
[10] Department of Hematology, Seoul St. Mary's Hospital, Leukemia Research Institute, The Catholic University of Korea, Korea

Background : In BCR-ABL1 tyrosine kinase inhibitor (TKI) treated chron
ic phase chronic myeloid leukemia (CP-CML), early molecular response (EMR) at 3 month is currently identified as being one of the most important prognostic factors. As dasatinib is a novel, oral tyrosine kinase inhibitor with improved potency, identification of very early molecular response (VEMR) would be beneficial.We evaluated the possibility of the VEMR at 1 month predicting long-term outcomes in newly diagnosed CP-CML patients treated with dasatinib.

Methods : In this multi-center, observational, open-label study, 102 patients with CP-CML were enrolled to receive dasatinib at a dose of 100 mg once daily. The primary end point was complete molecular response (CMR) by 18 months. Secondary end points including molecular response (MR) by 1, 3, 6, 12, 18, 24 month, time to and duration of MMR and CMR, and safety were tested. A receiver operating characteristic (ROC) curve from BCR-ABL1 transcript level on Day+28 was calculated to predict EMR and MMR at specific timepoints.

Results : Median age was 49 years (19-81 years) and 61 patients were male. With median follow-up duration of 28 months (0.9-33.8 months), 80 (78.4%) out of 102 patients were still on dasatinib treatment and 22 patients discontinued. The cumulative CMR by 18 months and MMR by 24 months were 20.5% and 79.6% respectively. The cut-off value of BCR-ABL1 transcript on Day+28 was 40% by ROC curve analysis. Among 95 patients who had available molecular data of both D+28 and 12 months, fifty nine (62.1%) patients had less than 40% of BCR-ABL1 transcript (VEMR) on Day+28. Among them, 49 (83.1%) patients achieved MMR at 12 months. However, only 27.8% (10 out of 36 patients) of patients without VEMR achieved MMR ($p<0.0001$). Overall survival (OS) & progression-free survival (PFS) rates were 98.0% and 95.1%, respectively. PFS rates for VEMR and no VEMR group were 98.4% vs. 88.8% respectively ($p=0.04$). More detailed data will be updated.

Conclusions : Our study shows that VEMR at 1 month can be a strong predictor for further molecular responses as well as long-term outcome. Therefore, it would be helpful to monitor BCR-ABL1 transcript level at 1 month in patients who treated with more potent TKIs.

Keyword : CML, Dasatinib, Very early molecular response

OP09-4

Deeper Molecular Response in Newly Diagnosed CML-CP Patients Receiving Radotinib: RERISE 3 Years FU

Youngrok Do, Jae-Yong Kwak, Jeong-A Kim, Hyeoung Joon Kim, Joon Seong Park, Sung-Hyun Kim, Dae Young Zang, Suk Joong Oh, Won Sik Lee, Dong-Wook Kim*

Department of Hematology and Oncology, Department of Medicine, Dongsan Medical Center, Keimyung University, Korea

Background : In RERISE phase 3 study, radotinib demonstrated significantly higher and faster rates of MMR than imatinib in patients with newly diagnosed CML-CP. By 12 and 24 months follow up, MMR and MR4.5 in radotinib 300 mg bid were higher than imatinib group. Also, EMR at 3- or 6- months could predict better outcomes in both radotinib or imatinib groups. To confirm the long-term benefits and risks of radotinib 300mg bid and imatinib 400mg qd, we update the results from RERISE phase 3 study based on a minimum follow-up of 36 months.

Methods : 241 patients were randomized 1:1:1 to radotinib 300 mg bid (n=79), radotinib 400 mg bid (n=81), or imatinib 400 mg once daily (qd) (n=81). Methods have been previously reported. We evaluated MMR, MR4.5, OS, and PFS by 36 months. Also, we analyzed the clinical impacts of early and deeper molecular response in radotinib and imatinib groups.

Results : By 36 months, MMR was significantly higher in patients receiving radotinib 300 mg bid compared with imatinib 400mg qd. The MR4.5 rate by 36 months was also higher for radotinib compared to imatinib (43% vs 28%; P=0.0538). More patients treated with radotinib achieved additional MMR and MR4.5 since 12 months and time to MR4.5 was faster in radotinib than imatinib (median 924 vs 1,095 days; P=0.2534). Of 59 patients who had MMR by 36 months, 18 patients achieved MMR, and of 34 patients who had MR4.5 by 36 months, 22 patients achieved MR4.5 since 12 months. Estimated OS and PFS rate at 36 months were not significantly different in two groups (98% vs 97%; P=0.0554, 99% vs 95%; P=0.4707). Treatment failure was lower in radotinib group compared with imatinib group. The safety profiles were consistent with those previously reported and most of AEs have developed within 12 months. Since 12 months, newly developed AEs such as rash, nausea/vomiting, pruritis, musculoskeletal pain, fatigue, hyperbilirubinemia, and ALT elevation, etc have shown minimal increase by 36 months FU.

Conclusions : With a 36 months follow-up, radotinib continued to demonstrate significantly higher rates of MMR and MR4.5 than imatinib in newly diagnosed CML-CP. Also, these responses with radotinib were earlier and deeper compared with imatinib. These results still demonstrate that radotinib can be one of the standards of care in newly diagnosed CML-CP and support the higher possibility of treatment- free remission (TFR) on frontline therapy.

Keyword : Radotinib, Frontline, CML, Imatinib

OP10-1

Gene Spectrum Analysis of Thalassemia Carriers Residing in Northern China

Wenzhe Zhou[1], Zhuo Yang[2], Quexuan Cui[1], Ling Qiu2, Bing Han*[1]

[1] Department of Hematology, Peking Union Medical Collage, Chinese Academe of Medical Science, China
[2] Department of clinical laboratory, Peking Union Medical Collage, Chinese Academe of Medical Science, China

Background : Thalassemia is one of the most pervasive monogenic diseases worldwide. The high frequency of this inherited hemoglobin variants is present in the area extending from sub-Saharan Africa to the Indian subcontinent and east and southeast Asia, especially the Mediterranean region. In China, southern provinces were known as high incidence areas of thalassemia. But thalassemia is now becoming increasingly common in northern China because of continued migration.

Methods : 1059 positive carriers were analyzed from 2136 suspected α and β-thalassemia carriers who were referred to Peking Union Medical College Hospital from 2012 to 2017, for diagnosis. Gap-PCR and RDB (reverse dot blot) analysis were applied for detections of common α and β-thalassemia gene mutations. Telephone follow-up survey was conducted on their ancestral information, to confirm whether these carriers residing in northern China have southern lineage.

Results : Mutation analysis was performed on all carriers. The α mutations account for 27.2% of the all northern thalassemia genes with 72.8% β mutations, while The percentage of α and β mutations in southern China were 37.6% and 62.4%, these two proportions were significantly different (P =0.001) by $\chi 2$ test. Analysis of the individual gene distribution of the south and north did not show significant difference either in α-thalassemia (P=0.221) or β-thalassemia (P=0.979).
We found that differences between gene distributions in provinces with similar average altitudes were relatively small. So we classified the 28 provinces according to their average altitude to explore the relationship between the gene distribution and the altitude. No significant statistical differences in the frequency of α mutation were found in different altitude levels. While in β thalassemia, the frequency of 6 most common mutations were significantly different by $\chi 2$ test ($P < 0.05$) in provinces with altitude below 500 meters, to above 1500 meters, and to about 500-1500 meters.

Conclusions : Chinese People with north lineage may have has higher frequency of α mutation than those originated from the south, while in both north and south China, the spectrum of α and β mutations may have no significant difference. People originate from regions with different level of altitudes may have different spectrum of β mutations.

Keyword : Thalassemia, Gene mutation, China, Spectrum, Altitude

OP10-2

Comparison of Gene Spectrum of Thalassemia in Northern, Southern China and Southeast Asia

Quexuan Cui[1], Zhuo Yang[2], Wenzhe Zhou[1], Ling Qiu[2], Bing Han*[1]

[1] Department of Hematology, Peking Union Medical Collage Hospital, Chinese Academe of Medical Science, China
[2] Department of clinical laboratory, Peking Union Medical Collage Hospital, Chinese Academe of Medical Science, China

Background : Thalassemia is a common genetic disorder. The high prevalence of thalassemia is found in South China, Southeast Asia, India, Middle East, African and Mediterranean area. Usually, thalassemia is thought to be found only in southern China, but increasing number of patients in northern China were found recently. Peking Union Medical Collage hospital is the only center to detect thalassemia gene mutations in northern China.

Methods : People who were suspected to carry thalassemia mutations in Peking Union Medical College Hospital from 2012 to 2017 were detected for common α and β-thalassemia gene mutations by gap-PCR and reverse dot blot (RDB) analysis. 1059 people with thalassemia mutations were analyzed retrospectively. With the help of hospital information system, we picked individuals with northern identity card numbers and conducted telephone follow-up survey in order to collect their ancestral information. We used 'thalassemia', 'mutation' 'Chinese' and southeast Asian countries as keywords to search potential related studies.

Results : All carriers include in our study reside in northern China. 17.3% were northern China origin according the ancestral information and 82.7% were identified to be the immigrant of southern China. Northern group had low percentage of α-thalassemia (49/191, 25.7%) compared to Southern group (356/915, 38.9%, P=0.001). Analysis of the individual gene distribution of the south and north did not show significant difference either in α-thalassemia or β-thalassemia, so we took south and north data together as a whole to compare them with the largest gene mutation meta-analysis data reported in China and in Southeast Asia. The distribution of α-thalassemia alleles were similar in northern and southern China. However, β-thalassemia gene spectrum were diverse in different regions. Besides, for β-thalassemia, similar gene mutation spectrum were found between Malaysia Chinese and Guangdong people, while other ethnic people in Malaysia, people in Indonesia and Thailand had totally different gene spectrum from that of Chinese people.

Conclusions : Chinese People originated from north may have lower percentage of α-thalassemia alleles compared to those originated from the south. Chinese people in different areas had similar gene mutation profile but Chinese people had large gene mutation distribution difference compared to other ethnic people in Southeast Asia.

Keyword : Thalassemia, Gene mutation, China, Southeast Asia

OP10-3

ThalPred: A Web-Based Decision Making Tool for Discriminating Thalassemia Trait and Iron Deficiency

Vishuda Laengsri[1], Watshara Shoombuatong[2], Warina Adirojananon[1], Chanin Nantasenamart[2], Virapong Prachayasittikul[2], Pornlada Nuchnoi[1]

[1] Department of Clinical Microscopy, Faculty of Medical Technology, Mahidol University, Thailand
[2] Center of Data Mining & Medical Informatics, , Faculty of Medical Technology, Mahidol University, Thailand

Background : The hypochromic microcytic anemia (HMA) commonly found in Southeast Asian are iron deficiency anemia (IDA) and thalassemia trait (TT). The high similarity of hematological laboratory results between TT and IDA with cost consuming for further special test such as hemoglobin typing and serum ferritin test. Accurate discrimination between IDA and TT is an important issue and better methods are urgently needed. Although considerable RBC formulas and indices with various optimal cut-off values have been developed, distinguishing between IDA and TT is still a challenging problem due to the diversity of various anemic populations. To address this problem, it is desirable to develop an improved and automated prediction model for discriminating IDA from TT.

Methods : We retrospectively collected laboratory data of HMA found in Thai adults. Three machine learnings, including decision tree, random forest (RF) and support vector machine (SVM), were applied to construct a discriminant model. Performance was assessed and compared with thirteen existing discriminant formulas and indices.

Results : The data of 186 patients (146 patients with TT and 40 with IDA) were enrolled. The interpretable rules derived from the RF model were proposed to demonstrate the combination of RBC indices for discriminating IDA from TT. A web-based tool 'ThalPred' was implemented using an SVM model based on seven RBC parameters. ThalPred achieved prediction results with an external accuracy, MCC and AUC of 95.59, 0.87 and 0.98, respectively.

Conclusions : ThalPred and an interpretable rule were provided for distinguishing IDA from TT. For the convenience of health care team, a web-based tool has been established at http://codes.bio/thalpred/ by which users can easily get their desired screening test result without the need to go through the underlying mathematical and computational details.

Keyword : Thalassemia Trait, Iron Deficiency Anemia, Discrimination Model, Laboratory Hematology, Laboratory Analytics, Artificial Intelligence

OP10-4

Epidemiology of Hereditary Hemolytic Anemia for 10 Years (2007-2016): RBC Disorder WP Study

Ye Jee Shim[1], Hye Lim Jung[2], Hee Won Chueh[3], Jin Yeong Han[3], Eu Jeen Yang[4], Young Tak Lim[4], Jae Min Lee[5], Ji Won Lee[6], Keon Hee Yoo[6], Hee Jo Baek[7], Hoon Kook[7], Hyun Joo Jung[8], Jun Eun Park[8], Eun Sil Park[9], Jae Young Lim[9], Seongkoo Kim[10], Jae Wook Lee[10], Nack-Gyun Chung[10], Bin Cho[10]

[1] Pediatrics, Keimyung University School of Medicine and Dongsan Medical Center, Korea
[2] Pediatrics, Sungkyunkwan University Kangbuk Samsung Hospital, Korea
[3] Pediatrics, Laboratory Medicine, Dong-A University College of Medicine, Korea
[4] Pediatrics, Pusan National University Children's Hospital, Korea
[5] Pediatrics, Yeungnam University College of Medicine, Korea
[6] Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[7] Pediatrics, Chonnam National University Hwasoon Hospital, Chonnam National University Medical School, Korea
[8] Pediatrics, Ajou University School of Medicine, Korea
[9] Pediatrics, Gyeongsang National University College of Medicine, Korea
[10] Pediatrics, The Catholic University of Korea Seoul St. Mary's Hospital, Korea

Background : Hereditary hemolytic anemia (HHA) occurs when the red blood cells (RBCs) are destroyed earlier than normal lifespan and removed from the circulating blood. HHA is generally classified as RBC membranopathies, hemoglobinopathies, and RBC enzymopathies, depending on the etiology. Recently, more accurate confirmation of HHA is possible by improving diagnostic techniques.

Methods : Patient information, clinical manifestations, and laboratory findings of Korean HHA patients from 2007 to 2016 were retrospectively collected using a survey questionnaire.

Results : Initially, a total of 363 cases were collected from the 33 hospitals. Among them, 9 duplicated patients, 2 AIHA, 1 PNH, 1 MDS, and 1 CDA were excluded. Finally, 349 HHA patients (male : female = 198 : 151) were investigated. RBC membranopathies were 253 (72.5%), hemoglobinopathies were 52 (14.9%), RBC enzymopathies were 21 (6.0%), and unknown etiology were 23 (6.6%). In RBC membranopathies, 242 patients were hereditary spherocytosis, 11 were hereditary eliptocytosis, and 112 had family history of HHA. Fifty-one HS patients were confirmed by genetic test; SPTB gene mutation was most common (23/51, 45.1%), and ANK1 gene mutation was the second (17/51, 33.3%). In hemoglobinopathies, 21 patients' mother were foreigner (12 Vietnam, 4 Cambodia, 1 China, 1 Thailand, 1 Singapore, 1 Venezuela, and 1 unknown) and 17 patients had family history of HHA. The 28 hemoglobinopathies were confirmed by genetic test; β-thalassemia minor 20, α-thalassemia minor 7, and unstable hemoglobin disease 1. In RBC enzymopathies, 1 patient was a foreigner (father from France and mother from Mauritius) and 1 patient' mother was a foreigner (Canada). Five patients had family history of HHA. Eighteen enzymopathies were confirmed by genetic or enzyme level test; 12 pyruvate kinase deficiencies, 5 glucose-6-phosphate dehydrogenase deficiencies, and 1 enolase deficiency.

Conclusions : The number of subjects with hemoglobinopathies or RBC enzymopathies are significantly increasing compare to the previous report, 1997-2006. As international marriages are increases, thalassemia traits are increasing. The increasing recognition of RBC enzymopathies is probably due to the development of diagnostic techniques, including genetic analysis. However, more accessible and accurate assays for the identification of unknown origin HHA are necessary.

Keyword : Nonimmune hemolytic anemia, Congenital hemolytic anemia, Hereditary spherocytosis, Thalassemia, Enzymopathy, Hemoglobinopathy

OP11-1

Nutritional Iron Deficiency Anemia: Magnitude and Its Predictors among School Age Children, Southwest, Ethiopia

Amare Desalegn Wolide
Biomedical Sciences, Hematology, Jimma University, Ethiopia

Background : Iron deficiency anemia (IDA) is a global public health problem among school age children, which retards psychomotor development and impairs cognitive performance. There is limited data on prevalence and risk factors for IDA.The aim of this study was to determine the prevalence, severity, and predictors of nutritional IDA in school age children in Southwest Ethiopia.

Methods : A community based cross-sectional study was conducted in Jimma Town, Southwest Ethiopia from April to July 2013. A total of 616 school children aged 6 to 12 years were included in the study using multistage sampling technique. A structured questionnaire was used to collect sociodemographic data. Five milliliter venous blood was collected from each child for hematological examinations. Anemia was defined as a hemoglobin level lower than 11.5 g/dl and 12 g/dl for age group of 5–11 years and 12–15 years, respectively. Iron deficiency anemia was defined when serum iron and ferritin levels are below 10 µmol/l and 15 µg/dl, respectively. Moreover, fresh stool specimen was collected for diagnosis of intestinal parasitic infection. Stained thick and thin blood films were examined for detection of Plasmodium infection and study of red blood cell morphology. Dietary patterns of the study subjects were assessed using food frequency questionnaire and anthropometric measurements were done. Data were analyzed using SPSS V-20.0 for windows.

Results : Overall, prevalence of anemia was 43.7%, and that of IDA was 37.4%. Not-consuming protein source foods [AOR=2.30, 95%CI(1.04,5.14)], not-consuming dairy products [AOR=1.83, 95%CI(1.14,5.14)], not-consuming discretionary calories [AOR=2.77, 95%CI(1.42,5.40)], low family income [AOR=6.14, 95%CI(2.90,12.9)] and intestinal parasitic infections [AOR=1.45, 95%CI(1.23, 5. 27)] were predictors of IDA.

Conclusions : Iron deficiency anemia is a moderate public health problem in the study site. Dietary deficiencies and intestinal parasitic infections were predictors of IDA. Therefore, emphasis should be given to the strategies for the prevention of risk factors for IDA

Keyword : Iron deficiency anemia , Anemia , Children

OP11-2

Prevalence of Inherited Hemoglobin Disorders and Relationships with Anemia and Micronutrient Status

Reina Engle-Stone*[1], Thomas N. Williams[2], Martin Nankap[3], Alex Ndjebayi[3], Yannick Oyono[4], Kenneth H. Brown[1,5]

[1] Department of Nutrition, University of California, United States
[2] KEMRI/Wellcome Trust Research Programme, KEMRI/Wellcome Trust Research Programme, Kenya
[3] Helen Keller International, Cameroon
[4] Medical Labortory Sciences, University of Buea, Cameroon / Centre Pasteur, Cameroon
[5] Department of Medical Pathology and Laboratory Medicine, UC Davis Medical Center, United States

Background : Information on the etiology of anemia is necessary to design effective anemia control programs. Our objective was to measure the prevalence of inherited hemoglobin disorders (IHD) in a representative sample of children in urban Cameroon, and examine the relationships between IHD and anemia.

Methods : In a cluster survey of children 12–59 months of age (n = 291) in Yaoundé and Douala, we assessed hemoglobin (Hb), malaria infection, and plasma indicators of inflammation and micronutrient status. Hb S was detected by HPLC, and ß+thalassemia (3.7 kb deletions) by PCR.

Results : Anemia (Hb < 110 g/L), inflammation, and malaria were present in 45%, 46%, and 8% of children. A total of 13.7% of children had HbAS, 1.6% had HbSS, and 30.6% and 3.1% had heterozygous and homozygous ß+thalassemia. The prevalence of anemia was greater among HbAS compared to HbAA children (60.3 vs. 42.0%, p = 0.038), although mean Hb concentrations did not differ, p = 0.38). Hb and anemia prevalence did not differ among children with or without single gene deletion ß+thalassemia. In multi-variable models, anemia was independently predicted by HbAS, HbSS, malaria, iron deficiency (ID; inflammation-adjusted ferritin <12 _g/L), higher C-reactive protein, lower plasma folate, and younger age.

Conclusions : Elevated soluble transferrin receptor concentration (>8.3 mg/L) was associated with younger age, malaria, greater mean reticulocyte counts, inflammation, HbSS genotype, and ID. IHD are prevalent but contribute modestly to anemia among children in urban Cameroon.

Keyword : Anemia, Hemoglobinopathy, Iron

OP11-3

Impact of Thrombocytopenia on In-Hospital Outcome in Patients with Acute STEMI

Ru Liu, Jingang Yang, Sida Jia, Yueyang Wu, Zhan Gao, Jue Chen, Lijian Gao, Lei Song, Yin Zhang, Xueyan Zhao, Shubin Qiao, Runlin Gao, Jinqing Yuan, Yuejin Yang*

Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, China

Background : Controversies exist on how thrombocytopenia (TP) effects in-hospital outcome of acute ST-segment elevated myocardial infarction (STEMI) patients.

Methods : A total of 16678 consecutive cases with STEMI from January 2013 to September 2014 at 108 hospitals that participated in the China Acute Myocardial Infarction (CAMI) registry were included. In-hospital outcomes were compared between patients with TP and those with normal platelet count, patients with mild TP and those with moderate/severe TP.

Results : There were 359 patients with baseline TP, accounted for 2.2% of total cohort. Compared with group with normal platelet count, the risk of in-hospital death (11.1% and 6.0%, P < 0.001), MACE (33.4% and 22.1%, P < 0.001) and bleeding (3.6% and 1.8%, P = 0.024) were significantly higher in group with TP. Patients with moderate/severe TP were associated with higher risk of in-hospital death (21.6% and 9.4%, P = 0.019) than patients with mild TP, while bleeding risk was similar between 2 groups (5.9% and 3.3%, P = 0.409). After multivariate adjustment, TP was an independent predictor of MACE (OR: 1.30; 95%CI: 1.01-1.67), but no independently associated with bleeding (OR: 1.44; 95%CI: 0.80-2.60), compared with patients with normal platelet count.

Conclusions : TP is independently associated with MACE in STEMI patients, but not independent predictor of bleeding during admission.

Keyword : Acute ST-Segment elevated myocardial infarction, Thrombocytopenia, In-Hospital death

OP11-4

Important Factors to Increase the Survival in Hemophilia Patient with Life-Threatening Hemorrhage

Kun Soo Lee, Ji Yoon Kim
Department of Pediatrics, Kyungpook National University School of Medicine, Korea

Background : Because the incidence and severity of intracranial hemorrhage (ICH) is closely and mainly related with the severity of disease, basic knowledge about hemophilia, rapid transportation to ER, quickly infusion of factor concentration at ER for surgery before history taking, blood examination and radiologic evaluation and maintenance of optimal blood factor level are very important to save the life and to minimize the sequelae.

Methods : Our regional patients to take care are 226 of 2,354 registered in Korea Hemophilia Foundation (2016). Annual routine examination including recovery test, home treatment, on-demand treatment and prophylactic treatment for severe type are recommended. Education and hot-line communication for emergency had been permitted for more than 30 years. We recalculated the dose based on the personal recovery rate for surgery case. To keep in vitro activity of concentrate for continuous infusion we freshly reconstitute lyophilized powder every 2-4 hour.

Results : All patients and parents were in good response with our education program and with routine examination including the recovery rate every year. They were in full satisfaction for hot-line communication with me in emergency. With hot-line communication we were always ready to infuse the calculate dose of concentrate before he were arriving at ER. In recovery test for 13 patients, 4 patients had results less than 80% at 15, 30 and 60 minutes. The consumption of factor VIII concentrates and hospitalization day in 22 patients whose recovery rate more than 80% or 100% with recalculated dose (A) were smaller dose and shorter day than in 5 patients whose recovery rate less than 80% but no adding dose because of late result (C). (A:C, $p<0.01$ and A:C, $p=0.015$). The in vitro activity after mixing concentrate was decreased in 5% for every 4 hours with 30% at 24 hours in 3 drugs uniformly.

Conclusions : Introducing our unique policy for handling hemophilia patients for more than 30 years, hot-line communication and optimal blood factor concentration are very important to minimize the sequelae of life threatening hemorrhage.

Keyword : Hemophilia, Life-Threatening hemorrhage

OP12-1

Comparison of Outcomes between Unrelated Donor and Haploidentical Transplantation in Aplastic Anemia

Sung-Eun Lee, Gi June Min, Sung Soo Park, Young-Woo Jeon, Jae-Ho Yoon, Byung-Sik Cho, Ki-Sung Eom, Yoo-Jin Kim, Seok Lee, Chang-Ki Min, Hee-Je Kim, Seok-Goo Cho, Dong-Wook Kim, Woo-Sung Min, Jong Wook Lee*
Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Background : We evaluated the clinical outcomes of haploidentical stem cell transplantation (h-SCT) compared with those of unrelated SCT (u-SCT) in adult patients with severe aplastic anemia (SAA).

Methods : Sixty-eight consecutive adult patients with SAA underwent SCT (37 h-SCT, 31 u-SCT) between June 2012 and May 2017. The conditioning regimen for u-SCT consisted of TBI (fractionated, 800~600 cGy) + cyclophosphamide (100 mg/kg) + ATG (2.5 mg/kg), and for h-SCT, we have optimized a dose of ATG (from 10 to 5 mg/kg) and TBI (from 800 to 600 cGy) in combination with fludarabine (30 mg/m2/day) for 5 days.

Results : Patients characteristics were similar in two groups, with the exception of a higher proportion of very severe at the time of SCT in h-SCT. There were some differences in transplantation characteristics, including graft source and CD3+ cell numbers. All patients achieved primary engraftment but two patients in h-SCT developed secondary graft failure. The incidence of acute GVHD (grade ≥2) in h-SCT and in u-SCT was 29.4% (10/37) and 29% (9/31) and chronic GVHD (≥ moderate) was 14.7% (5/37) and 19% (6/31), respectively. After a median follow-up of 22 and 32.6 months for h-SCT and u-SCT, the probability of overall survival was 84.3 and 89.8 % for h-SCT and u-SCT (P=0.661), respectively. The GVHD-free survival were 70.1% and 64.1% for h-SCT and u-SCT (P=0.518), respectively.

Conclusions : This study showed that survival of h-SCT is comparable to that of u-SCT. Especially, h-SCT could be considered in patients requiring urgent transplantation due to easy donor availability.

Keyword : Severe aplastic anemia, Unrelated donor , Related mismatched donor

OP12-2

Role of FDG PET for Evaluation of Bone Marrow Status and Prognosis Prediction in T-Cell Lymphomas

Go-Un Woo[1], Youngil Koh[1,2], Jung Min Lee[3], Jin Chul Paeng*[3], Jeonghwan Youk[1], Sung-Soo Yoon[1,4], Inho Kim[1,4], Dong-Yeop Shin[1,2], Junshik Hong[1,2], Gi Jeong Cheon[3], Dong Soo Lee[3], June-Key Chung[3,4]

[1] Department of Internal Medicine, Seoul National University Hospital, Korea
[2] Biomedical Research Institute, Seoul National University Hospital, Korea
[3] Department of Nuclear Medicine, Seoul National University Hospital, Korea
[4] Cancer Research Institute, Seoul National University College of Medicine, Korea

Background : We investigated the clinical value of FDG PET for evaluation of bone marrow (BM) tumor involvement status in peripheral T-cell lymphoma (PTCL) or extranodal NK/T-cell lymphoma (NKTCL).

Methods : Patients diagnosed with PTCL or NKTCL between 2008 and 2015, who underwent initial staging with FDG PET and BM biopsy were retrospectively retrieved. PET BM uptake was analyzed visually and quantitatively (bone marrow-to-liver ratio; MLR). The optimal cutoff value of MLR was obtained by receiver-operating-characteristic (ROC) analysis and the correlation between MLR and survival data was estimated using the Kaplan-Meier method.

Results : A total of 109 (63 PTCL and 46 NKTCL) patients were analyzed. BM biopsy revealed tumor involvement in 35.8% of cases. Sensitivity and specificity of PET for diagnosing positive BM biopsy were 58.5% and 77.9% by visual analysis; 64.1% and 72.9% by MLR. Diagnostic performance of PET for BM involvement was not different across lymphoma subtypes. Multivariate survival analysis revealed that BM PET finding, as well as BM biopsy result, was an independent prognostic factor for survival in PTCL and NKTCL. Moreover, MLR was a significant prognostic factor for both PFS and OS (P = 0.001 and 0.005) in BM biopsy-negative patients.

Conclusions : Although FDG PET findings fairly correlate with BM biopsy findings, PET could not replace BM biopsy in PTCL and NKTCL. However, BM finding on FDG PET is an independent prognostic factor in these tumors, suggesting the further biologic relevance of FDG PET findings to aggressiveness or covert BM involvement of tumor cells.

Keyword : T cell lymphoma, PET, Bone Marrow Involvement, Prognosis

OP12-3

Nutritional Status and Cardiovascular Risk Factors Affect Survival of DLBCL

Ji Hyun Lee[1], Sung Yong Oh[1], Ho-Jin Shin*[2]

[1]Department of Internal Medicine, Dong-A University College of Medicine, Korea
[2]Department of Hematology and Oncology, Busan National University Hospital, Korea

Background : Pretreatment nutritional status assessed by body mass index (BMI), total cholesterol (TC), albumin, total lymphocyte count (TLC) have been noted to have prognostic significance in diffuse large B-cell lymphoma (DLBCL) patients. Along with malnutrition, higher comorbidity score was observed to affect poor treatment outcome and treatment-related toxicity in the rituximab era. These factors have mostly been assessed in a small cohort of single center.

Methods : Five hundred and twenty-five patients with newly diagnosed DLBCL treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in 6 centers of South Korea from January, 2007 to March, 2016 were analyzed. Pretreatment nutritional status was assessed by controlling nutritional status (CONUT) score, which has been suggested to have strong prognostic impact in resectable solid cancer patients. The CONUT score was calculated by adding scores of the serum albumin concentration the TLC and the TC concentration. Cardiovascular risk factors screened for the analysis were: diabetes mellitus (DM), hypertension, previous history of myocardial infarction and cerebrovascular infarction.

Results : The median follow-up duration was 29.47 months (range: 0.60 – 139.03 months) and the median age was 62 years (range: 20-89 years). By univariate analysis, BMI ≤ 20 kg/m2 (hazard ratio [HR], 2.20; 95% confidence interval [CI], 1.32–3.66, p = 0.003), TC < 140 mg/dL (HR, 1.76; 95% CI, 1.11–2.79, p = 0.017), albumin < 3.0 g/dL (HR, 4.86; 95% CI, 2.80–8.46, p = 0.000), TLC < 1200 /mm3(HR, 1.69; 95% CI, 1.09–2.62, p = 0.019), CONUT score ≥ 4 (HR, 3.22; 95% CI, 2.03–5.10, p = 0.000), and cardiovascular risk factors ≥ 1 (HR, 2.53; 95% CI, 1.63–3.91, p = 0.000) significantly affected overall survival (OS). In multivariate analysis, BMI ≤ 20 kg/m2 (HR, 1.93; 95% CI, 1.12–3.33, p = 0.019), albumin < 3.0 g/dL (HR, 2.50; 95% CI, 1.27–4.94, p = 0.008), CONUT score ≥ 4 (HR, 2.32; 95% CI, 1.15–4.66, p = 0.019), and cardiovascular risk factors ≥ 1 (HR, 2.15; 95% CI, 1.34–3.45, p = 0.001) were significantly associated with OS.

Conclusions : Malnourishment status indicated by BMI ≤ 20 kg/m2 and CONUT score ≥ 4 and at least one or more cardiovascular risk factors at diagnosis poorly affect survival in DLBCL patients treated with Rituximab-based regimen.

Keyword : Nutritional status, Cardiovascular risk factors , DLBCL

OP12-4

Experience of Levetiracetam for Prevention of Busulfan-Induced Seizures in Adult HSCT Patients

Soo-Jeong Kim[1], Ji Eun Jang[1], Haerim Chung[1], Shin Young Hyun[2], Jung Yeon Lee[2], Yundeok Kim[1], Yu Ri Kim[1], Jin Seok Kim[1], June-Won Cheong[1], Yoo-Hong Min[1]

[1] Department of Internal Medicine, Yonsei University College of Medicine, Korea
[2] Department of Internal Medicine, Yonsei University Wonju College of Medicine, Korea

Background : Anti-seizure prophylaxis is routinely used during stem cell transplantation condition chemotherapy which includes busulfan. Most commonly used prophylaxis for busulfan-related seizure is phenytoin. However, phenytoin has several limitations; prolonged half-life, requirement of loading dose to get to effective serum concentration, acting as a potent inducer of cytochrome P450 hepatic enzymes which leads to increased clearance of busulfan, alteration of cyclophosphamide levels by affecting uridine glucuronosyltransferase enzymes. Levetiracetam has ideal pharmacokinetics for short-term use during stem cell transplantation; short half-life, dose-proportional steady-state pharmacokinetics, not affecting cytochrome P450 hepatic enzymes and enzymes related to metabolism of cyclophosphamide. We retrospectively analyzed our experience or levetiracetam use during hematopoietic stem cell transplantation among adult patients receiving busulfan containing conditioning regimens.

Methods : We reviewed medical records of all adult patient over > 18 years of age who received busulfan-containing condition regimen form January 2006 to December 2016. All patients received phenytoin or levetiracetam for seizure prophylaxis. Selection of prophylaxis was physician's choice. Levetiracetam was administered at 500mg every 12 hours orally, starting on the day before first busulfan infusion until the next day of final busulfan infusion.

Results : Total 508 patients(Male 316,Female 223) received busulfan based conditioning regimens from March, 2010 to June, 2017 in Severance Hospital, Seoul, Korea. Eighty-two patients received levetiracetam as anti-seizure prophylaxis and 457 patients received phynytoin. The underlying disease was AML 121, ALL 67, malignanat lymphoma 239, multiple myeloma 80, CML 8, MDS 18, myelofibrosis 5, HLH 1. The patients who received busulfan before year 2013, busulfan infusion was administered 4 times per day, after year 2013 busulfan infusion was administered once daily. The seizure rate showed no difference betwenn two groups (levetiracetam 1/82 vs. phenytoin 3/457). The rate of veno-occlusive disease and primary graft failure rate were similar between two groups. Total duration of anti-seizure prophylaxis and total cost including medication and blood level monitoring were lower in levetiracetam group.

Conclusions : Levetiracetam was well tolerated and efficacious in prevention of seizures

Keyword : Busulfan, Seizure, Levetiracetam, HSCT

OP12-5

Clinical Factors to Predict the Engraftment in Low CD34 Count Autologous Stem Cell Transplantation

Sang-A Kim, Dong-Yeop Shin*, Youngil Koh, Junsik Hong, Inho Kim, Sung-Soo Yoon
Department of Internal Medicine, Seoul National University Hospital, Korea

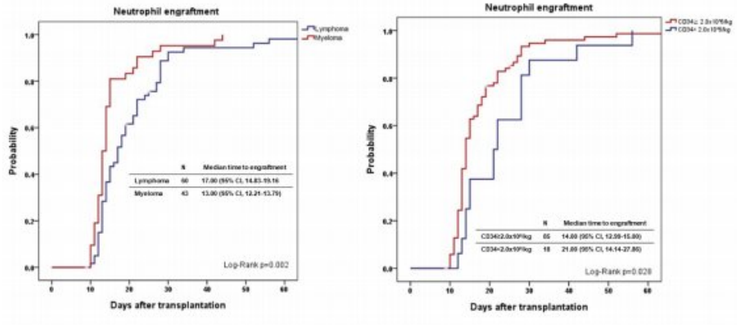
Background : Autologous stem cell transplantation (ASCT) is the essential treatment in high-risk lymphoma and multiple myeloma patients, and at least 3.0x106/kg of CD34 positive hematopoietic stem/progenitor cells (HSPC) are known to be optimal. But considerable patients fail to collect sufficient amount of HSPCs.We analyzed the factors associated with bone marrow engraftment in HSPC ASCT among the patients with myeloma and lymphoma.

Methods : We retrospectively reviewed the patients who received ASCT in Seoul National University Hospital from January 2008 to January 2017. Survival and risk factor analysis was conducted using Kaplan-Meier curve and Cox proportional hazard model.

Results : 60 lymphoma and 43 myeloma patients were included. With median follow-up duration of 42 months (range, 7.17-119.90), median overall survival was 105.70 months (95% Confidence interval (CI), 46.47-164.94) and median relapse-free survival was 39.97 months (95%CI, 27.24-52.70).
In the univariable analysis for neutrophil engraftment, lymphoma patients showed delayed engraftment compared to myeloma patients (p=.002). Patients with HSPCs less than 2.0x10^6/kg (p=.028), older age (≥50 years old, p=.003), more than one year from stem cell mobilization (SCM) to ASCT (p=.006) and previous heavy treatment history (>2 lines) (p=.028) and bone marrow harvest (p=.038) needed more time for neutrophil engraftment. Multivariable analysis revealed that lymphoma (p=.011, HR 1.79, 95%CI 1.14-2.82), more than 2 lines of previous treatment history (p=.017, HR 1.87, 95%CI 1.12-3.12), more than one year from SCM to ASCT (p=.021, HR 2.71, 95%CI 1.17-6.30) were the factors independently associated with neutrophil engraftment.
For the platelet engraftment, multivariate analysis revealed that lymphoma (p=.001, HR 2.33, 95%CI 1.44-3.77), age more than 50 (p=.045, HR 1.60, 95%CI 1.01-2.53) and less than 2.0 x10^6/kg of HSPCs (p=.005, HR 2.32, 95%CI 1.28 to 4.20) were clinically meaningful in predicting the platelet engraftment.

Conclusions : By this study focusing on low HSPC ASCT population, we concluded that we could predict the neutrophil and platelet engraftment using clinical information, suggesting we can plan patient-tailored strategy in ASCT.

Keyword : Autologous hematopoietic stem cell transplantation, CD34, Engraftment



OP12-6

Efficacy and Safety of Bendamustine Plus Rituximab as Early Salvage Treatment in Relapsed/Refractory NHL

Young-Woo Jeon, Jae-Ho Yoon, Sung-Eun Lee, Ki-Seong Um, Yoo-Jin Kim, Hee-Je Kim, Seok Lee, Chang-Ki Min, Jong-Wook Lee, Woo-Sung Min, Seok-Goo Cho*
Department of Hematology, Catholic Blood and Marrow Transplantation Center,Seoul St. Mary's Hospital, Korea

Background : Patients with relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL) are treated with salvage regimens and may be considered for high-dose chemotherapy and alternative autologous stem cell transplantation if disease is chemosensitive. However, for patients who are not eligible for intensive chemotherapy becaused of comorbidities, advanced age, treatment options are very limited and prognosis is poor. Bendamustine is active in indolent B cell lymphomas and chronic lymphocytic leukemia but has been extensively studied in aggressive lymphomas. So, this study examines the efficacy of the combination of bendamustine and rituximab as early salvage therapeutic option in relapsed/refractory NHL.

Methods : We retrospectively analyzed 27 patients with relapsed/refractory aggressive NHL treated with combination bendamustine and rituximab (BR) between August 2014 and July 2017 to evaluate overall response rate (ORR), progression-free survival (PFS), duration of response (DOR) and treatment safety.

Results : 27 patients consisted that diffuse large B cell lymphoma (10 patients), Mantle cell lymphoma (12 patients), and follicular lymphoma-grade 3 (5 patients). ORR was 51.9% (14 patients) with 48.1% CR (13 patients) and 3.8% PR (1 patient). SD was reported in 1 patient (3.8%) and PD in 12 patients (44.4%). At median follow up of 41 months (range 1-102.3 months), median PFS was 25.5 months for all patients (95% CI 4.1-58.0). the median DOR 31.2 months (95% CI 3.1-29.1). Grade 3/4 toxicity observed observed included hematologic events: lymphopenia (38.9%), neutropenia (42.1%), anemia (10.0%), and thrombocytopenia (11.1%).

Conclusions : BR regiement can be considered to have a role in the treatment of patients with relapsed/refractory aggressive NHL with limited therapeutic options, in that it can induce long-term remission in some patients with an acceptable toxicity profile.

Keyword : Bendamustine, Aggressive, Non-Hodgkin lymphoma

OP13-1

Quality of Life in Patients with Type I Gaucher Disease after Long Term Enzyme Replacement Therapy

Hongmin Li, Zhangbiao Long, Yali Du, Miao Chen, Junling Zhuang, Bing Han*
Hematology, Peking Union Medical College Hospital, China

Background : The chronic condition of type 1 Gaucher disease (GD1) and its weakening clinical manifestations can significantly affect patients' quality of life (QOL). This study aimed at investigating the survival status and QOL in patients with GD1, who underwent long-term imiglucerase enzyme replacement therapy (ERT) and to identify the possible relevant factors affecting QOL.

Methods : 22 patients with GD1 who received ERT (20-40U / Kg intravenously, twice a week) from January 1995 to July 2017 were included. Factors affecting QOL were analyzed based on their clinical data, survey of living conditions and SF-36 questionnaires.

Results : 22 GD1 patients consisted of 13 males and 9 females. The median age of onset, start of ERT treatment and current median age were 6 (1-38), 26 (6-41) and 40.5 (24-52) respectively. The median ERT treatment duration was 15.75 (7-22) years. Of the 22 patients, 68.2% lived in developing cities, 86.4% did not receive college education and 77.3% patients were with annual income <$4500. All dimensions but mental health (MH) of QOL were significantly poor ($P < 0.05$) in GD1 patients when compared to the normal Chinese population. History of splenectomy before treatment was an independent adverse factor affecting the physical health of patients ($P<0.05$), but not the mental health ($P>0.05$). ERT at early ages was beneficial in increasing patients' physical and mental health ($P < 0.05$). Presence of splenomegaly and bone involvement despite ERT had no effect on physical and mental health ($P > 0.05$).

Conclusions : Compared to the normal Chinese population, GD1 patients were associated with reduced QOL, which is consistent with their current living condition with poor education and income status. History of splenectomy and the age at the beginning of ERT emerged as key factors affecting the QOL of patients receiving long-term ERT.

Keyword : Gaucher disease, Quality of life, SF-36, Enzyme replacement therapy

OP13-2

Hematological Finding and Clinical Profile in Pulmonary Tuberculosis among HIV Patients

Petrus Kanisius Yogi Hariyanto[1], Muhammad Faisal Putro Utomo[1], Anindia Reina Yolanda[1], Nur Rizky Amaliah[1], Ni Made Dewi Dian Sukmawati[2], I Made Susila Utama[2]

[1] Faculty of Medicine, Udayana University, Indonesia
[2] Division of Tropical and Infectious Diseases, Department of Internal Medicine, Udayana University, Sanglah General Hospital, Indonesia

Background : Pulmonary tuberculosis (PTB) is the one of the most common opportunistic infection among HIV patients. Many patients before diagnosed with HIV came to the health center with complaint of TB symptoms. Studies are carried out on PTB and HIV in almost every aspect so as to develop new or improved systems in the early diagnosis and control of the comorbidity. Clinical and hematological profile associated with PTB with HIV infection play a major role, although a nonspesific one, in the diagnose and prognosis of PTB patients with HIV infection.

Methods : A cross-sectional study with a total 195 cases of HIV patients with pulmonary tuberculosis before antiretroviral treatment were conducted in Bali Province. Samples were consecutively selected from VCT/CST Clinic at Sanglah General Hospital. Secondary data collected from medical records. Data were then analyzed using SPSS version 20 and will show with table and diagram.

Results : A total of 195 cases were selected for the study, more males were in the study 141 (72,3%) than females 44 (27,7%). Most of age 31-40 years old 81 (41,5%) with total positive sputum examination 26 (13,3%). Almost half of the samples had CD4 count <50 cell/mm3 97 (49,7%), wasting syndrome 103 (52,8%), leucocyte count >4 .103 cell/µL 111 (56,9%) and most of them had hemoglobin >11 g/dL 129 (66,2%), limphocyte count >1.103 cell/µL 187 (95.9%), neutrophil count >1,5x103 cell/µL 177 (90,8%), and trombocyte count >150 103 cell/µL 185 (94,9%).

Conclusions : Clinical and hematological finding are important, simple, and cheaper method in analyzing the pattern of health status among PTB in HIV infection.

Keyword : Tuberculosis, HIV, Clinical Manifestation, Hematology, Infection

OP13-3

Cefepime versus Cefepime Plus Amikacin for Febrile Neutropenia in Pediatric Cancer Patients

Na Hee Lee[1], Ji-Man Kang[2], Ji Won Lee[3], Keon Hee Yoo[3], Ki Woong Sung[3], Hong Hoe Koo[3], Yae-Jean Kim*[3]

[1] Pediatrics, Cha Bundang Medical Center, Cha University, Korea
[2] Pediatrics, Center for Pediatric Cancer, National Cancer Center, Korea
[3] Pediatrics, Sungkyunkwan University School of Medicine, Samsung medical center, Korea

Background : Bacteremia in pediatric cancer patients with neutropenia is an important and urgent issue which needs prompt antimicrobial treatment. We investigated the treatment outcome of patients with bacteremia before and after the addition of amikacin to cefepime monotherapy as an initial empirical treatment in pediatric cancer patients with febrile neutropenia.

Methods : From January 2011 to December 2016, pediatric cancer patients who visited emergency room (ER) at Samsung Medical Center (SMC) due to chemotherapy induced febrile neutropenia were included. All bacteremia episodes occurred at ER were investigated by retrospective chart review. At SMC, the regimen of empiric antimicrobial treatment for febrile neutropenia at ER has been changed from cefepime to cefepime plus amikacin since September 2014 because increasing cefepime resistance rate was suspected.

Results : A total of 225 bacteremia episodes in 164 patients were evaluated. Approximately 54% of episodes (122/225) were treated with cefepime monotherapy and 37% of episodes (83/225) were treated with cefepime plus amikacin combination therapy. Remained 20 episodes were treated with other antimicrobial regimens. Gram-negative organisms accounted for 59% (132/225) and gram-positive organisms for 41% (93/225). There was no fungemia episode in this study. The bacteremia caused by cefepime-resistant gram-negative organisms occurred in 16% (11/69) before September 2014, and 21% (12/57) since September 2014 (P = 0.331). The percentage of appropriate empiric antimicrobial treatment increased from 62% to 83% since the additional administration of amikacin (P = 0.004). The duration of fever was shorter in the cefepime plus amikacin group than in the cefepime group (34 hours vs 22 hours, P = 0.014); however, the rate of septic shock and pediatric intensive care unit (PICU) hospitalization were not significantly different between two groups (septic shock 7% vs 7%, P = 0.968; PICU 3% vs 1%, P = 1.00). There was no differences in creatinine levels between two groups for 1 week follow-up period (P = 0.760). No infection related mortality was observed in both groups.

Conclusions : For gram-negative organisms, antimicrobial resistance rate to cefepime was around 18%. Although the percentage of appropriate empiric antimicrobial treatment increased by adding amikacin, no difference in progression to septic shock or PICU hospitalization were observed.

Keyword : Amikacin, Cefepime, Empirical treatment, Febrile neutropenia, Pediatric cancer

OP13-4

Detection of Bacteremia MRSA Using a Novel Isothermal Amplification with SPR Biosensor Methodology

Zhenbo Xu[1,2,3], Xuerui Bao[1], Bing Li[1,2], Lin Li[1,2]

[1] School of Food Sciences and Engineering, South China University of Technology, China
[2] Guangdong Province Key Laboratory for Green Processing of Natural Products and Product Safety, China
[3] Department of Microbial Pathogenesis, School of Dentistry, University of Maryland, United States

Background : Methicillin-resistant Staphylococcus aureus (MRSA) is one of the most important causes for nosocomial hematological infections as bacteremia, and its rapid and accurate detection from blood samples remains a major concern. In this study, 2 novel nucleic acids isothermal amplification assays, including loop- mediated isothermal amplification (LAMP) and rolling circle amplification (RCA), have been used in combination with surface plasmon resonance (SPR) biosensor, for the detection of bacteremia MRSA strains.

Methods : A total of 25 Staphylococcus strains were isolated from blood hemoculture specimens of clinical patients. Genomic DNA was extracted and conducted using LAMP and RCA amplification on the SPR platform for 542 bp, 823 bp and 374 bp DNA fragment of 16S rRNA, femA and mecA genes, respectively. All padlock probes for RCA amplification were designed by Primer Premier 5.0 and primers for LAMP amplification were designed online via PrimerExplorer. Besides, the irrelevant sequence inserted into padlock probes was fragment from Medicago truncatula calmodulin-domain kinase CDPK protein mRNA. Both of the isothermal amplification assays LAMP and RCA were carried out on the SPR sensor with specific chips to detect 16S rRNA, femA and mecA genes, in less reagents (6 μL) and shorter time about 15 min than that of conventional LAMP and RCA reactions.

Results : Curve results of LAMP- SPR and RCA- SPR amplification showed similar tendency with that of Q- PCR when DNA samples were positive in the detection loci. In total of 25 samples, all of them showed positive in 16S rRNA, which suggested that they all belonged to Staphylococcus. Besides, it has proved that totally 21 strains were positive in femA gene and 19 strains carried mecA gene according to SPR results.

Conclusions : This study for the first time has combined the isothermal amplification with SPR biosensor for the detection of bacteremia MRSA, with acquisition of high sensitivity, specificity, convenience and rapidity.

Keyword : Rolling circle amplification, Isothermal amplification, SPR, Methicillin-Resistant Sthphylococcus aureus, B- lactam resistance

OP14-1

Comparative Study of Porcine ALG and Rabbit ATG as a First-Line Treatment of Severe Aplastic Anemia

Miao Chen, Bing Han*

Department of Hematology, Peking Union Medical College Hospital, China

Background : Porcine anti-human lymphocyte immunoglobulin (pALG) and rabbit anti-human thymocyte immunoglobulin (rATG) are the only two ATGs for severe aplastic anemia (SAA) treatment in China.

Methods : 148 treatment-naïve SAA patients who received ATG combined with cyclosporine A (CsA) therapy were analysed retrospectively.

Results : The patients were divided into a pALG group (n = 114) and a rATG group (n = 34). After three months, the pALG and rATG groups had an overall response (OR) of 65.8% and 44.1%, respectively (P = 0.023); after six months, the OR reached 74.6% and 64.7%, respectively (P = 0.361). The pALG group had markedly better time-related efficacy than the rATG group (P = 0.03). The overall survival (OS) and event-free survival (EFS) between groups had no significant difference (P > 0.1). The pALG and rATG groups did not significantly differ in terms of recurrence (8.8% vs. 5.9%, P = 0.734) or PNH clonal transformation (5.3% vs. 2.9%, P = 1.000), whereas a significant difference was found in the incidence of MDS/AML transformation (2.6% vs. 11.8%, P = 0.049).

Conclusions : We found that pALG achieved a better time-related efficacy than rATG for the treatment of SAA; nonetheless, no significant difference in the OS or EFS of pALG compared with rATG.

Keyword : severe aplastic anemia, Immunosuppressive therapy, Porcine anti-Human lymphocyte immunoglobulin, Rabbit anti-Human thymocyte immunoglobulin

Table 1 Baseline characteristics of 148 patients received intensive IST

Characteristics	pALG group	rATG group	P value
Patients (n)	114	34	
Sex			0.609
Male—n(%)	66 (57.9%)	22 (64.7%)	
Female—n(%)	48 (42.1%)	12 (35.3%)	
Median age (range)(years)	30 (12-72)	35.5 (14-76)	0.353
≦40—n(%)	80 (70.2%)	24 (70.6%)	0.963
> 40—n(%)	34 (29.8%)	10 (29.4%)	
Severity of AA			
SAA—n(%)	77 (67.5%)	17 (50.0%)	0.097
VSAA—n(%)	37 (32.5%)	17 (50.0%)	
HAAA	6 (5.3%)	4 (11.8%)	0.172
Median duration from AA onset to therapy (range) (months)	1.5 (0.3-152)	2 (0.5-60)	0.362
With complications before intensive IST	56 (49.1%)	21 (61.8%)	0.270
Antifungal prophylaxis	53 (46.5%)	10 (29.4%)	0.116
CBC before intensive IST			
WBC(×109/L)	1.91±1.10	1.51±0.82	0.074
NEUT(×109/L)	0.46±0.46	0.26±0.24	0.046*
LYM(×109/L)	1.35±0.82	1.19±0.67	0.359
HGB(g/L)	67.10±18.24	63.12±18.56	0.754
MCV(fl)	91.83±8.18	90.80±6.67	0.788
RET(×109/L)	19.66±17.95	14.35±11.42	0.288
PLT(×109/L)	12.43±8.27	11.15±9.16	0.302
With PNH clone—n(%)	18(15.8%)	5(14.7%)	0.878
With symptomatic PNH—n(%)	2(1.8%)	0	0.592
Iron load before intensive IST			
SI		211.15±66.75	0.982
TIBC		257.32±71.73	0.524
TS		84.61±19.28	0.515
SF		1053.90±571.94	0.243

pALG porcine anti-lymphocyte immunoglobulin, rATG rabbit anti-thymocyte immunoglobulin, SAA severe aplastic anemia, VSAA very severe aplastic anemia, HAAA hepatitis-associated aplastic anemia, IST immunosuppressive therapy, CBC complete blood count, WBC white blood cell, NEUT neutrophil, LYM lymphocyte, HGB hemoglobin, MCV mean corpuscular volume, RET reticulocyte, PLT platelet, PNH paroxysmal nocturnal hemoglobinuria, SI serum iron, TIBC total iron binding capacity, TS transferrin saturation, SF ferritin.
* P<0.05

Table 2 Hematological responses

Time	Responses	pALG group	rATG group	P value
3 months	CR	6(5.3%)	2(5.9%)	0.055
	PR	69(60.5%)	13(38.2%)	
	NR	27(23.7%)	16(47.1%)	
	Death	12(10.5%)	3(8.8%)	
	OR (PR+CR)	75(65.8%)	15(44.1%)	0.023*
	No effect (NR+Death)	39(34.2%)	19(55.9%)	
6 months	CR	29(25.4%)	8(23.5%)	0.751
	PR	56(49.1%)	14(41.2%)	
	NR	16(14.0%)	8(23.5%)	
	Death	13(11.4%)	4(11.8%)	
	OR(PR+CR)	85(74.6%)	22(64.7%)	0.361
	No effect (NR+Death)	29(25.4%)	12(35.3%)	
Responses with time**	0	29	12	0.047*
	1	10	7	
	2	75	15	
At the end of follow-up	Relapse	10(8.8%)	2(5.9%)	0.734
	PNH transformation	6(5.3%)	1(2.9%)	1.000
	MDS/AML transformation	3(2.6%)	4(11.8%)	0.049*
	Death	22(19.3%)	10(29.4%)	0.238
	Loss to follow-up	9(7.9%)	3(8.8%)	1.000

pALG porcine anti-lymphocyte immunoglobulin, rATG rabbit anti-thymocyte immunoglobulin, CR complete response, PR partial response, NR none response, OR overall response, PNH paroxysmal nocturnal hemoglobinuria, MDS myelodysplastic syndrome, AML acute myeloid leukemia.
* P<0.05
** A new efficacy variable was defined by "response or not" and "time to response": 0 indicates "nonresponse" at both three and six months; 1 indicates "nonresponse" at three months but "response" at six months; and 2 indicates "response" at both three and six months.

Figure 1 Absolute lymphocyte changes of pALG group and rATG group in 1,3,6,12 months after intensive IST.

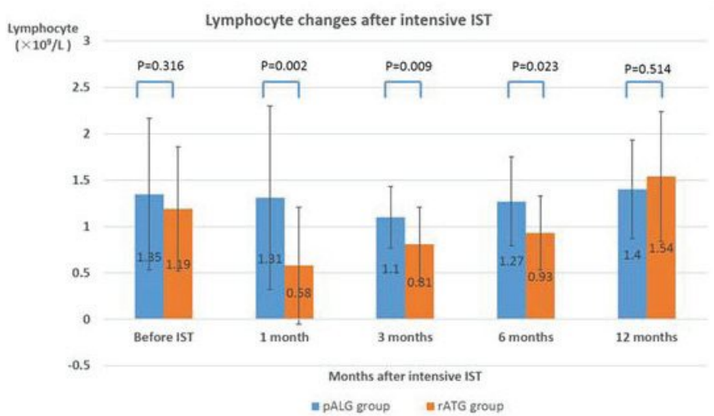


Figure 2A Kaplan-Meier survival curves of overall survival weighted by propensity score.
Figure 2B Kaplan-Meier survival curves of event free survival weighted by propensity score.

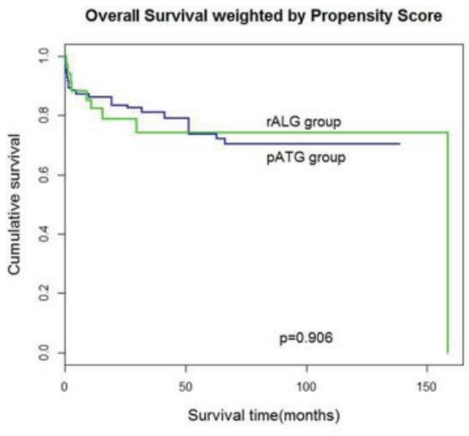


Fig 2A

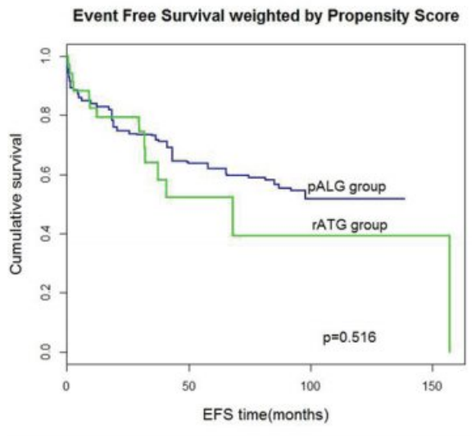


Fig 2B

OP14-2

PIGA Mutations as a Predictors of Treatment Response in PNH

Hee Sue Park[1], Seongmin Choi[2], Heewon Seo[3], Sung-Min Kim[4], Kyongok Im[5], Jiwon Yun[1], Dajeong Jeong[1], Jung-Ah Kim[6], Sang Mee Hwang[7], Kwangsoo Kim[2], Ju Han Kim[3], Dong Soon Lee*[1,4]

[1] Department of Laboratory Medicine, Seoul National University College of Medicine, Korea
[2] Division of Clinical Bioinformatics Biomedical Research Institute, Seoul National Hospital, Korea
[3] Division of Biomedical Informatics, Seoul National University College of Medicine, Korea
[4] Cancer Research Institute, Seoul National University College of Medicine, Korea
[5] Institute of Reproductive Medicine and Population Medical Research Center, Seoul National University, Korea
[6] Department of Laboratory Medicine, Chung-Ang University Hospital, Korea
[7] Department of Laboratory Medicine, Seoul National University Bundang Hospital, Korea

Background : The detection of extremely small clone (<0.01%) became possible through high-sensitive flow cytometry (FCM), but the clinical significance of small PNH clone has not been elucidated. To investigate a correlation of PIGA mutation and small PNH FCM clone, we measured PNH FCM clone size and mutant burden of PIG gene, with their correlation to treatment response.

Methods : A total of 89 specimens from 63 patients whose PNH clone size was ≥0.1% by FCM was enrolled (classic PNH 9, PNH related with bone marrow disorder 47, subclinical PNH 10). To detect minor cell population with PIG mutation, we adopted ultra-deep sequencing for PIGA, PIGM, PIGX and PIGT mutation

Results : Twenty two % of 63 patients with PNH FCM clone harbored PIG gene mutation and 92.8% of patients with PIG mutation had >10% PNH FCM clone in RBC and granulocyte. In classic PNH patients (n=6), the average of PNH FCM clone size was 56.8% in RBC and 89.6% in granulocyte, and all patients had PIG gene mutation. In patients with subclinical PNH clone, the average of PNH FCM clone was 1.8% in RBC and 3.3% in granulocyte, while PIG gene mutation was not detected. In the patients with coexisting bone marrow disorder (BMD), the average of PNH FCM clone size was 8.0% in RBC and 14.9% in granulocyte. Among 6 patients with Eculizumab treatment, hemoglobin increment and decrease of FCM RBC clone size correlated, while LDH decreased in all patients, irrespective of treatment response. Decrease of the ratio over 0.15 (type III/type II+III PNH clone in RBC) was a predictive factor for complete response at 6 months from treatment initiation. Of the 11 patients with consecutive results of PIG mutation, 88% of patients with PIG mutations was non-responsive to supportive treatment, while 33% of patients without PIG mutations was non-response (p=0.072). Mutant burden of PIG gene mutation were not changed during treatment irrespective of types of treatment.

Conclusions : The PIG gene mutation was detected only in patients with >10% FCM PNH clone and The mutation burden of PIG gene was related to the granulocyte FCM PNH clone size. The presence of PIG gene mutations was correlated with adverse treatment response. We suggest monitoring of PNH clone in RBC can be a potential predictor of treatment response as well as Hb during treatment with Eculizumab.

Keyword : Paroxysmal nocturnal hemoglobinuria, PIGA, Flow cytometry, Eculizumab

OP14-3

Prognostic Implications of Renal Dysfunction in Korean Patients with PNH

Jin Seok Kim[1], Jun Ho Jang[2], Deog-Yeon Jo[3], Yeung-Chul Mun[4], Jong Wook Lee*[5]

[1] Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Korea
[2] Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Korea
[3] Department of Internal Medicine, School of Medicine, Chungnam National University Hospital, Chungnam National University, Korea
[4] Division of Hematology and Oncology, Department of Internal Medicine, Collage of Medicine, Ewha Womans University, Korea
[5] Division of Hematology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Background : At the time of diagnosis of PNH, renal dysfunction was reported in 16% of Korean PNH registry. However, renal events may occur repeatedly during the clinical course of PNH. Therefore, the dynamics of renal dysfunction during PNH natural disease course should be evaluated.

Methods : Korean PNH patients (n=101) with PNH granulocyte clone size >10% and serum LDH >1.5-fold of upper limit of normal at the time of PNH diagnosis were retrospectively enrolled. Renal events such as acute kidney disease (AKD) or chronic kidney disease (CKD) were defined according to the definition of KDIGO. Medical records were reviewed until eculizumab was administered.

Results : During the 94.2 months of median follow up duration, the renal events were observed in 55 patients (54.5%). Median day of the first renal event from diagnosis of PNH was 79.3 months. The elevated levels of LDH at the time of first renal event were observed compared to the level of LDH at the time of diagnosis (r=-0.58, P=0.022 in the 1 renal event and r=-0.75, P=0.0002 in the renal events ≥2). The rate of TE was a higher trend in the patients with renal events ≥2 compared to those with renal events ≤1 (31.3% vs. 21.7%, P=0.303). The rate of recurrent TE was higher in patients with renal events ≥2 compared to those with renal events ≤1 (18.8% vs. 2.9%, P=0.012). The patients with renal events ≥2 showed a trend toward inferior OS compared to those with renal events ≤1 (P=0.124). The rate of TE was a higher trend in the patients with the patients with CKD+AKD compared to the other patients (45.5% vs. 22.2%, P=0.134). The rate of recurrent TE was higher in patients with CKD+AKD (3/11, 27.3%) compared to the other patients (5/90, 5.6%, P=0.040). The OS was inferior in the patients with CKD+AKD compared to the other patients (75.0% vs. 95.8% at 10 yr OS; P=0.011).

Conclusions : These data indicate that the rate of recurrent TE was higher in PNH patients with recurrent renal events, especially in patients with CKD+AKD group. The OS of PNH patients with recurrent renal events including CKD+AKD group has been shown to be lower than those of other patients. Therefore, physician should pay attention to evaluate the renal events during follow-up period.

Keyword : Paroxysmal nocturnal hemoglobinuria , Renal Dysfunction , Thromboembolism, Overall survival

OP14-4

Dynamics of PNH Clone in Adult Patients with PNH/Aplastic Anemia following Immunosuppressive Therapy

Sung-Soo Park, Gi June Min, Young-Woo Jeon, Jae-Ho Yoon, Sung-Eun Lee, Byung-Sik Cho, Ki-Seong Eom, Seok Lee, Hee-Je Kim, Chang-Ki Min, Seok-Goo Cho, Woo-Sung Min, Jong Wook Lee*

Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Background : The dynamic change of GPI-anchored proteins-deficient cell populations (PNH clone) in patients with acquired aplastic anemia who diagnosed paroxysmal nocturnal hemoglobinuria (AA/PNH) when administering immunosuppressive therapy (IST) is scarce. The aim of this study was to identify the dynamics of PNH clone in the context of AA with IST.

Methods : 71 consecutive adult patients with AA/PNH who received IST constructed initial cohort. After exclusions for various reasons, a cohort consisted of 66 patients were retrospectively analyzed. Hemolytic AA/PNH was defined as AA/PNH with elevated lactate dehydrogenase (LDH) ≥ 1.5 times the upper limit of normal (ULN). Available data of each PNH clone were collected at the time of diagnosis, 6, 12, 24, and 36 months after diagnosis of PNH clone. Particularly, patients were instructed to take a land mark visit at 6, 12, and 24 months from diagnosis of AA/PNH.

Results : The median age of patients was 46 (18-79) years. Concurrent IST of patients was as follows: 28 (40.1%) of antithymocyte gloubulin (Thymoglobulin®, ATG) with 2.5mg/kg/day for 5 days plus cyclosporine A (CsA), 14 (21.2%) of ATG with 3.5 mg/kg/day for 5 days plus CsA, and 24 (36.4%) of CsA only. With median follow-up of 36.0 (6.5-90.6) months of total patients, Hemolytic PNH was developed in 29 (43.9%) patients after median 1.2 (0-24.4) months from diagnosis PNH clone. Compared to PNH clone of other 37 patients (56.1%) with non-hemolytic PNH, those of hemolytic PNH/AA increased continuously with a statistical significance (p=0.002). LDH of hemolytic PNH also show significant trend of increment compared with those of non-hemolytic PNH (p=0.002). None of cases with minimal clone (<1%) at diagnosis (N=17) had a PNH clone reaching 3.5% (3.5 was the minimal value of clone in patients with clinical PNH). PNH clones in patients with PNH clone above the cut-off of 1% at diagnosis (N=17) showed consistently increasing compared with those of patients with minimal clone (<1%).

Conclusions : The value of 1% at diagnosis of PNH clone could be the cut-off that predicts the onset of hemolytic PNH in AA/PNH. Furthermore, periodic tracing of PNH clone should be necessary for AA/PNH patients whose PNH clone above 1% at diagnosis when administering IST.

Keyword : Paroxysmal nocturnal hemoglobinuria, Aplastic anemia, Antithymocyte globulin, PNH, AA, Dynamics

OP15-1

Analysis of Genetic Variants Related to the Hepatic Veno-Occlusive Disease in Pediatric Patients Receiving HSCT with Targeted Dose Busulfan Based Conditioning

Jung Yoon Choi[1], Heewon Seo[2,3], Yoomi Park[2,3], ByungJoo Min[2,3], Hyery Kim[4], Kyung Taek Hong[1], Che Ry Hong[1], Kyung¬Sang Yu[5], In¬-Jin Jang[5], Sang-Hoon Song[6], Hee Young Shin[1], Ju Han Kim[2,3], Hyoung Jin Kang*[1]

[1] Department of Pediatrics, Cancer Research Institute, Seoul National University College of Medicine, Korea
[2] Division of Biomedical Informatics, Seoul National University College of Medicine, Korea
[3] Systems Biomedical Informatics Research Center, Seoul National University, Korea
[4] Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center Children's Hospital, Korea
[5] Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Korea
[6] Department of Laboratory Medicine, Seoul National University College of Medicine, Korea

Background : Intensive monitoring and dose adjustment following therapeutic drug monitoring (TDM) of busulfan has improved outcomes after hematopoietic stem cell transplantation (HSCT). However, treatment toxicities such as veno-occlusive disease (VOD) still developed after TDM in some patients. In this study, we identified additional genetic variants related to hepatic VOD in pediatric patients.

Methods : Targeted once-daily for four days intravenous busulfan with pharmacokinetic modeling was performed. The first dose of busulfan was 120 mg/m^2 for patients aged ≥1 year and 80 mg/m^2 for patients aged < 1 year. The target area under the curve (AUC) was 18,750 mg•h/L/day for the first three days, and the AUC on the fourth day was decided as (75,000 – cumulative AUC during 3 days) mg•h/L/day. Targeted sequencing was conducted with DNA from patients' remission samples by a designed panel of 147 genes and 84 single nucleotide polymorphisms known to be involved in the pharmacokinetics or pharmacodynamics of multiple drugs. The relationship between sequenced genotypes and the occurrences of VOD was analyzed.

Results : A total of 123 patients with malignant diseases underwent allogeneic or autologous HSCT with targeted dose busulfan conditioning. VOD developed in 19 patients (15.4 %). The total AUC in patients with or without VOD was 70,456 to 87,448 mg•h/L/day (median, 75,157 mg•h/L/day) and 69,295 to 83,160 mg•h/L/day (median, 74,436 mg•h/L/day), respectively (P=0.20). The genotypes of rs17224367 (MSH2 [MutS Homolog 2], odds ratio [OR] = 4.4, P = 0.047), rs190420353 (ABCC1 [ATP Binding Cassette Subfamily C Member 1], OR = 59.2; P=0.0037), rs79242783 (UGT2B17 [UDP Glucuronosyltransferase Family 2 Member B17], OR = 15.6 ; P = 0.0030), and rs45547640 (XDH [xanthine dehydrogenase], OR = 5.83 , P = 0.013) were significantly associated with higher risk of hepatic VOD. MSH2, a member of the mismatch repair genes, has been implicated in sensitivities or resistances to alkylating agents such as busulfan. ABCC1, UGT2B17 and XDH are associated with multi-drug resistances and drug-related hepatic and renal toxicities.

Conclusions : Several genotypes were identified to be highly associated with hepatic VOD in pediatric patients. For these patients, more attention and prophylactic medications, such as defibrotide, are required. Further validation and replication studies in a larger group of patients are needed.

Keyword : Busulfan, Hepatic Veno-Occlusive Disease, Variants, Pharmacogenomic, Stem cell transplantation

OP15-2

Enhanced Immunosuppressive Properties of Human Mesenchymal Stem Cells Primed by Inflammatory Stimuli

Dae Seong Kim[1,2], Myoung Woo Lee[1,2], Ji Won Lee[2], Ki Woong Sung[2], Hong Hoe Koo[1,2,3], Keon Hee Yoo*[1,2,3]

[1] Stem Cell and Regenerative Medicine Institute for Future Medicine, Samsung Medical Center, Korea
[2] Department of Pediatrics, Sungkyunkwan University School of Medicine, Korea
[3] Samsung Biomedical Research Institute, Samsung Advanced Institute of Technology (SAIT), Samsung Electronics Co., Ltd, Korea

Background : A number of preclinical and clinical trials of human mesenchymal stem cells (MSCs) are currently in progress worldwide; however, their clinical benefit is often limited. Therefore, strategies to enhance MSCs' immunosuppressive properties need to be sought. In this study, the effects of ex vivo culture conditions such as the presence of inflammatory stimuli including IFN-γ, TNF-α, and poly(I:C) on the immunosuppressive properties of MSCs were investigated.

Methods : The gene expression profiles under IFN-γ, TNF-α, or poly(I:C) treatments were compared using RT-PCR analysis and microarray. In addition, the impact of IFN-γ treatment and regulation of IDO and PGES expression on MSCs' in vitro and in vivo function was analyzed.

Results : The expression of chemokine genes, immunomodulation-associated genes, anticancer effect-associated genes, and an adhesion-associated gene were significantly upregulated in IFN-γ-treated MSCs compared with TNF-α- or Poly(I:C)-treated MSCs. Furthermore, IFN-γ-treated MSCs significantly increased the survival rates of graft-versus-host disease (GVHD) mice compared with MSCs without IFN-γ stimulation. Downregulation of IDO in MSCs by shRNA resulted in restoration of T-cell proliferation in vitro and decreased the survival rates of GVHD mice. These results indicate IFN-γ produced by activated T-cells is correlated with induction of IDO expression in MSCs and IDO has a key role to suppress T-cell proliferation and alleviate GVHD in mice. In addition, the role of PGE2 pathway members in PGE2-mediated immunosuppression by BM-MSCs in response to inflammatory stimuli were investigated. The toll like receptor 3 (TLR3) stimulant poly(I:C) increased prostaglandin E synthase (PGES) compared with IFN-γ and TNF-α, resulting in a significant increase in PGE2 levels. Reduced PGE2 levels decreased MSC's capacity to inhibit hPBMC proliferation. Administration of MSCs with inhibited PGES expression into mice with GVHD did not reduce mortality. These results indicate that upregulation of PGES via TLR3 is critical for BM-MSCs-mediated immunosuppression by PGE2 secretion via the COX-2/PGE2 pathway.

Conclusions : These results suggest that IFN-γ or Poly(I:C) priming during culture expansion could be an effective strategy to enhance MSCs' immunosuppressive properties for the enhanced cell therapy in GVHD, thereby controlling culture condition.

Keyword : Mesenchymal stem cells, IFN-Gamma, IDO, PGES, Immunosuppression

OP15-3

Ruxolitinib Treatment for Steroid-Refractory Graft-Versus-Host Disease

Han-Seung Park, Je-Hwan Lee*, Jung-Hee Lee, Eun-Ji Choi, Sun-Hye Ko, Miee Seol, Young-Shin Lee, Young-Ah Kang, Mijin Jeon, Jin Yeong Im, Kyoo-Hyung Lee
Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea

Background : Steroid-refractory graft versus-host disease (GVHD) is one of the most lethal complications after allogeneic hematopoietic cell transplantation (HCT). Recent studies have shown that ruxolitinib, a Janus kinase 1/2 inhibitor, is effective in patients suffering from GVHD. Here, we report a retrospective result of ruxolitinib treatment for steroid-refractory GVHD.

Methods : All patients had received cyclosporine and a short course of methotrexate as GVHD prophylaxis. Antithymocyte globulin was added for unrelated or mismatched familial donor HCT. Ruxolitinib 5 mg twice daily was added to immunosuppressive treatment in patients with steroid-refractory GVHD.

Results : A total of 27 patients with GVHD (acute, 8, including 3 patients with donor lymphocyte infusion [DLI]-related; and chronic, 19) were included in the analysis. All patients had grade 3/4 acute GVHD or severe chronic GVHD at the time of ruxolitinib treatment.
Six (75.0%) of 8 patients with acute GVHD responded to ruxolitinib, including 3 with complete response. The median time to response was 13.5 days (range, 8-25). Nineteen patients received ruxolitinib for severe chronic GVHD, with the median of 3 involved organs (range 2-5). Fourteen patients (73.7%) showed response to ruxolitinib, including 4 CRs. The median time to response was 24 days (range, 12-138). Five responders discontinued ruxolitinib and 9 patients are still on the agent.
After a median follow-up duration of 8.7 months, 5 died (2 from relapse of disease, 3 from infection). The 1-year survival probability was 70.1%. Eleven of 20 responders discontinued ruxolitinib. GVHD relapsed in 3 of 11 patients at 14, 35, and 149 days after ruxolitinib discontinuation. Thrombocytopenia (12/27, Grade3/4; 4) was the most common adverse event of ruxolitinib. During treatment, 4 with grade 3/4 infectious adverse events occurred; 2 pneumonias, 1 brain abscess, and 1 liver abscess.

Conclusions : Ruxolitinib treatment seems to be effective for the treatment of steroid-refractory GVHD including long-standing chronic GVHD. The agent was well tolerated and relatively safe.

Keyword : Ruxolitinib, GVHD, Allogeneic HCT

OP15-4

Change of Gut Bacterial Diversity by Antibiotics Correlates with the Occurrence of Intestinal GVHD

Sung-Eun Lee[1], Ji-Young Lim[1], Da-Bin Ryu[1], Tae Woo Kim[1], Sung Soo Park[1], Young-Woo Jeon[1], Jae-Ho Yoon[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Hee-Je Kim[1], Seok Lee[1], Seok-Goo Cho[1], Dong-Wook Kim[1], Jong Wook Lee[1], Dong-Mi Shin[2], Chang-Ki Min[1]
[1] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, College of Medicine, Korea
[2] College of Human Ecology, Seoul National University, Korea

Background : Patients undergoing allogeneic stem cell transplantation (allo-SCT) frequently receive empiric antibiotics during the neutropenic period before engraftmen. Recently, several studies have shown that anaerobes in the intestine are important mediators of intestinal homeostasis and commensal bacteria can be potent modulators of the severity of acute graft-versus-host disease (aGVHD). However, correlation with broad-spectum antibiotics and the occurrence of aGVHD are not clear.

Methods : A total of 211 patients receiving allo-SCT were stratified into three groups; the patients who were not treated with any antibiotics during the neutropenic period (group 1, n = 43) and patients who were treated with cefepime only (group 2, n = 87) or broad-spectrum antibiotics, defined as meropenem or prepenem with/without prior cefepime therapy (group 3, n = 81). In addition, we examined the intestinal microbiota of patients pre- and post-transplant.

Results : Among a total of 211 patients, 95 patients (45%) developed aGVHD (≥grade 2) including 54 with intestinal aGVHD. The patients in group 3 had a trend for higher incidence of aGVHD (≥grade 2) (53.1%) compared with those of group 1 (32.6%) and group 2 (43.7%), respectively (P = 0.087). The incidence of intestinal aGVHD were also higher in broad-spectrum antibiotics group (P = 0.044). After adjusting for potential variable in univariate analysis, multivariate analyses revealed that broad-spectrum antibiotics use during the neutropenic period was associated with occurrence of intestinal aGVHD [HR (95% CI) 3.25 (1.13-9.34), P=0.029]. The patients without antibiotics showed no significant difference between pre- and post-transplant microbial diversity whereas the patients with antibiotics showed a marked decrease in the diversity. Interestingly, majority of the patients with aGVHD showed the loss of microbiota diversity.

Conclusions : Our data indicated that broad-spectrum antibiotics use during the neutropenic period was associated with a higher incidence of intestinal aGVHD via loss of microbiota diversity. Further studies are needed to determine whether maintaining bacterial diversity prevents aGVHD.

Keyword : Bacterial diversity , Antibiotics, Graft-Versus-Host-Disease

OP16-1

Mean Platelet Volume and Platelet Distribution Width Reflect the Pathophysiology of ITP and ET

Eunyup Lee, Kibum Jeon, Jiwon Lee, Miyoung Kim*, Han-Sung Kim, Hee Jung Kang, Young Kyung Lee
Department of Laboratory Medicine, Hallym University Sacred Heart Hospital, Korea

Background : Mean platelet volume (MPV) and platelet distribution width (PDW) may reflect the pathomechanism of Immune Thrombocytopenic Purpura (ITP) and Essential Thrombocythemia (ET).

Methods : Platelet count, MPV and PDW were measured in 153 healthy individuals using Advia 2120i and XN-3000, simultaneously. In ITP group, CBC was measured using either Advia 2120i or XN-3000 in 35 and 20 samples, respectively. In ET group, CBC was measured using either Advia 2120i or XN-3000 in 48 and 34 samples, respectively.

Results : MPV was significantly increased in ITP patients compared to healthy individuals, irrespective of the instrument used. MPV measured in both instruments was significantly decreased in ET patients compared to both ITP and healthy individuals. ET patients showed lower PDW values than healthy individuals when measured using Advia 2120i, but showed no difference in PDW values compared to healthy individuals when measured using XN-3000 (Fig. 1). Both MPV and PDW measured using Advia 2120i showed significantly higher values in ET patients with < 770×10^3/uL than in the ET patients with ≥770×10^3/uL (Table 1)

Conclusions : The thrombopoiesis and/or antibody-mediated platelet destruction occur in a complicated manner in ITP and ET, and it is reflected in MPV and PDW. In addition, MPV and PDW correlate with the platelet count in ITP and ET.

Keyword : Thrombopoiesis, Mean platelet volume, Platelet distribution width, Immune Thrombocytopenic Purpura, Essential Thrombocythemia

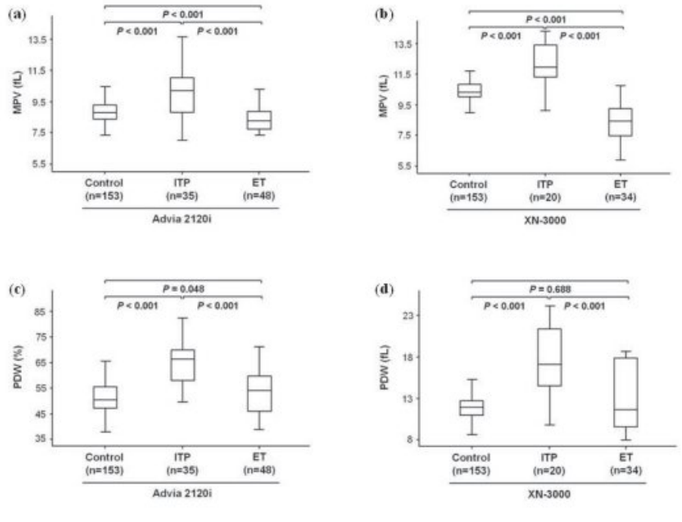


Table 1. Mean platelet volume (MPV), platelet distribution width (PDW) and platelet count in (a) immune thrombocytopenic purpura (ITP) and (b) essential thrombocythemia (ET)

(a)						
	ITP					
	Advia 2120i			XN-3000		
	PLT < 45×103/uL	PLT ≥ 45×103/uL	P value	PLT < 45×103/uL	PLT ≥ 45×103/uL	P value
	(n = 18)	(n = 17)		(n = 9)	(n = 11)	
MPV (fL)	10.5 (8.8 – 2.3)	9.4 (8.5 – 10.6)	0.215	11.3 (9.6 – 13.8)	12.0 (11.4 – 13.4)	0.543
PDW (% or fL)†	67.8 (58.4 – 72.0)	63.7 (57.1 – 69.0)	0.142	17.2 (12.7 – 21.3)	16.5 (14.9 – 21.6)	0.882
(a)						
	ET					
	Advia 2120i			XN-3000		
	PLT < 770×103/uL	PLT ≥ 770×103/uL	P value	PLT < 770×103/uL	PLT ≥ 770×103/uL	P value
	(n = 25)	(n = 23)		(n = 14)	(n = 20)	
MPV (fL)	8.5 (7.8 – 9.2)	8.1 (7.6 – 8.4)	0.042	8.8 (7.4 – 9.6)	8.1 (7.4 – 9.2)	0.616
PDW (% or fL)†	57.1 (52.2 – 64.3)	50.2 (41.7 – 57.3)	0.008	11.1 (9.0 – 17.8)	14.4 (9.6 – 17.7)	0.592

*Abbreviations: ITP, immune thrombocytopenic purpura; ET, essential thrombocythemia; MPV, mean platelet volume; PDW, platelet distribution width.
†PDW is expressed in % in Advia 2120i and in fL in XN-3000.
‡Values are shown as median (interquartile range).

OP16-2

Clinical Features and Outcomes of Borderline Thrombocytopenia: a Single Center Experience

Ik Chan Song, Hyewon Ryu, Yoon Seok Choi, Hyo Jin Lee, Hwan Jung Yun, Deog Yeon Jo*
Department of Internal Medicine, College of Medicine, Chungnam National University, Korea

Background : Clinical implications of platelet count between 100,000/uL and 150,000/uL (so called 'borderline thrombocytopenia') remain controversial, particularly in real practice. This study aimed to define clinical features and outcomes in individuals with borderline thrombocytopenia.

Methods : This retrospective study enrolled individuals with primary borderline thrombocytopenia who initially presented between January 2001 and December 2012 at Chungnam National University Hospital.

Results : Eighty-one individuals with a median age 51 (range, 19-79) years were enrolled, which accounts for 67.5% of all individuals with borderline thrombocytopenia. Borderline thrombocytopenia was detected during regular health check-up, health check-up for military recruit and preoperative check-up in 27 (33.3%), 9 (11.1%), and 5 (6.2%) individuals, respectively. Coexisting conditions or disorders of unlikely causative relationship, such as diabetes mellitus, hypertension, chronic kidney disease, ischemic heart disease, and osteoarthritis, were present in 50 (61.7%) individuals. Median platelet count at presentation was 113,500/ L (range, 102,000/ L – 148,000/uL). Of the 12 individuals who underwent bone marrow examination, 10 (83.3%) revealed hypocellular marrow for age. Sixty of the 81 (74.1%) individuals, who were followed-up for 6 or more months (median, 5.3 years; range, 0.5-14.7 years), were further analyzed for clinical course and outcome. Forty-six (76.7%) individuals experienced one or more episodes of fluctuations in platelet count (> 150,000/uL and/or < 100,000/uL). The fluctuation tended to be more frequent in the individuals having coexisting conditions or disorders. At the time of the last visit, 11 (18.3%) individuals revealed platelet count > 1500,000/uL, 33 (55.0%) individuals 100,000/uL – 150,000/uL, 15 (25.0%) individuals 50,000/uL - 100,000/uL, and 1 (1.7%) individual < 50,000/uL. One of the 3 individuals who were positive in urea breath test restored normal platelet count after H. pylori eradication therapy. Three (5.0%) individuals developed chronic ITP.

Conclusions : Borderline thrombocytopenia is a heterogeneous condition. Although clinical courses are modest in majority of individuals with borderline thombocytopenia, a population of the individuals experience a various degree decrease in platelet count with time, indicating that regular follow-up is necessary.

Keyword : Borderline thrombocytopenia, Immune thrombocytopenia

OP16-3

Genetic Confirmation of Platelet Function Disorders by Diagnostic Exome Sequencing (K-PHOG Study)

Ye Jee Shim[1], Heung Sik Kim[1], Jae Min Lee[2], Ho Joon Im[3], Hyery Kim[3], Eun Sil Park[4], Na Hee Lee[5], Jin Kyung Suh[6], Young Tak Lim[7], Eu Jeen Yang[7], Jung Woo Han[8], Jae Hee Lee[9], Hye Lim Jung[10]

[1] Pediatrics, Keimyung University School of Medicine and Dongsan Medical Center, Korea
[2] Pediatrics, College of Medicine, Yeungnam University, Korea
[3] Pediatrics, Asan Medical Center, Children's Hospital, University of Ulsan College of Medicine, Korea
[4] Pediatrics, Gyeongsang National University School of Medicine, Korea
[5] Pediatrics, Cha Bundang Medical Center, Cha University, Korea
[6] Pediatrics, Gachon University Gil Medical Center, Korea
[7] Pediatrics, Pusan National University Children's Hospital, Korea
[8] Pediatrics, Yonsei University College of Medicine, Korea
[9] Pediatrics, Chosun University School of Medicine, Korea
[10] Pediatrics, Sungkyunkwan University School of Medicine, Korea

Background : Congenital Platelet Function Disorders are very heterogeneous group with several categories of diseases. They should be exactly diagnosed for the appropriate management and genetic counseling. Thus we intended to confirm the diagnosis and find the causative genetic mutations in children with primary hemostasis problem by diagnostic exome sequencing (DES).

Methods : This is an ongoing multicenter study by Korean Pediatrics Hematology-Oncology Group (K-PHOG). Library preparation was performed with TruSight One sequencing panel (Illumina, USA), which enriches about 4,800 genes with clinical relevance. Massively parallel sequencing was conducted with NextSeq (Illumina). Diseases of primary interest were those associated with platelet dysfunction or coagulation; for VWF exons of either incomplete coverage or low mapping quality due to highly homologous region (exon 26, 24), additional Sanger sequencing was performed. Variants were annotated with population databases (1000 Genomes Project, Exome Variant Server, Exome Aggregation Consortium) and disease databases (OMIM). For missense variant, in-silico analysis was done with SIFT, PolyPhen-2, MutationTaster. Candidate variants were confirmed by Sanger sequencing in index patients and available family members.

Results : Nineteen index patients with primary hemostatic problems - easy bruising, frequent epistaxis, menorrhagia, postpartum bleeding or hematuria - and their family members were enrolled from 9 Korean medical centers. Among them, 6 unrelated index patients were confirmed as Glanzmann's thrombasthenia (GT), 7 patients were diagnosed as von Willebrand disease (vWD), 1 patients was confirmed as mild hemophilia A, and 1 patient was diagnosed as factor V deficiency, genetically. The clinical diagnosis, found variants, associated diseases, genetic confirmation, and the results of family studies were shown in Table 1.

Conclusions : DES is a valuable method for genetic confirmation of platelet function disorders. Further study is needed to find out unidentifiable mutations by this strategy.

Keyword : Glanzmann thrombasthenia, Von Willebrand disease, Next generation sequencing, Exome sequencing

Table 1. The clinical diagnosis, found genetic variants, associated disease, and the results of family studies in the patients with primary hemostatic problems.

ID	Clinical diagnosis	Found genetic variants	Associated disease	Genetic confirm	Family study
KM-01	GT	ITGB3 –c.1451G>T (p.Gly484Val) – Hetero ITGB3 – c.1913+5G>T (splicing) – Hetero	GT	Confirm	Parents carrier Sibling GT
KM-02	GT	ITGB3 – c.1913+5G>T (splicing) – Homo	GT	Confirm	Parents & Sibling carrier
KM-03	GT	ITGB3 – c.1913+5G>T (splicing) – Homo	GT	Confirm	Daughter & son carrier
KS-01	GT	ITGB3 – c.917A>C (p.His306Pro) – Hetero ITGB3 – c.1913+5G>T (splicing) – Hetero	GT	Confirm	ND
AS-01	GT	ITGA2B – c.257T>C (p.Leu86Pro) – Hetero ITGA2B – c.2333A>C (p.Gln778Pro) – Hetero	GT	Confirm	Parents carrier
AS-02	GT	ITGA2B – c.2390del (p.Gly797Valfs*29) – Hetero ITGA2B – c.2333A>C (p.Gln778Pro) – Hetero	GT	Confirm	ND
KM-04	vWD type 1	VWF – c.2008C>T (p.Arg670Cys) – Hetero	vWD type 1	Confirm	Mother vWD
KM-05	vWD type 1	VWF – c.1728G>T (p.Met576Ile) – Hetero	vWD type 1	Confirm	Father & sibling vWD
GG-01	vWD type 1	VWF – c.2540A>G (p.Asn847Ser) – Hetero	vWDtype 1	Confirm	Mother vWD
KM-06	vWD type 1 or 2	VWF – c.2574C>G (p.Cys858Trp) – Hetero VWF – c.3390C>T (p.Pro1127_Gly1180delinsArg) – Hetero	vWD type 1 and 2A combination	Confirm	Parents & Sibling vWD
YN-01	vWD type 2	VWF – c.5170+5G>A (exon 29 skipping) – Hetero	vWD type 2	Confirm	Father vWD Grandmother & Uncle same phenotype
YN-02	vWD type 2	VWF – c.3922C>T, p.(Arg1308Cys) – Hetero	vWD type 2B	Confirm	ND
CB-01	Platelet function disorder or vWD	VWF –c.790G>A (p.Ala264Thr) – Hetero VWF – c.6666C>A (p.Gly2222=) - Hetero	vWDtype 1	Confirm	Sibling same phenotype, same mutation; Mother & Aunt same phenotype
KM-07	vWD or hemophilia	F8 –c.3169G>A, p.(Glu1057Lys) – Hetero	Mild Hemophilia A	Confirm	Two cousin haemophilia A Mother & Aunt carrier
YN-03	Platelet function disorder of factor V deficiency	F5 – c.286G>C (p.Asp96His) – Hetero F5 – c.2032A>G (p.Lys678Glu) – Hetero F5 – c.5030A>G (p.Tyr1677Cys) - Hetero	Factor V deficiency	Confirm	Parents carrier
KM-08	vWD	P2RY12 – c.116G>C (p.Gly39Ala) – Hetero	platelet-type bleeding disorder 8	Under discussion	Mother same phenotype, same mutation
KM-09	Familial thrombocytopenia or megakaryocytic throbocytopenia	SLX4 – c.164G>A (p.Cys55Tyr) – Hetero SLX4 –c.3307C>T (p.Arg1103Cys) – Hetero FANCA – c.1049G>A (p.Arg350Gln) – Hetero	Fanconi anemia	Under discussion	Father same phenotype
YS-01	Platelet function disorder or factor XIII deficiency	ADAMTS2 – c.664G>A (p.Gly222Arg) – Hetero ADAMTS2 – c.2834C>T (Pro945Leu) – Hetero	Ehlers-Danlos syndrome, type VIIC	Under discussion	ND
AS-03	Platelet function disorder or factor XIII deficiency	KLKB1 - c.872C>G (p.Pro291Arg) – Hetero F2– c.13C>G (p.Arg5Gly) – Hetero	Fletcher factor (prekallikrein) deficiency and Thrombophilia due to thrombin defect	Under discussion	ND

OP16-4

Hot-Line to Increase the Survival in Hemophilia Patient with Life-Threatening Hemorrhage

Kun Soo Lee, Ji Yoon Klim
Pediatrics, Kyungpook National University School of Medicine, Korea

Background : Because the incidence, severity and healing of intracranial hemorrhage (ICH) is closely and mainly related with the severity of disease and blood factor level, rapid transportation and infusion of factor concentration at ER for surgery before history taking, blood examination and radiologic evaluation are very important to save the life and to minimize the sequelae. To fulfill this we had a hot-line communication between doctor and patient. A long time ago, we recommended hanging the tag of recognition for hemophilia to patients, but they refused because they didn't want to do.

Methods : Annual routine examination including recovery test, home treatment, on-demand treatment and prophylactic treatment for severe type are recommended. Education and hot-line communication for emergency had been permitted for more than 30 years. We evaluated the time to infuse the factor concentrator after arrival at ER between hot-line communication and no hot-line communication. To keep effective blood factor level we recalculated the dose based on the personal recovery rate for surgery case. To keep in vitro activity of concentrate for continuous infusion we freshly reconstitute lyophilized powder every 2-4 hour.

Results : With hot-line communication we were always ready to infuse the calculate dose of concentrate before he were arriving at ER. But in patient with no hot-line communication it took several hours to infuse factor concentrator with registration at ER, several times of preliminary history taking and physical examination and blood tests and radiologic and MRI or CT examination because diagnosis was not made.

Conclusions : Introducing our unique policy for handling hemophilia patients for more than 30 years, hot-line communication and optimal blood factor concentration are very important to minimize the sequelae of life threatening hemorrhage. Time is life.

Keyword : Hemophilia, Life-Threatening hemorrhage

OP16-5

Effect of Peramivir on Platelet Counts in Patients with Suspected or Confirmed Influenza Infection

Young-Gon Kim, Sun-Young Ko*, Chang Kyu Lee, Yunjung Cho, Dae-Won Kim
Laboratory Medicine, Korea University Medical Center, Korea

Background : Several cases and one retrospective study have been published recently of an increase of platelet count in patients with suspected influenza after oseltamivir treatment. The purpose of this study was to assess the effect of peramivir, an intravenous neuraminidase inhibitor which was approved by FDA in 2014, on platelet counts for the first time.

Methods : We retrospectively analyzed consecutive patients who were treated with peramivir or were tested for influenza from January 2015 to December 2017 in a tertiary hospital. Patients were divided into three groups: patients with peramivir treatment and proven influenza (group 1), with peramivir treatment but without influenza (group 2), and without peramivir treatment with proven influenza. The last group was redefined as patients with oseltamivir treatment with proven influenza (group 3), since most of the patients without peramivir treatment were treated with oseltamivir. Platelet counts were collected from three intervals: day (-30)-(-10) (baseline), day 0, and day 5-15 (after treatment). Day 0 was the day of peramivir injection in group 1 and 2 and was the first day of oseltamivir treatment in group 3.

Results : A total of 1,763 patients were treated with peramivir and 3,796 patients were tested positive for influenza. The number of patients in each group were 1,542, 221, and 2,162 and the number of patients whose platelet counts were available from all three intervals were 347, 93, and 88 for group 1, 2, and 3, respectively. Intragroup analysis revealed statistically significant decrease in platelet counts from baseline to day 0 in all groups (group 1: 261.6k vs. 204.7k, P<0.0001; group 2: 253.4k vs. 214.2k, P=0.0034; group 3: 249.2k vs. 197.4k, P<0.0001). After treatment, platelet counts of group 1 and group 2 recovered to that of the baseline while of platelet count of group 3 were significantly higher (group 1: 261.6k vs. 266.8k, P=0.3606; group 2: 253.4k vs. 252.2k, P=0.8411; group 3: 249.2k vs. 279.5k, P=0.0106).

Conclusions : The increase of platelet counts after treatment that exceeds that of the baseline was observed only in patient group treated with oseltamivir but not in those with peramivir. The reason for this different findings between the two neuraminidase inhibitors on platelet count needs further investigation.

Keyword : Peramivir, Platelet, Influenza, Oseltamivir, Neuraminidase inhibitor

OP16-6

Immature Platelet Fraction as a Predictor of Bone Marrow Cellularity in Thrombocytopenic Patients

Ha Jin Lim, Jun Hyung Lee, Yong Jun Kwon, Hyun-Jung Choi, Soo-Hyun Kim, Myung-Geun Shin*
Department of Laboratory Medicine, Chonnam National University Medical School and Chonnam National University Hwasun Hospital, Korea

Background : Immature platelet fraction (IPF) reflects newly formed young platelets and it is known to be related to thrombopoietic activity. So we suggest that this index could give us clues of the cause of thrombocytopenia and bone marrow cellularity. We aimed to compare the value of IPF in thrombocytopenic patients, especially in idiopathic thrombocytopenic purpura (ITP), aplastic anemia (AA) and myelodysplastic syndrome (MDS) patients. Furthermore, we studied about relationship between IPF and bone marrow cellularity in MDS patients.

Methods : A total of 60 whole blood samples which were obtained at the time of first diagnosis from thrombocytopenic patients were tested. Study groups included the patients with idiopathic thrombocytopenic purpura (n=15), aplastic anemia (n=7) and myelodysplastic syndrome (n=38). The level of IPF was measured on the XN-1000 automated hematology analyzer (Sysmex Corp., Kobe, Japan).

Results : A total of 60 whole blood samples were tested with the Sysmex XN-1000 for IPF level. When comparing the value of IPF in three groups of thrombocytopenic patients, the median IPF% was 14.7% (range from 3.4% to 34.1%), 4.8% (range from 2.9% to 7.3%) and 8.9% (range from 2.3% to 63.2%) in idiopathic thrombocytopenic purpura, aplastic anemia and myelodysplastic syndrome group with having significant differences (p=0.016). In addition, we divided MDS patients by their cellularity of bone marrow into hypercellular/normocellular and hypocellular group. As a result hypocellular MDS (n=8) has a lower IPF level (7.0 ± 4.8%) than its value (18.5 ± 16.0%) of hypercellular/normocellular MDS (n=30), (p value=0.002). And it had a positive correlation between IPF levels and bone marrow cellularity in MDS group (R=0.507, p=0.001), also when bone marrow cellularity was adjusted by age (R= 0.379, p=0.021).

Conclusions : The IPF count can be helpful in predicting cellularity of MDS patients, which is important for treatment and prognosis prediction, as well as differential diagnosing in thrombocytopenic patients. Therefore, it can be used as a supportive index for thrombocytopenic patients.

Keyword : Immature platelet fraction, Myelodysplastic syndrome, Bone marrow cellularity

OP17-1

Expression of Inhibitory Receptors on T cells and Inhibitory Ligands on Leukemic Blasts in Childhood Acute Leukemia

Kyung-Nam Koh[1], Nayoung Kim[2], Hyun Ju Hwang[2], Sung Han Kang[1], Jae Won Yoo[1], Eun Seok Choi[1], Hyery Kim[1], Ho Joon Im[1], Jong Jin Seo[1]

[1] Division of Pediatric Hematology/Oncology, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea
[2] Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Korea

Background : Clinical implication of the inhibitory immune checkpoint pathways is still to be explored in hematologic malignancies. This study was performed to investigate the differences between expression of inhibitory receptors and ligands and their impact on prognosis in childhood acute leukemia.

Methods : The expressions of inhibitory receptors, programmed-death 1(PD-1), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and B- and T-lymphocyte attenuator (BTLA)on alpha beta T cell and gammadelta T cellfrom patients with newly diagnosed ALL (n = 9) and AML (n = 12), and healthy volunteers(n = 7) were determined by flow cytometry. The expression of inhibitor ligands, PD-L1, B7-1, B7-2, and herpesvirus-entry mediator (HVEM) on leukemic blasts were determined by flow cytometry and real-time PCR.

Results : Expression of inhibitory receptors on alpha beta T cell and gamma delta T cell between healthy volunteers and patients with ALL and AML were not significantly different. Expression of PD-1 on alpha beta T cell and gamma delta T cell were significantly higher in patients with ALL compared to those with AML (p = 0.003 and < 0.001, respectively), and expression of CTLA-4on alpha beta T cell and gamma delta T cell seemed modestly higher in patients with ALL (p = 0.077 and 0.077, respectively). Expression of inhibitory ligandson blasts were not significantly different between patients with ALL and AML. In ALL, expression of PD1 and CTLA-4 on gamma delta T cell were significantly and modestly higher, respectively(p = 0.032 and 0.063)in high-risk patients. In ALL, higher expression of CTLA-4 on gamma delta T cell and higher expression of PD-L1 on blasts were significantly associated poor relapse-free survival (p = 0.049).In AML, higher expression of B7-1 on blasts were modestly associated with poor relapse-free survival (p = 0.066).

Conclusions : This study suggests that PD-1 and CTLA-4 signaling pathways may have different effects on the pathogenesis of ALL and AML. Expression of CTLA-4 and PD-L1 were associated with prognosis in ALL, and expression of B7-1 seemed to be associated with prognosis in AML. These results suggest that blockade of these pathways may be a potential target in ALL and AML.

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OP17-2

Reversal of Cytarabine Resistance in AML-OCI2 Cell Line after Na/H Exchanger 1 Modulation

June-Won Cheong[1], Eun Jung Na[2], Shin Young Hyun*[3]

[1] Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Korea
[2] Avison Biomedical Researcch Center, Yonsei University College of Medicine, Korea
[3] Division of Hematology and Oncology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Korea

Background : Na/H exchanger 1 (NHE1), an important participant in the precise regulation system of intracellular pH (pHi), is known to be involved in pathological processes of the neoplastic disease. In this study, we evaluated the intracellular (pHi) and NHE1 expression in Acute myeloid leukemia (AML) cell lines and whether it contributes the resistance to cytarabine (AraC)

Methods : We evaluated the pHi and NHE1 expression in AML cell lines AraC sensitive OCI-AML2 (AS-OCI) and AraC resistant OCI-AML2 (AR-OCI) cells. To modulate the NHE1 activity, the NHE1 inhibitor, 5-(N,N-hexamethylene) amiloride (HMA), and NHE1 activator, phorbol 12-myristate 13-acetate (PMA), was used. The level of apoptosis and proliferation induced by NHE1 inhibitor or activator with/without AraC was assessed at 24 hr after treatment by the annexin V assays and the CCK-8 assay.

Results : The pHi of AR-OCI cells was significantly higher than AS-OCI cells (7.839 vs 7.589, P=.045). Compared with AS-OCI cells, AR-OCI showed significantly higher NHE1 expression by western blot analysis, and NHE1 mRNA levels (1.565 vs 0.039, P<.001) by qRT-PCR. After 24hr treatment with HMA 10 ~ 30 μM, the proliferation of leukemic cells was inhibited and the apoptosis was induced in a concentration-dependent manner, and higher concentration of HMA (30 μM) could induced apoptosis on most of AR-OCI cells. When treated with PMA 0.1~10 uM, proliferation of leukemic cells was inhibited in a concentration-dependent manner but apoptosis was not induced. The addition of HMA 10 μM that concentration did not cause apoptosis of AR-OCI cells when treated alone to AraC treatment resulted in a significant increase in the fraction of apoptosis in AR-OCI cells (P<.001) as compared with that of AraC treatment alone (26.33% vs 7.11%, P<.001). Also, the addition of PMA 1 μM to AraC treatment resulted in a significant increase in the level of apoptosis in AR-OCI cells as compared with that of AraC treatment alone (45.70% vs 7.11%, P<.001).

Conclusions : These findings suggest that NHE1 is involved in the leukemogenesis and mechanism of the resistance to AraC. Further experimental studies are needed to elucidate the detailed signaling pathway after modulation of NHE1 activity. Then, targeting the NHE1 pathway could be an effective therapeutic strategy for overcoming resistance to AraC in AML.

Keyword : Acute myeloid leukemia, Resistance, Cytarabine, Na/H exchanger 1

OP17-3

The Role of Myeloid-Derived Suppressor Cell-Like Blasts in Acute Myeloid Leukemia

Shin Young Hyun[1], Eun Jung Na[2], June-Won Cheong*[3]

[1] Division of Hematology and Oncology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Korea
[2] Avison Biomedical Researcch Center, Yonsei University College of Medicine, Korea
[3] Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Korea

Background : Myeloid-derived suppressor cells (MDSC) have an ability to suppress T-cell function and have been known to facilitate tumor growth. We elucidated the immune suppressive function of leukemic blasts which resembled MDSC phenotype and their role in the growth of leukemic cells.

Methods : CD11b+CD33+HLA-DR- blast (MDSC-like blast) were isolated using flow-cytometry from primary acute myeloid leukemia (AML) samples. To evaluate the immune-suppressive ability, CD8+ T cells from healthy donor and MDSC-like blasts were co-cultured with/without phytohemagglutinin A (PHA) and proliferation of T cells was measured after 3 days of culture. To assess the ability to restore the proliferation of leukemic cells which suppressed by T cells, various leukemic cell lines were co-cultured with jurkat T cells and/or MDSC-like blasts enriched primary AML cells from patients. The level of cell proliferation was assessed by the CCK-8 assay after 1 and 3 days of culture. To define the prognostic impact, AML patients (n=63) were divided into 'High MDSC' or 'Low MDSC' group based on the median fraction of MDSC-like blasts (12.64%), and clinical outcomes were compared.

Results : MDSC-like blasts showed higher expression of Arg1 and iNOS. CD8+ T cell proliferation induced by PHA was significantly suppressed when co-cultured with MDSC-like blasts ($P < 0.01$) . Among the various AML cell lines, the proliferation of NB4 cells were significantly suppressed when co-cultured with jurkat T cells on day 3 ($P < 0.01$) and the proliferation of NB4 cells was partially restored when co-cultured with MDSC-like blasts (P=0.022). Patients with 'High MDSC' had a significantly shorter overall survival (331±42 vs. 758±114 days, P=0.027) and also tended to have shorter leukemia-free survival (341±47 vs. 730±116 days, P=0.062). Multivariate analysis showed that higher fraction of MDSC-like blast cells (Hazard ratio 2.966, 95% CI 1.086-8.095, P=0.034) were poor prognosis factors for short overall survival.

Conclusions : MDSC-like blasts subpopulation which expressed the iNOS and Arg1 existed in AML. These blasts showed ability to suppress the T cell proliferation and restore the inhibited NB4 cell proliferation by T cells. Clinically, higher fraction of MDSC-like blasts at diagnosis has adverse effect on the prognosis. MDSC-like blasts might play a certain role in immune-escape mechanism of AML.

Keyword : Myeloid-Derived suppressor cells, Acute myeloid leukemia, Prognosis, Immune

OP17-4

The Clinical Implication of Cytogenetic Clonal Evolution Pattern in Relapsed Adult ALL Patients

Ji Hyun Lee[1], Sung-Hyun Kim[1], Hyo- Jin Kim[1], Yoo Jin Lee[2]

[1] Department of Internal Medicine, Dong-A University College of Medicine, Korea
[2] Department of Internal Medicine,, Kyungpook National University School of Medicine, Korea

Background : Adult acute lymphoblastic leukemia (ALL) patients commonly relapse after allogeneic stem cell transplantation (Allo-SCT) and chemotherapy. ALL relapse has been related to clonal cytogenetic evolution, but there is no study which focuses on the cytogenetic pattern or its clinical implications after treatment.

Methods : Two hundred and twenty-four ALL was diagnosed as ALL in two centers in South Korea between January, 2000 and December, 2016. Among these patients, 181 patients were able to proceed to treatment (80.8%) and among 104 patients (57.5%) achieved complete remission (CR) after allo-SCT or chemotherapy only. 63 patients (60.6%) relapsed after CR and finally 51 patients who had cytogenetic results both at initial diagnosis and at relapse were analyzed.

Results : banding analysis combined with fluorescent in situ hybridization. The male to female ratio was 31:20 and the median age in allo-SCT group and conventional chemotherapy only group was 34.0 years (20-54 years) and 46 years (20-76 years) respectively. At diagnosis, aberrant karyotypes were more frequent
in the HSCT than in the chemotherapy cohort (14 of 18; 77.8% versus 16 of 33; 48.5%; P = 0.042).
Clonal changes from diagnosis and relapse were more frequent in the allo-SCT group
(15 of 18; 83.3% versus 20 of 31; 64.5%) compared with the conventional chemotherapy only group (not significant), mostly due to the clonal evolution. Appearance of new ≥3 cytogenetic alterations was more frequent in the allo-SCT group (4 of 18; 22.2% versus 3 of 33; 9.1%, not significant). The mean number of cytogenetic alterations was increased from 1.94 (standard deviation, SD ± 1.47) at diagnosis to 4.39 (SD ± 1.47) at relapse in the allo-SCT group, but in the conventional chemotherapy only group, 2.06 (SD ± 5.12) to 2.35 (SD ± 3.21) (at diagnosis, P = 0.047, at relapse, not significant). Clonal change did not correlate to overall survival.

Conclusions : Clonal change and cytogenetic complexity was more frequently observed in the hematopoietic stem cell recipient group. The change of karyotype did not correlate to the overall survival of adult ALL patients, which might be affected the innate poor prognosis in this group of patients.

Keyword : Acute lymphoblastic leukemia, Relapse, Cytotogenetics

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POSTER PRESENTATION

PP-01

Statin Promotes Apoptosis by Activating JNK Signaling in FLT3-ITD Acute Myeloid Leukemia Cells

Ji Eun Jang [1], So-Young Seol[2], Dohyu Hwang[3], Ju-In Eom[2], Hoi-Kyung Jeung[2], Soo-Jeong Kim[1], Jin Seok 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
[3] Department of Internal medicine, Catholic Kwndong University, Korea

Background : The FLT3-ITD mutation is frequently observed in acute myeloid leukemia (AML) and is associated with poor prognosis due to their intrinsic resistance to chemotherapeutic agents. With the recent understanding that statin drugs may have anti-cancer properties, our investigations have focused on the ability of statins to inhibit the growth and cytotoxicity of the FLT-ITD AML cell line.

Methods : We evaluated the levels of apoptosis, endoplasmic reticulum (ER) stress and autophagy by simvastatin and lovastatin in AML cell lines. FLT3 wild type (WT) (RS4:11), FLT3-ITD mutation (MV4:11 and Molm13) and FLT3 inhibitor-resistant Molm13 (Molm13/ACR) human AML cell lines were used. Molm13/ACR cell line was established in our laboratory by exposing parental Molm13 cells to stepwise increasing concentrations of FLT3 inhibitor, AC220.

Results : Both statin compounds effectively reduced cell proliferation and induced apoptosis in a concentration-dependent manner in FLT3-ITD AML cell lines. However, in Molm13/ACR cells, lovastatin induced little apoptosis although inhibited cell proliferation. In contrast, simvastatin induced apoptosis in a concentration-dependent manner in all of 3 cell lines (MV4:11, Molm13 and Molm13/ACR) irrespective of resistance to FLT3 inhibitor and was ineffective in FLT3 WT cell line. To demonstrate the mechanism by which death occurs in FLT3-ITD AML cells with statin treatment, we examined the activation of various signaling pathways in WT and FLT3-ITD cells after simvastatin treatment. Phosphorylation of eIF2a and LC3 II accumulation were increased in both of WT and FLT3-ITD cells, suggesting that activation of ER-stress and autophagy as a pro-survival signaling pathway is not involved in the cell death observed. Interestingly, caspase-3 and c-Jun NH2-terminal kinase (JNK) were selectively activated in FLT3-ITD cells compared to WT cells.

Conclusions : These results revealed that statins, a class of drugs already approved by the US Food and Drug Administration, might be repurposed for the management of FLT3-ITD AML. Furthermore, our findings suggest that it is required to demonstrate the role of JNK pathway in statin-induced apoptosis in FLT3-ITD AML cells to establish the foundation of further study for novel therapeutic target of FLT3-ITD AML cell.

Keyword : FLT3-ITD, Acute myeloid leukemia, Statin

PP-02

The Synergistic Effect of DMNT Inhibitors and Nutlin-3 on Apoptosis of TP53 Wild Type AML in Vitro

Ji Eun Jang[1], Ju-In Eom[2], Hoi-Kyung Jeung[2], Haerim Chung[1], So-Young Seol[2], Soo-Jeong Kim[1], Jin Seok 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

Background : The majority of patients with acute myeloid leukemia (AML) are elderly and have a poor prognosis despite induction therapy. DNA methyltransferase (DMNT) inhibitors that can reverse aberrant DNA methylation and induce differentiation and apoptosis of leukemic cells, is a well-tolerated alternative to aggressive chemotherapy. Recently, it has been reported that clinical responses to decitabine were highly correlated with the presence of TP53 mutations.

Methods : We investigated the effect of DMNT inhibitors (decitabine and SGI-110) and pharmacologic activation of p53 by MDM2 antagonist in AML cell lines. NB4 and Kasumi-1 cells were used as TP53 mutation AML cell lines and MV4;11, Molm13, OCI-AML2, and OCI-AML3 cells were used as TP53 wild type (WT) cell lines.

Results : We examined that the effects of DMNT inhibitors on cell proliferation and death in AML cells. Apoptotic cell death was minimal in TP53 WT cell lines, especially OCI-AML2 and OCI-AML3 cells. Western blotting showed that tumor suppressor protein p53 was activated after decitabine treatment in a concentration-dependent manner in TP53 mutation AML cell lines and MV4;11, Molm13 among TP53 WT AML cell lines. However, decitabine did not increased expression of p53 in DMNT inhibitor-resistant cell line, OCI-AML3 cells (TP53 WT). After treatment of Nutlin-3, MDM2 antagonist in OCI-AML3, p53 expression was markedly increased. We examined whether p53 activation contributed to survival in DMNT inhibitor-resistant cells. The addition of Nutlin-3 to decitabine treatment resulted in a significant increase in the level of apoptosis in OCI-AML2 ($P = 0.0007$) and OCI-AML3 ($P = 0.0034$) as compared with that of decitabine treatment alone. Similar results were obtained after co-treatment of SGI-110 and Nutlin-3 in DMNT inhibitor-resistant cells. The addition of Nutlin-3 led to a significant increase in the extent of SGI-110-induced apoptotic cell death in OCI-AML2 ($P < 0.0001$) and OCI-AML3 ($P = 0.0026$).

Conclusions : These findings support that activation of p53 is associated with DMNT inhibitor sensitivity. Activation of p53 by MDM2 antagonist could be an effective therapeutic strategy for combating resistance to DMNT inhibitors in AML. The mechanisms underlying the sensitivity of AML cells with p53 activation to DMNT inhibitors are unclear at present and are needed to define in further studies.

Keyword : MDM2 antagonist, TP53 wildtype AML, DMNT inhibitor, Synergism

PP-03

Calcium Blocker-Induced Interference Effects on Steroid Resistance in Acute Lymphoblastic Leukemia

Hyun Joo Jung[1], Eunhee Han[2], Jun Eun Park*[3]

[1] Department of Pediatrics, Ajou University Hospital, Ajou University School of Medicine, Korea
[2] Department of Pediatrics, Ajou University School of Medicine, Korea
[3] Department of Pediatrics, Ajou University Hospital, Ajou University School of Medicine, Korea

Background : Acute lymphoblastic leukemia (ALL) is one of the most common cancers in both children and adults. Although the overall survival rate of patients with ALL is approaching to 90%, quite q few patients still die. And, Steroid resistance is one of the major cause of their death. To improve survival for patients with ALL, it is necessary to develop innovative therapeutic strategies to overcome steroid resistance.

Methods : We used biochemical and molecular methodologies to demonstrate the intracellular pathway of tissue transglutaminase (TG2) - nuclear factor-κB (NF-κB) and the cell survival to evaluate the effect of calcium blockers on the steroid resistance in ALL cells.

Results : We generated steroid-adapted subclones of ALL cell lines that were extremely more resistant to steroid than the parent cells. We found that calcium blockers not only altered TG2 activity but also affected NF-κB expression in this steroid-resistant ALL cells. Calcium blockers interfered in the expression of NF-κB target genes in steroid-adapted ALL cells. We also found that calcium blockers reduced the steroid resistance and promoted apoptosis-mediated cell death in steroid-resistant ALL cells.

Conclusions : This study shows that calcium blockers affect the cell survival as well as the steroid resistance on steroid-resistant ALL cells via the change of TG2 and NF-κB signaling pathway. The combination of calcium blockers with conventional chemotherapeutic agents may be a new alternative to overcome steroid resistance and increase the survival rate of ALL patients.

Keyword : Acute lymphoblastic leukemia, Steroid, Calcium blocker

PP-04

Role of High-Dose Cytarabine as Consolidation Therapy before Allogeneic HCT for AML without CBF

YooJin Lee[1], SangKyun Sohn*[1], JoonHo Moon[1], DongWon Back[1], Hyeoung-Joon Kim[2], Jae-Sook Ahn[2], Seo-Yeon Ahn[2], Sung-Hoon Jung[2]

[1] Hematology, Kyungpook National University Hospital, Korea
[2] Hematology, Chonnam National University Hwasun Hospital, Korea

Background : The optimal number of high-dose cytarabine (HDAraC) consolidation cycles before allogeneic hematopoietic cell transplantation (allo-HCT) for acute myeloid leukaemia (AML) is not fully standardised. This study evaluated the therapeutic value of the number of HDAraC consolidation cycles before transplantation for AML in the first complete remission (CR).

Methods : We retrospectively reviewed the medical records of 241 patients who received allo-HCT for AML without the core-binding factor (CBF) between 1998 and 2014 in Korea. All the patients received 3+7 induction chemotherapy. After 186 patients (77.2%) achieved CR, they were reclassified into three subgroups: the C0 (0 cycle of HDAraC, n=21), C1 (1 cycle, n=116), and C2 (2 cycles, n=52) groups, according to the number of HDAraC consolidation cycles.

Results : The median age at diagnosis was 43 years (range, 15–67 years). Thirty-two patients (17.2%) had high-risk and 154 (82.8%) had intermediate-risk cytogenetics. The cumulative HDAraC dose was 3 g/m2 (range, 3–9 g/m2) in the C1 and 12 g/m2 (6–18 g/m2) in the C2 groups. Ten patients (5.4%) had a relapse before transplantation: 3 (14.3%) in the C0, 3 (2.6%) in the C1, and 4 (7.8%) in the C2 groups.
The median time from CR to allo-HCT was 126 days, 118 days (range, 60–174) in C0, 113 days (range, 84–214) in C1, and 158 days (range, 75–270) in C2. Ninety-nine patients (53.2%) received myeloablative conditioning regimens. The median follow-up duration was 1135 days. The 2-year relapse-free survival (RFS) was 47.2% ± 11.7%, 71.6% ± 4.4%, and 79.9% ± 5.% in the C0, C1, and C2 groups, respectively (p=0.032). The 2-year overall survival and non-relapse mortality did not significantly differ. The adverse cytogenetic risk group had a benefit from HDAraC consolidation (hazard ratio [HR] = 0.467; 95% confidence interval [CI], 0.221–0.988; p=0.015). In the multivariate analysis, the following factors were associated with RFS: adverse cytogenetic risk (HR, 2.407; 95% CI, 1.372–5.930; p=0.002), no HDAraC consolidation (HR, 3.008; 95% CI, 1.381–6.550; p=0.006), and chronic graft-versus-host disease (HR, 0.361; 95% CI, 0.166–0.783; p=0.010).

Conclusions : The use of HDAraC consolidation as a pre-HCT strategy had a positive role in AML without CBF. One or two cycles of HDAraC seemed to maximise the following HCT outcome in AML patients.

Keyword : Acute myelogenous leukemia, Cytarabine, Allogeneic hematopoietic stem cell transplantation

PP-05

The Efficacy of Daily ATRA Monotherapy as Maintenance Therapy for Newly Diagnosed APL

Yoojin Lee, Sangkyun Sohn, Joonho Moon, Dongwon Back
Hematology, Kyungpook National University Hospital, Korea

Background : All-trans retinoic acid (ATRA) added during all treatment period have been reported to improve the outcomes of newly diagnosed acute promyelocytic leukemia (APL). However, the benefits of post-remission maintenance chemotherapy are uncertain and bone marrow suppression, especially when including chemotherapy (CT), is a major problem. This study evaluated the efficacy and safety of maintenance therapy by daily ATRA monotherapy of newly diagnosed APL.

Methods : We retrospectively reviewed the medical records of 85 patients with newly diagnosed APL between Feb 2002 and Feb 2015 in Kyungpook National University Hospital. They received daily ATRA (45 mg/m2/day in 2 equally divided doses until complete remission or 90 days) plus idarubicin (± cytarabine) as induction, followed by three intensive consolidation chemotherapy. Maintenance therapy consisted of either ATRA 45 mg/m2/day for 15 days every 3 months with continuous low-dose 6 mercaptopurine and methotrexate (ATRA-CT) for 2 years or daily ATRA 45 mg/m2 for 2 years.

Results : The median age at diagnosis was 47 years (range, 17 – 80 years). Thirteen patients (15.3%) had high-risk and 44 (51.8%) had intermediate-risk by Sanz risk score. Seventy seven patients (90.6%) achieved hematologic complete remission (CR) and 2 patients had leukemic resistance. During induction chemotherapy, 14 patients (16.5%) had bleeding complications and 6 patients (7.1%) suffered an early death. ATRA syndrome occurred in 37 patients (43.5%) and was fatal in 5 cases. 1 patient died because of septic shock during consolidation. There was no difference in characteristics for 66 patients who received maintenance therapy. ATRA-CT was 31 patients (47%) and ATRA daily was 35 (53%). Myelosuppression occurred in 10 patients (32.3%) with ATRA-CT only (p=0.001). The relapse-free survival, and overall survival did not significantly differ between ATRA-CT and daily ATRA monotherapy (p=0.74 and p=0.68). There was no statistically significant difference in survival outcomes between the two groups in the high-risk group.

Conclusions : Compared with ATRA-CT as a maintenance therapy for newly diagnosed APL, daily ATRA monotherapy can be a feasible and effective choice in terms of bone marrow suppression. To elucidate best maintenance regimen for APL, a large scale study will be needed.

Keyword : Acute promyleocytic leukemia, Maintenance, ATRA

PP-06

MiR-424/-503 Regulates Expression of Cobll1 in Chronic Myeloid Leukemia

Seung hun Han[1], Soo-Hyun Kim[2], Hyoung-June Kim[1], Yoonsung Lee[3], Soo-Young Choi[2], Do-Hyun Kim[4], Aram Lee[5], Kibeom Park[1], Jongmin Kim[5], Je-Min Choi[4], Yonghwan Kim[5], Kyungjae Myung[3], Hongtae Kim[1], Dong-Wook Kim*[2,6]

[1] Department of Biological Sciences, Sungkyunkwan University, Korea
[2] Leukemia Research Institute, The Catholic University of Korea, Korea
[3] Center for Genomic Integrity Institute for Basic Science (IBS), Ulsan National Institute of Science and Technology, Korea
[4] Department of Life Science, Hanyang University, Korea
[5] Department of Life Systems, Sookmyung Women's University, Korea
[6] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

Background : Up- or down-regulation of many miRNAs plays an important role in chronic myeloid leukemia (CML), however underlying mechanisms remain to be elucidated.
In previous our study, Cobll1 is a novel oncoprotein to associate with drug resistance and CML progression and highly expressed in blast crisis (BC). Cobll1expression does not correlate with BCR-ABL1. So, we searched for miRNAs that can regulate the expression level of Cobll1 to examine potential regulators of Cobll1.

Methods : 41 CP and 40 BC samples is analyzed to determine the levels of Cobll1 or miRNAs using Western blot and qRT-PCR. K562 transfection was performed using a microporator. A negative miRNA and miRNA 424/-503 were purchased from Ambion.

Results : To find candidate miRNAs of Cobll1, we were predicted to miRNAs by the algorithm in the TargetScan software. To validation target miRNA of Cobll1, we analyzed the expression levels of these miRNAs using qRT-PCR. Interestingly, miR-424/-503 expression were significantly reduced in BC.
We next performed that eighty one CML samples (41 CP and 40 BC) were analyzed to determine the levels of the Cobll1 protein and miR-424/-503 by Western blotting and qRT-PCR. Amazingly, we found that miR-424/-503 were significantly downregulated highly expressed Cobll1 BC samples (n=21) compared to Cobll1 less expressed BC samples (n=19) and CP samples (n=41). Interestingly, there were down-regulations in expression of miR-424/-503 that had co-relation with Cobll1 expression in CML progression. These results suggest that miR-424/-503 regulate Cobll1 expression in CML.
To assess the effects of miR-424/-503 regulates Cobll1 expression, we make ectopically expressing plasmids of Cobll1 3'-UTR WT and Cobll1 3'-UTR mutant. Transfection of miR-424/-503 reduced Cobll1 3'-UTR WT luciferase activity, but not a Cobll1 3'-UTR mutant . Consistently, overexpression of miR-424/-503 significantly reduced the endogenous Cobll1 levels in K562 cells. In addition, the knockdown of Cobll1 by the miRNAs sensitized to nilotinib-induced apoptosis in K562 cells.

Conclusions : Our findings suggest that miR-424/-503 plays a critical role CML by targeting directly targeting the Cobll1. These results provide the clue of miR-424/-503 as a potential therapeutic target for CML progression by regulating the Cobll1 expression.

Keyword : Chronic myeloid leukemia, Cobll1, MiR-424/-503, TKI resistance

PP-07

Comparison of Treatment Strategies in CML Patients with Suboptimal Molecular Response to Imatinib

Sung-Eun Lee[1,9], Soo-Young Cho[1], Soo-Hyun Kim[1], Saengsuree Jootar[2], Hyeoung-Joon Kim[3], Sang-Kyun Sohn[4], Joon Seong Park[5], Sung-Hyun Kim[6], Dae-Young Zang[7], Suk-Joong Oh[8], Dong-Wook Kim*[1,9]

[1] Leukemia Research Institute, The Catholic University of Korea, Korea
[2] BMT Program, Ramathibodi Hospital, Mahidol University, Thailand
[3] Department of Hematology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Korea
[4] Department of Oncology/Hematology, Kyungpook National University Hospital, Korea
[5] Department of Hematology/Oncology, Ajou University School of Medicine, Korea
[6] Department of Internal Medicine, Dong-A University, College of Medicine, Korea
[7] Department of Internal Medicine, Hallym University College of Medicine, Korea
[8] Department of Internal Medicine, Kangbuk Samsung Hospital, Korea
[9] Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Background : The aim of this study was to investigate the efficacy of nilotinib (NIL) versus high-dose imatinib (IM) versus sustained standard-dose IM for patients with chronic phase (CP) chronic myeloid leukemia (CML) with suboptimal molecular response to first-line IM therapy.

Methods : Patients with early CP CML who achieved complete cytogenetic response (CCyR) but not major molecular response (MMR) after 18 to 24 months on first-line IM therapy were enrolled and divided into three treatment cohorts: NIL 800 mg/day (Cohort 1) and IM 800 mg/day (Cohort 2) in the RE-NICE study, and sustained IM 400 mg/day (Cohort 3) in clinical practice.

Results : Using a data cutoff date of 7 Dec 2016, a total of 108 patients were evaluated: 28 in Cohort 1, 28 in Cohort 2, and 52 in Cohort 3. Median follow-up duration from enrollment for each cohort was 36 months (range, 1-36), 45 months (range, 21-63), and 90 months (range, 14-159), respectively. When data were collected on patients who crossed over to the alternative therapy, the cumulative incidence of MMR by 36 months was significantly higher in Cohort 1 than Cohort 3 (83.1% vs. 57.1%, P=0.021), but there were no significant differences in Cohort 1 vs. 2 (P=0.195) and Cohort 2 vs. 3 (P=0.297). In subgroup analyses among patients enrolled in the RE-NICE study, a different profile for adverse events was observed between NIL and high-dose IM therapy.

Conclusions : In conclusion, NIL 800 mg/day therapy showed better efficacy than standard-dose IM for the treatment of patients with suboptimal molecular response to first-line IM.

Keyword : Chronic myeloid leukemia, Suboptimal response, Nilotinib, Imatinib

PP-08

Compound Mutations are the Major Components of Multiple Mutations Detected in TKI Resistant CML

Ki-Hoon Kang[1], Soo-Hyun Kim[1], Soo-Young Choi[1], Sung-Eun Lee[1,2], Hae-Lyun Yoo[1], Mi-Young Lee[1], Hye-Young Song[1], Kyung-Mi Kee[1], Ji-Hyung Suh[1], Seon-Young Yang[1], Eun-Jung Jang[1], Dong-Wook Kim*[1,2]

[1] Leukemia Research Institute, The Catholic University of Korea, Korea
[2] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

Background : ABL1 kinase domain mutations are a major mechanism of tyrosine kinase inhibitor (TKI) resistance in patients with chronic myeloid leukemia (CML). One of the characteristics patients with multiple mutations have poorer prognosis than patients with a single mutation. Although multiple mutations can be firstly detected by Sanger sequencing, it is not possible to determine whether mutations are in the same clone (compound mutations) or in different clones.

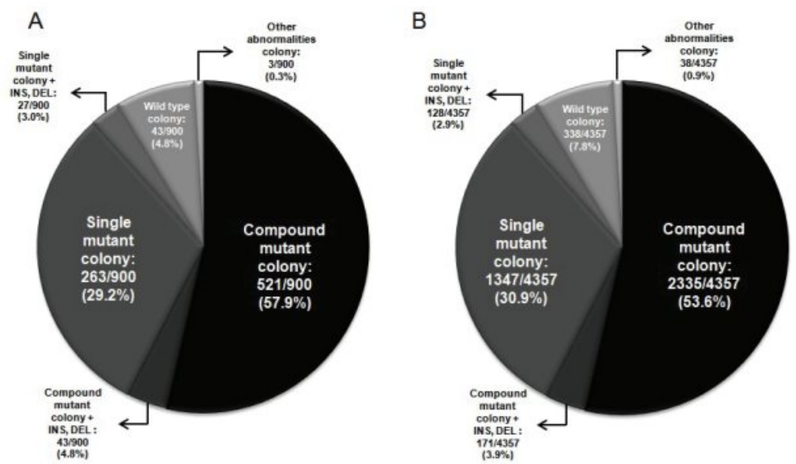
Methods : Between 2002 and 2015, 735 CML patients had been screened for mutation analysis due to suspicious resistance to various TKIs and ABL001 using Sanger sequencing. Among them, 45 patients had multiple mutations. We performed Sanger sequencing and subcloning sequencing using 218 peripheral blood samples from the patients. For subcloning sequencing, at the least 20 colonies were selected at random and sequenced from all samples except 3 samples, and in total 4357 colonies from 218 serial samples are analyzed.

Results : The component of mutation by subcloning sequencing is shown in Figure 1. Among 900 colonies with subcloning sequencing, A total of 552 mutant types were detected and the higher frequencies were in order T315I (324 colonies; 36.0%), E255K (132 colonies; 14.7%), Y253H (63 colonies; 7.0%), G250E (60 colonies; 6.7%), M351T (59 colonies; 6.6%) and E255V (48colonies; 5.3%).
In additional analysis with 4357 colonies of 218 serial samples on further treatment, 2506 colonies (57.5%) had compound mutation and the composition of non-compound mutation was also similar with that of baseline samples. Of 2506 colonies with compound mutation, a majority of colonies had double (53.4%) or triple (28.7%) mutations. The T315I and P-loop mutations were in 29.4% and 28.5% respectively. Known ABL001 resistant mutations were detected in 65 clones (1.5%).

Conclusions : The majority of multiple mutations were in compound mutations, and T315I and P-loop mutation were the major component of multiple mutation. As some minor mutations were detected; thus, more sensitive sequencing assays are needed in patients with multiple mutations.

Keyword : Multiple mutations, Compound mutation, Minor mutation, Resistance, Tyrosine kinse inhibitor

Figure 1. The component of mutation by subcloning sequencing. (A) with 900 colonies from 45 samples at baseline (B) with 4357 colonies from 218 serial samples during follow-up



PP-09

Optimal Time Point for BCR-ABL1 KD Mutation Analysis in CML Patients; Based on 2013 ELN Guideline

Hea-Lyun Yoo[1], Soo-Hyun Kim[1], Soo-Young Choi[1], Mi-Young Lee[1], Hye-Young Song[1], Ki-Hoon Kang[1], Kyoung-Mi Ki[1], Sun-Young Yang[1], Dong-Wook Kim[*1,2]

[1] Leukemia Research Institute, The Catholic University of Korea, Korea
[2] Department of Hematology, The Catholic University of Korea Seoul St. Mary's Hospital, Korea

Background : BCR-ABL1 kinase domain (KD) mutations are closely related to tyrosine kinase inhibitor (TKI) resistance in chronic myeloid leukemia (CML). Although mutation analysis has been suggested in CML patients with treatment failure, there is no standard guideline according to landmark responses at specific timepoints of European LeukemiaNet (ELN) recommendation.

Methods : From 605 newly diagnosed chronic phases CML patients, 961 peripheral blood samples were analyzed for BCR-ABL1 KD mutation and all of patients were treated with frontline imatinib for at least 3 months. The patients with atypical transcripts were excluded. Hematologic, cytogenetic, and molecular responses on 3, 6, and 12 months were also assessed by ELN criteria. To determine appropriate timepoint for mutation analysis, the frequency and type of BCR-ABL1 KD mutation were analyzed using Sanger sequencing and were assessed by achieving landmark responses at specific timepoints.

Results : Of the 605 patients, BCR-ABL1 KD mutations were detected in 28 patients (4.6%) and a total of 33 mutations were detected. Of the 33 mutations, 23 mutations (69.7%) were highly resistant mutations of T315I and P-loop. In cytogenetic response criteria, the mutation frequencies of optimal, warning and failure group were 0.7% (5/671 samples), 1.8% (2/110 samples) and 16.0% (17/106 samples) respectively and were 0.7% (3/425 samples), 3.6% (13/359 samples) and 7.6% (13/172 samples) respectively in molecular response criteria. Under 18 different response criteria of ELN recommendation, there was a higher incidence of mutations among patients with 12 month-cytogenetic treatment failure (21.8%; 12/55 patients), 3 month-cytogenetic treatment failure (20.0%; 3/15 patients) and 12 month-molecular treatment failure (9.3%; 10/107 patients). Interestingly, mutations were also detected in 5 optimal cytogenetic responders (2/280 patients at 6 month-criteria and 3/241 patients at 12 month-criteria; 1 G250E, 2 Y253H, 1 V280M and 1 M351T)

Conclusions : We conclude that some patients with treatment failure, especially with cytogenetic criteria, should be warranted for mutation analysis. Furthermore, the majority of patients with warning criteria may be enough only with a close monitoring without routine mutation analysis. However, as a few patients with optimal response had mutation, mutation analysis should not be totally excluded.

PP-10

The Impact of Early Molecular Response on Long-Term Survival in CML Patients following TKIs Therapy

Sung-Eun Lee[1,2], Soo-Young Choi[2], Soo-Hyun Kim[2], Hye-Young Song[2], Kyung-Mi Kee[2], Hea-Lyun Yoo[2], Mi-Young Lee[2], Ki-Hoon Kang[2], Ji-Hyung Suh[2], Seon-Young Yang[2], Eun-Jung Jang[2], Dong-Wook Kim*[1,2]

[1] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea
[2] Leukemia Research Institute, The Catholic University of Korea, Korea

Background : The aim of this study is to evaluate the impact of 3-month early molecular response (EMR) on long-term outcomes of CML patients treated with imatinib (IM) and second-generation tyrosine kinase inhibitors (2G-TKIs), as additional information to guide clinical decisions on switching to a different TKI.

Methods : 646 new CP CML patients who were treated with frontline IM (n = 362) or 2G TKIs (n = 284) were analyzed.

Results : A total of 646 patients were treated with IM (n = 362), dasatinib (DAS; n = 117), nilotinib (NIL; n = 85), and radotinib (RAD; n = 82). The median age was 43 years (range, 11-87). With a median follow-up of 75.4 (IM; range, 4.4-195.9) and 34.1 (2G-TKIs; range, 5.2-138.4) months, 383 (59.3%; 168 IM and 215 2G-TKIs) patients continue on the frontline therapy and 263 (40.7%) patients were permanently discontinued or changed to other TKIs due to intolerance (72 IM, 26 DAS, 2 NIL, 21 RAD), ELN failure (36 IM, 3 DAS, 2 RAD), progression (3 IM, 1 DAS, 2 NIL, 1 RAD), death (1 IM, 1 DAS, 1 NIL), and others (10 warning, 9 pregnancy, 59 treatment-free remission study, and 13 follow-up loss). In 362 patients treated with IM, patients achieving BCR-ABL1 ≤ 10% at 3 months (n = 270, 74.6%) had a better outcomes in terms of 8-y failure-free survival (FFS) (91.7% vs 64.4%, P<0.001), 8-y progression-free survival (PFS) (95.5% vs 84.2, P<0.001), and 8-y overall survival (OS) (97.0% vs 83.2%, P <0.001) compared with those of the patients with BCR-ABL1 >10%. In 284 patients treated with 2G-TKIs, achievement of 3-month EMR (n = 252, 88.7%) was associated with a higher 6-y FFS (95.5% vs 82.1%, P = 0.001), 6-y PFS (97.2% vs 36.0, P<0.001), and 6-y OS (100% vs 66.2%, P <0.001). The prognostic impact of 3-month EMR was observed in both IM and 2G-TKIs treated groups. However, in IM treated group, 3-month EMR failure showed relative risk (RR) of 4.96 (P <0.001) for PFS and 4.54 (P = 0.001) for OS, respectively, whereas in 2G-TKIs treated group, 3-month EMR failure showed RR of 10.71 (P <0.001) for PFS and 26.42 (P = 0.005) for OS, respectively.

Conclusions : Our data showed the 3-month EMR provided long-term prognostic information in patients treated with frontline IM and 2G-TKI. However, the prognostic impact of 3-month EMR failure was enhanced in the patients treated with 2-G TKIs. However, further investigations in a larger patient population with longer follow-up are needed.

Keyword : Chronic myeloid leukemia, Chronic myeloid leukemia, Tyrosine kinase inhibitors

PP-11

Outcomes of CML Patients who Have Achieved CCyR but Not MMR after 24 Months on Frontline Imatinib

Sung-Eun Lee[1,9], Won-Sik Lee[2], Young Rok Do[3], Jae-Yong Kwak[4], Suk Joong Oh[5], Sung Hyun Kim[6], Jeong-A Kim[7], Dae Young Zang[8], Soo-Young Choi[9], Dong-Wook Kim*[1,9]

[1] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea
[2] Department of Internal Medicine, Inje University College of Medicine, Inje University Busan Paik Hospital, Korea
[3] Division of Hematology-Oncology, Keimyung University, School of Medicine, Keimyung University Hospital, Korea
[4] Division of Hematology-Oncology, Chonbuk National University Medical School, Chonbuk National University Hospital, Korea
[5] Department of Internal Medicine, School of Medicine, Sungkyunkwan University, Kangbuk Samsung Hospital, Korea
[6] Department of Internal Medicine, Dong-A University College of Medicine, Dong-A University Hospital, Korea
[7] Department of Hematology, The Catholic University of Korea, St. Vincent's Hospital, Korea
[8] Department of Internal Medicine, Hallym University College of Medicine, Hallym University Hospital, Korea
[9] Leukemia Research Institute, The Catholic University of Korea, Korea

Background : Although failure to achieve molecular response milestones on tyrosine kinase inhibitors (TKIs) therapy for chronic phase (CP) chronic myeloid leukemia (CML) means that switching to a different TKI is needed to limit the risk of progression and death, there is insufficient data to show long-term outcomes in the patients who were in a molecular failure after 24 months. The aim of this study was to evaluate long-term survival end points and identify predictive factors for an achievement of overall major molecular response (MMR) in the patients who have achieved complete cytogenetic response (CCyR) but not MMR after 24 months on frontline IM therapy.

Methods : 280 newly diagnosed CP CML patients who were in CCyR but not MMR after 24 months on frontline IM therapy were evaluated.

Results : With a median follow-up of 134.2 months (range, 25.6–195.0 months), 163 (58%) patients continued IM and maintained at least a CCyR, while 117 patients permanently discontinued IM due to intolerance (n = 31), warnings according to ELN 2013 recommendation with adverse events (n = 43), and treatment failure (n = 17), progression (n = 9), death (n = 1), enrollment of treatment-free remission (TFR) study (n = 10), and others (n = 6). Among them, 98 (84%) switched to 2G TKIs. The CI rates of MMR by 3, 4, and 5 years were 27.9 ± 2.8%, 53.6 ± 3.3%, and 71.8 ± 3.0%, respectively, and the CI rates of CMR by 3, 4, and 5 years were 1.9 ± 0.8%, 5.0 ± 1.4%, and 10.8 ± 2.1%, respectively on IM therapy. The 10-year FFS, PFS, and OS were 89.3 ± 2.2%, 96.0 ± 1.3%, and 98.5 ± 0.9%, respectively. Transcript type of b2a2 and high Sokal risk were independent factors for failure of overall MMR on IM therapy.

Conclusions : This study demonstrated long-term survival outcomes in the patients who have achieved CCyR but not MMR after 24 months on frontline IM therapy. In addition, the predictive factors may provide additional information to guide clinical decisions on selecting patients who would benefit from switching to 2G TKIs in molecular failure.

Keyword : Chronic myeloid leukemia, Molecular response, Imatinib

PP-12

Pegylated L-Asparaginase Induced Cholestatic Jaundice and Treated with Oral L- Carnitine: A Case Report

Asma Nasir Mahmud[1], Huma Asif[1], Ayisha Imran[1], Tasneem Farzana*[2]

[1] Department of hematology, Chughtai Lab lahore, Pakistan
[2] National centre for blood diseases, National hospital and medical centre , Lahore, Pakistan

Background : Acute lymphoblastic leukemia (ALL) is a heterogeneous clonal malignant disorder affecting lymphoid progenitor cells. It can present in both children and adults and a peak age of presentation is 2-5 years. It is treated with a variety of intensive combination chemotherapeutic regimens. More precise understanding of the molecular basis of the disease may help in developing targeted therapy for the disorder. However, currently available majority of the therapeutic regimens are associated with systemic toxicities. L-asparaginase is a commonly used drug in combination chemotherapy for ALL. It is a bacterial enzyme which can be obtained from two different bacteria i.e. Escherichia coli and Erwinia carotovora. Normal cells can produce their own asparagine (amino acid) whereas malignant cells (e.g. lymph oblasts) acquire asparagine from blood to support their own growth. L-asparaginase helps to deaminate asparagine into aspartate hence, deprives the tumor cells from essential amino acid. Native E-coli asparginase and PEG-asparginase (pegylated form) both are obtained from E-coli and Erwinia asparginase is obtained from Erwinia carotovora. Commonly observed side effects of E. coli-asparginase are hypersensitivity, hepatotoxicity, thrombosis, pancreatitis and hyperglycemia. PEG preparation produces prolonged depletion of asparagine and shows less frequency of hypersensitivity reaction. Liver injury caused by asparaginase can present with mild- moderate Cholestatic jaundice, macro vesicular steatosis or fatal liver failure. We here describe a patient who developed Cholestatic jaundice after induction chemotherapy for ALL.

Methods : Case Report

Results : He gradually improved over a period of 10 days.
Based on the scenario we ruled out other potential causes of cholestatic liver injury and concluded him as having L-Asparginase induced Cholestatic jaundice

Conclusions : Cholestatic jaundice is an infrequently observed adverse effect of L-asparginase. Early identification, with holding chemotherapy and good supportive care can prevent worsening of the condition as well as helps in the recovery of the patient.

Keyword : L-Asparaginase, Cholestatic jaundice, Chemotherapy, Acute lymphoblastic leukemia

His improved labs showed:

Hb 10.5 g/dl

TLC 4.7 x103/l

PLATELET 251 X103/L

LFTs:	
Total billirubin	2.3
Conjugated billirubin	1.7
Unconjugated billirubin	0.6
ALT	126
AST	32
ALKALINE PHOSPHATASE	220
GAMMA GT	138
TOTAL PROTEIN	6.9
ALBUMIN	2.2
GLOBULIN	4.7
ALBUMIN /GLOBULIN RATIO	0.5

PP-13

Molecular Docking to Identify a Novel Inhibitors for Tyrosine Kinase in CML from Alkaloids

Shah Md Shahik[1,2]

[1] Genetic Engineering and Biotechnology, University of Chittagong, Bangladesh
[2] Chronic Disease, Biomedical Research Foundation Bangladesh, Bangladesh

Background : Chromosomal abnormality so-called Philadelphia chromosome is the hallmark of chronic myelocytic leukemia (CML). More than 90% of CML caused by Philadelphia chromosome which mainly causes by a fusion gene called BCR-ABL1 coding for a hybrid protein: a tyrosine kinase signaling protein that is, causing the cell division uncontrollably. Targeting this signaling molecule is a novel approach for the resist of CML.

Methods : In the recent year virtual high throughput screening has emerged as a widely accepted powerful technique in the identification of novel and diverse lead. The high-resolution X-ray structure of tyrosine kinase signaling protein has opened the way to introduce new small molecular inhibitors by structure-based virtual screening.

Results : In this study using different alkaloid molecules as potential novel inhibitors of tyrosine kinase signaling protein and proposed three candidate compounds with high scoring function.

Conclusions : Thus from complex scoring and binding ability, it is clarified that these alkaloids might be developed as novel lead compounds to design new drugs against CML.

Keyword : Chronic myelocytic leukemia (CML), Philadelphia chromosome, Cancer, Alkaloids, Drug likeness, Molecular Docking

PP-14

Erdheim–Chester Disease (ECD) is an Uncommon Aggressive, Multisystem Immunological Disease among Arab Males

Abdalla Bowirrat
Neuroscience and Genetic, Emms Hospital, Palestine

Background : Erdheim–Chester disease (ECD) is an uncommon aggressive, multisystem form of non-Langerhans' cell histocytosis, which was firstly reported by Jakob Erdheim and William chester in 1930. The disease pathological features encompass an aberrant multiplication, overproduction and accumulation of white blood cells called histiocytes within multiple tissues and organs. Herein, we present three cases of ECD owing to the rarity of this disease (roughly, 550 cases have been described in the literature to date). We discussed the clinical course, diagnostic evaluations, and the possible treatments. Our cases were encountered in an Arab males in there 30's who have suffered from an ongoing bones pain for years. At our rheumatologic department, we compiled there recent medical history, which consisted of diagnosis of central diabetes insipidus, hyperprolactinemia and secondary hypogonadism along with the previously conducted laboratory evaluations and imaging which brought to our mind the possibility of an infiltrative disease such as ECD.

Methods : The diagnosis of ECD was done based on the combinations of pathognomonic radiographic osteosclerosis, neuroimaging, bones biopsies along with a careful clinical evaluation. Given the protean clinical manifestations, interferon-α was considered as our first line treatment of ECD, consequently our patient improved noticeably.

Conclusions : Clinical presentation, imaging studies, distinctive pathological findings, followed by bone biopsy showed a non-Langerhans cell histiocytosis, supported by immunohistochemistry exams are essential for the diagnosis. Radiation therapy and Bisphosphonates in addition to cladribine, anakinra, infliximab and vemurafenib (BRAF Inhibitors) are currently advocated as promising second line treatment for patients whose response to interferon-α is unsatisfactory

Keyword : Erdheim–Chester disease, Multisystem disease, Array

PP-15

Adverse Drug Reactions to Anti-TB Drugs: Pharmacogenomics Perspective for Identification of Host Genes

Kamal Kishor
Analytical , Institute of Pesticide Formulation Technology, India

Background : Adverse drug reactions (ADRs) are associated with clinical morbidity and, in severe cases, even mortality. Globally billions of dollars are spent on managing these ADRs for common and uncommon diseases. The developing world suffers from a high burden of tuberculosis, which requires 6-8 months of multi-drug treatment. In spite of most cases being treatable the problem persists mainly due to a high attrition rate associated with ADR mediated complications. Due to these reasons drug resistant strains have emerged and are now a serious challenge to TB eradication. To effectively deliver the available treatment regimen and ensure patient compliance it is important to manage ADRs more efficiently. Recent studies have demonstrated that drug outcomes are patient-specific and can, therefore be predicted. A few of these drugs, including a few administered for TB, have shown excellent correlation with response rates and development of ADRs. In this review, we profile information available in public domain for existing anti-TB drugs to understand the genesis of ADRs and patient response. Additionally, human genome variation databases have been used to correlate the frequency of these markers and their genomic variants in different populations.

Methods : ADRs selected based on frequency of occurrence (≥1%). Anti-TB drugs were reviewed to identify the candidate genes (DMETs, HLA). Genes analysed with different web tools and databases to extract their SNPs. MAF >0.01 shortlisted using NCBI Gene and dbSNP databases (built 141). SNPs which lay in a functional domain of the gene were prioritized using SNPinfo web server (www.snpinfo.niehs.nih.gov/). Additionally, same analysis was done for Indian population.

Results : 10 genes identified which maybe directly linked to ADRs to various anti-TB drugs, 4 of these have been documented earlier. Nearly 47 genes were identified for indirect association with ADRs by virtue of them being off-targets of the drugs. 5 genes were reported for their allelic association with anti-TB DIH.

Keyword : Adverse Drug Reactions, Anti-TB Drugs, Pharmacogenomics

PP-16

Survey of Titanium Dioxide Nanoparaticles Exposure during Pregnancy on Hematological Parameters

Cyrus Jalili[1], Faramarz Jalili[2], Mahdi Taghadosi[3], Mohammad Reza Salahshoor[4]

[1] Department of Anatomy and Cell Biology, Medical Biology Research Center, Kermanshah University of Medical Sciences, Iran
[2] Students Research Committee, Students Research Committee, Kermanshah University of medical Sciences, Iran
[3] Department of Immunology, Department of Immunology, Kermanshah University of Medical Sciences, Iran
[4] Department of Anatomy and Cell Biology, Medical Biology Research Center, Kermanshah University of Medical Sciences, Iran

Background : Nanotechnology is a developing technology whose use is increasing in different aspects. Among various nanostructures that are widely used, we can refer to titanium dioxide nanoparticles (Tio2-np), which are applied in water and wastewater treatment, antibacterial and antifungal substances, and self-cleaning surfaces; however, due to passing of the particles through placenta and blood–brain barrier, it may cause pathological damages in infants and affect the future generations' health.

Methods : In this experiment, 30 female mice were divided into three groups, including the control group who received no substance, the solvent group who received drug carrier on the 3rd, 7th, 10th, and 14th days of pregnancy, and the treatment group who received subcutaneously 10 µL of titanium dioxide nanoparticles of 1 mg/mL concentration in the 3rd, 7th, 10th, and 14th days after mating. Afterwards, among the offspring of each group, 10 male and 10 female offspring were chosen to evaluate hematological parameters and lipid profile on the 42nd day.

Results : The results demonstrated that offspring exposure to prenatal titanium dioxide particles (Tio2-NP) in the treatment group causes changes in hematological parameters and lipid profile levels in male and female offspring; however, changes were greater in female offspring.

Conclusions : Since previous studies have shown that titanium dioxide nanoparticles have the ability to cross the placenta and blood–brain barrier. After passing the barriers, they cause damages to various organs including liver and kidney and also changes in gene expression levels in different parts of the body including brain and bones. In addition, they result in producing free radical in the body and developing disorders in globules production and lipid metabolism.

PP-17

Apoptotic Genes Expression Changes of Mice Tissues Exposed to Nicotine

Faramarz Jalili[1], Cyrus Jalili[2]

[1] Students Research Committee, Students Research Committee, Kermanshah University of medical Sciences, Iran
[2] Department of Anatomy and Cell Biology, Medical Biology Research Center, Kermanshah University of medical Sciences, Iran

Background : Smoking is the leading preventable cause of various diseases such as blood cancer, lung cancer, chronic obstructive pulmonary disease and cardiovascular disease. Nicotine, one of the major toxic components of tobacco, contributes to the pathogenesis of different diseases.

Methods : Given the controversy about nicotine toxicity, the present study was conducted to determine apoptotic effects of nicotine on the heart, kidney, lung and liver of male mice. Real-time PCR was performed to identify mRNA expression changes in apoptotic-related genes between nicotine treated and control mice.

Results : In the heart and lung, nicotine caused significant decrease in P53, Bax and Caspase-3 mRNA expression levels compared to the control group. However, in the kidney and liver, the result was significant increase in Bax, Caspase-2, Caspase-3 and a significant decrease in P53 mRNA expression ($p<0.01$). DNA fragmentation assays indicated no fragmentation in the heart and lung, but in the kidney and liver of nicotine treated mice, isolated DNA was fragmented.

Conclusions : Our study provided insight into the molecular mechanisms of nicotine anti-apoptotic effects on the heart and lung as well as pro-apoptotic effects on kidney and liver via a P53-independent pathway.

Keyword : Nicotine, Apoptosis , Caspase-2, P53

PP-18

Prevalence of Glucose-6-Phosphate Dehydrogenase Deficiency among Lao Theung Ethnic Group

Amkha Sanephonasa[1,2], Kamonlak Leecharoenkiat*[1], Chalisa Louicharoen Cheesunthorn[3], Issarang Nuchprayoon[4,]
Naly Khaminsou[2], Onkham Savongsy[2]

[1] Department of clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, Thailand
[2] Deparment of Laboratory , Faculty of Medical Technology, University of Health Sciences, Laos
[3] Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Thailand
[4] Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Thailand

Background : G-6-PD deficiency is an X-linked recessive disorder. Glucose-6-phosphatedehydrogenase (G-6-PD) is an enzyme that protects red blood cell hemolysis from excess free radical. The prevalence of G-6-PD deficiency varies worldwide with a higher prevalence rate in malarial endemic region. Recently, the information about prevalence and genotype of G-6-PD deficiency in Lao population is limited with the data from only few reports and still lacking data from the minority group. This study aims to determine the prevalence of G-6-PD deficiency in Lao Theung which is a large ethnic group in Lao PDR.

Methods : The G-6-PD enzyme activity was measured in EDTA blood samples collected from 252 Lao Theung participants by using Trinity Biotech kit. Eight common Asian G6PD variants were detected by multiplex allele specific PCR.

Results : Based on the enzyme activity, the prevalence of G-6-PD deficiency in Lao Theung group is 13.5 %, including 14.10 % of maleand 13.2 % of female. Five of 8 G-6-PD variants were detected in this cohort. The G-6-PD Viangchan (1.2%) and Union (1.2 %) types are the most common variants followed by Mahidol(0.8%), Kaiping (0.8%) and Canton (0.4%) genotype.

Conclusions : This finding is the first report of G-6-PD genotype in Laos's ethnic group. We found that the prevalence of G-6-PD Mahidol and Union type in Lao Theung group is higher than the data from previous studies. The prevalence of G-6-PD deficiency and its genotype will apply for the development of prevention procedure to protect patients from acute hemolysis in the Lao PDR.

Keyword : G-6-PD deficiency, G-6-PD activity, G-6-PD genotype, Laos, Lao Theung, Prevalence

PP-19

Prognostic Factors and Response to the Hypomethylating Agents in Hypocellular Myelodysplastic Syndromes: A Retrospective Study from the Korean Society of Hematology AML/MDS Working Party

Jungmin Jo[1], Sung Hwa Bae[1], Jinny Park[2], Hong-Ghi Lee[3], Chul Won Choi[4], Yong Park[5], Ho Sup Lee[6], Sung-Hyun Kim[7], Won-Sik Lee[8], Soo-Mee Bang[9], Jun-Ho Jang[10], Inho Kim[11], Je-Hwan Lee[12], June-Won Cheong[13], Seongkyu Park[14], Jong-Ho Won[15], Min Kyoung Kim[16], Hyeok Shim[17], Yeung-Chulmun[18], Jae-Sook Ahn[19], Deog-Yeon Jo[20], Dae Young Zang[21]

[1] Daegu Catholic Univ. Medical Center, Daegu, Korea, Republic of (South);
[2] Gil Medical Center Gachon University, Inchon, KOR;
[3] Konkuk University School of Medicine, Seoul, Korea, Republic of (South);
[4] Korea University, Guro Hospital, Seoul, Korea, Republic of (South);
[5] Korea University, Anam Hospital, Seoul, Korea, Republic of (South);
[6] Kosin University Gospel Hospital, Busan, South Korea;
[7] Department of Internal Medicine, Dong-A University College of Medicine, Dong-A University Hospital, Busan, Korea, Republic of (South);
[8] Inje Univ. Busan Baik-Hospital, Busan, Korea, Republic of (South);
[9] Seoul national university, Bundang hospital, Seongnam-si, Gyeonggi-do, Korea, Republic of (South);
[10] Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South);
[11] Seoul national university hospital, Seoul, Korea, Republic of (South);
[12] Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South);
[13] Yonsei University College of Medicine, Severance Hospital, Seoul, KOR;
[14] Hematology/Oncology, SoonchunhyangUniveristyBucheon Hospital, Bucheon, Korea, Republic of (South);
[15] Soonchunhyang University Hospital, Seoul, Korea, Republic of (South);
[16] Department of Internal Medicine, Yeungnam University Medical Center, Daegu, Korea, Republic of (South);
[17] Wonkwang University Hospital, Iksan, KOR;
[18] Department of Internal Medicine, EwhaWomans University School of Medicine, Seoul, Korea, Republic of (South);
[19] Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun-Gun, Korea, Republic of (South);
[20] Department of Internal Medicine, Chungnam National University College of Medicine, Daejeon, Korea, Republic of (South);
[21] Department of Internal Medicine, Hallym University College of Medicine, Hallym University Hospital, Anyang, Korea, Republic of (South)
Korean Society of Hematology AML/MDS Working Party

Background : Hypocellular myelodysplastic syndrome (h-MDS) comprised approximately 10-20% of total MDS cases. The difference in clinical features and prognosis between h-MDS and normo/hypercellular MDS (NH-MDS) remains uncertain and the treatment strategy of h-MDS patients has not been well-defined in epigenetic therapy era.

Methods : We collected clinical and laboratory data from web-based Korean MDS registry. A total of 1976 evaluable MDS patients, who were diagnosed between the years 1993 and 2014, form 28 Korean hospitals were registered in Korean MDS Registry. Hypocellularity was defined as less than 30% of cellularity in patients <70 years, and <20% in patients 70 years or older in the bone marrow biopsy specimens.

Results : We identified 358 (18.1%) h-MDS patients among 1976 evaluable MDS patients. Gender, performance status, Hemoglobin, platelet counts, prior transfusion and bone marrow blast percentage did not differ between h-MDS and NH-MDS patients. However, h-MDS patients were younger, more neutropenic, with lower level of LDH. There was no difference in overall survival (OS) between the h-MDS and the NH-MDS patients and 9% of h-MDS patients and 15.1% NH-MDS patients transformed to acute leukemia.
The IPSS and IPSS-R were able to identify different risk groups within each group and were not significantly different between the groups. The IPSS-R was a lesser ability to predict OS for h-MDS patients. Of the 358 h-MDS patients, 141 h-MDS patients were treated with HMA. The median OS after the treatment of HMA was 31.4 months and 32 months for h-MDS and NH-MDS patients and leukemic transformation rate at 3 years was 24.1% and 27.6%, respectively.
At univariate analysis to define prognostic factors in h-MDS, the factors associated with a poor overall survival were age, poor performance status, low albumin, anemia , neutropenia, prior transfusion and high LDH. Using the Cox proportional hazard regression model, older age, neutropenia, low albumin and prior transfusion were independent prognostic indicators. Based on those independent factors, h-MDS patients were divided into 3 risk groups and it discriminated 3 groups with distinct survival rates.

Conclusions : IPSS-R was less powerful in detecting difference for h-MDS and h-MDS patients had a different pattern from those of NH-MDS regarding prognostic factors. Further study and validation are warranted to stratify the risk of h-MDS patients.

Keyword : MDS, Hypomethylating agents, Prognostic factor

PP-20

Increased Proportion of Th17/Treg T Cells for Early Prediction of Chronic Immune Thrombocytopenia in Children

Hao Gu, Zhenping Chen, Jingyao Ma, Lingling Fu, Jie Ma, Runhui Wu*
Beijing Children Hospital, Capital Medical University, China

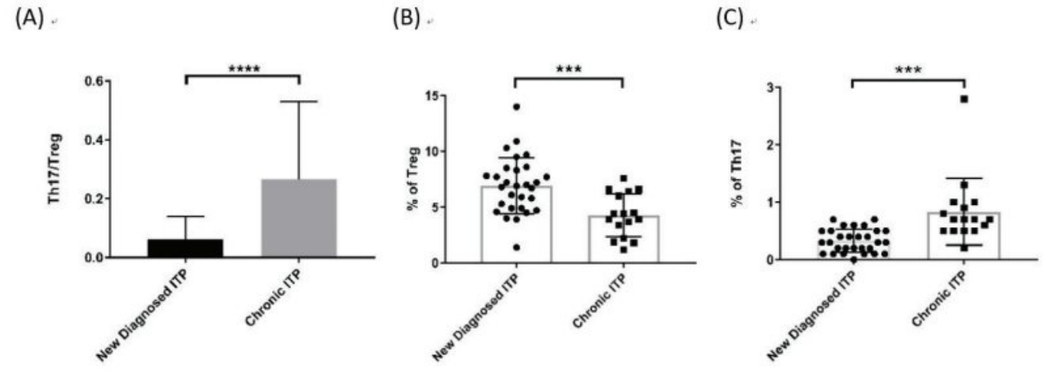
Background : Chronic immune thrombocytopenia (CITP) is an autoimmune disease with many immune dysfunctions including T helper type 17 cell (Th17) /regulatory T cells (Tregs) imbalance. Low quality of life and side effects of drugs is severe especially in pediatric. This study aimed to determine the Th17/Treg polarrization in pediatric CITP when first diagnose ITP and evaluate their potency as predict marker for pediatric CITP.

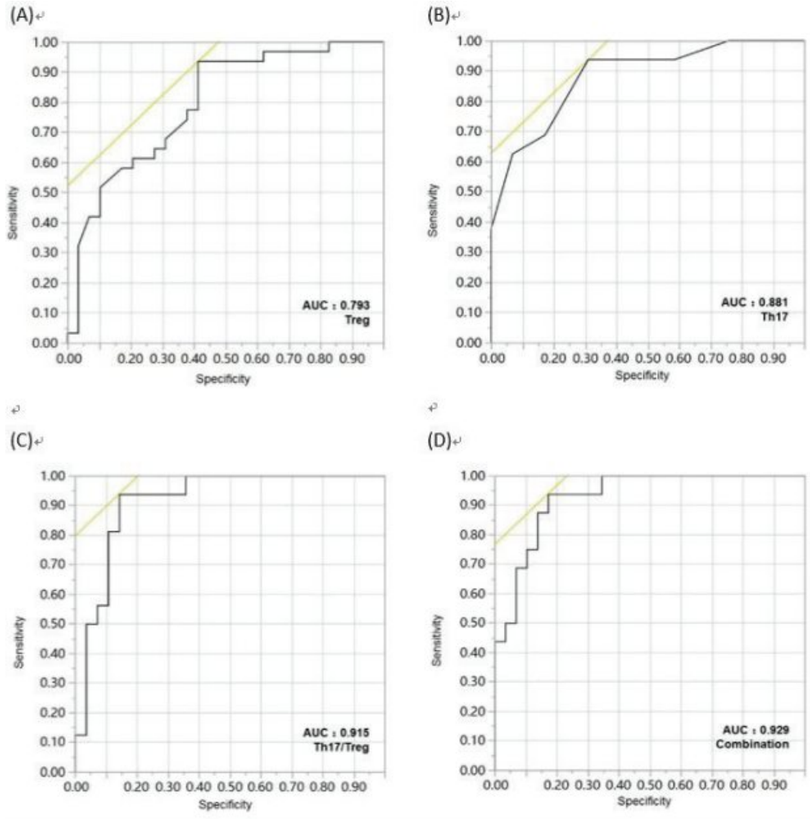
Methods : This is a prospective observation study. The percentage of Treg cells and Th17 cells were quantified by flow cytometry when patient first came. The association between the Th17/Treg and CITP was analyzed statistically.

Results : The percentage of Treg cells and Th17 cells were lower(p=0.0008) and higher(p=0.0001) respectively in CITP group than in the New Diagnosed ITP group at primary ITP stage. Using receiver operating characteristic analysis, it was shown that the area under the curve (AUC) of Treg and Th17 was 0.793 and 0.881 respectively. The combination of Treg and Th17 exhibited the largest AUC of 0.929.

Conclusions : Thus, Treg and Th17 may play an important role in the pathogenesis of CITP. they are promising predictive markers for CITP, and may facilitate the management of patient care.

Keyword : CITP, Th17/Treg ratio, early prediction





PP-21

Torque Teno Virus/Torque Teno-Like Minivirus in Kikuchi-Fujimoto Disease

Yosep Chong[1], Seung Bum Hong[2], Ji Young Lee[1], Eun Jung Lee*[1]

[1] Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Korea
[2] Department of Genetic Analysis, Crimininal Investigation Command, Ministry of National Defense, Korea

Background : Kikuchi-Fujimoto disease (KFD) is necrotizing lymphadenitis that mainly involves cervical lymph nodes of young women with unknown etiology. Although a range of infectious etiology has been postulated, any of possible human pathogens have not shown statistically significant association to KFD. Recently, Torque teno virus/Torque teno-like mini virus (TTV/TLMV), which is a genus of circoviridae that causes necrotizing lymphadenitis in pigs, has been described as a potential pathogenic virus in human. This study aims to detect the loadof TTV/TLMV in KFD and to find its association to KFD.

Methods : We performed two-step quantitative polymerase chain reaction (PCR) specific to TTV/TLMV with formalin-fixed, paraffin-embedded tissue of 100 KFD patients and compare the relative quantity of viral load with 50 normal controls. Consequent direct sequencing was done for confirmation with PCR products.

Results : Mean age of KFD patients was 23.5 years (range 3 ~ 61 years). The male to female ratio was 1:2.4. The lymphohistiocytic subtype was most common (54%). PCR amplification of TTV was found in 85 out of 100 KFDs while only 9 out of 50 was found in normal controls, which is significantly different (85% vs. 18%, p<0.000). Likewise, PCR amplification of TLMV was found in 91 KFDs while only 12 was found in normal controls (91% vs. 24%, p<0.000).

Conclusions : Although TTV and TLMV are often found in normal hosts, this finding strongly suggests that the possible implication of TTV/TLMV in the pathogenesis of KFD. Animal or in vivo experiment design should be followed in the future.

Keyword : Kikuchi Fujimoto disease, Torque teno virus, Torque teno like minivirus, Quantitative polymerase chain reaction, Necrotizing histiocytic lymphadenitis

PP-22

Genotype-Phenotype Study on Familial HLH in Korea: A Study from Korea Histiocytosis Working Party

Hyery Kim[1], Kyung Nam Koh[1], Ho Joon Im[1], Hyung Jin Kang[2], Hee Young Shin[2], Jae Wook Lee[3], Nak Gyun Chung[3], Bin Cho[3], Ji Won Lee[4], Kun Hee Yoo[4], Ki Woong Sung[4], Hong Hoe Koo[4], Hee Jo Baek[5], Hoon Kook[5], Kyung Mi Park[6], Eu Jeen Yang[6], Young Tak Lim[6], Eun Sun Yoo[7], Kyung-Ha Ryu[7], Jong Jin Seo*[1]

[1] Pediatrics, University of Ulsan College of Medicine, Asan Medical Center, Korea
[2] Pediatrics, Seoul National University College of Medicine, Korea
[3] Pediatrics, The Catholic University of Korea College of Medicine, Korea
[4] Pediatrics, Sungkyunkwan University School of Medicine, Korea
[5] Pediatrics, Chonnam National University Hwasun Hospital, Korea
[6] Pediatrics, Pusan National University College of Medicine, Korea
[7] Pediatrics, Ewha Womans University College of Medicine, Korea
[8] Pediatrics, Yonsei University College of Medicine, Korea
[9] Pediatrics, Ajou University School of Medicine, Korea
[10] Pediatrics, Yeungnam University College of Medicine, Korea

Background : Hemophagocytic lymphohistiocytosis (HLH) is a genetically heterogeneous disorder, and evidences on genotype-phenotype correlations are emerging. In this study, the correlation between clinical features and genetic subtypes in Korean familial HLH (FHL) was investigated.

Methods : FHL data from 10 hospitals were retrospectively collected. Patients diagnosed with FLH according to the HLH-2004 diagnostic criteria, and with causative gene mutation identified were included.

Results : A total of 48 FHL patients were reported. There were 7, 36, 1, 2, and 2 patients with PRF1, UNC13D, STX11, STXBP2, and SH2D1A gene mutations. Most prevalent causative gene mutation was UNC13D which was identified in 73.5% of Korean FHL patients, and it was followed by PRF1 gene mutation (14.3%). Median age at diagnosis 3.2 months (range, 7 days-13 years), and 77.0% of the patients were diagnosed under the age of 1 year. There was no statistical difference in the clinical presentations and laboratory findings at diagnosis between genotype groups. Most of the patients received HLH-2004 based chemotherapy, and 30 patients (62.5%) reached complete remission at the end of induction. Eighteen patients showed reactivation, and there was no difference in reactivation rates by genotype. Eight patients died before hematopoietic stem cell transplantation (HSCT). The 5-yr overall survival (OS) rate of 36 transplanted patients was 75.0%, whereas that of 12 who didn't receive HSCT was 25.2% (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 OS by genotype. Among the 26 FHL3 patients, 5 with biallelic splicing mutations showed significantly lower OS (20% vs. 71.1%, P=0.012) and lower reactivation free survival rates (0% vs. 65.7%; P=0.011) compared to other patients.

Conclusions : Our study showed that the unique predominance of an UNC13D mutation in Korean FHL patients and patients with biallelic splicing mutation in UNC13D gene was associated with poor survival. Although HSCT conferred a significant survival benefit to FHL patients, some patients could achieve stable remission status with chemotherapy alone. Further investigation for HSCT indication in FHL patients and functional studies for the understanding of molecular pathophysiology are needed in the future.

Keyword : Familial hemophagocytic lymphohistiocytosis, Genotype, Phenotype, Survival

PP-23

Prevalence of Anemia among Chronic Kidney Disease Patients in India: Evidence from a Meta-Analysis

Md Salman Hussain[1], Abul Kalam Najmi[2]

[1] Department of Pharmaceutical Medicine, Jamia Hamdard (Hamdard University), India
[2] Department of Pharmacology, Jamia Hamdard (Hamdard University), India

Background : Anemia is one of the most common complications in chronic kidney disease (CKD) patients. Anemia in CKD is associated with poor quality of life, increased risk of mortality and cardiovascular complications and is generally unrecognized. So, this meta-analysis is aimed to estimate the exact prevalence of anemia in CKD patients in India.

Methods : This meta-analysis was conducted in accordance with the PRISMA guidelines. PubMed and Embase database was searched for relevant articles using a combination of keywords related to "anemia AND chronic kidney disease." Search period was from inception to December 2017. Risk of bias among the included studies was judged using modified Newcastle-Ottawa scale. Articles were identified based on pre-specified inclusion criteria. The primary outcome was to calculate the pooled prevalence of anemia. Secondary outcomes include subgroup analysis based on anemia prevalence on the basis of CKD stages. Comprehensive meta-analysis software version 2 was used for all the statistical analysis.

Results : This meta-analysis comprised of 7095 CKD patients from nine eligible studies. Majority of the included studies were of high quality. Mean age of the patients was 41.10 ± 8.36 years. Anemia among Indian CKD patients lie in the range of 40.7 – 100%, with an overall pooled prevalence of 76.5% (95% CI: 60.3% – 87.5%) {Fig.1}. Random effect model was applied since there was evidence of substantial heterogeneity across the studies (I2= 98%, p = 0.00). Subgroup analysis revealed the pooled prevalence of anemia in early stages (Stage 1 – 3) of CKD and late stages of CKD (Stage 4 – 5) around 51.6% (95% CI: 42.8% – 60.4%) and 72.1% (95% CI: 57.6% – 83.1%) respectively.

Conclusions : High prevalence of anemia was found among Indian CKD patients. Effective measures should be taken to prevent and treat this devastating co-morbid condition.

Keyword : Anemia, Chronic Kidney Disease, Epidemiology, India, Systematic Review, Meta-Analysis

PP-24

Cell Bead: Affordable Counting Bead by Flow Cytometry

Duangdao Palasuwan, Attakorn Palasuwan

Clinical Microscopy, Faculty of Allied Health Sciences, Department of Clinical Microscopy, Chulalongkorn University, Thailand

Background : Activation of vascular endothelium and blood cells in a range of inflammatory and infectious diseases is associated with the formation of cell-derived microparticles (MPs), which are membrane vesicles with diameter <1.5 micron. Analysis of circulating MPs is becoming more refined and clinically useful. The standard single-platform flow cytometric testing that uses the known reference microbeads is expensive; more affordable alternatives are therefore needed. In this study, we validated a quantitative method called "cell bead (CB)" to measure circulating MPs in the peripheral blood of patient with Glucose-6-phosphate dehydrogenase deficiency (G6PD).

Methods : Citrated blood samples were collected from 34 patients with G6PD Vaingchan (871 C→T), 4 patient with G6PD Mahidol (487 G→A), 2 patient with G6PD Union (1360 C→T), and 2 patient with double mutation variant of G6PD Mahidol-Vaingchan and Vaingchan-Union. AnnexinV-FITC, a specific marker for phosphatidylserine, was used to distinguish MPs from nonspecific noise. The cellular origin of MPs was identified using an antibody to a specific surface marker of the cells, PE-conjugated anti-glycophorin A was used for RBCs, PE-conjugated anti-CD51 for endothelial cell, and PE-conjugated anti-CD41a for platelet and counted by FACsCalibur flow cytometer. The absolute MPs numbers were measured by CB and the results were compared with the known reference microbeads (Trucount TM). Statistical correlation and agreement were analyzed using linear regression and Bland-Altman analysis.

Results : Linear regression analyses revealed an excellent correlation of the CB with the standard microbead method (r(2) > 0.9; absolute counts, r(2) > 0.9. Mean percent bias for the CB method was +1.35% [limits of agreement (LOA): -2.86% to +3.57%].

Conclusions : The use of CB is comparable with the use of commercial microbeads. This has resulted in major cost savings to resource-limited countries where the health care system is under increasing pressure to operate cost effectively. AFM demonstrated that MPs are shed by the discoid RBCs. This might reflect the capability to remove damaged cell components for the viability of the discoid RBC.

Keyword : Cell bead, Flow cytometry, Deformability, Microparticles, Counting bead

PP-25

Red Blood Cell Deformability in Patients with Hematologic Neoplasms

Yu Kyung Kim[1], Jae Min Lee[2], Ji Yeon Ham[1], Jang Soo Suh*[1]
[1] Clinical Pathology, Kyungpook National University School of Medicine, Korea
[2] Pediatrics, College of Medicine, Yeungnam University, Korea

Background : Red blood cell (RBC) deformability is the ability of RBCs to adapt their shape to the flow conditions to enable passage through the capillaries, which are narrower than RBCs, and to minimize resistance to blood flow. Several studies have demonstrated that reduced RBC deformability is related to microcirculatory disease, such as diabetes mellitus, sickle cell anemia, and malaria. However, there is no repot regarding the association of RBC deformability in various hematologic disorders including clonal hematologic malignancies. The objective of this study was to evaluate RBC deformability in in patients with leukemic disease.

Methods : The deformability of the RBCs was measured by the microfluidic ektacytometer, Rheoscan-D. The elongation index (EI) of erythrocytes is defined as (L-W)/(L+W), where L and W are the major and minor axes of the ellipse, respectively. RBC deformability was evaluated on 469 patients comprising 57 with acute myeloid leukemia (AML), 31 with acute lymphoid leukemia (ALL, including Burkitt leukemia), 23 with chronic myelogenous leukemia (CML), 29 with myelodysplastic syndrome (MDS), 42 with myeloproliferative disease (MPD, except CML), 30 with aplastic anemia (AA), 9 with chronic lymphocytic leukemia, 56 with plasma cell neoplasm, 23 with BM involvement of malignancy (including lymphoma), 169 with normal bone marrow at initial diagnosis of time.

Results : The mean values and standard deviations of RBC deformability in each study subjects are shown in Table 1. RBC deformability of AML, ALL, CML and MDS were significantly lower than that of normal BM.

Conclusions : In the group of AML, ALL, CML and MDS, RBC deformability was significantly decreased as compared to the normal control group and other hematologic disease. Thus, RBC deformability test may be used to reflect the aggressiveness of clonal hematologic diseases.

Keyword : RBC deformability, Leukemia, Rheology

Table 1. RBC deformability (Elongation Index) in the 469 study patients

	N	Elongation Index		P
		mean	SD	
Normal BM	169	0.3015	0.0241	
AML	57	0.2699	0.0422	<0.01
ALL	31	0.2786	0.0323	<0.01
CML	23	0.2727	0.0376	<0.01
MDS	29	0.2777	0.0238	<0.01
MPD (except CML)	42	0.2954	0.0365	0.310
Plasma cell neoplasm	56	0.2997	0.0243	0.630
BM involvement of malignancy (including lymphoma)	23	0.2955	0.0328	0.403
Aplastic anemia	30	0.2895	0.0340	0.073
CLL	9	0.0306	0.0189	0.494

PP-26

Bone Marrow and Laboratory Findings in Light Chain Amyloidosis in a Single Center Study

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

Background : Light chain (AL) amyloidosis is the most common form of systemic amyloidosis. The aims of this study were identifying bone marrow (BM) features in AL amyloidosis and comparing BM findings with other diagnostic tests used for AL amyloidosis.

Methods : We retrospectively studied patients who were newly diagnosed with amyloidosis by pathologic examination from 2005 to 2015 and who underwent BM study. The diagnosis of AL amyloidosis was based on a combination of immunohistochemistry (IHC) and other diagnostic tests used for detecting monoclonality. Amyloid deposits were graded as 1+, blood vessel only; 2+, interstitial deposition of ≤2 high-power fields (HPF), 3+; interstitial deposition of >2 HPF. The identification of amyloid deposits was based on the slides of Congo red and PAS. Results of serum and urine immunofixation electrophoresis (IFE), protein electrophoresis (PEP), serum free light chain (SFLC) ratio and flow cytometric (FCM) assay were reviewed using medical records.

Results : For 11 years, 108 patients were diagnosed as amyloidosis and BM study was performed. 2 patients turned out inflammatory (AA) amyloidosis and 5 patients showed no monoclonality. There were insufficient slides for 3 patients. Finally 98 cases were reviewed. The monoclonality (λ, 64; κ, 34) was identified. Plasma cell dyscrasia was diagnosed in 85% by IHC of the BM biopsy or clot section. Significant correlation between a high plasma cell percentage (>10%) and the BM amyloid deposition was not identified. Serum IFE (62%), urine IFE (69%), serum PEP (46%), urine PEP (45%) and SFLC ratio (80%) detected presence of monoclonality. The types of monoclonality between the tests were concordant. FCM assay identified aberrant plasma cells in 93%. Amyloid deposits were identified in 25 BM study. Among 25 cases, Congo red positive and PAS positive cases were 23 and 18 cases respectively. The results of amyloid deposit according to grade were as follows: 1+; 10, 2+; 12, 3+; 3. None of the tests for monoclonality showed significantly associated results with BM amyloid deposits.

Conclusions : Congo red stain of BM section is still an important tool for diagnosing BM deposits of amyloidosis. PAS stain can be helpful in diagnosing few cases of Congo red negative amyloidosis. The sensitivity of BM IHC study was relatively higher than other diagnostic tests for detecting monoclonality in AL amyloidosis.

Keyword : Light chain (AL) amyloidosis, Bone marrow, Immunohistochemistry, Monoclonality

PP-27

Synergistic Effect but Acquisition of Resistance for Danusertib and BKM120 in BL Cell Lines

Jun Liu[1], Junshik Hong*[1,2], Kwang-Sung Ahn[3], Sung-Soo Yoon[1,2]

[1] Cancer Research Institute, Seoul National University College of Medicine, Korea
[2] Department of Internal Medicine, Seoul National University Hospital Seoul National University College of Medicine, Korea
[3] PDXen Biosystems Co., Korea

Background : Burkitt Lymphoma (BL) is one of the fastest growing tumors and the growth largely depends on the process of mitosis. Aurora Kinase act as essential regulators of mitosis and is often amplified and/or overexpressed in human lymphomas. PI3K/Akt pathway plays an important role the in lymphomagenesis of BL in conjunction to MYC. A recent study showed that an AKT inhibitor AZD5363 resulted in synergistic effect with VX-680, an aurora kinase inhibitor (AURKi) in AURKi -resistant cell lines (J Biol Chem. 3:292:1910). This study aimed at defining synergistic effect between a PI3K inhibitor BKM120 and a pan-AURKi danusertib in two BL cell lines (Namalwa and BJAB). In addition, we tried to elucidate by what mechanism this combination could become eventually resistant.

Methods : Cell viability was measured by MTT assay. Cell counting and live cell ratios were given by auto-cell counter. Protein expression levels were detected by western blotting. IL-6 concentration was measured by ELISA. Further, we conducted partial resistance cell experiment by treating the two inhibitors for 3 cycles consecutively in each cell line, to increase the population of chemoresistant BL cells. Cell viability, protein expression, and IL-6 concentration was then measured in the chemoresistant cells.

Results : The combination treatment showed synergistic effect in Namalwa but not in BJAB cell line. P-STAT and p-ERK was overexpressed in BJAB but not in Namalwa, suggesting that JAK/STAT and MEK/ERK pathway would be related to the resistant mechanism. Notably, in partial resistance experiment, Namalwa, which was more sensitive at the 1st cycle, became more resistant at the 3rd cycle. On the other hand, BJAB became less resistant than Namalwa at the 3rd cycle. In chemoresistant cells obtained from the 3rd cycle of partial resistant experiment, p-STAT and p-ERK was overexpressed in Namalwa but not in BJAB, as elevation of IL-6 and hyperactivation of NK-κB pathways.

Conclusions : Danusertib and BKM120 combination initially showed synergistic effect on Namalwa BL cell line. However, Namalwa has become more resistant after partial resistant cell experiment and the resistance was contributed by expression of p-STAT and p-ERK, IL6 release, and NF- κB activation, as initially BJAB did.

Keyword : Burkitt Lymphoma, Danusertib, BKM120, Synergy, Chemoresistance

PP-28

Development and Validation of Mobile Application of Machine Learning Expert Supporting System "ImmunoGenius" for Diagnosis Presumption of Lymphoid Neoplasms Using 1000 Immunohistochemistry Dataset

Yosep Chong[1], Gyeongsin Park[1], Ji Young Lee[1], Myungjin Choi[2], Eun Jung Lee[1]

[1]Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]DasomX, Seoul, Korea

Background: In the pathologic diagnosis of hematolymphoid neoplasms, immunohistochemistry (IHC) has been playing a great role during the past decades, especially for the determination of the cell origin by visualizing the protein expression of tumor cells. However, exponentially increasing IHC data is becoming a big challenge to the pathologists, even to the subspecialists. This study targets the need foran expert supporting system that can quickly provide accurate IHC data and accelerate more efficient use based on mobile platform.

Methods: We designed to develop a mobile application for iOS and Android using probabilistic decision tree algorithm that was priorly confirmed to show a relevant accuracy and efficiency for diagnosis presumption in hematolymphoid neoplasms regarding the computer complexity and information complexity. Using over a dozen of major textbook including WHO classification of tumours series and open literature data, the IHC expression database for each diseasewas built. An IHC profile database was prepared based on WHO classification by reviewing the literature. We trained the algorithm with a real case data of 639 lymphomas and validate with a data of 392 lymphomas to compare the presumption accuracy.

Results: The IHC expression data of over 2009 diseases (150 lymphoid neoplasms) and 584 antibodies was built. The initial features for this prototype application include IHC expression data search by disease and antibody name and the generation of IHC profile table and diagnosis presumption with antibody test results. The presumption accuracy using 639 training dataset was 94.7% and that of 329 validation dataset was 95.7%, which is not significantly different.

Conclusion: Better usage of IHC expression data in perspective of precision medicine can be achieved by the aids of computer expert systems. Further enhancement might be possible by adopting artificial neural network algorithm, deep learning,with a larger magnitude of the training dataset.

PP-29

Seasonal Variation in PE but Not DVT Incidence: A Korean Nationwide Epidemiology Study

Junshik Hong[1], Ju Hyun Lee[2], Ji yun Lee[2], Won-Il Choi[3], Soyeon Ahn[4], Yun Hee Lee[5], Soo-Mee Bang*[2], Doyeun Oh[6]

[1] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[2] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Korea
[3] Department of Internal Medicine, Keimyung University School of Medicine, Keimyung University Dongsan Medical Center, Korea
[4] Medical Research Collaborating Center, Seoul National University Bundang Hospital, Korea
[5] Environmental Health Center, Seoul National University College of Medicine, Korea
[6] Department of Internal Medicine, CHA university School of Medicine, CHA Bundang Medical Center, Korea

Background : Seasonal variation is an environmental factor proposed to affect the incidence of venous thromboembolism (VTE). However, VTE seasonal variation is not well studied in Asian populations, which have different genetic determinants of VTE compared to Westerners.
Objectives: The present study aimed at investigating seasonal variation of VTE occurrence and the effect of various demographic factors (i.e., age, gender, and co-morbidities) on variation.

Methods : VTE seasonal variation was evaluated in 59,626 index cases (from January 2009-December 2013) in the Korean Health Insurance Review and Assessment Service (HIRA) database. We quantified and compared VTE occurrence across four seasons, and additionally assessed monthly through a chronobiological analysis.

Results : VTE incidence varied both seasonally and monthly, with new cases peaking in the winter (January and February) and the lowest incidence in the summer (August and September). After adjusting for sex, age, type of VTE, and combined cancer diagnosis, winter remained a significant independent factor driving VTE incidence. Additionally, seasonal variation was prominent in patients aged 60 years or older and in patients with pulmonary embolism, but not in patients of aged less than 60 years and patients with deep vein thrombosis.

Conclusions : Seasonal variation was a weak but independent contributor to VTE incidence in a Korean population diagnosed from 2009 to 2013, especially in those individuals suffering from a pulmonary embolism.

Keyword : Venous thromboembolism, Deep vein thrombosis, Pulmonary embolism

PP-30

Reevaluation of Initial Antiphospholipid Antibody Positivities

Jin-Yeong Han, In-Wha Jeong, Gyu-Dae An, Hyeon-Ho Lim, Kwang-Sook Woo

Laboratory Medicine, Dong-A University College of Medicine, Korea

Background : Laboratory detection of antiphospholipid antibody (aPL) associated with APS includes lupus anticoagulant (LA), anticardiolipin (aCL), and anti-$\beta_2$glycoprotein-I (a$\beta_2$2GPI) IgG or IgM antibodies. In this study, we evaluated whether the presence of aPL was transient or could be replicated upon repeat tests after three months. The changes in patterns of positive profiles were also evaluated.

Methods : Starting from 2006, the initial positive cases of aPL diagnosed using one or more tests were recommended to get repeat tests done after 3 months, in order to exclude the possibility of transient positivity. The patients who underwent repeat aPL tests more than once were included in the study. LA was measured using diluted Russell viper venom time (DRVVT). aCL and a$\beta_2$2GPI antibodies were initially tested by ELISA, and from 2014onwards, both the parameters were measured by automated chemiluminescence assay.

Results : During a 10-year-period, a total of 136 patients tested positive for aPL initially one or more of the diagnostic tests. These patients then underwent at least one confirmatory test after 12 weeks. The patients were classified into five different groups: triple-positive (LA+, aCL+, a$\beta_2$2GPI +, same isotype), double-positive (LA-, aCL+, a$\beta_2$2GPI +, same isotype), and others (any other triple-, double-, or single-positive cases); the number of cases in each group was 17, 4, 6, 19, and 90, respectively. After 12 weeks, aPL was confirmed in all 17 cases (100%) with initial triple positivity, while only 3 out of 4 double-positive patients (75.0%) were diagnosed with the antibody. Among other combination groups, however, only in 44 of 115 cases (38.3%) were diagnosed positive. Female gender, IgG isotype, and thromboembolic events were more prevalent in triple-positive group.

Conclusions : The study confirmed the presence of triple-positive aPL repeat tests in all the cases. In fact, in some patients, aPL persisted over 2 to 4 years. Further research is warranted to predict the persistence of aPL based on the initial positive profiles and to conduct anti-thrombotic treatment without delay in patients at high-risk.

Keyword : Antiphospholipid syndrome, Antiphospholipid antibody, Lupus anticoagulant, Anticardiolipin antibody, Anti-B2 glycoprotein-I antibody

PP-31

Platelet Proteome and Hypercoagulable State of Non-Splenectomized β-Thalassmia/HbE Patients

Puangpaka Chanpeng[1], Kamonlak Leecharoenkiat*[1], Saowaros Svasti[2], Duncan R. Smith[3], Kittiphong Paiboonsukwong [2], Wannapa Sornjai[3], Wasinee Kheansaard [2]

[1] Department of Clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, Thailand
[2] Thalassemia Research Center, Institute of Molecular Biosciences, Mahidol University, Thailand
[3] Molecular Pathology Laboratory, Institute of Molecular Biosciences, Mahidol University, Thailand

Background : β-thalassemia/HbE is an inherited hemolytic anemia caused by defect in β globin synthesis resulting in accumulation of excess α globin chain in red blood cell. Hypercogulable state leading to high risk of thromboembolic event is one of the most common complication observed in this disease, particularly in the patients with splenectomy. Previous study suggested that increased platelet activation and coagulation factors in splenectomized β-thalassemia/HbE intermediate patients promote the hypercoagulable state. However, the hypercoagulable state as well as the molecular mechanism regarding this pathogenesis in non-splenectomized β-thalassemia/HbE is not yet well understood.

Methods : Fifteen non-splenectomized β-thalassemia/HbE patients and 20 normal subjects were included in this study. The hypercogaulable parameters including detection levels of P-selectin and prothrombin fragment 1+2 were analyzed by flow cytometry and ELISA assay, respectively. The proteomic analysis was conducted to compare platelet proteome between the patients and normal subjects. The differential protein spots were identified by LC/MS/MS method.

Results : The non-splenectomized β-thalassemia/HbE showed significant higher levels of P-selectin (6.4±1.6% vs 3.1±0.7%) and prothrombin fragment 1+2 (1.5±0.7 vs 0.5±0.2) than normal subjects and the levels of P-selectin and prothrombin fragment 1+2 in the patients are strongly correlated (r =0.8479, p<0.0001). Moreover, the platelet proteome revealed 20 differential spots including up-regulation of chaperone (HSC70), purine metabolism (PNP), chemotaxis protein (CXCL7 and Integrin αIIB) and down-regulation of cytoskeleton proteins (TPM1, TPM4 and CAPZA1) and antioxidant enzyme (PRDX6 and GST).

Conclusions : The data from this study suggested that the hypercoagulable state is not only detected in the patients with splenectomy, but also the non-splenectomized patients, indicating that these patients may also have a risk for thrombosis. The platelet proteome data suggested that may play an important role in the biological pathogenesis of the hypercoagulable state observed in β-thalassemia/HbE patients and lead to the possibility of improved treatment modalities as well as the development of thrombosis predictive markers for the patients.

Keyword : Platelet proteomics, B-Thalassaemia/HbE, Thalassemia, Platelet activation, Hypercoagulable state, Protein profiling

PP-32

Von Willebrand Antigen Levels in Blood Group 'O' and Non-O Individuals

Asma Nasir Mahmud, Huma Asif*, Ayisha Imran, Nauman A. Malik
Department of hematology, Chughtai lab lahore, Pakistan

Background : Von willebrand factor (VWF) is a large mutimeric glycoprotein produced by endothelial cells and megakaryocytes. VWF plays dual role in normal homeostasis as it is a carrier molecule for Factor VIII and prevents its early degradation in plasma secondly; it helps in platelet to platelet and platelet to vessel wall interaction for the formation of primary haemostatic plug after vessel wall injury. Levels of VWF antigen varies considerably in association with age, race, ABO blood group, estrogen, pregnancy, hyperthyroidism and as a part of acute phase response. It is established that ABO blood group locus at chromosome 9 (9q34) exerts a major qualitative effect on plasma VWF.

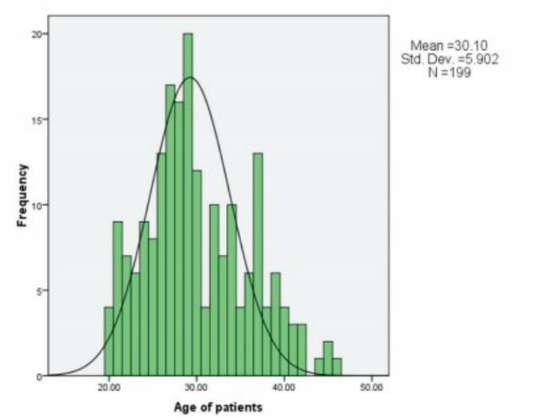
Methods : This comparative Cross sectional study was conducted at Department of Hematology, Chughtai Lab from April2017 to October 2017. Total 200 cases fulfilling inclusion criteria were enrolled in study. Venous blood sample was drawn for blood grouping and VWF antigen levels. Blood group was determined by standard test tube method; forward and reverse grouping was performed. VWF antigen levels were determined quantitatively by Sysmex Coagulation Analyzer (CA600). Levels of VWF Ag in blood group O Vs non O were determined and recorded in a pre-designed proforma.

Results : Mean age of the patients enrolled in this study was 30.10±5.92 years. Majority of the cases were male 184(92%) while lesser female 16(8%). Blood group 'O' was noted in 57 (28.5%) of cases, B was found in 79(39.5%), A in 58(29%) and AB in 6 (3.0%). Mean von willebrand antigen levels were lower 86±19.75 in blood group O while higher in blood group non 'O' 107±33.63, the difference was statistically significant.

Conclusions : Mean Von Willebrand antigen levels are significantly lower in Blood Group O individuals and the results of our study are comparable to the internationally published data. However, none of our blood group O individual showed levels of VWF antigen below 50 IU.

Keyword : VON WILLEBRAND ANTIGEN, ABO BLOOD GROUP, VON WILLEBRAND FACTOR

Distribution According to the Age



Distribution of Gender in the Study Population

	Frequency	Percent
Male	184	92.0
Female	16	8.0
Total	200	100.0

Distribution of Different Blood Groups in Cases Enrolled

	Frequency	Percent
A	58	29.0
AB	6	3.0
B	79	39.5
O	57	28.5
Total	200	100.0

Mean Von willebrand Factor Antigen levels in Blood Group 'O' Vs Non 'O'

	Blood group	Mean	Std. Deviation	P-value
Vonwillebrand antigen levels	Group O	85.9982	19.75535	
	Group non O	107.7090	33.63437	0.001

PP-33

Nonstroke Arterial Thromboembolism in Pediatric Patients: A Single Institution Experience in Korea

Hyoung Soo Choi, Chang Won Choi, Heon Min Kim, Young Hwan Song
Pediatrics, Seoul National University Bundang Hospital, Korea

Background : Arterial thromboembolism (ATE) occurring outside of the CNS, remains a rare event in infants and children. The pathophysiology of arterial disease in pediatric patients has not been adequately explored. The aim of this study is to investigate the prevalence, etiology, diagnosis, management and outcome of ATE in a single tertiary pediatric center in Korea.

Methods : We retrospectively analyzed consecutive ATE patients from 0 to 18 years in Seoul National University Bundang Hospital from April 2003 to March 2016.

Results : Among 70,462 hospitalizations of pediatric patients, 5 males with ATE were identified (0.71 per 10,000 admissions) over a 13-year period. The median age at diagnosis was 7 year 6 months. Locations of thrombosis included 1 intracardiac, 1 coronary artery, 1 renal and splenic artery, 1 femoral artery, and 1 intracardiac and peripheral artery. Underlying clinical conditions were present in all 5 patients including 1 congenital heart disease, 1 Kawasaki disease, 1 trauma and 2 infections. Prothrombotic risk factors including protein C, protein S, or anti-thrombin deficiency were not found. Unfractionated heparin or low molecular weight heparin (LMWH) followed by warfarin was used in 2 patients. Thrombectomy and thrombolysis followed by LMWH was performed in 1 patient. One patient underwent a leg amputation.

Conclusions : This study demonstrated that pediatric ATE occurred with very low frequency compared with venous thromboembolism in the pediatric population of our institution (3.27 per 10,000). The majority of arterial thrombi in children occur as secondary events; therefore, effective preventive strategies are necessary. Multicenter collaboration is warranted to evaluate the epidemiology and clinical outcome of pediatric ATE in Korea.

Keyword : Arterial thromboembolism, Epidemiology, Children

PP-34

Screening of HIV, HBsAg, HCV and VDRL among Voluntary Blood Donors of Western Region of Nepal

Mukunda Raj Kalouni, Arnav Ghosh*
Clinical Pathology, Manipal Teaching Hospital, Nepal

Background : Blood safety remains a major public health problem in our country. Many of the diseases were transmitted through blood transfusion.
The aim of the study was to determine the seroprevalence of HIV, HBsAg, HCV, and VDRL among blood donors of Manipal Teaching Hospital and Blood transfusion centre (Nepal Redcross Society) Pokhara, Nepal.

Methods : Retrospective research design was used to carry out the study between July 2016 to March 2017. Among 9505 blood donors 8172 (85.97%) were male and 1333 (14.02%) were female which were screened for HIV, HBsAg, HCV and VDRL. HIV and HCV were screened by tridot rapid test kit. HBsAg was tested by hepacard spot test kit. VDRL was detected by Veneral Disease Research Laboratory Test. Seropositive samples were confirmed by Enzyme Linked Immunosorbent Assay (ELISA). Data was analyzed by using Excel 2007.

Results : A total of 9505 blood donors were included in this study. The overall seroprevalence was found to be 0.55%. The seroprevalence of HIV, HBsAg, HCV and VDRL were found to be 0.06% (n=6), 0.34% (n=33), 0.12% (n=12) and 0.04% (n=2) respectively. All the HIV, HCV, and VDRL positive donors were males. HBsAg positive donors were males and females. Out of 9505 donors 33 were seropositive for HBsAg. We found a higher prevalence of HbsAg positive donors as compared to HIV,HCV and VDRL. Males have higher prevalence than females.

Conclusions : This study found a low prevalence of transfusion transmitted infections. Thus standard procedures should be used to diagnose the infectious diseases for the safety of the recepient.

Keyword : HIV, HBsAg, HCV, VDRL, Blood donors

Table 1: Pattern of seropositivity of HIV, HBsAg, HCV and VDRL among blood donars at Manipal Teaching Hospital and Nepal Redcross Society

Number of Donar	Male N (%)	Female N (%)	HIV positive N (%)	HBsAg positive N (%)	HCV positive N (%)	VDRL positive N (%)
9505	8172(85.97%)	1333(14.02%)	6(0.06%)	33(0.34%)	12(0.12%	02(0.04%)

PP-35

Prevalence of Anemia among Type 2 Diabetes Mellitus Patients: A Pilot Study

Abul Kalam Najmi[1], Salman Hussain[2]
[1] Department of Pharmacology, Jamia Hamdard, India
[2] Department of Pharmaceutical Medicine, Jamia Hamdard, India

Background : Diabetes mellitus is one of the leading causes of anemia development. Anemia in diabetic patients increase mortality rate, impair quality of life and also responsible for the diabetic complications.

Methods : This was an observational study conducted in Hakeem Abdul Hameed Centenary (HAHC) Hospital, Jamia Hamdard, New Delhi, India. Study duration was of four months. Study was approved by Jamia Hamdard Institutional ethics committee. The main outcome of this study was to estimate the anemia prevalence and its correlates among diabetic patients attending HAHC medicine outpatient department. Data are presented in descriptive analysis. Statistical analysis was performed using SPSS version 20.

Results : A total of 100 participants participated in the study out of 135. Response rate was of 74%. Mean age of the participants was 51.75 ± 11.8 years, while mean duration of diabetes was 5.2 ± 2.4 years respectively. The number of patients diagnosed with mild, moderate and severe anemia was found to be 67%, 27% and 6% in male patients and 51.72%, 27.58% and 20.70 in female patients. Overall anemia prevalence was 78%. Higher odds of anemia were reported in female patients and in elderly patients. Iron, vitamin B12 and folic acid and its combination was the most commonly prescribed to overcome the anemia.

Conclusions : High prevalence of anemia was reported in this pilot study. Iron, vitamin B12 and folic acid and its combination was the most commonly prescribed medication.

Keyword : Anemia, Chronic Kidney Disease, Diabetes

PP-36

Prospsective Phase II Pilot Study to Evaluate the Use of Intravenous Iron in the Treatment of Anemia

Youjin Kim, Jun Ho Jang*, Silvia Park, Chul Won Jung
Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Background : Iron deficiency anemia (IDA) are common complications in cancer patients. Evidence on intravenous (IV) iron for treatment of chemotherapy-induced anemia (CIA) is emerging. Herein, we evaluated the efficacy of IV iron for improvement of anemia in cancer patients.

Methods : This prospective single arm phase II study aims at evaluation of efficacy of IV iron without additional Erythropoiesis-stimulating agents (ESA) for correction of anemia in cancer patients. Patients received Ferinject® (ferric carboxymaltose) 1000mg injection on the first day (visit 1) of chemotherapy or target therapy. Thereafter, hemoglobin (Hb) response defined by increase of Hb ≥ 1.0g/dL was assessed at visit 1, visit 2 and visit 3. To identify biochemical parameter predictive for Hb response, transferrin saturation(TSAT), soluble transferrin receptor (sTFR), hepcidin, erythropoietin (EPO), interleukin-6 (IL-6), CRP were also assessed at each visit.

Results : Between Oct 2010 and Jul 2017, a total of 104 patients were enrolled, and 92 patients was available for and 92 patients was available for injection, Hb response was observed in 36, 53 and 61 patients at visit 1 (39.1%), visit 2 (57.6%) and visit 3 (66.3%), respectively. When excluding 19 patients (20.6%) with absolute IDA defined by ferritin <30ng/mL or TSAT <20%, Hb response rate was 83.5% (61/73). Of 73 patients without absolute IDA, there were i) 56 patients whose serum ferritin 30- 500 ng/ml , ii) 6 patients whose serum ferritin 500-800 ng/ml and TSAT < 50 % , and iii) 10 patients whose ferritin levels >800ng/mL or TSAT ≥ 50%. In each population of i), ii) and iii), Hb response was observed in 60.7% (34/56), 50% (6/6), and 50%(5/10), respectively. Regarding anemia related biochemical parameters, responders had significantly lower levels of hepcidin (13.5 vs. 35.2 ng/mL, p = 0.007), CRP (0.7 vs. 2.5mg/mL, p = 0.044) and ferritin (249.2 vs. 575.3 ng/mL, p = 0.048). When comparing Hb response by baseline hepcidin level, there were significantly more responders in low hepcidin group (58/61, 95.1%) compared to high hepcidin group (3/61, 4.9%) at the cut off value of 34.1 ng/mL (p=0.002).

Conclusions : IV iron supplementation alone showed promising result in improving anemia in cancer patients. Hepcidin may predict response to IV iron in cancer and chemotherapy induced anemia, and is superior to TSAT or ferritin for this purpose

Keyword : Cancer, Hepcidin, Anemia, Soluble transferrin receptor

PP-37

SFKs Inhibitor Bosutinib and Dasatinib Enhances ATRA or ATO Induced NB4 Cell Differentiation

Hee-Jeong Cheong[1], Min Young Lee[2], Kyoung Ha Kim[2], Namsu Lee[2], Sung Hee Lim[2], Jina Yoon[2], Se Hyoung Kim[2], Chan-Kyu Kim[2], Sung Kyu Park[2], Dae Sik Hong[2], Han Jo Kim[2], Sang-Cheol Lee[2], Sang Byung Bae[2], Kyu Taeg Lee[2], Jong-Ho Won*[2]
[1] Institute for Clinical Molecular Biology Research, Soonchunhyang University Hospital, Korea
[2] Division of Hematology-Oncology, Department of Internal Medicine, Soonchunhyang University Hospital, Korea

Background : Leukemic promyelocytes have the unique ability to undergo differentiation with exposure to all-trans-retinoic acid (ATRA) and both differentiation and apoptosis with exposure to arsenic trioxide (As2O3, ATO). Emerging evidence has implicated Src family kinases (SFKs) as regulator of proliferation and survival of myeloid lineage cells. Recent studies showed that inhibition of SFKs resulted enhancement of retinoic acid induced myeloid differentiation. Dasatinib and bosutinib are US Food and Drug Administration (FDA)-approved compound that was developed as an inhibitor of ABL and SFKs. According to our data, we expect the addition of clinically available SFK inhibitors to combination of ATRA and ATO will be more effective than combined ATRA and ATO without additional toxicity.

Methods : In this study, we investigated that bosutinib (2 uM) and dasatinib (2 uM) enhance the differentiation of NB4 cells when combination with ATO (0.5 uM) as well as ATRA (1 nM) by flow cytometric analysis of the myeloid differentiation marker CD11b. These results were confirmed in morphologic analysis by Wright stain and NBT staining.

Results : Treatment of NB4 cells with bosutinib alone, ATRA alone, or ATO alone for 72 hours resulted in only 25.65%, 3.03% or 3.15% of CD11b-positive cells, respectively. However, co-treatment with ATRA plus bosutinib, and ATO plus bosutinib resulted in significant enhancement of CD11b-positive cells (54.60%, and 32.18%, respectively). The synergistic effect of bosutinib combined with ATRA was more significant than that of bosutinib combined with ATO. Treatment of NB4 cells with dasatinib alone, ATRA alone, or ATO alone for 72 hours resulted in only 8.35%, 3.03% or 3.15% of CD11b-positive cells, respectively. However, co-treatment with ATRA plus dasatinib, and ATO plus dasatinib resulted in significant enhancement of CD11b-positive cells (66.53% and 34.25%, respectively). The synergistic effect of dasatinib combined with ATRA was more significant than that of dasatinib combined with ATO.

Conclusions : Our data showed that bosutinib and dasatinib enhanced myeloid differentiation. The synergic effect of SFKs inhibitor on NB4 myeloid leukemia cell differentiation was strong when combined with ATRA than ATO. These studies suggest the combination of SFKs inhibitor (bosutinib and dasatinib) and ATRA or ATO treatment may be therapeutically beneficial in AML.

Keyword : Acute promyelocytic leukemia (APL), All-Trans-Retinoic acid (ATRA), Arsenic trioxide (As2O3, ATO), Bosutinib, Dasatinib, Cell differentiation

PP-38

Advanced Serological Evaluation of a Case of Evans Syndrome with Anti D Autoantibody Induced AIHA

Nitin Agarwal, Prashant Pandey
Transfusion Medicine and Transplant immunology, Jaypee Hospital, India

Background : AIHA is usually caused by IgG antibodies that bind to RBC antigens and result in erythrophagocytosis by macrophages or Kupffer cells. Here we present a case where we found anti-D antibody in aRh (D) positive patient and subsequently, found it to be an auto antibody against D antigen.

Methods : ABO Blood grouping, Rh phenotyping, antibody screening (Capture ready screen) and identification (Capture-R Ready-ID) were performed by SPRCA on NEO (Immucor, USA). DAT and Elution of DAT positive cells with Gamma Elukit-II (Immucor, USA) were performed using conventional tube technique (CTT).

Results : A 56 yrs. old woman was admitted in ICU for breathlessness and malena for 2 days. Two units of Packed Red Cells (RC) were requested as her hemoglobin was gradually decreasing (from 8.6 to 6.7 gm/dl in 2 days) with increasing bilirubin (0.8 to 2.1mg/dl) and LDH(160 to 510 IU/L) and severe thrombocytopenia (platelet count 16000). PBS showed few Spherocytes and few large platelets indicating in vivo hemolysis and some platelet abnormality. Bone marrow biopsy showed increased number of megakaryocyte suggesting ITP.
Patient blood group was B Rh(D) Positive but cross matching with multiple B Positive Packed Red Cell showed 2+ incompatibility.Irregular antibody screening showed possibilities of Anti-D, C, E, Jka, M and S antibodies and identification confirmed the presence of anti-D. DAT (poly) and auto control were positive. Monospecific DAT was positive for anti-IgG only. Eluate showed anti-D specificity on antibody identification. Patient Rh D typing was reconfirmed using 5 different manufacturer's/clone [Series-5, Novaclone (Immucor, USA), Bioclone (OCD), Rhofinal (Tulip), Seraclone (BioRad)] antisera to detect any suspected reaction for D variant. But, all showed strong 4+ reaction, confirming D antigen (not any suspected weak-D or partial-D). Patient's Rh phenotyping was CCee. To exclude anti-G, patient serum was tested with rare rGr cell and found negative.Patient was transfused with two D negative units and her hemoglobin responded well. Patient was treated further considering it a case of Evans syndrome (AIHA + ITP) and responded well to the treatment.

Conclusions : As patient had warm reacting IgG antibodies, auto control positive and lab tests showing signs of hemolysis and thrombocytopenia,this was a case of Evans syndrome (AIHA due to an autoantibody against self Rh (D) antigen+ITP).

Keyword : AIHA, Autoantibody, Evan's syndrome

PP-39

Serum NLR and PLR as a Systemic Inflammatory Marker among HIV-TB before Antiretroviral Therapy

Muhammad Faisal Putro Utomo[1], Anindia Reina Yolanda[1], Nur Rizky Amaliah[1], Petrus Kanisius Yogi Hariyanto[1], Ni Made Dewi Dian Sukmawati[2], I Made Susila Utama[2]
[1] Faculty of Medicine, Udayana University, Indonesia
[2] Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Udayana University, Sanglah General Hospital, Indonesia

Background : Acquired immunodeficiency syndrome (AIDS) in Human immunodeficiency virus (HIV) patient can lead to opportunistic infections such as pulmonary tuberculosis infection. Mycobacterium tuberculosis infection is known to cause inflammation to lead lung damage, the condition more severe in patients with immunocompromised. Recently, some hematological parameter associated with some biomarker that increased inflammation response. High values of neutrophil-to-lymphocytes ratio (NLR) and platelet-to-lymphocytes ratio (PLR) indicated increasing systemic inflammation. Until now, data which support the condition still unclear. This study was aimed to investigate the association between NLR and PLR as a systemic inflammatory marker among HIV patients with pulmonary tuberculosis.

Methods : This is an analytic observational study who involved 210 HIV patient. Secondary data were taken from medical record and extracted using extraction form. Baseline data such as demographic data, stage HIV, opportunistic infection, BTA sputum results, radiographic examination, CD4 count, and complete blood count results were documented. Data were analyzed using univariate and bivariate analysis (Mann-whitney Test).

Results : A total of 210 cases were conducted for the study. Most of cases in the study were males (70,1%) Most of age range between 31-40 years old 41.5%, with total positive pulmonary tuberculosis were 21.2%. Nutritional status of 27.2% samples were assessed to be underweight. Majority of CD4 examination of these samples were <50 (54.5%). The mean value of NLR was 4.609±13.84, mean value of PLR was 287.287±227.47. In this study, there was significantly higher in HIV-TB group than in control group (p=0.035). and PLR was also significantly higher in HIV-TB group than in control group (p=0.008).

Conclusions : The results of this study indicated that NLR and PLR significantly difference between HIV-TB group than the other. This finding should be consider for systemic inflammatory biomarker as an simple examination, specifically in rural/peripheral healthcare setting.

Keyword : Hematology, Tuberculosis, HIV

PP-40

Association between Immunological Status with Hematological Findings among TB-HIV Patients

Anindia Reina Yolanda, Muhammad Faisal Utomo, Yogi Haryanto, Nurrizky Amaliah
Medical Student, Udayana University, Indonesia

Background : Tuberculosis (TB) often happen secondary in HIV patients because of their declining immunological status. TB may increase morbidity as it worsens prognosis and decrease patient condition even more. Currently, the most used method to diagnose TB is based on clinical symptoms and sputum test. However, in many cases, people with TB-HIV develop negative result in sputum test, makes it more difficult to recognize. Our study objective was to see their hematological profile to predict possibility of TB in HIV patients.

Methods : A cross-sectional study with a total of 206 Care Support and Treatment (CST) clients was conducted in Bali Province from March to June 2016. Samples were consecutively selected from CST Clinic at Sanglah General Hospital. Data were collected by extracting it from the medical records using extraction form. Data were then analyzed using univariate analysis, Chi-square.

Results : Among 206 samples there are 58 (28.2%) patients who are diagnosed as TB-HIV yet only 23 (11.2%) of them who develop positive sputum test. The study showed that there is a positive correlation between CD4 count and hemoglobin (p=0.000), thrombocyte (p=0.006), and lymphocyte (p=0.011) among TB-HIV patients.

Conclusions : Hematology profile might be useful to predict TB in HIV patients, besides sputum test. Therefore, HIV patients need to undergo screening for TB sputum test, also hematological profile monitoring. The findings from this study can be used to predict complications for HIV/AIDS patients so early prevention can be taken as soon as possible.

Keyword : HIV, Tuberculosis, Hematology

PP-41

Clinical Characteristics, Treatment Patterns, and Outcome of Lymphoplasmacytic Lymphoma

Jang Ho Cho[1], Silvia Park[1], Young Hyeh Ko[2], Hee-Jin Kim[3], Sun-Hee Kim[3], Kihyun Kim[1], Won Seog Kim[1], Seok Jin Kim*[1]
[1] Medicine, Samsung Medical Center, Korea
[2] Pathology, Samsung Medical Center, Korea
[3] Laboratory Medicine, Samsung Medical Center, Korea

Background : Lymphoplasmacytic lymphoma (LPL) is an extremely rare subtype of B-cell NHL with various clinical behaviors. LPL is clinically overlapped with Waldenstrom's macroglobulinemia because LPL is commonly associated with IgM monoclonal gammopathy. As paraproteinemia can influence multiple organs such as peripheral nerves, liver, and kidney, the treatment outcome of LPL may be affected by the extent of organ involvement as well as type of organ-associated symptoms and signs. However, there are limited data about the outcome of LPL patients due to its rarity.

Methods : We retrospectively analyzed 50 patients who were pathologically diagnosed with LPL at the Samsung Medical Center between 1996 and 2017. Clinical characteristics and treatment outcomes of patients with LPL were analyzed and their survival outcomes were compared according to the type of organ involvement including the presence of amyloidosis.

Results : Male (68%) was predominant with a median age of 63.2 years (range 26-86) at diagnosis. The most common clinical presentation was anemia (32%) and lymph node enlargement (32%). Bone marrow involvement was found in most patients (86%), and 78% of patients had IgM paraproteinemia. The most commonly used regimen in first-line treatment was chlorambucil (22%). Chlorambucil was preferred for elderly patients. Its response rate was 45% (5/11), and disease control rate was 91% (10/11). CHOP or CHOP-like combination chemotherapy was frequently used as a first-line treatment. After 2016, bendamustine plus ribuximab regimen was applied for elderly patients. The response rate was 80% (4/5), and two patients showed CR (2/5, 40%). In salvage treatment, various regimen was used including fludarabine-based regimen. The median overall survival was 62.0 months (95% CI: 48.03-75.97). IPI score (p=0.002), B symptoms (HR 4.541, 95% CI : 1.430-14.419, P=0.010), and ECOG PS (HR 6.989, 95% CI: 1.571-31.090, P=0.011) were independent predictors of OS. The OS of patients with AL amyloidosis was significantly worse than that of patients without AL amyloidosis (4.0 months vs. 65.0 months, HR 0.09 (0.02-0.34), P < 0.001).

Conclusions : We analyzed the clinical characteristics, treatment patterns and outcome of LPL in Korea. This report is the largest study focusing on LPL in East Asia. However, responses to currently used chemotherapy were still not satisfactory.

Keyword : Lymphoplasmacytic lymphoma , Outcome, Amyloid

PP-42

Thrombocytopenia due to Dengue and Vitamin D

Narendra Gemawat
Pediatrics-School health, Hindustan Chamber Chikitsalaya, India

Background : Dengue viral fever (DENV) is recent public health and epidemiological concern. DENV infection has reported from over 100 countries,.The path-physiology of host's immune response is not well understood.,thrombocytopenia being common finding. An immune mechanism of increased platelet destruction appears a risk for concurrent bacteremia. and bleeding .Vitamin D believes to plays role in platelet aggregation ,immune response regulation and dendritic cell maturation. We report our observation in dengue fever with thrombocytopenia ,who showed remarkable increase in platelet count and clinical recovery .with supplementation of vtamin D..as supplementation adjuvant therapy could resulting clinical cure..

Methods : We studied 22 children (10-15 years age) suffering from dengue fever, with normal growth ,health and without associated complication or debility, during a health program in a semirural area during month of June to Oct . who had evidence of thrombocytopenia (count of 50000 -100000 /.cmm), All children were managed with hydration ,paracetamol if needed and were followed up clinical observation with platelets count on 1,2,4 and 6 day. Vitamin D of 60000 iu orally was advised ,on 0,2,4,and 6 day 0f follow-up

Results : It was observed that out of 22 children , only 12 were taking regular vitamin D supplementation .And overall clinical and platelets counts improvement was noted in all these children in 24 hrs only, as compared to non vitamin supplemented group who has shown improvement only on 2-4th day

Conclusions : The observation of early recovery in clinical and thrombocytopenia in dengue viral fever in the vitamin D supplemented children shows a possible role of vitamin d as a immunomedulation , to play an essential role in the immune system.Vitamin D has been shown to promote both innate and adaptive immunity through a number of mechanisms, such as T-cell activation and monocyte differentiation. Many additional cells of the immune system (including B cells, monocytes, and dendritic cells) also respond to the immunomodulatory effects. Vitamin D supplementation In recent research also showed success in helping to treat other viral infections, such as influenza. We wish for further studies with more elaborative scientific data to study further the role of vitamin D in thrombocytopenia of dengue fever.

Keyword : Denv, Vitamin D, Thrombocytopenia

PP-43

Clinical Characteristics of Young-Age Venous Thromboembolism: A Nationwide Study in Korea

Chang-Hun Park[1], Inho Kim[2], Soo-Mee Bang[3], Ho-Young Yhim[4], Yeo-Kyeoung Kim[5], Yang-Ki Kim[6], Won-Il Choi[7], Chul Won Jung[8], Doyeun Oh[9], Sun-Hee Kim[1], Hee-Jin Kim[*1]

[1] Department of Laboratory Medicine & Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[2] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Korea
[3] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Korea
[4] Department of Internal Medicine, Chonbuk National University Medical School, Korea
[5] Department of Internal Medicine, Chonnam National University College of Medicine, Korea
[6] Department of Internal Medicine, Soonchunhyang University School of Medicine, Korea
[7] Department of Internal Medicine, Keymyung University College of Medicine, Korea
[8] Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[9] Department of Internal Medicine, School of Medicine, CHA University, Korea

Background : Venous thromboembolism (VTE) typically occurs in advanced ages, and there have been limited data on VTE in young-age (or early-onset). In this study, we investigated the clinical and laboratory characteristics of young-age VTE in Korea.

Methods : We analyzed the national VTE registry data (from August, 2001 to June, 2016) collected by the Korean Venous Thromboembolism Working Party. The clinical and laboratory data of young-age (YA, <45 years at onset of VTE) were analyzed as compared with those of VTE patients with an onset age ≥45 years (old age, OA). The parameters included demographic profiles, clinical presentation and management data, comorbid conditions, and laboratory data including lipid and thrombophilia.

Results : The YA group consisted of 69 patients, and they were compared with 301 patients in the OA group (≥45 years). The analysis showed that the YA group showed a significantly higher proportion of male patients (p=0.0015) and lower rates of medical comorbidities of coronary heart disease, hypertension, and diabetes mellitus (p<0.0001) and the history of cancer (p<0.0001). In YA group, the VTE involving unusual sites (abdominal cavity, upper limbs, neck, etc), idiopathic VTE, use of thrombolytic agent were significantly more frequent than OA group (p=0.0062, p<0.0001, and p=0.0018, respectively). The duration of symptoms of pulmonary embolism was shorter in YA group (p=0.0488).

Conclusions : Korean VTE registry data showed significantly different clinical and laboratory characteristics of VTE in young age, which could benefit the risk assessment and management planning in these patients.

Keyword : Venous thromboembolism, Deep vein thrombosis, Pulmonary embolism, Multi-Center, Korea

PP-44

Effect of the Hydro-Alcoholic Extract of Falcaria Vulgaris on Liver Parameters of Diabetic Rats

Faramarz Jalili[1], Cyrus Jalili[2]

[1] Department of Anatomy and Cell Biology, Students Research Committee, Kermanshah University of medical Sciences, Iran
[2] Department of Anatomy and Cell Biology, Department of Anatomy and Cell Biology, Kermanshah University of medical Sciences, Iran

Background : Diabetes mellitus is a metabolic disorder as old as mankind and its incidence is considered to be high all over the world. Oxidative stress is strongly associated with development and the complications of diabetes. Antioxidant agents, especially with the origin of plants, are of more importance in the treatment of diabetic complications. The main objective of the present study was to evaluate the effect of hydro-alcoholic extract of falcaria vulgaris on serum levels of nitric oxide, insulin, weight, blood sugar and investigated the change heypatocyte and central vein diameter, Liver tissue and AST,ALT , ALP and cholesterol levels in liver tissue in streptozotocin induced diabetic rats.

Methods : In this study, 68 male rats were divided in to 8 groups:control, STZ-treated group (55mg/kg/day); hydro-alcoholic extract of falcaria vulgaris -treated groups (50, 100, 150 mg/kg./day); and stz and hydro-alcoholic extract of falcaria vulgaris treated group were administration orally for 28 consequent days. These mice were randomly assigned to 8 groups(n=8). After 24 hours animal were killed the liver was sampled:tissue sections were prepared and examined by light microscopy. Blood glucose, insulin, nitric oxide serum level and body weights were measured. Finally, we estimated the Hepatocyte and central vein diameter, and weight liver, and AST,ALT , ALP and cholesterol levels were analyzed (one-way ANOVA). Then data were P<0.05 was considered significant.

Results : The results indicated that STZ administration significantly increased cholesterol level, ALT,AST,ALP and nitric oxide compared to saline group(P<0/05). Histopatology of the liver confirmed the changes induced by STZ and the hepatoprotective effect of hydro-alcoholic extract falcaria vulgaris. However, hydro-alcoholic extract falcaria vulgaris treatment significantly increased insulin, nitric oxide compared to control group(p<0.05). oral administration of hydro-alcoholic extract falcaria vulgaris resulted in significant reduction in the level blood sugar(p<0.05).

Conclusions : hydro-alcoholic extract falcaria vulgaris may improve liver dysfunction in Streptozotocin-induced diabetic rats by modulation of detoxification enzymes and its antioxidant effects.

Keyword : Falcaria vulgaris, STZ, Hepato protective

PP-45

Expression of PD-1 in Pediatric Patients with Haploidentical SCT Not Correlates with GVHD

Eunkyoung You[1], Seongsoo Jang*[1], Ari Ahn[1], Min Young Lee[1], Young-Uk Cho[1], Chan-Jeoung Park[1], Yu Jin Lee[2], Nu-Ree Park[2], Eun Seok Choi[3], Hery Kim[3], Kyung Nam Koh[3], Ho Joon Im[3], Jong Jin Seo[3]

[1] Department of Laboratory Medicine, Asan Medical Center and University of Ulsan College of Medicine, Korea
[2] Asan Clinical Research Center, Asan Medical Center and University of Ulsan College of Medicine, Korea
[3] Department of Pediatrics, Asan Medical Center and University of Ulsan College of Medicine, Korea

Background : In a tumor microenvironment, overexpression of PD-1, an inhibitory receptor on the surface of T cells, can lead to dysfunction of antitumor effector cells. Recent studies show PD-1 is associated with graft-versus-host disease (GVHD) and relapse after stem-cell transplantation (SCT). However, studies on PD-1 in patients received SCT are rare. The aim of this study was to evaluate pediatric patients undergoing haploidentical hematopoietic stem-cell transplantation (HHSCT) to determine expression levels of PD-1 and to investigate the association between PD-1 and GVHD and relapse.

Methods : Between April 2017 and January 2018, a total of 147 peripheral blood samples with 34 patients with hematologic malignancies (n=18) and non-malignancies (n=16) were enrolled. Seventeen patients were experienced acute GVHD and 4 patients were experienced engraftment failure and 2 patients were expired. Flow cytometric analysis of PD-1 expression on T cells was performed by means of a Navios™ flow cytometer and Kaluza® Flow Analysis Software (Beckman Coulter, Miami, FL, USA).

Results : Patients within 14 days after graft infusion showed significantly lower level of PD-1 on CD8+ and CD4+ T cells than before HHSCT (P = 0.000 and P = 0.009). However, PD-1 expressions were not correlated with time after HHSCT. PD-1 expression on CD8+ T cells was higher in hematologic malignancies patients than non-malignancies patients (P = 0.027). No significant differences were observed in the expressions of PD-1 between GVHD and non-GVHD group. In addition, no difference in PD-1 was observed between patients with engraftment and patients with engraftment failure. However, PD-1 expressions on CD8+ T cells and CD4+ T cells were significantly correlated quantitative chimerism results (P = 0.000 and P = 0.000).

Conclusions : In this study, PD-1 did not seem to be significantly associated with GVHD, but it might be related to HHSCT setting. Recent studies have reported cases of severe GVHD in PD-1 blockade clinical trials in patients receiving SCT. Interestingly, there was no case of GVHD in patients who received HHSCT.

Keyword : PD-1, Haploidentical stem cell transplantation , GVHD

PP-46

Successful Renal Re-Transplant after Desensitization with Plasmapheresis & IVIG in High Risk Patient

Nitin Agarwal, Prashant Pandey
Transfusion Medicine and Transplant Immunology, Jaypee Hospital, India

Background : Antibody-mediated rejection (AMR) remains the major cause of graft failure after kidney transplantation. The presence of donor specific anti-human leukocyte antigen (HLA) increases the risk of AMR after kidney transplant. However, a desensitization protocol enables renal transplantation in such type of high risk patients, particularly in a repeat transplant cases where patient doesn't have other donor. The aim of this study was to investigate the role of TPE in a case where patient demonstrated antibody against both class I and class II HLA donor specific antigens

Methods : All the therapeutic procedures were done using a fully automatic cell separator (COM. TEC Fresenius kabi). 1.2 to 1.5 volume of plasma exchange was done with replacement of albumin and 0.9% normal saline. The tissue typing of the patient and donor (A, B, DR) was performed by low-resolution PCR-SSO method (ImmucorGamma,USA). DSA(Immucor Gamma, USA) and flow cross match(FCXM) (BD FACSVerse™) were done before, during and after the plasmapheresis to monitor effectiveness of plasmapheresis. LSA (LIFECODES Single Antigen) class I and II were also performed by using Lifecodes fluoroanalyzer (Immucor Gamma, USA).

Results : A 34-yr-old male presented for evaluation for a second kidney transplant in March 2016 (first transplant at the age of 30). Patients kidney function was highly deranged (urea=258 mg/dl, sodium=128 mmol/l, potassium=4.4 mmol/l, creatinine=10.1 mg/dl). His CDC-XM was negative but FCXM was positive for both T- and B-cells. The tissue typings of the recipient was haploidentical to the donor (3/6). Luminex DSA (Luminex XM with donor lysates) was negative for class I but positive for class II with mean fluorescence index (MFI) > 5000. Moreover, LSA class I and class II were also positive against donor's HLA antigens. The patient was treated with 6 sessions of plasmapheresis and IVIG before renal transplant. After couple of days of plasmapheresis his flow cross match and DSA Class II became negative (MFI<500) and renal transplant was done on 3rd day of last session of plasmapheresis. Post renal transplant two plasmapheresis were done on day 1 and day 3. At the day 10 repeat DSA was done and found negative and patient was discharged. Graft kidney biopsy done after 6 months and found to be doing well.

Conclusions : Plasmapheresis is a very effective modality for reducing antibody loads to prevent AMR

PP-47

Patients with Therapy-Related Myeloid Neoplasm Harboring Normal Karyotype Showed Better Outcomes

Sang-A Kim[1], Junshik Hong*[1], Go-Un Woo[1], Youngil Koh[1], Dong-Yeop Shin[1], Inho Kim[1], Dong Soon Lee[2], Sung-Soo Yoon[1]
[1] Department of Internal Medicine, Seoul National University Hospital, Korea
[2] Department of Laboratory Medicine, Seoul National University Hospital, Korea

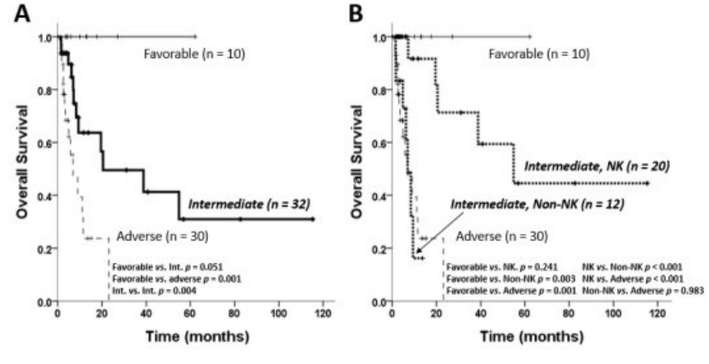
Background : Currently, any myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) developed after previous exposure to chemotherapy and/or radiation (CT/RT) are defined as therapy-related myeloid neoplasms (tMNs). However, this medical history-oriented definition has an inherent uncertainty and although it is known that prognosis of tMNs generally follows risk stratification criteria of de novo AML (for example, tAPL or core binding factor (CBF)-tAML has favorable prognosis), it has not been extensively investigated in t-MNs.

Methods : From July 2002 to June 2017, 103 adult patients were diagnosed tMDS or tAML in single institute. After excluding 13 patients with tAPL and 18 patients who received supportive care only after dignosis of tMNs, 72 patients (45 tAML and 27 tMDS; median age 53 years) were retrospectively analyzed.

Results : During median follow-up period of 10.0 months from the diagnosis of tMNs, median allo-HSCT censored-overall survival (AC-OS) was 20.5 months (95% CI 8.1-32.9 months). Patients with male sex, age at tMNs diagnosis ≥ 70 years, and tMDS showed poorer AC-OS compared to female, age at diagnosis < 70 years, and tAML, respectively. Patients who had complex karyotype or monosomal karyotype showed significantly inferior AC-OS compared to their counterparts. The European Leukemia Network (ENL) 2017 risk stratification effectively separated patients into 3 groups according to their AC-OS, however, among patients with intermediate risk category (n = 32), patients with normal karyotype (NK; n = 20) showed better AC-OS compared to non-NK intermediate risk patients. Patients with non-NK showed OS nearly equivalent to that of patients classified into adverse risk (Fig 1). Multivariate analysis showed that patients with female sex, age < 70 years, and favorable + NK risk category showed independently better AC-OS

Conclusions : Among patients with tAML and tMDS, patients with NK showed AC-OS compared to those with non-NK intermediate cytogenetic risk according to ELN 2017 risk category.

Keyword : Therapy-Related myeloid neoplasms, Acute myeloid leukemia, Myelodysplastic syndromes



PP-48

Micafungin Prophylaxis for Acute Myeloid Leukemia Patients Undergoing Induction Chemotherapy

Hyunkyung Park[1], Jiwon Jeong[1], Jeonghwan Youk[2], Wan Beom Park[1], Dong-Yeop Shin[1,3], Junshik Hong[1,3], Inho Kim[1,3], Nam Joong Kim[1], Sung-Soo Yoon[1,3], Youngil Koh*[4]

[1] Internal Medicine, Seoul National University Hospital, Korea
[2] Korea Advanced Institute of Science and Technology, , Korea
[3] Cancer Research Institute, Seoul National University College of Medicine, Korea
[4] Biomedical Research Institute, Seoul National University Hospital, Korea

Background : Micafungin is a tolerable and effective prophylactic antifungal agent used during allogeneic stem cell transplantation. In this prospective, we aimed to evaluate the potential efficacy and safety of micafungin as a prophylactic agent during first induction chemotherapy in acute myeloid leukemia (AML) patients.

Methods : Patients received 50mg of micafungin intravenously once daily from initiation of induction chemotherapy to recovery of neutrophil count (absolute neutrophil count > 500/μg for consecutive days) or suspected fungal infection or occurrence of drug-related toxicity (ClinicalTrials. Gov number, NCT02440178). Additionally, we compared the outcomes with observational study using prophylactic posaconazole in our institution.

Results : A total of 32 patients (median age 57.0 years, male:female = 18:14) were enrolled in this study. The median treatment duration of micafungin was 26 days (range 1.0-68 days). Proven invasive fungal disease occurred in 1/32 patients (3.1%) and possible fungal infection occurred in 1/32 patients (3.1%). Overall, 17/32 patients (53.1%) discontinued prophylactic micafungin and 16/32 patients (50.0%) changed micafungin to other antifungal agents; 2 patients (6.3%) for fungal infection, 1 patient (3.1%) for adverse event and 13 patients (40.6%) for prolonged neutropenic fever. For safety, 2/32 patients (6.3%) experienced adverse events: 1 patient for liver function abnormality and 1 patient for allergic reaction (grade 2). Induction-related mortality occurred in 3 patients, where 1 event was caused by invasive aspergillosis pneumonia. The period of from initiation of micafungin to change to other antifungal agents was 33 days (95% CI 21-45 days). Additionally, there was no fungal infection caused by resistant organism after induction chemotherapy. When compared to the results of separate observational study using prophylactic posaconazole for AML induction in our institution, there were no significant differences in the incidence of fungal infections, the rate of discontinuation of antifungal agent and safety (probable invasive fungal infection: 2/39 (5.1%), p=1.000; discontinuation: 20/39 (51.3%), p=0.877; adverse events 4/39 (10.3%), p=0.683 in patients treated with prophylactic posaconazole).

Conclusions : Likewise posaconazole, micafungin could be used effectively and safely as prophylactic regimen in AML patients undergoing induction chemotherapy.

Keyword : Acute leukemia, Induction chemotherapy, Prophylaxis , Antifungal agents

PP-49

SET-NUP214 Fusion in Acute Myeloid Leukemia with Massive Hyperdiploidy

Gyu-Dae An[1], In-Hwa Jeong[1], Hyeon-Ho Lim[1], Kwang-Sook Woo[1], Kyeong-Hee Kim[1], Jeong-Man Kim[1], Ji-Hyun Lee[2], Jin-Yeong Han*[1]

[1] Department of Laboratory Medicine, Dong-A University College of Medicine, Korea
[2] Division of Hematology-Oncology, Department of Internal Medicine, Dong-A University College of Medicine, Korea

Background : The SET-NUP214 fusion gene mutation is most frequently observed in T-cell lymphoblastic leukemia and acute undifferentiated leukemia. In acute myeloid leukemia (AML), SET-NUP214 fusion gene mutation is very rarely observed. Here, we report a case of SET-NUP214 fusion in AML with massive hyperdiploidy.

Methods : A 46-year-old man was admitted to our hospital for anemia, leukocytosis, thrombocytopenia and weight loss. Hemoglobin was 5.3g/dL, platelets were 12×109/L, and WBCs count was 17.11×109/L. Differential counts revealed 1% segmented neutrophils, 3% lymphocytes, 2% monocytes, 94% blasts. So, we performed bone marrow examination and biopsy. For further evaluation, we conducted flow cytometric analysis, reverse transcription polymerase chain reaction (RT-PCR), chromosome analysis, SET-NUP214 FISH and sequencing.

Results : The aspirated bone marrow showed 88.0% blast cells characterized by pleomorphic appearances with a large size, a high N/C ratio, irregular nuclear membranes and convolutions, and cytoplasmic projections. Bone marrow biopsy was diluted, but tiny portion showed markedly hypercellular parts and fibrosis. Flow cytometric analysis on bone marrow showed that the cells were positive for cytoplasmic MPO (72.72%), CD33(58.52%), CD7(86.87%), CD34(91.00%) and CD71(68.43%). RT-PCR analysis showed SET-NUP214 fusion transcripts. The chromosome analysis was not fully completed, but showing a massive hyperdiploidy, almost tetraploidy. He was diagnosed as AML without maturation. SET-NUP214 FISH and sequencing results are pending. He is being treated for AML and infection.

Conclusions : AML with SET-NUP214 fusion was very rare, especially combined with massive hyperploidy was not reported. So, we report a case of SET-NUP214 fusion in AML with massive hyperdiploidy.

Keyword : SET-NUP214 fusion, AML, Hyperdiploidy

PP-50

Evaluation and Application of RNA Fusion Gene Panel for the Patients with Acute Leukemia

Borahm Kim[1], Saeam Shin[4], Jieun Jang[3], Soo Jeong Kim[3], Seung-Tae Lee[1], June-Won Cheong[2], Chuhl Joo Lyu[3], Yoo Hong Min[2], Jong rak Choi*[1]

[1] Department of Laboratory Medicine, Yonsei University College of Medicine, Korea
[2] Department of Pediatrics, Yonsei University College of Medicine, Korea
[3] Department of Internal Medicine, Yonsei University College of Medicine, Korea
[4] Department of Laboratory Medicine, Hallym University College of Medicine, Kangnam Sacred Heart Hospital, Korea

Background : The assessment of gene fusion is essential in diagnosis and treatment of patients with acute leukemia, but currently used tests reverse transcription-PCR (RT-PCR) or fluorescence in-situ hybridization (FISH) have several limitations. The application of next-generation sequencing (NGS) technology would be helpful in this group of patients.

Methods : We have evaluated the clinical validity of two commercially available RNA fusion panels, the TruSight RNA fusion panel (Illumina, USA) and FusionPlex Pan-Heme Kit (ArcherDx, USA). The correlation with conventional methods and the limit of detection were confirmed. We applied these NGS-based RNA panels to 46 diagnostic samples.

Results : The two commercial RNA fusion panels showed superior clinical sensitivity to conventional tests, detecting KMT2A-AFF1 gene fusion with unusual breakpoint and rare gene fusions such as DDX3X-MLLT10 and NUP98-HOXC1. The limit of detection was somewhat not satisfactory, ranging from 10-1 to 10-2. Among 46 patients with acute leukemia, 13 had gene fusions. Four of the positive results were those cannot be detected by RT-PCR. Three were rare or novel gene fusions, ETV6-EIF4B, USP42-RUNX1, and PAX5-CBFA2T3. P2RY8-CRLF2 gene fusion indicating Philadelphia-like ALL was detected in a patient with B-cell lymphoblastic leukemia.

Conclusions : RNA fusion panels showed superior clinical utility in detecting gene fusions in patients with acute leukemia. They were suitable for the initial diagnosis, however, for follow-up samples, conventional RT-PCR should be selected.

Keyword : Acute lekemia, Gene fusion, NGS RNA fusion panel

PP-51

A Case of Lineage Conversion with Clonal Evolution from Acute Lymphoblastic Leukemia to Acute Myeloid Leukemia

Heerah Lee[1], Chan-Jeoung Park*[1], Eunkyoung You[1], Hyery Kim[2], Jong Jin Seo[2]

[1] Laboratory medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea
[2] Pediatrics, University of Ulsan College of Medicine and Asan Medical Center, Korea

Background : Therapy related acute myeloid leukemia (t-AML) cases are frequently reported and our understanding regarding the genetic pathways leading to their development is well established. On the other hand, there are rare published cases of complete switch between lymphoid and myeloid lineages during the course of acute leukemia treatment.

Methods : Two shows somewhat similar clinical course but are different concerning whether the leukemic blasts arise from the leukemic clones. T-AML can be diagnosed by establishing a clearly distinct cytogenetic/molecular pattern from the original disease. In contrast, a true lineage conversion within the same disease requires the confirmation of involvement of the same clone (remaining same cytogenetic/molecular alteration) despite the phenotypic changes. Here, we report a case of lineage conversion with clonal evolution from ALL to AML.

Results : A previously healthy 13-year-old boy was referred from a primary clinic with the impression of acute leukemia. CBC showed WBC of 7,000/uL with 46% blasts, Hb of 7.8 g/dL and platelet of 46k/uL. Bone marrow (BM) study revealed 100% cellularity composed of 95% lymphoblasts with typical L1 morphology, expressing pro-B cell immunophenotype with aberrant myeloid antigens (CD19 92%, cytoplasmic CD22 50%, CD13 33%, CD33 93%) and positive FLT3-ITD in molecular study. Cytogenetic analysis showed 46,XY,t(2;16)(p11.2;p11.2),i(12)(q10)[20], and the deletion at ETV6 was also noted by FISH. He achieved complete remission (CR) after the induction chemotherapy and maintained CR state.

Conclusions : 15 months later he was readmitted to our hospital presenting metabolic acidosis signs. CBC showed WBC of 1,500/uL with 11% blasts, Hb of 9.9 g/dL and platelet of 48k/uL. In BM study, blasts displayed monocytic morphology, positivity for CD13(23.7%), CD33(39.2%), CD65(87.8%), CD15(71.3%), and CD14(90.1%) by immunophenotyping. Cytogenetic study revealed a karyotype of 49,XY,t(2;16)(p11.2;p11.2),+6,+8,+12[25]/46,XY[5] and abnormal gain of ETV6. Therefore the conversion of the leukemic cell lineage with clonal evolution from B-ALL to AML (acute monocytic leukemia) was diagnosed. The induction chemotherapy for AML was started accordingly, but failed to achieve remission. He died of multi-organ failure within a month of the diagnosis of the lineage conversion to AML.

Keyword : Clonal evolution, Acute lymphoblastic leukemia, Acute myeloid leukemia

PP-52

Inhibition of Mitochondrial Respiration by Treatment of PDTA Entails Depletion of ATP Content in AML

Ilhwan Ryu[1,2,3], Jeongsu Han[1,3], Yunseon Jang[1,2,3], Soo Jeong Kim[1,2,3], Min Joung Lee[1,2,3], Xianshu Ju[2,3], Byeong Hyeon Yoo[1,2,3], Yu Lim Lee[1,2,3], Min Jeong Ryu[1,4], Woosuk Chung[6], Gi Ryang Kweon[1,2,4], Jun Young Heo*[1,2,3]

[1] Department of Biochemistry, Chungnam National University School of Medicine, Korea
[2] Department of Medical science, Chungnam National University School of Medicine, Korea
[3] Infection Control Convergence Research Center, College of Medicine, Chungnam National University, Korea
[4] Research Institute for Medical Science, Chungnam National University School of Medicine, Korea
[5] Brain research Institute, Chungnam National University School of Medicine, Korea
[6] Department of Anesthesiology and Pain Medicine, Chungnam National University Hospital, Korea

Background : Acute myeloid leukemia (AML) is a hematopoietic malignant neoplasm that characterized by continuous proliferation of myeloid progenitor cells. A large number of discoveries for genetic mutation in immature myeloid cells make it hard to specific targeting therapy of AML. In accordance with evidence about somatic mutation can alter the metabolic flow in cancer cells, we focused on the mitochondrial metabolism for inducing anti-leukemic activity against the complex and variable genetic mutation.

Methods : Cytotoxic effect tested with CCK-8 assay and count the cell numbers with hemocytometer. Mitochondrial respiration measured oxygen consumption rate by XF24 analyzer. Monoamine oxidase-A and B (MAO-A and B) activity was based on the flurometric detection of H2O2, one of the product of MAO enzyme reaction. Intracellular total ATP content assessed with luminescence assay that detect the light with ATP, luciferase and D-luciferin.

Results : Parkinson's disease therapeutic agent (PDTA) has been known to inhibit the MAO-B activity which localized in mitochondrial outer membrane. Interestingly, PDTA has potent anti-leukemic activity in KG-1α, U937 cells, even though AML cells have low MAO-A and B activity. To verify the underlying mechanism of cytotoxic effect, we assessed mitochondrial respiration that control the intracellular energy metabolism. Expectedly, PDTA treatment suppressed the mitochondrial activity and lead to ATP depletion.

Conclusions : We discovered small molecule as a new candidate for the treatment of acute myeloid leukemia by inhibition of mitochondrial respiration, regardless of MAO-B.
(2014R1A6A1029617), (2016R1A2B4010398), (2016R1D1A1B03932766), (2017R1A5A2015385)

Keyword : Monoamine oxidase-B, Acute myeloid leukemia, Mitochondrial respiration, Anti-Leukemic activity

PP-53

Single Center Experience of Blinatumomab for Relapsed/Refractory B Cell Acute Lymphoblastic Leukemia

Soo-Jeong Kim[1], Ji Eun Jang[1], Hae Rim Chung[1], Chul-Joo Yoo[2], Jin Seok Kim[1], June-Won Cheong*[1], Yoo Hong Min[1]

[1] Department of Internal Medicine, Yonsei University College of Medicine, Korea
[2] Department of Pediatrics, Yonsei University College of Medicine, Korea

Background : The complete remission rate of acute lymphoblastic leukemia (ALL) reaches 85 to 90%, however for adult patients long term survival rates range 30 to 50%. Although lont term survival rate of pediatric patients are much better than adult patients, the prognosis of relapsed/refractory patients are not favorable. Previous salvage regimens showed remission rates around 20 to 45%, and median duration of remission was mostly less than 6 months regardless of chemotherapeutic combinations. The vast majortiry of B cell precursor ALL blasts express CD19 antigen. Blinatumomab is a bispecitic T-cell engager antibody which simutaneously binds to CD3 antigens of cytotoxic T cell and CD19 antigens of ALL blasts. The TOWER trial has shown much improved remission rate and longer survial of blinatumomab treatment for relapsed/refractory B cell ALL patients. We reviewed single center experience of blinatumomab.

Methods : The medical records of the patients who received blinatumomab were reveiwed.

Results : Total 15 patients (Male 8, female 7)received blinatumomab for salvage treatment of relapsed/refractory ALL from October 2016 to December 2017. The age of patients ranged from 5 to 62 years. The median number of previous treatment lines were 3. Five patients (33.3%) experienced allogeneic stem cell transplantation before blinatumomab treatment. The median cycle number of blinatumomab was 2 cycles. Complete remission was documented in 6 patients (40%).Among five patients who had simutaneous bone marrow relapse and extramedullary relapse(BM+EM), only 1 patient achieved CR. One patient who has solitary extramedullary relapse failed to achieve CR. Nine patients had bone marrow relapse only and 5 of them achieved complete remssion. For 6 patients who achieved CR has allogeneic stem cell transplantation followed. Two patients who failed CR with blinatumomab received MEC salvage treatment followed by allogeneic stem cell transplantation. Currently median follow up duration after starting blinatumomab is 6 months. Eight patients who received Blinatumomab or MEC salvage regimen followed by allo HSCT are alive in CR.

Conclusions : Blinatumomab response r in Korean patients were similar to the TOWER trial. BM+EM relapse type was associated with poor response. Further data collection is required to find factors related to better response with blinatumomab.

Keyword : ALL, Blinatumomab

PP-54

Acute Myeloid Leukemia Classification in an Era of the WHO 2016 Diagnostic Criteria

Jung Jin, Eunhee Han, Myungshin Kim*, Yonggoo Kim, Kyungja Han
Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea

Background : The diagnosis of acute myeloid leukemia (AML) has been developed over the past 15 years into a disease characterization largely based on cytogenetic and molecular analysis. Since the World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues included genetic entities, abundant genetic knowledge associated with AML has been accumulated. The recent update of WHO classification incorporated new clinical, prognostic, morphologic, immunophenotypic, and genetic data to improve the characterization of AML. Thus, we reviewed our leukemia database and reclassified 610 patients previously diagnosed as AML with the consideration of 2016 revision criteria.

Methods : AML patients who were diagnosed and treated in Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea between Jan 2014 and June 2017 were included. Karyotype analysis was performed on short-term cultures from diagnostic bone marrow specimens and described according to International System for Human Cytogenetic Nomenclature guidelines. The mutations in CEBPA, NPM1 and RUNX1 genes were analyzed by Sanger sequencing.

Results : Seven patients (1.1%) were categorized as myelodysplastic syndrome with excess blasts because the definition of myeloid neoplasms with erythroid predominance has been modified shifting the main criteria for calculating blast percentage from non-erythroid cells to all nucleated marrow cells. Two (0.3%) were classified into myeloid neoplasms with germline predisposition because they harbored germline CEBPA mutation. AML with recurrent genetic abnormalities were 57.4% (345/601). Among them, AML with mutated NPM1 (16.5%, n=99) and AML with biallelic mutations of CEBPA (8.3%, n=32) were newly included. Two provisional entity: AML with BCR-ABL1 and AML with mutated RUNX1 were 0.7% (n=4) and 0.2% (n=1).

Conclusions : The classification of AML is improving through application of comprehensive genetic analysis. We anticipate that the implementation of the WHO 2016 classification of AML will not pose major difficulties. Future studies with incorporation of molecular mutation status with prognosis would provide a better tool for risk stratification and development of new therapeutic strategy.

Keyword : AML, Classification, Gene mutation, CEBPA, NPM1

PP-55

Clinical Dissection of Infectious Event following ATG Treatment for Aplastic Anemia and Hypoplastic Myelodysplastic Syndrome

Hee Ryeong Jang [1], Youngil Koh*[1], Sung-Soo Yoon[1], Inho Kim[1], Soo-Mee Bang[2], Jeong-Ok Lee[2]
[1] Internal Medicine , Seoul National University Hospital, Korea
[2] Internal Medicine, Seoul National University Bundang Hospital , Korea

Background : Infection is the leading cause of death in patients with aplastic anemia (AA) and hypoplastic myelodysplastic syndrome (hMDS). While the responses of immunosuppressive treatment (IST) occur after 3-6months after ATG treatment, aggravation of transient neutropenia and lymphopenia is provoked. As such, increasing of mortality associated with infection is obviously predictable following ATG treatment. In this study, we studied the relation between invasive fungal infection (IFI) and treatment outcome and predictive factor of IFI after ATG treatment for AA and hMDS.

Methods : We retrospectively reviewed the medical records of AA and hMDS patients who were treated with rATG based IST between January 2005 to July 2016 in two institutions (Seoul National University Hospital and Seoul National University Bundang Hospital). The response was evaluated at 3 and 6 months after IST. Assessment of response to IST was performed according the criteria of EBMT.Infection events occurred within 6 months after rATG administration were studied. Only proven and probable IFIs were considered according to the EORTC/MSG criteria. OS was defined as the time of IST treatment to death . WBCs, ALC and ANC of the initiation of treatment, 3months and 6months after IST were analyzed by using receiver operating characteristics curves to assess the optimal value.

Results : A total of 139 patients (median age, 51.0; range 15-82, male:female 75:64) were evaluated.A total of 88 infection events were observed in 75 patients and the most frequent infection was bacterial infection (40 cases, 45.4%). IFIs were observed in 26 cases and invasive aspergillosis was the most common fungal infection (23 cases, 88.4%). IFIs following ATG was significantly related with shorter OS (HR 4.4; CI 1.925-10.074; p <0.0001). ALC less than 500/ml (sensitivity 71.4%; specificity 76.9%; AUC 0.768 CI95 0.630-0.906; P=0.002) at 3months after IST was a significant predictive factor for IFIs related death (OR 8.3; CI 2.167-32.044; P=0.002). Interestingly, infections other than IFI were not significantly related to infection related death or shorter OS.

Conclusions : IFI is the leading cause of death in patients who receive IST for AA or hMDS. Our findings strongly suggest need for antifungal prophylaxis such as posaconzole following ATG based IST in this population.

Keyword : Aplastic anemia, Fungal infection , ATG

PP-56

Diagnostic Considerations for the Recently Described Entity, MDS/MPN-RS-T: A Review of 6 Cases

Min Young Lee, Seongsoo Jang*, Chan-Jeoung Park, Young-Uk Cho, Eunkyoung You, Ari Ahn
Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea

Background : Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) is a new entity that was introduced as a full entity in the 2016 revision of the WHO classification. Previously it was classified as refractory anemia with ring sideroblasts with marked thrombocytosis (RARS-T), which was a provisional entity under the MDS/MPN, unclassifiable (U) group. It is characterized by thrombocytosis of ≥450 x 10^9/L and RS ≥15% of erythroblasts. In this study, we investigate the characteristics of morphologic and laboratory features through analysis of 6 cases that can be categorized as MDS/MPN-RS-T.

Methods : We reviewed the bone marrow study of patients with the disease code as RARS and MDS/MPN, not classifiable from Jan, 2008 to Dec, 2017.

Results : A total of 6 cases were diagnosed with MDS/MPN-RS-T according to the 2016 WHO classification. The data of cases were described in Table 1. In PB findings, large/giant platelets were frequently found. The platelet counts were less than 450,000 with the results by the automated hematologic instrument in 3 cases, however all were over 450,000 in the manual count.
A patient had a diagnosis of RARS-T, followed by bicytopenia and dysplasia in 3 lineages, and MDS RCMD was diagnosed at follow-up. Before the revision, RCMD can be given regardless of presence of RS. If current criteria are applied, the patient should consider to be maintaining MDS/MPN-RS-T. The other patient has a history of MDS RCMD with RS followed by a diagnosis of RARS-T. As in the previous MDS/MPN-U criteria, there should be no MDS history, while in the current MDS/MPN-RS-T criteria, the history of MDS-RS is not exceptionally exclusion criteria, such a series of disease progress is possible.

Conclusions : MDS/MPN-RS-T has recently been fully established, so there is little understanding. It is worth noting that in patients having RS, manual counting of the platelet should be performed. Conversely, for patients suspected ET, evaluation of the RS through careful observation of the iron stained slide is essential. Since the independent evaluation of RS was reflected in the revised classification, the blurred disease entity becomes more clear and consistent.

Keyword : MDS/MPN-RS-T, RARS-T, MDS/MPN-U, 2016 WHO classification

Table 1. RBC deformability (Elongation Index) in the 469 study patients

Case No.	Sex/Age (y)	WBC Count (× 109/L)	Hb Level (g/L)	Platelet Count (× 109/L) (manual count)	Cellularity (%)	Ring sideroblast (%)	JAK2V617F mutation	SF3B1 mutation
1	M/71	5300	6.3	349k (450k)	70 (5-90)	30	NT	NT
2	M/21	4400	8.6	277k (600k)	70	81	Negative	NT
3	M/55	5290	7.3	504k (930k)	90	72	Negative	NT
4	M/55	6700	9.3	738k	90	24	Negative	positive
5	M/80	3000	6.4	347k (600k)	45 (20-70)	30	Negative	NT
6	M/67	5200	9.4	791k	75	32	positive	NT

PP-57

A Rare Case of MPN with a Coexistence of JAK2 V617F Mutation and BCR/ABL1 Translocation

Sang Hyuk Park[1], Ji-Hun Lim*[1], Joseph Jeong[1], Sun-Ho Lee[1], Yunsuk Choi[2], Jae-Cheol Cho[2], Young-Uk Cho[3], Sang-Hyun Hwang[3], Seongsoo Jang[3], Chan-Jeoung Park[3]
[1] Department of Laboratory Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Korea
[2] Department of Hematology and Cellular Therapy, University of Ulsan College of Medicine, Ulsan University Hospital, Korea
[3] Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea

Background : Although revised 2016 WHO classification does not include myeloproliferative neoplasm (MPN) with more than 1 genetic aberration as a distinct disease entity, some cases with coexistence of JAK2V617F mutation and BCR/ABL1 translocation have been reported and up to 28 cases have been previously reported. Among them, the majority of the patients either had pre-existing BCR/ABL1-positive chronic myeloid leukemia (CML) and developed JAK2V617F mutation while undergoing tyrosine kinase inhibitor (TKI) treatment, or developed BCR/ABL-positive CML with a pre-existing JAK2V617F mutation-positive MPN. In contrast, cases with simultaneous occurrence of both JAK2V617F mutation and BCR/ABL1 translocation at the diagnosis of CML, without pre-existing CML or other philadelphia-negative MPN, is rarely reported. We report here a rare case of MPN with a simultaneous coexistence of JAK2V617F mutation and BCR/ABL1 translocation in a patient without pre-existing CML or other philadelphia-negative MPN.

Methods : A 65 years-old man visited author's institution at November 2016 with the symptom of cough and epigastric pain. The patient's hemogram results at first visit were as follows: white blood cells, 26.3 × 109/L, Hb, 16.2 g/dL, and platelets, 2,333 × 109/L.

Results : The peripheral blood smear (PBS) revealed neutrophilia, basophilia, and marked increase in the platelets. The bone marrow aspiration showed hypercellular marrow with granulocytic, eosinophilic and megakaryocytic hyperplasia, and the bone marrow biopsy showed hypercellular marrow (cellularity 85.0%) with granulocytic, eosinophilic and megakaryocytic hyperplasia (7.0/high power field), accompanied with frequent cluster formation of megakaryocytes demonstrating nuclear atypia and occasional platelets pooling. Subsequently performed real-time PCR using Real-Q BCR-ABL1 probe & primer set (Biosewoom Inc., Seoul, Korea) for the detection of BCR/ABL1 fusion transcript showed the presence of major BCR/ABL1 fusion transcript (b3a2 type). Additionally performed real-time PCR using Real-Q JAK2 V617F kit (Biosewoom Inc., Korea) for the detection of JAK2V617F mutation also shows the presence of JAK2V617F mutation (heterozygous type).

Conclusions : On the basis of these findings, the patient was diagnosed as CML in chronic phase with simultaneously harbored JAK2V617F mutation and initiated to treat with imatinib mesylate.

Keyword : BCR/ABL1, Chronic myeloid leukemia, Coexistence, JAK2 V617F, Myeloproliferative neoplasm

PP-58

Very Early Molecular Response at 1 Month is a Predictor of the Outcome of CP-CML Treated with TKIs

Hye-Young Song[1], Soo-Young Choi[1], Sung-Eun Lee[2], Soo-Hyun Kim[1], Hea-Lyun Yoo[1], Mi-Young Lee[1], Ki-Hoon Kang[1], Kyung-Mi Kee[1], Ji-Hyung Suh[1], Seon-Young Yang[1], Dong-Wook Kim*[1,2]

[1] Leukemia Research Institute, The Catholic University of Korea, Korea
[2] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

Background : The early molecular response (EMR) by tyrosine kinase inhibitors is important to predict optimal response and survival in chronic phase chronic myeloid leukemia. However, EMR achievement can be affected by various clinical factors such as dose intensity, adverse events, blood level and risk scores. However, innate intrinsic sensitivity to TKIs of CML clones has not been considered.
To define the optimal molecular response at early time point of treatment initiation with minimal dose interruption, we identified the optimal BCR-ABL1 transcript level measured at 4 weeks after TKI initiation and assessed the clinical impact.

Methods : In this single center study, 258 newly diagnosed CML-CP patients were treated with various TKIs (130 imatinib and 128 second generation TKIs; 80 dasatinib, 33 nilotinib, 13 radotinib, and 2 bosutinib) and BCR-ABL1 transcript level were analyzed at 4 weeks (28 + 3 days) after frontline TKI initiation.
All of patients had e13a2 or e14a2 transcript and a receiver operating characteristic (ROC) curve from BCR-ABL1 transcript level on Day+28 was calculated to predict EMR at 3 months and major molecular response (MMR) at specific time-points. The results of qRT-PCR were analyzed with at least 4.5-log sensitivity in the central laboratory (Leukemia Research Institute, The Catholic University of Korea, Seoul, Korea).

Results : At 4 weeks, the cut-off values of BCR-ABL1 transcript for achieving 12 month-MMR was 40.89% (very early molecular response; VEMR, $P < 0.0001$) by ROC curve analysis. One hundred thirty four patients achieving VEMR (<40.89% at 4 weeks) had significantly higher 7-year probabilities of Event-free survival (63.2% vs 57.9%; P=0.081), and deep molecular response (62.6% vs 59.5%; P=0.017) than no VEMR patients. Various predictive factors for achieving VEMR including age, sex, risk score, initial WBC, basophils, splenomegaly, baseline BCR-ABL1 transcript level were analyzed and low leukocytes ($p<0.001$) and low level of baseline BCR-ABL1 transcript ($p<0.0001$) were significantly associated with VEMR achievement.

Conclusions : The very early molecular response assessment could be important to predict long term outcomes and may provide additional information about innate intrinsic sensitivity to individual CML clone. As it also allows for the prediction of DMR, VEMR can be used as one of the important tools to select candidates for treatment free remission.

Keyword : Chronic Myeloid Leukemia, Early Molecular Response, Tyrosine Kinase Inhibitors, Major Molecular Response

PP-59

Dasatinib-Induced Pulmonary Arterial Hypertension Diagnosed by Echocardiography in CML

Jee Hyun Kong[1], Sung-Eun Lee[2], Young-Woo Jeon[2], Soo Young Choi[3], Soo-Hyun Kim[3], Eun-Jung Jang[3], Hae-Eok Jung[4], Dong-Wook Kim*[2,3]

[1] Hematology-Oncology, Wonju Christian Hospital, Yonsei University College of Medicine, Korea
[2] Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea
[3] Leukemia Research Institute, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea
[4] Cardiology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

Background : Pulmonary arterial hypertension (PAH) is rare complication of dasatinib, which requires invasive right heart catheterization. With introduction of the Doppler echocardiography, approximate evaluation of pulmonary arterial pressure (PAP) became feasible. Thus, we reviewed echocardiography of dasatinib treated chronic phase chronic myeloid leukemia patients (CP-CMP), and we evaluated the clinical application of non-invasive echocardiography for PAH.

Methods : Between March 2005 and June 2015, 359 CP-CML patients were treated with dasatinib, 302 of them performed echocardiography. We defined dasatinib induced PAH (D-PAH) as right ventricular systolic pressure (RVSP) >40mmHg by echocardiography with relevant symptoms and the absence of other specific etiologies known to evoke PAH.

Results : A total 664 echocardiographys were performed randomly at baseline (200), or on/after dasatinib (464). Median 46.6 (13.5-96.6) months after dasatinib, high RVSP was detected in 23 patients (6.4%), and 12 patients (3.3%) were diagnosed as D-PAH. The estimated cumulative incidence of D-PAH at 3-year was 6.5% (95% C.I. 6.2 –20.5). All symptoms and RVSPs of D-PAH were improved in after holding or dose reduction of dasatinib, and 5 RVSP were normalized completely (42%).
Median RVSP (26mmHg (11-108) measured during dasatinib medication was higher than baseline (24 mmHg (12-46)) (p=0.002). During medication, patients treated with dasatinib longer than 2 years had higher RVSP (28mmHg (14-108)) than those who treated less than one year (25.5mmHg (11-49))(p=0.001).

Conclusions : As RVSP significantly increased with dasatinib treatment and discontinuation of dasatinib was important for reversion of D-PAH, serial echocardiography may be important in patients with relevant symptoms. However, the regular RVSP monitoring is not recommended for all dasatinib-treated patients. In addition, if a patient who had relevant clinical manifestations, non-invasive echocardiography will be fast way for early diagnosis as well as for evaluation of D-PAH.

Keyword : Chronic myeloid leukemia, Dasatinib, Pulmonary arterial hypertension, Echocardiography

PP-60

Therapeutic Targeting of BCR-ABL in Chronic Myelogenous Leukemia by Modulating NAD Levels

Jeongsu Han[1,2,3,4], Soo Jeong Kim[1,2,4], Min Joung Lee[1,2,4], Ilhwan Ryu[1,2,4], Xianshu Ju[1,2,4], Byeong Hyeon Yoo[1,2,4], Yu Lim Lee[1,2,4], Yunseon Jang[1,2,4], Min Jeong Ryu[1,2,3], JunYoung Heo[1,2,4,5], Gi Ryang Kweon*[1,2,3]

[1] Department of Biochemistry, Chungnam National University School of Medicine, Korea
[2] Department of Medical Science, Chungnam National University School of Medicine, Korea
[3] Research Institute for Medical Science, Chungnam National University School of Medicine, Korea
[4] Infection Control Convergence Research Cente, Chungnam National University School of Medicine, Korea
[5] Brain Research Institute, Chungnam National University School of Medicine, Korea

Background : Mutations of Bcr-Abl protein reduce sensitivity of imatinib treatment for chronic myelogenous leukemia. The resistance of imatinib treatment to CML patients' needs to develop a direct target drug of Bcr-Abl fusion protein itself through another mechanism. Here we describe the modulation of NAD+/NADH ratio effect on CML cell line (k562 cells) that down regulates Bcr-Abl protein expression level.

Methods : Modulation of cellular NAD+/NADH ratio has been identified as the therapeutic target responsible for Bcr-Abl degradation by molecular biologic methods including measurement of cell viability, western blot and enzyme activity.

Results : When k562cells changed with cellular NAD+/NADH ratio, Bcr-Abl degradation was detected, followed by decreasing of procaspase-3 and cleavage of PARP, means that cellular DNA damaged and apoptotic stimuli was activated. Quinone oxidoreductases [NAD(P)H:quinone Oxidoreductase 1 (NQO1) and NRH:quinone oxidoreductase2 (NQO2)] are the major enzymes involved in modulating NAD+/NADH ratio. For the functional study of NQO1 and NQO2 in Bcr-Abl degradation, we used inhibitors for each enzymes, dicumarol and quercetin. Interestingly, Bcr-Abl degradation was inhibited by dicumarol, but it was accelerated by quercetin.

Conclusions : Collectively, our results demonstrate that modulation of cellular NAD+/NADH ratio destruct the Bcr-Abl fusion protein mediated by NQO1 and NQO2 and it expected synergic effect by co-treatment of NQO2 inhibitor in treating CML. (2014R1A6A1029617), (2016R1A2B4010398), (2016R1D1A1B03932766), (2017R1A5A2015385)

Keyword : BCR-ABL, Chronic myelogenous leukemia, NAD levels

PP-61

Quantification of BCR-ABL1 Using Digital PCR in CML Patients for TKI Discontinuation

Hee-Jung Chung[1], Hye-Won Lee[2], Mi-Kyoung Han[2,3], Hyun-Seok Um*[2]

[1] Laboratory Medicine, Konkuk Medical Center, Korea
[2] Internal Medicine, Center for Hematologic Malignancy, National Cancer Center Hospital, Korea
[3] Division of Convergence technology, Immunotherapeutics Branch, National Cancer Center Research institute, Korea

Background : Quantification BCR-ABL1 fusion transcripts is an important clinical test for the monitoring of patients with chronic myeloid leukemia. Recent therapeutic issues are discontinuation of tyrosine kinase inhibitors (TKI). Related analytical sensitivities became important to detect low level of BCR-ABL (less than 0.001~0.0001 IS%) in patient who reached deep molecular remission.
Droplet Digital PCR (ddPCR) is highly sensitive PCR by amplifying single tube conventional PCR reaction to thousand PCR reactions by droplets within single tube.

Methods : We developed and validated the ddPCR assay with homebrew primer and probe. BCR-ABL1 major rearrangement and / BCR were set as target / control genes, respectively. Primer 3 plus was used for design of primer and probe.
We quantified Certified Reference Material (CRM) with certified BCR-ABL1 level. Calibration was performed with IS calibrator to serve commutable standard results. The imprecision was tested and IS calibration curve was confirmed in every batch. We compared the results of the newly developed real-time RT-PCR (Ipsogen BCR-ABL1 Mbcr IS-MMR DX Kit) and the newly developed ddPCR using BCR-ABL positive patient samples with low concentrations.

Results : The developed method was able to detect and quantify major BCR-ABL1 up to 5-log in analysis with CRM and patient samples. Assay range was 0.001 ~ 10 ^ 5 IS%. Imprecision in five repeated tests was 6.8% CV.
Real-time RT-PCR results and ddPCR results were compared. Comparison of patient samples showing 4 log ~ 3 log concentrations revealed 0.67 of correlation coefficient. Results of 5 samples at undetectable level on Real-time RT-PCR showed 3~5 log concentrations.

Conclusions : We developed in-house laboratory IS calibrated ddPCR assay quantifying BCR-ABL1 fusion transcripts. The results revealed digital PCR had better analytical sensitivity than real-time RT PCR. We expect the droplet digital RT-PCR is a promising method for quantification of BCR-ABL1 fusion transcripts to clinical laboratory. By quantifying BCR-ABL1 fusion transcripts even down to 5-log or more, physicians can be more informed in selecting TKI discontinuation candidate.

Keyword : BCR-ABL1, Digital PCR, Chronic myeloid leukemia, limit of detection, Analytical sensitivity, Droplet PCR

PP-62

Performance of Automated Imaging Cell Analyzer Vision Hema for White Blood Cell Differentials

Sumi Yoon, Mikyoung Park, Hanah Kim*, Mina Hur
Department of Laboratory Medicine, Konkuk University School of Medicine, Korea

Background : Vision Hema (West Medica, Perchtoldsdorf, Austria), an automated imaging cell analyzer, has been newly developed. We evaluated the performance of Vision Hema for white blood cell (WBC) differentials in comparison with manual count.

Methods : In a total 200 peripheral blood smear samples (100 normal and 100 abnormal samples), concordance and agreement were evaluated between Vision Hema pre-classification and verification for WBC differentials. WBC pre-classification and verification by Vision Hema were compared with WBC differentials by manual count respectively. The manual count was performed according to the Clinical and Laboratory Standards Institute guidelines (H20-A2).

Results : The overall concordance between Vision Hema pre-classification and verification for WBC differentials was 95.4%. The agreement between Vision Hema pre-classification and verification was almost perfect (κ = 0.949) for WBC five-part differentials and strong (κ = 0.827) for all cells including non-cells, immature granulocytes (IGs), blasts, and nucleated red blood cells (nRBCs). Vision Hema pre-classification and manual count showed very high or high correlations (r = 0.706 to 0.947) except basophils (r = 0.601) and IGs (r = 0.699). After verification, the correlation between Vision Hema and manual count was very high or high for all cells (r = 0.717 to 0.952).

Conclusions : Vision Hema showed reliable analytical performance for WBC differentials with improvement after verification. Vision Hema could be helpful for the workflow in hematology laboratory.

Keyword : Vision Hema, Performance, White blood cell (WBC) differentials, Comparison, Manual count

PP-63

Performance Evaluation of the Automated Digital Cell Morphology Analyzer DI-60 in Pediatric Patients

Gyu-Dae An[1], In-Hwa Jeong[1], Hyeon-Ho Lim[1], Sung-Suk Cho[2], Kwang-Sook Woo[1], Kyeong-Hee Kim[1], Jeong-Man Kim[1], Hee-Won Chueh[3], Jin-Yeong Han*[1]
[1] Department of Laboratory Medicine, Dong-A University College of Medicine, Korea
[2] Department of Laboratory Medicine, Dong-A University Hospital, Korea
[3] Department of Pediatrics Medicine, Dong-A University College of Medicine, Korea

Background : Cell morphology analysis is an important and essential test for diagnosis of several hematologic diseases. It requires technical expertise and is time consuming. On the contrary, DI-60 is a fully automated digital cell morphology analyzer by Sysmex Co., Kobe, Japan, which can help report efficient and accurate results. It is easy to standardize, and thus, is convenient for even unskilled inspectors. We evaluated the performance of DI-60 in pediatric patients.

Methods : A total of 174 samples were analyzed. Among these, 102 samples were obtained from neonates and 72 samples were obtained from infants and juveniles. First, DI-60 was used to classify white blood cells (WBCs); the initial DI-60 results were corrected and confirmed. To compare manual differential counts, 100 WBCs were classified as segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils, immature cells, nucleated red blood cells (RBCs) by two researchers, followed by calculation of the average from their results. We analyzed correlation between each cell morphology type as observed from DI-60 and manual differential counts.

Results : Overall, the performance of DI-60 was excellent. The correlations between DI-60 and manual differential counts in segmented neutrophils and lymphocytes were very strong (R=0.945; P <0.0001, R=0.939; P <0.0001, respectively). Correlations between DI-60 and manual differential counts in monocytes and immature cells were also strong (R=0.741; P <0.0001, R=0.767; P <0.0001, respectively). Despite of low cell counts, correlations between DI-60 and manual differential counts in eosinophils and nucleated RBCs were observed (R=0.705; P <0.0001, R=0.642; P <0.0001, respectively). When further divided into two groups as neonates and infants, similar correlation results were observable.

Conclusions : The DI-60 is an automated differential analyzer, so it can reduce testing and analyzing time; furthermore, it is also useful to train unskilled and new inspectors. It enables the standardization of cell morphology analysis, too. However, we evaluated only samples from pediatrics patients. So, there is a need to analyze other disease groups and patients.

Keyword : DI-60, Automated digital cell morphology analyzer, Differential count

PP-64

A Case of Iron-Refractory Iron Deficiency Anemia with Autoimmune Chronic Gastritis

Hyunjung Kim[1], Der Sheng Sun*[2], Joonhong Park[1], Myungshin Kim[1]
[1] Laboratory Medicine, College of Medicine, The Catholic University of Korea, Korea
[2] Internal Medicine, College of Medicine, The Catholic University of Korea, Korea

Background : The celiac disease, autoimmune atrophic gastritis, Helicobacter pylori gastritis, and hereditary iron-refractory iron deficiency anemia (IRIDA), is uncommon cause of iron deficiency anemia (IDA). Anti-parietal cell antibodies (APCAs) are usually associated with pernicious anemia because they are necessary for the absorption of vitamin B12. Here, a case of phenotypic IRIDA in a patient with APCA and autoimmune chronic gastritis has been reviewed.

Methods : A 42-year-old woman with fatigue and vomiting, but no obvious symptoms of disease, was diagnosed with IDA; her laboratory tests showed WBC 8.55×103/μL, hemoglobin (Hb) 5.3 g/dL, hematocrit 21.6%, MCV 54.7 fL, MCH 14.9 pg, MCHC 27.2 g/dL, platelet count 679 ×103/μL, ferritin 2.3 ng/ml, iron 11 μg/dL, TIBC 550 μg/dL, transferrin 504 mg/dL, transferrin saturation 2%, slightly increased erythropoietin, and normal levels of vitamin-B12 and folate. A bone marrow biopsy revealed 50% cellularity and some of erythroid precursors reveal microcytic change. There was no occult blood in the stool, no Helicobacter pylori antibody, no hemorrhagic focus anywhere in the body, however atrophic gastritis was found in the gastric endoscopy. The patient did not respond to oral iron therapy, and showed only a slight response to IV iron therapy.

Results : We firstly suspected hereditary IRIDA, however, sequencing of TMPRSS6 revealed no pathogenic mutations. Whole exome sequencing revealed a heterozygous mutation in BMP6, which is involved in iron metabolism, and revealed no mutations for myelodysplastic syndrome. We could not conclude that BMP6 heterozygous mutation was the pathogenic mutation in this patient, because IRIDA is autosomal recessive disorder. Then we fine other rare condition such as autoimmunity, APCA and homogenous pattern of auto-antibody (1:800) were present in the patient.

Conclusions : Previously, there have been a few reports on the association of autoimmune chronic gastritis with IDA. However, iron refractoriness in autoimmune gastritis is seldom reported, and is also a very difficult condition for doctors to treat in IDA patients, while being a painful experience for the patient. Therefore, for IDA patients with iron refractoriness, in addition to genetic testing, autoimmune testing is also needed for proper diagnosis and management.

Keyword : Iron-Refractory, Autoimmune gastritis, Iron deficiency , IRIDA

PP-65

Performance Evaluation of Automatic Image Analyzer for Differential Count of Bone Marrow Cells

Yong Jun Kwon, Jun Hyung Lee, Ha Jin Lim, Hyun Jung Choi, Soo Hyun Kim, Myung Geun Shin*
Departments of Laboratory Medicine, Chonnam National University Medical School and Chonnam National University Hwasun Hospital, Korea

ackground : Although differential count of bone marrow is essential in diagnosing hematological disorders, it can be time-consuming and laborious. Recently, automatic image analyzer for bone marrow, Vision Hema Bone Marrow 4Pro (West Medica, Austria) is introduced. This study was to evaluate its performance in analyzing slides of bone marrow aspiration smear.

Methods : We tested 76 samples of bone marrow from patients with variant hematologic disorder and measured the time it took for the image analyzer to analyze the slides. To test its precision, 4 slides that are closest to normal differential count were selected to be evaluated for between run and within run, and we performed 10 tests for each slide. Total of 500 nucleated cellular elements of bone marrow were counted by the image analyzer and the percentages of them were compared with those of manual differential count using Pearson correlation analysis.

Results : For analysis 500 bone marrow cells, the image analyzer took 392.5 seconds. The coefficient of variation (CV) of nucleated cellular elements were less than 20% for between run and less than 10% for within run, except for the cells that accounted for less than 5% of normal bone marrow (myeloblasts, promyelocytes, basophils, eosinophils, plasma cells, proerythroblasts, and basophilic erythroblasts). CV of granulocytes, erythroblasts (NRBC), and myeloid to erythroid ratio (M:E ratio) were less than 5%, 20%, 20% and 2%, 5%, 5% for between run and within run, respectively. Correlation coefficients for nucleated elements except basophils, proerythroblasts were 0.52-0.91, for granulocytes, immature neutrophils (promyelocyte, myelocytes, metamyelocytes), mature neutrophils (band neutrophils, segmented neutrophils), NRBC, M:E ratio were 0.87, 0.73, 0.92, 0.83, 0.57, respectively.

Conclusions : Both the CV and the correlation to manual differential count of automatic image analyzer are acceptable based on this study. This automatic image analyzer expected to be helpful for saving time and labor in analyzing bone marrow.

Keyword : Automatic Image Analyzer, Bone Marrow Cells, Vision Hema

PP-66

Relapsed Acute Myeloid Leukemia Preceded by Discrepant Morphologic and Molecular Evaluations

Sumi Yoon, Hanah Kim, Mina Hur*
Department of Laboratory Medicine, Konkuk University School of Medicine, Korea

Background : Bone marrow (BM) evaluation is mandatory to decide remission or relapse of acute myeloid leukemia (AML), and morphologic evaluation is considered less sensitive than molecular evaluation.

Methods : We present a case of relapsed AML preceded by discrepant status between morphologic and molecular evaluations. A 26-year-old man with therapy-related AML showed relapse after receiving scheduled chemotherapy and allogeneic peripheral blood stem cell transplantation (allo-PBSCT). He underwent regular BM evaluations over chemotherapy and second allo-PBSCT.

Results : Five months after relapse, leukemic cells were 6.8% of all nucleated cells in BM. Flow cytometric analysis, fluorescence in situ hybridization (FISH), cytogenetic study, and short tandem repeats PCR (STR-PCR), however, showed molecular complete remission (CR). With discrepancy between morphologic and molecular evaluations, he was in morphologic partial remission that preceded relapse (leukemic cells, 52.7%) one month later. Increased leukemic cells were evident in flow cytometric analysis (16.2% of total cells), FISH analysis (7q deletion in 304/500 cells [60.8%]), and cytogenetic analysis (44~45,XY,t(3;12)(q26.2;p13),-7,-18,+6~7mar[cp2]/46,XY[11]). Mixed chimerism (38% - 50%) was observed in STR-PCR.

Conclusions : Even with molecular CR, remained leukemic cells can precede the relapse of AML. This case underscores the importance of morphologic evaluation and multimodal approaches in the monitoring of AML.

Keyword : Relapse, Acute myeloid leukemia, Discrepancy, Morphologic evaluation, Molecular evaluation

PP-67

VisionHema is Useful for Nucleated Cell Differentials in Bone Marrow Aspirates without Abnormalities

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

Background : The VisionHema system (West Media Austria, Perchtoldsdorf, Austria) was developed as an automated digital cell morphology analyzer for determination of nucleated cell differential counts in bone marrow aspirates (BM) as well as peripheral blood (PB). This system automatically scans slides as well as identifies and pre-classifies BM cells. Here we present our experience of performing automated differential counts of BM cells using this system.

Methods : A total of 27 BM samples (16 abnormal; 11 normal) were analyzed in this study. The 16 abnormal BM aspirates, including those from patients of acute leukemia (n=5), plasma cell myeloma (PCM) (n=4), lymphoma (n=3), chronic myeloid leukemia (n=2), eosinophilia (n=1), and hemophagocytic lymphohistiocytosis (HLH) (n=1), were used. For each sample, manual differential counts were performed by hematopathologists. Wright-stained BM aspirates were used for both automated and manual counts, and a total of 500 cells were counted. Correlations and discrepancies between the two methods were assessed along with their ability to pre-classify BM cells.

Results : The correlation coefficients for each cell component as measured using the manual and automated methods were variable and ranged from 0.217 to 0.877. In the 11 normal samples, automated and manual counts were in good agreement, overall. In the 16 samples with abnormalities, counts for eosinophil (r=0.985), band neutrophil (r=0.918), segmented neutrophil (r=0.843), and blasts (r=0.837) showed good correlation. In the patients with leukemia, there was a difference in the blast percentages measured using the two methods. However, there was still a good correlation (0.794) and all cases of the automated counts reported blasts to be more than 5%, which was useful to screen for abnormalities. In the PCM samples, plasma cells were measured to be lower via the automated count as compared to the manual count; they were also misclassified, mainly as lymphocytes or basophilic erythroblasts.

Conclusions : The VisionHema system is expected to be useful for differential counting of BM samples without abnormalities. In samples with abnormalities, VisionHema system could be used to screen for them. However, in this study, the number of samples was too small to be evaluated. Thus, the accuracy and ability of this system should be evaluated in larger patient samples in future studies.

Keyword : Automated analyzer, VisionHema, Bone marrow

PP-68

Clonal TCR Rearrangements in Patients with Hemophagocytic Lymphohistiocytosis without Malignancy

Heyjin Kim[1], Keon Hee Yoo[2], Silvia Park[3], Seok Jin Kim[3], Duck Cho[1], Sun-Hee Kim[1], Hee-Jin Kim*[1]

[1] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[2] Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[3] Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Background : Hemophagocytosis in bone marrow is an important finding for the diagnosis of hemophagotyic lymphohistiocytosis (HLH) and can be associated with such conditions as malignancy and infection. Clonal TCR gene rearrangement typically reflects malignant T-cell clone. In this study, we investigated the clonality of TCR gene rearrangement in bone marrow (BM) samples in HLH patients without malignancy.

Methods : Study subjects were the patients diagnosed with HLH without evidence of malignancy from Nov 2016 to Dec 2017 at Samsung Medical Center, Seoul, Korea. Molecular tests for clonality of TCR gene rearrangement was performed by using IdentiClone™ TCRG Gene Clonality Assay 2.0 Kit (InVivoScribe Technologies, San Diego, CA, USA) on DNA extracted from BM cells. Data were analyzed by fragment analysis after PCR amplification, and clonality was determined according to the standard protocol.

Results : Total 18 patients were diagnosed with HLH without malignancy based on clinical/laboratory and pathology findings including BM study during the period, and 10 were tested for TCR gamma (TCRG) gene rearrangement. Clonal TCRG rearrangement was detected in 8 (80%); 6 were infection-associated, 1 was familial (UNC13D mutations), and 1 was idiopathic HLH. Flow cytometry analysis was performed in 7 of those 8 patients, and 3 showed loss of CD5 and/or CD7 of T cells. Two patients without clonal TCRG rearrangement had idiopathic HLH.

Conclusions : HLH patients without malignancy had a high frequency of clonal TCR rearrangement, reflecting expansion of clonal T-cells associated with infection or genetic background. Cautious clinicopathological correlation is warranted in the interpretation of clonal TCRG rearrangement in patients suspected to have HLH. Clinical implications of non-malignant clonal T cells need to be determined.

Keyword : Hemophagocytic lymphohistiocytosis, Hemophagocytosis, TCR, TCRG, Clonal rearrangement, Infection

PP-69

MYC and BCL2 Coexpression is Not Related with Inferior Outcome in the Diffuse Large B-Cell Lymphoma

Yu Ri Kim[1], Sun Ochyoon[2], Soo-Jeong Kim[3], June-Won Cheong[3], Haerim Chung[3], Jung Yeom Lee[4], Ji Eun Jang[3], Yundeok Kim[1], Woo-Ick Yang[2], Yoo Hong Min[3], Jin Seok Kim*[3]

[1] Division of Hematology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Korea
[2] Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Korea
[3] Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Korea
[4] Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University, Wonju College of Medicine, Korea

Background : MYC and BCL2 protein double expressed diffuse large B-cell lymphoma (DLBCL), double-expressor lymphoma (DEL), was related with inferior prognosis to standard rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) chemotherapy. It was uncertain whether MYC and BCL2 co-expression was related with inferior outcome for DLBCL patients received upfront autologous hematopoietic stem cell transplantation (ASCT).

Methods : Forty-three DLBCL patients received upfront ASCT following R-CHOP chemotherapy were retrospectively analyzed. All enrolled patients were advanced stage and elevated lactic dehydrogenase and have the results of MYC and BCL2 protein expression by immunohistochemistry (IHC).

Results : Median age of 43 patients was 52.0 years (range, 23 ~ 64 years). The 3-year OS was 79.0% and the 3-year PFS was 70.0%. Twelve (27.9%) patients expressed both MYC and BCL2 by IHC, these patients were classified to DEL. The 3-year OS of the patients with DEL was not different to non-DEL, 79.0% versus 79.0% (P = 0.906). The 3-year PFS of the patients with DEL was not different to non-DEL, 80.0% versus 66.0% (P = 0.562). Ten (23.3%) patients were classified as the germinal center B-cell (GCB) subtype and 33 (76.7%) were classified as the non-GCB subtype, there was no survival difference between GCB and non-GCB subtype. DEL showed the comparable OS and PFS compared to the patient with non-DEL both GCB and non-GCB subtype patients.

Conclusions : In conclusion, MYC and BCL2 co-expression did not have the poor prognostic impact among the high-risk DLBCL patients treated with upfront ASCT regardless of molecular classification. Upfront ASCT could be considered as currently available therapeutic option for DEL patients.

Keyword : Diffuse large B-Cell lymphoma, Autologous hematopoietic stem cell transplantation, Double-Expressor lymphoma

PP-70

Different Role of Surveillance 18FDG-PET/CT according to Histologic Subtypes in Patients with NHL

Yu Ri Kim[1], Soo-Jeong Kim[2], June-Won Cheong[2], Yundeok Kim[1], Ji Eun Jang[2], Huynsoo Cho[2], Haerim Chung[2], Yoo Hong Min[2], Woo Ick Yang[3], Arthur Cho[4], Jin Seok Kim*[2]

[1] Division of Hematology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Korea
[2] Division of Hematology, Department of Internal Medicine, , Severance Hospital, Yonsei University College of Medicine, Korea
[3] Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Korea
[4] Department of Nuclear Medicine, Severance Hospital, Yonsei University College of Medicine, Korea

Background : Although the use of surveillance 18-fluorodeoxyglucose (FDG) positron emission tomography/computerized tomography (PET/CT) is discouraged in malignant lymphoma, its role according to aggressiveness or international prognostic index (IPI) is unclear.

Methods : We evaluated the positive predictive value (PPV) of FDG-PET/CT accoording to aggressiveness and IPI based on histologic confirmation. Seventy-seven (49.0%) of 157 patients were true positive, the other 80 (51.0%) patients including eight (5.1%) patients with secondary malignancies were confirmed as false positive.

Results : The PPV of aggressive B-cell non-Hodgkin's lymphoma (NHL) was lower than that of indolent B-cell NHL (P = 0.003). The PPV of aggressive B-cell NHL patients with low/low-intermediate baseline IPI was significantly lower than that of indolent B-cell NHL (P = 0.006) and aggressive T-cell NHL (P = 0.013). The patients with low/low-intermediate risk secondary IPI was related with low PPV (P = 0.001), this finding was significant only in aggressive B-cell NHL (P = 0.005). Among patients with low/low-intermediate risk in the secondary IPI, the PPV of aggressive B-cell NHL was lower than that of indolent B-cell NHL (P = 0.001).

Conclusions : In conclusion, the role of the surveillance FDG-PET/CT differed according to the aggressiveness of lymphoma and IPI. Surveillance FDG-PET/CT would not be beneficial in patients with aggressive B-cell NHL compared with the patients with indolent B-cell NHL, especially in aggressive B-cell NHL patients with low/low-intermediated risk of baseline or secondary IPI. Repeated biopsy should be recommended for the diagnosis of relapse in patients with positive surveillance FDG-PET/CT.

Keyword : FDG-PET/CT, Lymphoma, Surveillance

PP-71

Efficacy and Safety of Once-Weekly Bortezomib in Relapsed/Refractory Multiple Myeloma Patients

Sang Eun Yoon, Yeung-Chul Mun*, Chu-Myong Seong, Eun-Mi Nam, Kyoung-Eun Lee, Soon-Nam Lee
Department of Internal Medicine, Ewha Womans University, Hemoto-Oncology, Korea

Background : Bortezomib therapy in multiple myeloma (MM) was significantly superior to a previous standard of care. Because peripheral neuropathy (PN) leading to dose modification and drug discontinuation seems to be dependent on dose and exposure of bortezomib, the some schedules of botezomib were reduced from twice-weekly to once-weekly infusion.

Methods : We compared the outcomes and safety of once- and twice-weekly bortezomib as a second line in MM in our hospital from Janurary 2001 to August 2016, retrospectively.

Results : Forty-two multiple myeloma patients were enrolled including 24 patients who received once-weekly bortezomib on day 1, 8, 22 and 29 of the cycles and 18 patients who received twice-weekly bortezomib on day 1, 4, 8 and 11 of the cycles. Dexamethasone alone (n=33), melpahalan with prednisolone (n=5), and thalidomide with dexamethasone (n=4) were administered combined with bortezomib. Median cumulative dose of bortezomib were 32.9 (10-83) mg/m2 and 14.0 (5.91) mg/m2 in once- and twice-weekly group (p=0.015). The incidence of grade 3/4 PN was similar (45.8% vs 33.3%, p=0.426) in both group. There was some difference in the median time-to-onset of grade 3/4 PN without statistical significance (8.0 months in once-weekly vs 3.9 months in twice-weekly, p=0.073). There was some difference in overall response rate (above PR) without statistical significance (70.8% in once-weekly vs 44.4% in twice-weekly, p=0.089). The overall survival of the patients who received once-weekly bortezomib was superior to the overall survival of the patients who received twice-weekly bortezomib (11.0 months vs 6.0 months, p=0.005) by Kaplan-Meier analysis.

Conclusions : Our data showed that the once-weekly bortezomib has a clinical benefit in terms of survival, response and PN compared with those of the twice-weekly bortezomib. In conclusion, once-weekly bortezomib treatment could be a potential therapeutic approach for patient with relapsed/refractory MM.

Keyword : Multiple myeloma, Bortezomib, Once weekly

PP-72

Thalidomide/Dexamethasone Maintenance after Autologous Stem Cell Transplantation in Multiple Myeloma

Sang-A Kim[1], Youngil Koh*[2], Dong-Yeop Shin[2], Jin Seok Kim[3], Kihyun Kim[4], Chang-Ki Min[5], Hyeon-Seok Eom[6], Je Jung Lee[7], Jeong-Ok Lee[8], Soo-Mee Bang[8], Sung-Soo Yoon[2]

[1] Department of Internal Medicine, Seoul National University Hospital, Korea
[2] Division of Hematology, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Korea
[3] Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Korea
[4] Division of Hematology, Department of Internal Medicine, Samsung Medical Centre, Sungkyunkwan University School of Medicine, Korea
[5] Division of Hematology, Department of Internal Medicine, Seoul St Mary's Hospital, The Catholic University of Korea, College of Medicine, Korea
[6] Hematology-Oncology Clinic, Department of Internal Medicine, National Cancer Center, Korea
[7] Division of Hematology, Department of Internal Medicine, Chonnam National University Hwasun Hospital, Korea
[8] Division of Hematology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Korea

Background : Maintenance is a part of standard practice in multiple myeloma patients receiving induction chemotherapy followed by autologous stem cell transplantation (ASCT). In this open-label, prospective multi-center phase II trial, we evaluated the efficacy and toxicity of thalidomide-based maintenance therapy in Korean myeloma patients.

Methods : The patients received maintenance treatment of 100mg thalidomide daily for 28 days and 40mg dexamethasone for 4 days. The induction therapy was continued for one year unless there were disease progression, unacceptable toxicity, or consent withdrawal. The primary endpoint was 1-year event-free-survival (EFS). Progression-free survival (PFS), overall survival (OS), drug tolerability and safety were also evaluated.

Results : A total of 43 patients were enrolled. 1-year EFS rate was 60.47% (95% confidence interval (CI), 44.34-73.26). Progression-free survival (PFS) was 86.05% at 1-year and 72.09% at 2-year. Overall survival (OS) at 1-year and 2-year was 90.70% and 88.37%, respectively.
Among 21 patients who did not acquire complete response (CR) after ASCT, 4 patients reached CR after maintenance therapy. The maintenance treatment was discontinued in 15 patients (34.9%), mainly due to the adverse events (6 patients) and progression (4 patients). In each cycle, up to 23.3% of patients experienced dose reduction or delayed medication because of the adverse event and physician's decision. The most common grade 3 or 4 adverse events (AE) was the upper respiratory infection (20 patients, 46.5%) followed by peripheral neuropathy (19 patients, 44.2%). But only ten percent of the neuropathy patients experienced more than grade 3 symptom. On the other hand, all neutropenia cases (18 patients, 41.9%) were more than grade 3. Two patients experienced serious adverse events (pneumonia and fulminant hepatitis). Aspirin was administered in 37 patients (86.0%) for thromboprophylaxis and 1 patient developed deep vein thrombosis during the maintenance.

Conclusions : Thalidomide and dexamethasone (TD) maintenance for transplant eligible, newly diagnosed Korean multiple myeloma patients showed comparable outcome with the reports from western countries. TD maintenance was tolerable in Korean patients, although high hematologic toxicity draws concern. We concluded that thalidomide-based maintenance therapy is one of the suitable options for transplant-eligible Asian NDMM patients.

Keyword : Multiple myeloma, Thalidomide, Maintenance, Asian

PP-73

Prognostic Role of Myeloid-Derived Suppressor Cells in Transplant-Eligible Multiple Myeloma

Sung-Soo Park[1,2], Gi June Min[1,2], Young-Woo Jeon[1,2], Jae-Ho Yoon[1,2], Seung-Ah Yahng[3], Seung-Hwan Shin[4], Sung-Eun Lee[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], Jong Wook Lee[1], Chang-Ki Min*[1,2]

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

Background : Previous studies have shown that granulocytic myeloid-derived suppressor cell (MDSC) are increased in patients with multiple myeloma (MM) and have bidirectional interaction with malignant cells in microenvironment of MM. However, prognostic impact of MDSC in patients with newly-diagnosed MM remains uncertain.

Methods : The peripheral 117 blood samples from newly diagnosed and transplant-eligible MM patients were taken between July 2014 and December 2016. After exclusions for various reasons, a cohort including 96 samples and characteristics of patients were analyzed. circulating MDSC (Lineage-HLA-DR-CD33+CD11b+) at the time of diagnosis were identified from each sample using flow cytometry.

Results : The median age was 58 years (38-64). And median proportion of MDSC among mononuclear cell was 0.141% (0.0-1.450). With a median follow-up of 22.3 (2-40.3) months, overall survival (OS) was significantly lower in patients with higher MDSC (≥0.141%, n=48) than those with lower MDSC (<0.141%, n=48) (p=0.006) whereas time to progression (TTP) was not different according to frequency of MDSC (p=0.494). Survival after progression according to MDSC frequency in the subgroup patients (N=44) who progressed after first treatment was significantly worse in patients with higher MDSC (≥0.141%, n=24) than those with lower MDSC (<0.141%, n=20) (p=0.009). In multivariate analysis, female (HR=0.270, p=0.047), advanced ISS staging (HR=3.007, p=0.015) and higher MDSC (HR=5.538, p=0.026) were significant factors affecting OS.

Conclusions : Our data demonstrate that circulating MDSC subset at diagnosis could be relevant prognostic factor in transplant-eligible patients with newly diagnosed MM.

Keyword : Multiple myeloma, Transplant-Eligible, MDSC, Myeloid-Derived suppressor cells, Prognosis

PP-74

Prognostic Impact of 18F-FDG PET/CT at Diagnosis in Newly Diagnosed Multiple Myeloma

Sung-Hoon Jung, Seo-Yeon Ahn, Seung-Shin Lee, Deok-Hwan Yang, Jae-Sook Ahn, Yeo-Kyeoung Kim, Hyeoung-Joon Kim, Je-Jung Lee*

Department of Hematology-Oncology, Chonnam National University Hwasun Hospital , Korea

Background : Although the Revised International Staging System (R-ISS) was validated in an analysis of an independent cohort of unselected patients with multiple myeloma (MM), stage II problematic increased and included a more heterogeneous population with various risk factors. Therefore, we evaluated the prognostic role of 18F-FDG PET/CT at diagnosis in newly diagnosed patients with MM classified as stage II.

Methods : We retrospectively analyzed the records of 160 patients with newly diagnosed MM between February 2012 and December 2016 at Chonnam National University Hwasun Hospital.

Results : Using the R-ISS, 13.1% of patients were R-ISS I, 67.5% were R-ISS II, and 19.4 % were R-ISS III. ISS was not prognostic for progression free survival (PFS) and overall survival (OS) when applied to the all patients, but the median PFS and OS were significantly different by the three stages of R-ISS. In addition, patients with more than 3 hypermetabolic focal lesion (FL) at baseline PET/CT showed significantly inferior PFS and OS than other patients (PFS, 29.6 months vs. 16.8 months, P = 0.001; OS, not reached vs. 51.1 months, P = 0.017). In patients with R-ISS II, 50 patients (46.2%) had more than 3 hypermetabolic FL at baseline PET/CT, and the presence of hypermetabolic FLs (>3) was associated with shorter PFS and OS (PFS, 31.0 months vs. 16.7 months, P = 0.011; OS, not reached vs. 51.1 months, P = 0.042). In multivariate analysis, the presence of >3 hypermetabolic FLs at baseline PET/CT was significantly associated with inferior PFS in patients with R-ISS II (HR 2.439, 95%CI 1.402-4.243, P = 0.002).

Conclusions : In conclusion, PET/CT at diagnosis may be useful for determining the survival outcomes of patients with R-ISS II.

Keyword : Multiple myeloma, PET, Prognosis

PP-75

Single Center Experience of Pomalidomide Plus Low-Dose Dexamethasone in Patients with Refractory and Relpased Multiple Myeloma

Sung Won Lim[1], Silvia Park[1], Seok Jin Kim[1], Jun Ho Jang[1], Won Seog Kim[1], Chul Won Jung[1], Hyo Jung Kim[2], Kihyun Kim[1]

[1] Division of Hematology-Oncology, Department of Medicine, Amsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[2] Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Korea

Background : The patients with multiple myeloma who are refractory to proteasome inhibitors and immunomodulatory drugs has poor prognosis. Pomalidomide plus low-dose dexamethasone has shown significantly longer progression free survival (PFS) and overall survival (OS), and a greater number of responses compared with high-dose dexamethasone in patients with advanced refractory or relapsed and refractory multiple myeloma. However, cytopenia is of concern to many patients in real world.

Methods : A total 56 patients with refractory to proteasome inhibitors and immunomodulatory drugs started pomalidomide plus low-dose dexamethasone with or without cyclophosphamide at Samsung Medical Center from December 2015 to September 2017 were retrospectively analyzed. Patients were given 28 day cycles of pomalidomide (4mg/day on days 1-21, orally) plus low-dose dexamethasone (40mg/day on days 1, 8, 15, and 22, orally). The primary end point was the rate of adverse events and the secondary endpoints were response rate, progression free survival, and overall survival.

Results : At baseline characteristics, median age was 63.5 year-old, 53.6% (n=30) of patients were male. Patients were having a median number of four previous treatments (range 2-14). Cytopenia which was defined as less than 1000/μL of absolute neutrophil count or 50,000/μL of platelet was present in 48.2% of patients at baseline. The median cycles of pomalidomide plus low-dose dexamethasone was 4 (range 1-16). 23 patients (41.0%) were received cyclophosphamide also. The median PFS was 5 months (95% CI, 3.5-6.4) and median OS was 7 months (95% CI, 2.8-11.1). The overall response rate was 28.6% (n=16). There were 77% of grade 4 neutropenia and 73% of grade 4 thrombocytopenia, and 62.5% of grade 3 anemia. Treatment-related mortality was occurred in six patients (10.7%).

Conclusions : Pomalidomide plus low-dose dexamethasone improve PFS and OS in heavily treated patients and is convenient because they are oral agents. However, a large number of patients trying to use pomalidomide already have cytopenia in real clinical situation because of multiple treatments and disease itself. Therefore, severe adverse events were much more frequent than previous clinical trials, especially cytopenia.

PP-76

The Use of mTOR Inhibitor in Patients with Activated PI3K δ Syndrome 1; A Case Series in Korea

Ji-Man Kang[1,2], Su Kyung Kim[1], Hyeon-Jin Park[3], Sae Rom Choi[1], Yeon Jung Lim[4], Soon Ki Kim[5], Meerim Park[6], Youn-Soo Hahn[6], Byung-Kiu Park[2], Weon Seo Park[8], Young Hye Ko[7], Sung Yoon Cho[1], Dong-Kyu Jin[1], Yon Ho Choe[1], Ji Won Lee[1], Keon Hee Yoo[1], Yae-Jean Kim*[1]

[1] Pediatrics, Sungkyunkwan University School of Medicine, Samsung Medical Center, Korea
[2] Center for Pediatric Cancer, National Cancer Center, Korea
[3] Pediatrics, Seoul National University College of Medicine, Korea
[4] Pediatrics, College of Medicine, Chungnam National University, Korea
[5] Pediatrics, Inha University Medical Center, Korea
[6] Pediatrics, College of Medicine, Chungbuk National University, Korea
[7] Pathology, Sungkyunkwan University School of Medicine, Samsung Medical Center, Korea
[8] Pathology, National Cancer Center, Korea

Background : Activated phosphoinositide 3-kinase δ syndrome (APDS) 1 is caused by gain-of-function mutations of PIK3CD gene which encodes the catalytic p110δ subunit of the phosphatidylinositol-3-OH kinase (PI(3)K). This rare primary immunodeficiency disease clinically manifests with recurrent respiratory tract infections, lymphadenopathy, autoimmune cytopenia, enteropathy, CMV and/or EBV infection and EBV-related lymphoma. Here we described first four patients with APDS 1 who were diagnosed in Korea.

Methods : We investigated the clinical manifestations in all APDS patients and collected data on the efficacy and safety profile of three patients receiving sirolimus, mTOR inhibitor, which is a pathway-specific targeted medicine. The genetic diagnosis was performed by NGS technique.

Results : The PIK3CD mutation was detected in four patients. Three of them (patient 1-3) have the most common mutation (NM_005026.3: E1021K, heterozygous), whereas one patient (patient 4) have another known mutation (NM_005026.3: C416R, heterozygous). Median age at genetic diagnosis was 9 years (range, 4-23 years) and female to male ratio was 1:1. The remaining three patients, except one patient with lymphoma (patient 4), experienced an excellent clinical response to sirolimus treatment including amelioration of lymphoproliferation with the reduction of lymph node sizes and spleen, and the improvement of nodular mucosal lymphoid hyperplasia in the gastrointestinal tract. Two patients who required a high-dose, short interval regular immunoglobulin replacement (IVIG) experienced the reduction of the requirement IVIG dose and prolonged regular IVIG interval from 2-3 weeks to 4 weeks. The median trough level of sirolimus was 5.5 ng/mL (range 2.8-7.5 ng/mL) at a dose of 2-2.5 mg/m2.

Conclusions : We diagnosed first four patients with APDS 1 and observed mTOR inhibitor, sirolimus, alleviated clinical manifestations and immune dysfunctions in three patients with APDS 1. Large-scale international studies are needed to demonstrate the safety and the effectiveness of sirolimus, including long-term data.

Keyword : Activated PI3-Kinase δ syndrome (APDS), PIK3CD, Sirolimus, MTOR inhibitor , Trough level , Primary immunodeficiency

PP-77

Efficacy of Darbepoetin Alfa for Chemotherapy-induced Anemia in Solid Cancer Patients

Jang Ho Cho, Jun Ho Jang, Silvia Park, Jong-Mu Sun, Jeeyun Lee, Yeon Hee Park, Jin Seok Ahn, Chul Won Jung*
Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Background : Chemotherapy induced anemia in patients with solid cancers affects the quality of life in patients receiving chemotherapy. Although erythropoiesis stimulating agent (ESA) is recommended for anemia in patients with receiving chemotherapy according to the NCCN guideline, we do not have enough information of ESAs for anemia in patients with solid cancer in Korea.

Methods : Solid cancer patients receiving chemotherapy and having chemotherapy induced anemia (hemoglobin 8~10 g/dℓ) was eligible for this study. Darbepoetin alfa (Aranesp®), a long acting ESA, was injected subcutaneously 2.25 mcg/kg once weekly or 6.75 mcg/kg once every three weeks for a total of 12 weeks or more. Primary objective was to evaluate red cell transfusion requirement during ESA treatment. Secondary endpoint was to evaluate major or minor hematopoietic response. Major response was defined as an increase in Hb level of 2.0 g/dℓ or more compared to before ESA injection or a hemoglobin level of 11.0 g/dℓ or more without transfusion for 4 weeks. Response evaluation was analyzed by two periods; 1 - 4 weeks (first period) versus 5 - 12weeks (second period).

Results : 70 patients were enrolled, but 25 patients within the first four weeks due to patient's withdrawal of consent or physician's discretion were excluded that 45 patients were evaluable. 36% (16/45) of the patients had at least one red cell transfusion (range, 1-3 times). Red cell transfusion requirement was higher in the second period (15.6% vs 20.0%, p=0.022). During the first period, none of the patients reached major hematopoietic response. However, more patients achieved major response the second period compared to the first period (13.3% vs 0%). The median change in hemoglobin concentration in the first period was -0.3 g/dℓ (range, -2.7 to 1.5) and that was 0.6 g/dℓ (range, -3.2 to 3.5) in the second period (p=0.06). Patients who received cisplatin containing chemotherapy had more transfusions compared to those who received non-cisplatin containing chemotherapy (44% vs 15%, p=0.09).

Conclusions : Darbepoetin alfa reduced the need for red cell transfusions in more than half of solid cancer patients receiving chemotherapy. Major hematopoietic response was achievable usually at 4 weeks or later of ESA treatment.

Keyword : Darbepoetin alfa, Anemia, Solid cancer, Chemotherapy

PP-78

The Implementation of Next Generation Sequencing in Myeloid Neoplasm Clinical Diagnostics

Smbat Daghbashyan[1], Aline Aywaz[1,2]

[1]Hematology Center after Prof. Yeolyan, Yerevan, Armenia,
[2]Molecular genetics and immunophenotyping laboratory in Hematology Center after Prof. Yeolyan, Yerevan, Armenia,

Background : The rapid progress of molecular genetic methods in modern medicine promotes new approaches to the quality of diagnostic methods. Due to Next generation sequencing /NGS/ method, the diagnostic, preventive and therapeutic problems began to be observed at molecular level by studying the nucleic acids and their expression products. [5] This method contributes to deepen modern ideas about the genome structures and their functional interactions, which provide different states of organisms in normal and pathological conditions. [5,10]
MPL, TET2, ASXL1, DNMT3A, CBL, LNC, IDH, CARL, RAD21, HRAS and other gene mutations are detected in 5-20% cases of myeloproliferative disorders. ASXL1 is a very commonly mutated gene. It is found in solid tumors and all types of myeloid neoplasms [1,3]. ASXL1 participates in chromatin remodeling. It interacts with the PRC2 complex [1,3]. ASXL1 mutations are considered as "frameshift" or "non-sense"
heterozygous mutations. They are mainly found in the 13th exon and lead to PHD loss of carbon dioxide domain (Plant Homeodomain) involving in methylated lysines connection. They also associated with the decrease or loss of protein expression [1,2,3,4]. The most common mutation is Guanine nucleotide insertion at position 1934 (c.1934dupG), which leads to frameshift and resultant premature stop codon 12 codons downstream of the insertion (Gly646TrpfsX12). This mutation is not somatic, and its role is still discussed in malignant processes [11]. However, it has a poor prognostic significance [1,2].
The rarely ASXL1 mutation can occur in the 9th exon or ASXL1 gene can be lost by long arm chromosome 20 deletion (del (20q)[1,2,3,7].
ASXL1 mutations occur rarely in cases of Polycythemia vera (PV), Essential thrombocytopenia (<7%). They are frequently encountered in Primarily Myelofibrosis (PMF) (34.5%) and later stages of myelodysplastic syndrome (MDS), as well as in secondary acute myeloid leukemia (AML) (30%) and chronic myelomonocytic leukemia (CMML) (~ 45%) [7]. The ASXL1 mutation has been rarely described in juvenile myelomonocytic leukemia (JMML).
ASXL1 mutations may be associated with other mutations, such as JAK2V617F, MPL, TET2 or EZH2 [9,11]. These mutations appear in the chronic phase and precedes the presence of JAK2 or MPL. In case of MDS as well as CMML or CML, ASXL1 has no favorable prognosis [6].
The aim of study is to detect point mutations by using NGS in myeloproliferative disorders and evaluate the importance this method in diagnosis, monitoring and prognosis.

Materials and Methods: 5 patients with the suspect of myeloproliferative disorder were admitted to Hematology Center of Armenia. Peripheral blood samples were taken from 5 patients with chronic myeloproliferative diseases, DNA extraction has been performed and then sequencing of 54 targeted genes [table – 1] true sight myeloid panel by using MiniSeq new generation sequencing from (Illumina).

Results and Conclusion: The 5 patients with chronic myelopoliferetive diseases were adults. First one was suffering from chronic myeloid leukemia (CML) and was in the treatment stage. The second case had chronic eosinophilic leukemia (CEL), CHIC2 deletion by FISH method was negative. The third patient had a myelopoliferetive disease and was getting Hydroxyurea for 3 years. At the time of diagnose JAK2 gene mutation was detected by qualitative PCR method. Minimal Residual Disease (MRD) test has been performed by using NGS. The forth case was patient with myelopoliferetive disease; BCR / ABL translocation by PCR method was negative. The fifth patient was also suffering from myelopoliferetive disease JAK2 by PCR was negative.
Frameshift mutation in ASXL1 gene was found in 3 cases (tab.2), because of insertion of Guanine nucleotide at position 1934 (c.1934dupG) and resultant premature stop codon p.(Gly646TrpfsTer12). This mutation was located in exon 13 and was heterozygote.
So, we could concluded, that the detection of genetic mutations by NGS, for the patients with oncohematological diseases, is indispensable. The use of this method will give opportunity to raise the effect of therapy, because the detection of particular mutations will allow to include target medicines in the strategy of therapy. This, in turn, will help extend the life expectancy of patients and improve the quality of life.

Keywords : New generation sequencing, ASXL1, myeloproliferative disorders, frameshift mutation

Patient No.	Diagnose	NGS test result
N1	Chronic Myeloid Leukemia (CML)	**ASXL1** Frameshift indels NM_015338.5 (Transcript) c.1934dupG (HGVS cDNA) p.(Gly646TrpfsTer12) (HGVS AA) Exon: 13 Heterozugous Prediction: Likely pathogenic
N2	Chronic Eosinophilic Leukemia (CEL) CHIC2 deletion by FISH method negative	**ASXL1** Frameshift indels NM_015338.5 (Transcript) c.1934dupG (HGVS cDNA) p.(Gly646TrpfsTer12) (HGVS AA) Exon: 13 Heterozugous Prediction: Likely pathogenic
N3	Myelopoliferetive disease with presence of Jak 2 mutation	No pathogenic or likely pathogenic variant.
N4	Myelopoliferetive disease BCR / ABL translocation by PCR negative	**JAK2** Missense NM_004972.3 (Transcript) c.1849G>T (HGVS cDNA) p.(Val617Phe) (HGVS AA) Exon: 14 Homozygous Prediction: pathogenic
N5	Myelopoliferetive disease	**ASXL1** Frameshift indels NM_015338.5 (Transcript) c.1934dupG (HGVS cDNA) p.(Gly646TrpfsTer12) (HGVS AA) Exon: 13 Heterozugous Prediction: Likely pathogenic

PP-79

Evaluation of the Immature Platelet Fraction in the Diagnosis of ITP and Other Various Diseases

Dong Jin Park[1], Sooyoung Kim[1], Yeongsic Kim[1], Jeong-A Kim[2], Young Hoon Park[2], Dong Jin Park*[1]

[1] Laboratory Medicine, The Catholic University of Korea, St. Vincent's Hospital, Korea
[2] Division of Hematology, Department of Internal medicine, The Catholic University of Korea, St. Vincent's Hospital, Korea

Background : The immature platelet fraction (IPF) is a predictive factor in increased platelet production associated with platelet immunomediated consumption or platelet destruction which results from the suppression of bone marrow production. We evaluated the value of immature platelet fraction (IPF) in distinguish between immune thrombocytopenic purpura (ITP), aplastic anemia (AA) and myelodysplastic syndrome (MDS). In addition, in order to assess its potential use as a diagnostic marker in other hematologic disease including myeloproliferative neoplasm, IPF was measured in essential thrombocythemia (ET).

Methods : 10 patients with ITP were compared with 11 patients with AA, 6 patients with MDS, 6 patients with ET, and 80 age- and sex-matched healthy controls. Complete blood count tests including IPF, platelet distribution width (PDW), mean platelet volume (MPV), platelet large cell ratio (P-LCR), plateletcrit (PCT) were performed using Sysmex XN-2000 (Sysmex, Kobe, Japan).

Results : Mean IPF was 16.1% in patients with ITP, 4.3% in patients with AA, 6.5% in patients with MDS, 2.5% in patients with ET, and 3.1% in the control group($p<0.05$). ITP patients showed high IPF, PDW, MPV, and P-LCR compared with other groups, while PCT was lower in ITP patients than other groups.

Conclusions : We found highly elevated IPF in disorders related to increased platelet production, particularly associated with platelet destruction such as ITP. AA and MDS patients resulting from the decreased platelet production associated with bone marrow suppression showed slightly increased IPF rather than healthy controls. ET showed normal ITP comparing with healthy controls. The IPF is highly recommended to evaluate the thrombopoietic status of bone marrow in thrombocytopenia patients.

Keyword : Immune thrombocytopenic purpura, Immature platelet fraction, Diagnosis

PP-80

Association of HSV to Chemotherapy-Induced Oral Mucositis in Patients with Hematologic Malignancies

Junshik Hong[1], Youngnim Choi[2], Ji-Yeob Choi[4], Dong-Yeop Shin[1], Youngil Koh[1], Hee Kyung Park[3], Inho Kim*[1], Sung-Soo Yoon[1]

[1] Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Korea
[2] Department of Oromaxillofacial Infection & Immunity, School of Dentistry and Dental Research Institute, Seoul National University, Korea
[3] Department of Oral Medicine and Oral Diagnosis, School of Dentistry and Dental Research Institute, Seoul National University, Korea
[4] Department of Biomedical Sciences, Seoul National University College of Medicine, Korea

Background : The relationship of infections in oral cavity to chemotherapy-induced oral mucositis (CIOM) in patients with hematological malignancies (HM) undergoing intensive chemotherapy (IC) or hematopoietic stem cell transplantation (HSCT) has been suggested but not concluded and there is no mention on prophylactic use of antimicrobials for the prevention of CIOM for those population in the current guidelines.

Methods : To prospectively determine the relationship of human herpes virus (HSV) reactivation and colonization with Candida in oral cavity to CIOM in patients with HM undergoing high dose chemotherapy, patients aged ≥ 19 years with HM undergoing IC or HSCT were enrolled. In each enrollment, evaluations of HSV and Candida in the oral cavity along with CIOM were performed at baseline, second, third, and fourth weeks. CIOM was estimated and graded according to the WHO's oral toxicity scale and the NCI-CTCAE v3.0. The sample was obtained by placing a sterilized transfer Membrane on the buccal mucosa for 30 seconds. DNA was isolated from the sampled membrane. Reactivation of HSV-1 and -2 was determined by PCR using HSV 1/2 PCR kit.

Results : A total of 70 enrollments from 56 patients were analyzed. CIOM was observed 23 out of 70 enrollments (32.9%), with a higher incidence in cases of HSCT (17 of 35 enrollments, 48.6%) compared to those of IC (6 of 35 enrollments, 8.6%). Reactivation of HSV-1 was significantly associated with increased incidence of CIOM and higher REU score, after data were adjusted to age, sex, type of disease, and treatment stage. Higher viral load of HSV-1 showed stronger association to increased incidence and severer CIOM. Presence of Candida was not associated with CIOM (Table 1).

Conclusions : In conclusion, HSV reactivation in oral cavity was highly associated with the incidence and severity of CIOM in patients with HM undergoing high dose chemotherapy.

Keyword : Hematologic malignancies, Oral mucositis, Herpes simplex

Table 1. Relationship of HSV-1 and -2 reactivations to the incidence and severity of CIOM

Category of viral load (numbers of evaluation)		CIOM (yes vs. no) *			REU score†		
		Odds Ratio‡	95% CI‡	*p*‡	*β*‡	95% CI‡	*p*‡
HSV-1	0 (n = 130)	Reference			Reference		
	1 (n = 46)	3.693	1.032 ~ 13.213	0.045	0.432	-0.654 ~ 1.519	0.435
	2 (n = 48)	16.913	3.922 ~ 72.929	< 0.001	2.694	1.601 ~ 3.788	< 0.001
	1+2 (n = 94)	7.660	2.762 ~ 21.242	< 0.001	1.553	0.668 ~ 2.438	0.001
HSV-2	0 (n = 217)	Reference			Reference		
	1+2 (n = 7)	13.370	0.962 ~ 185.727	0.053	-0.181	-2.744 ~ 2.382	0.890
Candida	Negative (n =184)	Reference			Reference		
	Carrier (n =20)	0.591	0.129-2.716	0.499	-0.057	-0.223-0.108	0.498
	Positive (n =17)	0.435	0.045-4.161	0.470	-0.052	-0.237-0.134	0.583

CIOM, chemotherapy-induced oral mucositis
*According to multiple logistic regression analysis; †According to multiple linear regression analysis; ‡Adjusted to age, sex, type of disease, and treatment stage

PP-81

Efficacy of Olanzapine-Containing Antiemetic Regimen in ASCT Patients with TBC Conditioning

Bobae Kim[1], Youree Jung[1], Eunjeong Shin[1], Sungyun Suh[1], Yoonsook Cho[1], Ju-Yeun Lee[2], Youngil Koh*[3]

[1] Pharmacy, Seoul National University Hospital, Korea
[2] College of Pharmacy, Hanyang University, Korea
[3] Hematology , Seoul National University Hospital, Korea

Background : The purpose of this study was to show the efficacy of prophylactic olanzapine-containing antiemetic regimen, which consists of olanzapine (OLN), palonosetron (PAL) and dexamethasone (DEX), for the prevention of nausea and vomiting in patients receiving high dose anticancer agents as conditioning for autologous hematopoietic stem cell transplantation (ASCT).

Methods : A retrospective study was performed in patients receiving thiotepa, busulfan and cyclophosphamide (TBC) as conditioning for ASCT. The OLN, PAL, DEX (OPD) regimen consisted of 10 mg of OLN, 0.25 mg of PAL, and 8 mg of DEX on day 1, and 10 mg of OLN alone on days 2-3. Patients who received OPD regimen for emesis prevention during TBC conditioning in Seoul National University Hospital from November 2016 to November 2017, all of whom received OPD in this center, were included.

Results : We analyzed 15 patients (Male:Female=10:5, median age 54 years). For underlying disease, 6 patients had multiple myeloma and 9 patients had non-Hodgkin lymphoma (7 B-cell and 2 T-cell lymphoma). In terms of emesis control, complete response (CR, no vomiting) was achieved in 80% during the early period (the first 72 hours of conditioning) and in 40% for the overall period (from day 1 to 13). Patients with response (PR, no vomiting or grade 1 vomiting by NCI-CTCAE) were 93% and 60% for the early and overall period respectively. No serious toxicities have occurred.
We compared our results with the data of 27 primary central nervous system lymphoma patients who as well received TBC based ASCT with different antiemetic regimen (Asan Medical Center in Korea, from December 2012 to July 2015): Antiemetic regimen in Asan Medical Center does not contain OLN but includes lorazepam (Table 1). Antiemetic regimen without OPD resulted in 11% CR and 63% PR while 40% and 60% of our patients achieved CR and PR respectively during the overall period. CR was achieved more frequently in patients with OPD containing regimen (p=0.049).

Conclusions : OPD has remarkable antiemetic potential during TBC conditioning. We assume that OPD could also be considered as an effective antiemetic therapy in various highly-emetogenic chemotherapies including conditioning for ASCT.

Keyword : Olanzapine, Palonosetron, Dexamethasone, Antiemetics, Prophylaxis

Table 1. Conditioning schedule and antiemetic regimen in each center

	Anticancer agents	Antiemetic regimen of SNUH	Antiemetic regimen of AMC
Day 1	Thiotepa	OLN, PAL, DEX	LRZ
Day 2	Thiotepa	OLN	LRZ
Day 3	Thiotepa	OLN	LRZ
Day 4	Busulfan	SRA	SRA, LRZ
Day 5	Busulfan	SRA	SRA, LRZ
Day 6	Busulfan	SRA	SRA, LRZ
Day 7	Cyclophosphamide	NK1RA, SRA, DEX	NK1RA, SRA, DEX, LRZ
Day 8	Cyclophosphamide	NK1RA, DEX	NK1RA, SRA, DEX, LRZ
Day 9	None	NK1RA, DEX	NK1RA, DEX, LRZ

PP-82

Prevention of PTLD in Children Using Preemptive Rituximab Therapy

Bo Kyung Kim, Hyoung Jin Kang*, Kyung Taek Hong, Jung Yoon Choi, Hong Yul An, Che Ry Hong, Hee Young Shin
Department of Pediatrics, Cancer Research Institute, Seoul National University College of Medicine, Korea

Background : Post-transplant-lymphoproliferative disease (PTLD) is one of the most common post-transplant malignancies. PTLD occurs in 1-3.5% after hematopoietic stem cell transplantation in pediatric patients. Rituximab (anti-CD20 monoclonal antibody) is used for prophylaxis and treatment of EBV- PTLD, but the efficacy of the preemptive treatment using rituximab has not yet been fully elucidated. The purpose of this study was to prove the effects of preemptive treatment with rituximab for EBV related PTLD after HSCT in pediatric patients.

Methods : We analyzed 16 pediatric patients undergoing allogeneic HSCT at Seoul National University Children's Hospital from 2005 to 2017 who developed high EBV DNAemia. We administrated rituximab preemptively to patients with EBV load ≥10,000/105 peripheral blood mononuclear cells (PBMCs) (375 mg/m2, once daily). We excluded patients who had EBV infection before HSCT or were administrated rituximab after occurring PTLD. We investigated EBV titer in peripheral blood after rituximab infusion and checked PTLD incidence, and side effects.

Results : Underlying diseases of patients were 9 acute leukemia (56.3%), 2 aplastic anemia (12.5%), and the other genetic rare diseases (31.3%). Median EBV titer just before rituximab treatment was 155,476 copies/105 PBMCs (range, 13,153-267,203 copies/ 105 PBMCs). Rituximab was infused on median 50.9 days (range, 9-214 days) after EBV DNAemia. In all 16 patients EBV DNAemia were eradicated after median 6.5 days (range, 1-12 days) and PTLD did not occur in all patients. B cell counts recovered normally and serum IgG level remained at the pre-transplantation level even after the administration of rituximab. There was no patient with above CTC grade III side effects. HSCT related mortalities occurred in 2 patients not by EBV infection or PTLD but by acute graft versus host disease and severe venous occlusive disease. Other 14 patients are still alive without disease after median 50 months (range, 4.8-111months) after transplantation.

Conclusions : Preemptive therapy with rituximab was effective and safe for the treatment EBV DNAemia after HSCT in pediatric patients. This preemptive therapy is expected to reduce the incidence of PTLD after HSCT and improve post-transplantation outcomes. However, large-scale and long-termfollow up studies are needed

Keyword : Epstein-Barr virus, Rituximab, Post-Transplant-Lymphoproliferative disease, Hematopoietic stem cell transplantation

PP-83

A Comparative Analysis of Efficiency Among the Different Donor Groups in Stem Cell Collection Result According to Injected with GCSF on Unrelated Peripheral Blood Stem Cell Donors

Ok-Ja Hyoung[1], Min-Jung Kawk[1], Tai-Gyu Kim[1], Young-Shin Lee[2], Min-Jin Choi[3]

[1] Catholic Hematopoietic Stem Cell Bank, Department of coordination, Catholic University of Korea, Korea
[2] Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Korea
[3] Department of Internal Medicine, Samsung Medical Center, Korea

Background : Since 2000, PBSC (Peripheral Blood Stem Cell) collection has increasedremarkablyup to 90% of stem cell source in KOREA. Then gradually interest in G-CSF mobilization method increased. Most of the donors are administrated for up to 4 or 5 days. In this article, we will analyzewhether 3~4days hypodermic G-CSF medication is enough. To evaluate the current status of PBSC mobilization and collection, and assess efficiency of procedures between two groups(G1,G2), promoted a retrospective cooperative study. Moderate PBSC procedure which proposed in this study will be helpful among the Korean Transplant centers and unrelated donors.

Study Design and Methods : Effective injection period can be suggested by 475donors of unrelated stem cell in CHSCB from 2007-2014 excepting 164 pediatric patients and 103 bone marrow donors and 24 international donors into two groups (G1,G2). Two groups are divided by the amount of WBC growth factor injection period : 3~4 days for 120 donors and 4~5 days for 355 donors.

Results : The donors of each group received G-CSF for mobilizing with different schedules(time,period) according to each collection center policy. A range of 1-2 apheresis per donor were run not 3 days apheresis 3. All donors follow-up after stem cell collection 7~14days. For the case of CD34+ was, over 74% donors were reached to the target amount of 3.0*10^6/patient body weight in both cases on 1st collection day. But 79.5% of G1 group, 21.4% of G2 group were requested additional stem cell collection.
For the 54% of G1 group, 65% of G2 group donors were reached to the target amount of 4.0*10^6/patient body weight in both cases on 1st collection day. But 72.3% of G1 group, 14.7% of G2 group were requested additional stem cell collection.
For the 41% of G1 group, 52% of G2 group donorswere reached to the target amount of 5.0*10^6/patient body weight in both cases on 1st collection day. But 63.2% of G1 group, 12% of G2 group were requested additional stem cell collection.It was revealed that there was no standard for unrelated stem cell collection method in KOREA.

Interpretation and Conclusion : If target amount of CD34+ collected is set as 3~5 *10^6/kg, injecting stimulator for 3~4 days(4th day collection after G-CSF administration) would be efficient for many patients and donors. Futhermore, if the cell count of 1st collection day is enough, don't ask to get additional collection for donors. The positive experience has a beneficial effect on latent volunteer donors. This process will be avoid prolonged exposure to G-CSF and decrease unpaid leave of donor. So donor agreement rate will be increased and cost-effective process method.However, only clinical careful analysis of donors and international cooperation will help to definitively assess the donor safety for G-CSF mobilization and patients transplant effectiveness of PBSC.

Keywords: PSBC, G-CSF, duration of G-CSF administration, unrelated stem cell donor, hematopoietic stem cell and CD 34+

PP-84

Granulocyte Transfusions in Pediatric Patients with Neutropenic Fever: A Single Center Experience

Eu Jeen Yang[1], Kyung Mi Park[1], Hyun-Ji Lee[2], Young Tak Lim*[1]

[1] Pediatrics, Pusan National University Children's Hospital, Korea
[2] Laboratory Medicine, Pusan National University Yangsan Hospital, Korea

Background : Neutropenic fever is the most important complication of chemotherapy and hematopoietic stem cell transplantation. The granulocyte transfusion (GT) has been used in neutropenic patients with severe bacterial infection. However, the data regarding the efficacy of GT and the results are limited in children. The purpose of this study was to analyze factors affecting granulocyte collection and to evaluate the efficacy of GT in pediatric patients with neutropenic fever, especially gram-negative sepsis.

Methods : This study was retrospectively identified in Department of Pediatrics, Pusan National University Children's Hospital, from July 2014 to June 2017. The granulocyte were collected by automated apheresis and approved healthy donors who matched blood types applied 300 ug of G-CSF 12 hours before apheresis.

Results : Donor lymphocyte count (P=0.039) and immature granulocyte fraction of collection (P<0.001) were significantly associated with yield, whereas age, monocyte, and immature granulocyte fraction of donor were not. For 11 patients with neutropenic fever, GT was performed at an average of 1-13 courses per episode, a total of 70 courses. Four of the patients were boys and seven were girls, median age was 12.36 years (range, 4.6–18 years). Median duration of neutropenic fever was 9.42 days. Infection were classified primary bacterial infection (81.8%, n=9) included gram-negative sepsis (72.7%, n=8) and clinically suspected infection (72.7%, n= 8). The median granulocyte yield was 2.22 x 1010/unit. The median increment in white blood cell (WBC) count and absolute neutrophil count (ANC) were 275.35 and 192.96 x 103/uL, correlated with the granulocyte yield, yield per kilogram body mass, immature granulocyte fraction of collection and donor lymphocyte count. All 15 patients of the control group received a broad-spectrum antibiotics therapy alone, diagnosed gram-negative sepsis. 10 of 15 controls survived, and eight of nine received GT for revealed gram-negative sepsis survived (P=0.037).

Conclusions : Overall, higher donor lymphocyte count and immature granulocyte fraction of collection were strongly correlated with yield and hematologic response. Our study also documents that GT is safe and effective in pediatric hemato-oncology patients with neutropenic fever. Additionally, the GT combined with antibiotics improved survival from gram-negative sepsis in pediatric patients with neutropenia.

Keyword : Granulocyte transfusion (GT), Neutropenic fever, Children

PP-85

Low Rate of Rh Alloimmunization after Rh-Incompatible Solid Organ Transplantations

Ari Ahn[1], Duck Cho[2], Sang-Hyun Hwang*[1]

[1] Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Korea
[2] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunwan University School of Medicine, Korea

Background : Anti-D is present in more than 50% of Rh-negative recipients transfused with Rh-positive blood, indicating the necessity of Rh immunoglobulin (RhIG) prophylaxis. Rare complications with high-dose RhIG, causing severe intravascular hemolysis, DIC, and renal failure have been reported; however, there are no guidelines for the dose of RhIG administered in Rh-incompatible (Rh-i) transplantation.

Methods : We reviewed a total of 33 Rh-negative patients who had received Rh-i solid organ transplantation included kidney (KT; n=12), liver (LT; n=20), and heart (HT; n=1) . We divided the patients into an RhIG-administered group and non-administered group. To detect anti-D after transplantation, serial Rh-antibody titer was followed up by the tube method in the RhIG-administered group. An antibody screening test was conducted by an automated method, using IH-1000 system (Bio-Rad, Hercules, USA) in the RhIG non-administered group. Graft function was monitored with serum creatinine or bilirubin, and renal or hepatic biopsy, whenever rejection was suspected.

Results : Median age of transplant recipients was 48 years (range, 4-69) and 66.7% patients were male. Median follow-up time after transplantation was 46 months (1-228). RhIG administration was greater in LT (90.0%, n=18) than in KT (33.3%, n=4) or HT (0%) (P=0.023). The amount of RhIG administered at one time varied from 600IU to 9,000IU, regardless of organ volume and patient age; frequency of administration also. In the RhIG-administered group, 86.4% patients (19/22) underwent an Rh-antibody titer test; most patients were followed-up the test for 1 month. Anti-D was detected for various periods in each patient (2 weeks–5 months) according to their follow-up time. In the RhIG non-administered group, 45.5% patients (5/11) underwent an antibody screening test; anti-D was not detected in all the patients. Total graft survival was 60.6%; 5 patients were lost to follow-up. Causes of graft-loss were renal abscess (n=1), rejection (n=5) and recurrence of original disease (n=2). The RhIG non-administered group showed higher graft survival rate than RhIG-administered group (P=0.227).

Conclusions : The low rate of Rh alloimmunization is associated with the immunosuppressive state of the patients. Excepting female patients in the reproductive age group, further multicenter studies should establish the optimal dosage of RhIG prophylaxis in Rh-i transplantation.

Keyword : Rh-Negative, Rh-Incompatible transplantation, Rh immunoglobulin prophylaxis, Anti-D, Rh Alloimmunization

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Sung-Eun Lee (The Catholic University of Korea)

Hyery Kim (University of Ulsan)

Sang Mee Hwang (Seoul National University)

ICKSH 2018
& 59th ANNUAL MEETING

Otsuka

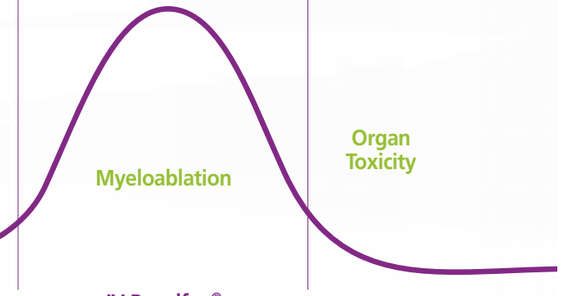
IV Busulfex® (busulfan) Injection

IV Busulfex (Busulfan)

- **IV Bu** formulation to **achieve absolute dose assurance** associated with its controlled administration[1]
- The combination of Cy with **IV Bu** administration appeared **safer compared with that of oral Bu.**[1]
- Significantly lower incidence of HVOD with IV Bu compared with oral Bu.[1]

- **Cy :** Cyclophosphamide, **Bu :** Busulfan, **HVOD :** Hepatic veno-occlusive disease

Target AUCss with precision



IV Busulfex®
Therapeutic Window = 900-1500 μMol/min[1]
(Target AUC values)

Reference 1. *Biol Blood Marrow Transplant.* 2009 May;15(5):523-36.

INFORMATION

제품명 : 부설펙스 주(바이알)(부설판)(성분명 : Busulfan) 성상 : 이 약은 바이알에 충전된 무색의 액상주사제입니다. **성분·함량 :** 이 약 1바이알(10ml)중 (주성분) 부설판(USP) : 60.0mg (첨가제) 폴리에틸렌글리콜400 6.7mL, 디메틸아세트아미드 3.3mL **효능·효과 :** 다음 질환에 대하여 시클로포스파미드 와 병용하여 조혈모세포 이식시 전처치요법으로 사용한다 : 급성 백혈병, 만성 골수성 백혈병, 림프종, 골수 이형성증후군 **용법·용량 :** 1) 성인 0.8 mg/kg으로서 이상 체중 또는 그 보다 낮은 실제 체중을 적용하여 4일간 매 6시간마다 16회를 중심 정맥 카테터를 통하여 2시간 동안 투여한다. 시클로포스파미드는 이 약 16회째 요법이 완료된 6시간 후, 골수이식 개시 3일전에 60 mg/kg용량으로 한시간 동안 이틀간 주입한다. 과체중 혹은 심각한 비만 환자의 경우, 교정 이상 체중(AIBW)에 근거하여 용량을 산정하여야 한다. 이상 체중(IBW)은 다음과 같이 계산된다.(단위 : 신장 cm, 몸무게 kg) IBW(남성) = 50 + 0.91 ×(신장 - 152) IBW(여성) = 45 + 0.91 ×(신장 - 152) 교정 이상 체중(AIBW)은 다음과 같이 계산된다. AIBW = IBW + 0.25 ×(실제체중 - IBW) 이 약은 교정 이상 체중 (AIBW)을 근거로 한 용량을 투여하였을 때 가장 좋은 클리어런스를 예상할 수 있다. 마른환자, 정상 및 비만 환자들의 경우 실제 체중, 이상체중(IBW) 또는 다른 인자들을 근거로 하여 투여했을 경우, 클리어런스에 유의성 있는 차이를 나타낼 수 있다. 이 약은 뇌혈관 장벽을 통과하여 발작을 일으키는 것으로 알려져 있기 때문에 모든 환자는 페니토인으로 이를 예방하여야 한다. 페니토인은 부설판의 혈중농도- 시간곡선하면적(AUC)를 15% 감소시킨다. 다른 항경련제를 사용하면 부설판의 혈장 AUC가 높아지므로 간정맥 폐쇄성질환(VOD) 또는 발작의 위험성이 높아진다. 다른 항경련제를 사용할 경우에는 혈장 부설판 노출을 모니터해야 한다. 5-HT3계열의 구토억제제를 이 약 초회 사용 이전에 투여하여야 하며, 이 약의 계획된 투여 기간동안 계속 투여하여야 한다. 최적의 치료를 위하여 가능한한 약동학적 모니터링을 실시하는 것이 좋다. 2) 소아 소아(n=24)에 대한 약물동태학적 결과에 근거한 권장용량은 환자의 실제 체중(ABW)을 적용하여 12 kg 이하일 경우 1.1 mg/kg, 12 kg 초과일 경우 0.8 mg/kg를 4일간 매 6시간마다 16회를 중심 정맥 카테터를 통하여 2시간 동안 투여한다. 이 약의 초회 투여 후, 투여용량의 조절 및 치료 약물농도 모니터링(TDM)의 실시가 권장된다. 시클로포스파미드는 이 약 16회째 요법이 완료된 후, 골수이식 개시 5일전부터 50 mg/kg용량으로 1일 1회, 4일간 주입한다. ※ 치료 약물농도 모니터링에 근거한 소아 환자의 투여용량의 조절 초회 투약 후 목표 AUC(1,125 μM·min)에 도달하기 위한 소아 환자의 교정 투여용량은 다음과 같이 계산된다. 교정투여용량(mg) = 실제 투여용량(mg) × 목표 AUC (μM·min) / 실제 AUC (μM·min) 3) 정맥 내 투약을 위한 준비 이 약은 60mg의 부설판을 6mg/ml의 농도로서 함유하고 있는 10ml 무균 용액이며, 일회용 유리 바이알로 공급된다. 이 약은 사용 전 0.9% 생리식염수 주사액 또는 5% 포도당 주사액에 희석되어야 한다. 희석액의 양이 이 약 부피의 10배가 되어야 하며, 최종농도가 약 0.5mg/ml 으로 유지되어야 한다.
KD Code : 649900341 **포장단위 :** 10ml x 1, 8바이알 **저장방법 :** 2~8℃보관, 밀봉용기 **사용기한 :** 제조일로부터 30개월
* 기타 상세한 사항은 최신제품설명서를 참조하시기 바랍니다.

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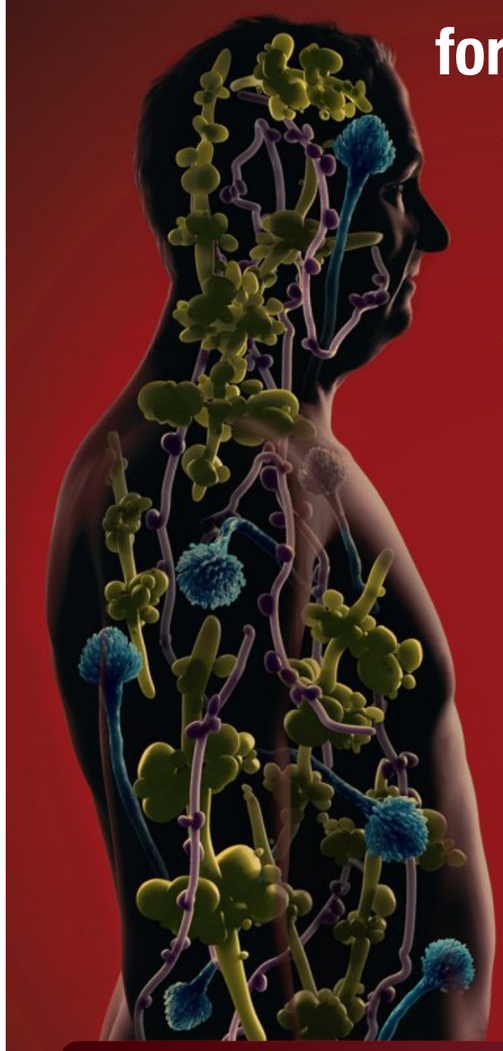
0-BUS-17-AD-001-01
Date of approval : 10 May 2017



Simple Solution for Today's Complex Patients

- **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.[‡]

* 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[¶], absence of any breakthrough fungal infection[§] 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]

¶ Baseline infections were those present on or before day 2 of the study.
§ 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 coadministered (see 1.Warnings).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. Pediatric 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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MYCAMINE® : approved, recommended and effective antifungal prophylaxis in HSCT recipients

- MYCAMINE® is the only echinocandin licensed for antifungal prophylaxis in HSCT recipients[1]
- The overall efficacy of MICAFUNGIN was superior to that of fluconazole as antifungal prophylaxis during the neutropenic phase after HSCT (p=0.03)[2]

Reference: 1. 마이카민 제품설명서 (작성일 : 2015년 12월 9일) 2. Van Burik JA,et al Clin Infect Dis 2004;39:1407-16

AMYC-17-A-10

[제품명] 트룩시마®주 500mg/50mL, Truxima® (리툭시맙) (단클론항체, 유전자재조합) **[원료약품 및 그 분량]** 1 바이알 (50 mL) 중 Rituximab 500 mg **[성상]** 무색 또는 미황색이고 투명에서 탁한 용액이 무색 투명한 바이알에 든 주사제 **[효능·효과]** 1) 림프종 : 재발성 또는 화학요법 내성인 여포형 림프종(3세포 비호지킨 림프종 WF분류중 B, C, D형) / 이전에 치료받은 적이 없는 여포형 림프종에서 화학요법과 병용투여 / 여포형 림프종에서 유도요법 실시 후 유지요법 / CD20 양성의 미만형 대형 B세포 비호지킨 림프종(DLCL)[CHOP화학요법 (cyclophosphamide, doxorubicin, vincristine, prednisolone 으로 구성, 8주기 투여)과 병용하여 투여해야 한다.] 2) 만성 림프구성 백혈병 3) 류마티스 관절염 4) 베게너육아종증 및 현미경적 다발혈관염 **[용법·용량]** (주입방법) 별도의 전용관을 써서 정맥 점적 주입하며 매회 30~60분전 해열제 및 항히스타민제 투여하에야 하고 비호지킨 림프종 및 만성림프구성 백혈병 환자의 치료계획 중 글루코르티코이드가 포함되어 있지 않은 경우 전처치를 고려해 보아야 한다. 1차 주입 시 초기 주입 속도는 50 mg/hr이 권장되며 30분마다 50 mg/hr씩 속도를 높여 최고 400 mg/hr까지 증가할 수 있다. 이후 이 약의 주입 속도는 100 mg/hr에서 시작하여 30분마다 100 mg/hr씩 증가시켜 최고 400 mg/hr까지 높일 수 있다. (림프종) 치료기간 중 용량 감량은 바람직하지 않으며 이 약을 표준 화학요법과 병용투여하는 경우 화학요법제의 감량지침을 적용하도록 한다. ① 여포형 비호지킨 림프종 1) 병용요법 : 이전에 치료받은 적이 없거나 재발성/불응성인 환자에게 유도요법으로 화학요법과 병용할 경우 권장용량은 375 mg/m²이며 8주기까지 투여한다. 이 약은 글루코르티코이드 장액 투여 후(해당되는 경우만) 매 화학요법 투여 주기 제1일에 투여한다. 2)유지요법 : 이전에 치료받은 적이 없고 유도요법에 반응하는 환자는 2개월에 한번씩 375 mg/m²(유도요법 최종 투여로부터 2개월 후 유지요법 시작)을 재발성/불응성이고 유도요법에 반응하는 환자는 3개월에 한번씩 375 mg/m²(유도요법 최종 투여로부터 3개월 후 유지요법 시작)을 질환 진행 시까지 또는 최대 2년간 유지요법으로 투여한다. 3)단독요법 : 재발성/불응성 환자에서 유도요법으로 투여할 경우 권장용량은 375 mg/m²이며 매주 1회씩 4주에 걸쳐 투여한다. 1차 치료 시 반응했던 환자가 재발한 경우 재투여하였으며 이때 반응률은 처음과 유사하였다. 권장용량은 375 mg/m²이며 매주 1회씩 4주에 걸쳐 투여한다. ② 미만형 대형 B세포 비호지킨 림프종 : CHOP 화학요법과 병용투여한다. 권장용량은 375 mg/m²이며 매 화학요법 투여 주기의 제1일에 투여한다. 화학요법 구성약물들은 이 약 주입 후에 투여해야 한다. ※ 만성 림프구성 백혈병, 류마티스 관절염, 베게너육아종증 및 현미경적 다발혈관염의 용법·용량 및 제품에 대한 보다 자세한 정보는 제품설명서를 참조하시거나 아래의 연락처로 문의하여 주시길 바랍니다.

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NSCT, non stem cell transplant; NDNN, newly diagnosed multiple myeloma

Reference 1. Bahlis NJ, et al. Leukemia 2017;31:2435-42.

MKT/MM/REV/2017.12/01

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- Low Incidence of Nephrotoxicity, even in High Dose Therapy [4]
- Broad Spectrum Fungicidal Action Including in Neutropenic Patients [5]
- Impressive Response in Invasive Aspergillosis [6]

KRAM80048_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(titer)/kg/day is usually administered, the dosage can be gradually increased to 5.0 mg(titer)/kg/day, if required. • Fever of unknown origin show in patients with neutropenia: 1.0 mg(titer)/kg/day is administered as initial dose, which can be increased to 3.0 mg(titer)/kg/day according to symptoms. • Visceral leishmaniasis: 1.0~1.5 mg(titer)/kg/dayis administered for 21 days or 3.0 mg(titer)/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, bronchospasm, 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 Euljiro 5-gil, Jung-gu, Seoul, 100-210, Korea, 02-6030-3330) **[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: Sobel 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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브이펜드는 IA† 1차 치료제입니다.[1,2]

- 브이펜드는 **IA† 치료 국제 가이드라인***에서 **1차 약제 중 하나로 권고**되고 있습니다.[1,2]
- 브이펜드는 **IA† 1차 치료제로써 타 항진균제 대비 높은 생존율**을 보였습니다.[3,4]

† IA : Invasive Aspergillosis
* 주요 국제 가이드라인 : IDSA 2016, ECIL 6 2017

[주요 안전성 정보] 보리코나졸 투여와 관련하여 흔하게 보고된 이상반응은 시각 이상이었으며, 이러한 시각 이상은일 시적이고 대부분 60분 이내에 자연적으로 완전히 회복되었습니다.

References 1. Patterson TF, Thompson III GR, Denning DW et.al: Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America: Clinical Infectious Diseases 2016;63(4):e1 – 60 **2.** Frederic Tissot, Samir Agrawal, Livio Pagano et. al, ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients, Haematologica 2017 Volume 102(3):433–444 **3.** Nivoix Y, Velten M, Letscher-Bru V, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis. 2008;47(9):1176–84. **4.** Lortholary O, et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005 – 2007). Clin Microbiol Infect 2011;17:1882–9.

브이펜드®주 200mg, 브이펜드®정 200mg (보리코나졸)

[적응증/용법·용량] 적응증: 1. 침습성 Aspergillus 감염 및 Scedosporium apiospermum과 Fusarium속에 의한 중증 진균감염 1) 부하용량: 주사제 -6 mg/kg을 12시간 간격으로 투여(최초 24시간 동안) 2) 유지용량: ① 주사제: 4 mg/kg을 12 시간 간격으로 투여 ② 정제: 200 mg을 12시간 간격으로 투여 2. 호중구감소증이 없는 환자에서의 칸디다혈증 및 다른 심부 조직의 칸디다 감염 1) 부하용량: 주사제: 6 mg/kg을 12시간 간격으로 투여(최초 24시간 동안) 2) 유지용량: ① 주사제: 3~4mg/kg을 12시간 간격으로 투여 ② 정제: 200 mg을 12시간 간격으로 투여 3. 식도 칸디다증: 1) 주사제: 식도칸디다증 환자에 대해 평가되지 않았습니다. 2) 정제: 200 mg을 12시간 간격으로 투여. 4. 급성백혈병(급성 골수성 백혈병, 급성 림프성 백혈병, 골수형성이상증후군), 림프종 치료실패 또는 만성골수성백혈병으로 인한 조혈모세포 이식환자에서의 침습성 진균 감염증의 예방: 1) 주사제: 4 mg/kg을 12시간 간격으로 투여 2) 정제: 200 mg(5 mL)을 12시간 간격으로 투여 **[사용상 주의사항]** 1. 다음 환자에는 투여하지 말 것 ① 보리코나졸이나 다른 부형제 성분에 과민반응 있는 환자 ② St John's Wort 투여 환자 ③ Rifampicin, carbamazipine, phenobarbital과 병용 ④ 고용량 ritonavir와 병용 ⑤ CYP3A4 효소의 기질인 terfenadine, astemizole, cisapride, pimozide, quinidine 등과 병용 ⑥ Sirolimus와 병용 ⑦ CYP3A4 효소의 기질인 ergot 알칼로이드와 병 용 ⑧ Efavirenz 400 mg(1일 1회 투여) 이상의 용량과 병용투여 하지 않음 2. 다음 환자에는 신중히 투여할 것 ① 다른 아졸계 약물에 과민반응 있는 환자 ② 심혈관계:심전도상의 QT 연장과 관련이 있다. 부정맥 가능성이 있는 환자, 전해질 장애가 있는 환자에 신중 투여 ③ phenytoin, nifabutin, 저용량의 ritonavir, methadone과 병용 투여 3. 임상시험에서 가장 높은 빈도로 보고된 이상반응: 시각장애, 간기능검사이상, 발열, 발진, 구토, 구역(주사제), 오심(정제), 설사, 두통, 말초 부종 및 복통. 임상시험들에서 시각장애(시야흐림, 눈부심, 녹색시, 색시증, 색맹, 청색시, 안질환, 달무리보임, 야맹증, 뗄림보기, 광시증, 섬광암점, 시력저하, 시력발음, 시야결손, 유리체부유물, 황색시 포함)가 매우 흔하게 보고되었습니다. 이러한 시각이상은 일시적이고 대부분은 60분 이내에 자연적으로 완전히 회복되었으며, 임상적으로 유의할 정도의 장기간에 걸친 시각장애는 관찰되지 않았습니다. 제품개봉년월일: 주사제 2017년 1월 18일, 정제 2017년 1월 18일

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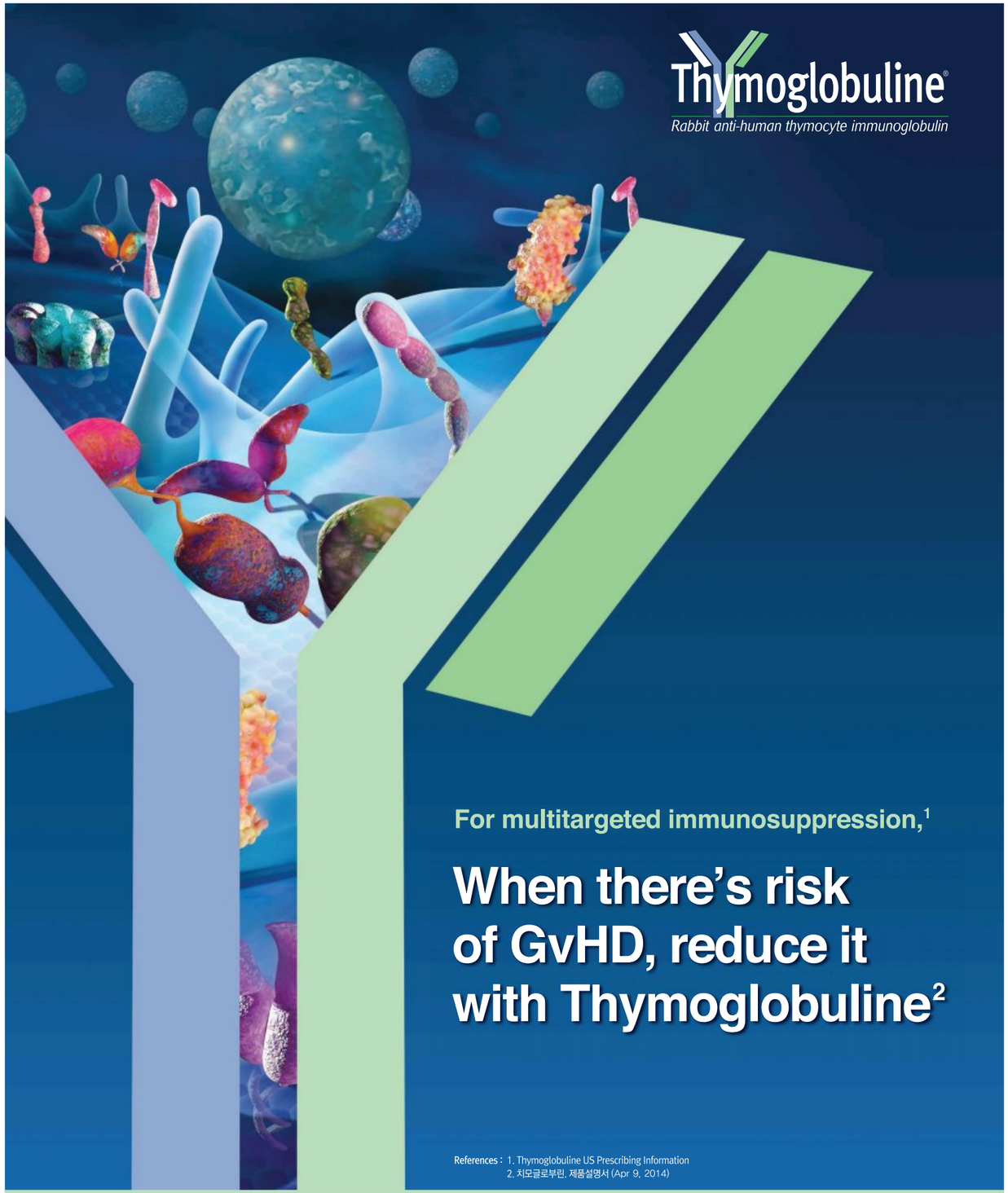

For multitargeted immunosuppression,[1]

When there's risk of GvHD, reduce it with Thymoglobuline[2]

References : 1. Thymoglobuline US Prescribing Information
2. 치모글로부린. 제품설명서 (Apr 9, 2014)

SANOFI

치모글로부린®주사 (인체흉선세포로 면역시킨 래빗트의 항흉선 면역 글로부린)

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자세한 사항은 제품설명서 또는 회사 홈페이지(www.sanofi.co.kr)를 참조해주십시오.

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- ✔ 투여시간 **단축**

Product Information

【성상】 무색 또는 담황색이고 투명 또는 약간 혼탁한 액이 무색 투명한 바이알에 든 주사제입니다. 【원료약품의 분량】 1mL 중 주성분 : 사람면역글로불린-지 (병규) 100mg, 안정제 : 글리신 (KP) 18.8mg, 용제 : 주사용수 (EP) 적 량 【효능 · 효과】 1. 저 및 무감마글로불린혈증 2. 중증감염증에 항생물질 병용 3. 특발혈소판감소자색반병(타제가 무효로서 현저한 출혈경향이 있고, 외과적 처치 또는 출산 등 일시적 치혈관리를 필요로 하는 경우) 4. 길랑바레 증후군(급성특발다발신경염) 5. 가와사키병(관상동맥합병증 예방목적) 【용법 · 용량】 1. 저 및 무감마글로불린혈증 : 1회 사람면역글로불린-지로서 체중 kg당 200~600mg을 3~4주 간격으로 점적 정맥주사 또는 직접 정맥주사합니다. 2. 중증감염증에 항생물질 병용 시 : 1회 사람면역글로불린-지로서 성인 2,500~5,000mg, 소아 50~150mg/kg을 점적 정맥주사 또는 직접 정맥주사합니다. 3. 특발혈소판감소자색반병 : 이 약으로서 1일 1000mg/kg, 2일간 사용하여도 증상의 개선이 보이지 않으면 중지합니다. 4. 길랑바레 증후군 : 400mg/kg 1일 1회 5일간 투여합니다. 5. 가와사키병 : 1일 400mg/kg, 5일간(증감). 혹은 2,000mg/kg을 1회 점적 정맥주사합니다 (적의감량). 가와사키병에 사용하는 경우에는 발병 후 7일 이내에 투여를 개시하는 것이 바람직합니다. 2,000mg/kg를 1회 투여할 경우 기본적으로 아래 투여속도를 준수하는 것으로 하지만 기준으로서는 12시간 이상에 걸쳐 점적 정맥주사합니다. 투여속도 초기 30분 동안은 0.01~0.02mL/kg/min으로 투여하고 (예, 체중 60kg 인 경우 0.6~1.2mL/min 투여) 환자의 상태에 이상이 없으면 0.06mL/kg/min까지 점차적으로 투여속도를 증가할 수 있습니다. 투여 후 환자의 상태를 충분히 관찰하고, 만약 투여속도 증가로 인해 환자의 상태에 이상이 발생할 경우 즉시 투여속도를 줄이거나 증상이 호전될 때까지 투여를 중단합니다. 【사용상의 주의사항】 1. 경고 1) 이 약은 사람 혈장으로부터 제조되어 현재의 과학기술 수준에서 혈액 매개 바이러스 또는 다른 종류의 감염원(이론적으로 CJD)의 감염 위험을 완전히 배제할 수 없습니다. 따라서 혈우병 환자 또는 면역기능이 현저히 저하된 환자는 A형 간염 백신 등 적절한 백신 접종이 권장되며, 동 제제 투여 시 의사는 정기적으로 감염 여부를 모니터 해야 합니다. 또한 사람 혈액을 원재료로 하고 있는 것에 의한 감염증 전파의 위험을 완전히 배제할 수 없으므로 투여시 환자에게 충분히 설명을 하고 질병 치료상의 필요성을 충분히 검토한 후에 필요한 최소한의 사용에 그치도록 합니다, 2) 이 약 투여를 통한 혈전증 발생 위험은 완전히 배제할 수 없으며, 위험요인 및 투여 경로에 무관하게 발생할 수 있습니다. 고령자 등 혈전증 발생 위험요인이고령. 장기간 부동상태, 과음과 상태, 정맥 또는 동맥 혈전증 병력, 에스트로겐 사용, 중심정맥카테터 삽입, 고점도 및 심혈관질환에 위험요인이 있는 환자의 경우, 가능한 최소농도를 최저 주입속도로 신중 투여하여야 합니다. 또한 투여 전 환자가 적절한 수분을 섭취할 수 있도록 하여야 하며, 투여 후 혈전증 증상 및 징후를 관찰하고 고점성 위험이 있는 환자의 혈액점성을 평가하는 등 환자의 상태를 관찰하여야 합니다. – 첨부문서 참조. 【포장단위】 10, 25, 50, 100, 200 mL/Vial × 1 【저장방법 및 유효기간】 밀봉용기에 넣어 1~-25℃ 에서 차광하여 보관 제조일로부터 18개월까지입니다. ※ 유효기한 또는 사용기한이 경과되었거나 변질, 변패 또는 오손된 제품은 약국, 병 · 의원, 도매상에 한하여 각 영업소에서 교환하여 드립니다. ※ 이 첨부문서의 작성일자(2017년 07월 03일) 이후 변경된 내용은 홈페이지(www. greencross.com)나 소비자 상담실 (☎ 080-260-8232)로 문의하시기 바랍니다.

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  (만성기 CML 2차 치료)
- 2011.8 임상 3상 시험 개시
  - 아시아 4개국, 24개 GCP 기관
  (만성기 CML 1차 치료)
- 2012.1 식약처(MFDS) 의약품 품목허가
  (국산 18호 신약, 대한민국신약개발상 대상수상)
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1. 이전에 한 가지 이상의 치료를 받은 경험이 있는 외투세포 림프종.
2. 이전에 한 가지 이상의 치료를 받은 경험이 있는 만성 림프구성 백혈병

【용법・용량】 이 약은 매일 같은 시각에 물과 함께 1일 1회 경구 투여한다. 캡슐을 물과 함께 통째로 삼켜야 하며 캡슐을 열거나 부수거나 씹지 않도록 한다. 이 약은 자몽주스와 복용해서는 안된다. 이 약은 질병이 진행되거나 환자의 내약성이 지속될 수 없을 때까지 계속 복용하여야 한다. 1. 외투세포 림프종 이 약의 권장 용량은 1일 1회 560mg(140mg 캡슐 4개)이다. 2. 만성 림프구성 백혈병 이 약의 권장 용량은 1일 1회 420mg(140mg 캡슐 3개)이다.

【사용상의 주의사항】 1. 다음 환자에는 투여하지 말 것 이 약의 주성분 또는 첨가제에 과민성의 병력(아나필락시스 반응, 아나필락시스양 반응)이 있는 환자 2. 이상반응 단발적으로 백혈구 올혈이 발생한 사례가 관찰되었다. 1) 외투세포 림프종 가장 흔하게 발생하는 비혈액학적 이상반응은 설사, 피로, 오심, 말초부종, 호흡곤란, 변비, 상기도 감염, 구토, 식욕저하 등이었다. 가장 빈번하게 보고된 혈액학적 이상반응은 호중구 감소증, 혈소판 감소증, 빈혈이었다. 2) 만성 림프구성 백혈병 가장 흔하게 발생하는 약물 이상반응은 설사, 근골격계 통증, 상기도감염, 멍, 발진, 오심, 발열, 호중구 감소증 및 빈혈이었다. 3. 일반적 주의 1) 출혈 2) 백혈구올혈 3) 감염 4) 혈구감소증 5) 간질성 폐질환 6) 심방세동 7) 종양용해 증후군 8) 비흑색종 피부암 4. 임부, 수유부, 수태능 1)임부 이 약은 임신 중에는 복용해서는 안된다. 2) 수유부 이 약의 치료기간 동안 수유를 중단하여야 한다. 3) 수태능 남성은 이 약을 투여하는 기간과 복용이 끝나고 3개월 동안은 아이를 갖지 않도록 권고되어야 한다.

【수입판매원】 ㈜한국얀센

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TFR, treatment-free remission; **DMR,** deep molecular response; **Ph+,** Philadelphia chromosome-positive; **CML,** chronic myeloid leukemia; **CP,** chronic phase.

Reference 1. TASIGNA® (nilotinib) Product Information. **2.** Hochhaus A, *et al. Leukemia.* 2016;30(5):1044-54 (Epub 2016 Feb 3). **3.** Hochhaus A, *et al. Leukemia.* 2017;31(7):1525-1531 (Epub 2017 Feb 20).

타시그나캡슐 150mg, 200mg (닐로티닙염산염일수화물) [효능 효과] 1. 새로 진단된 안성기의 필라델피아 염색체 양성 만성골수성백혈병(Ph+CML) 성인 환자의 치료. 이 약의 유효성은 주요 분자학적, 세포유전학적 반응률을 근거로 하고 있다. 2. 이전에 치료를 받은 적이 없는 만성기 또는 가속기의 필라델피아 염색체 양성 만성골수성백혈병(Ph+CML) 성인 환자의 치료. 이 약의 유효성은 세포유전학적, 혈액학적 반응률을 근거로 하고 있다. 3. 재발하거나 난치성인 중증 개선되나 생존율 증가의 같은 임상적 유익성을 나타낸 임상시험은 없다. **[용법 용량]** 1. 새로 진단된 안성기의 필라델피아 염색체 양성 만성골수성백혈병(Ph+CML) 성인 환자의 치료: 1일 2회, 1회 300mg 2. 이전에 닐로티닙을 포함하는 선행요법에 저항성 또는 불내성을 보이는 만성기 또는 가속기의 필라델피아 염색체 양성 만성골수성백혈병 (Ph+CML) 성인 환자의 치료: 1일 2회, 1회 400mg이 약은 약 12시간의 간격을 두어야 하고, 음식과 함께 복용해서는 안된다. 최소한 식사 1시간 전, 또는 2시간 후에 복용한다. 캡슐을 물과 함께 그대로 삼킨다. 캡슐을 삼키기 어려운 환자인 경우, 캡슐을 열어 내용물을 1 티스푼의 사과소스(으깬 시럽)에 뿌려 즉시 복용한다. 1 티스푼 이상의 사과소스나 시과소스(으깬 시럽) 이외의 다른 음식물 사용해선 안 된다. 다음 환자에게는 투여하지 말 것: 1) 이 약의 주성분 또는 다른 성분들에 과민증 환자 2) 갑작스으로 불내성, Lapp 유당분해효소 결핍증 또는 포도당-갈actose으로 흡수장애 등의 유전적인 문제가 있는 환자 3) 저칼륨증, 저마그네슘증, 또는 QT 연장증후군이 있는 환자 다음 환자에게는 신중히 투여할 것: 1) 이 약이 투여는 이 약과 음식의 병용 투여는 반드시 피해야 하며, 이 약과 강력한 CYP3A4저해제 및/또는 CT를 연장시킬 가능성이 있는 의약품과의 병용투여를 피해야 한다. 환자에게 저칼륨증과 저마그네슘혈증이 있을 경우 이러한 QT연장의 위험이 증가할 수 있다. 이 약은 QTc 연장의 유의한 위험이 있는 환자(선천적 long QT syndrome, 조절되지 않거나 또는 유의한 심장 질환(최근의 심근경색, 울혈성 심부전, 불안정성 협심증 또는 임상적으로 유의한 서맥 포함)이 있는 환자)에게는 주의하여 사용되어야 한다. 임상시험에서 급사가 한적지 않은 사례 (0.1-1%)로서 보고되었으며, 이는 과거 심장질환의 병력이나 유의한 심장 위험 요인을 가진 환자 군에서 나타났다. 이 약은 강력한 CYP3A4 저해제 및 항 부정맥 약물과 같이 QT간격을 연장시킬 수 있는 약물과의 병용투여를 피해야 한다. 이와 같은 약물을 투여해야 하는 경우, 가능하면 이 약의 투여를 중단하는 것이 권장된다. 2) 간장애 환자에서 닐로티닙 노출도는 증가한다. 경증-중증의 간장애 환자에서 낮은 초기 용량이 요구되며, QT 간격 모니터링을 차주해야 한다. 3) 혈청 리파이제이 상승이 관찰되었으며 췌장염의 병력이 있는 환자에게 주의가 요구된다. 리파이제이 상승이 복부증상을 동반할 경우, 췌장염이 발생하지 않도록 투여를 중단하고 적절한 진단을 고려한다. 4) 간에 위장애을을 보인 환자들에서 닐로티닙의 생체내 이용률이 감소될 수 있으며, 이러한 환자들에서 더욱 빈번한 추적 관찰이 고려되어야 한다. 5) 이 약을 투여 받은 환자들에서 종양용해증후군(TLS)이 보고되었으며, 몇몇 용량에 따라 모니터링 한다. 6) 새로 진단된 CML 환자에 대한 3상임상시험에서 하루에 두 번 400mg을 투여한지을 때, 1.1% 의 환자들에서 총 3/4등급의 콜레스테롤 수치 상승이 관찰되었다. 이 약으로 치료하기 전 지질 프로파일이 측정되어야 하며, 치료를 시작한 뒤, 3개월과 6개월 후, 그리고 안성치료기 동안 적어도 1년에 한번은 지질프로파일이 평가되어야한다. HMG CoA 환원효소 억제제들이 CYP3A4경로에 의해서 대사가 되므로, 만일 HMG CoA 환원효소 억제제와 같은 지질 수치를 낮추는 약물이 요구되면 치료를 시작하기 전 이 약과의 상호작용을 고려해야 한다. 7) 새로 진단된 CML 환자에 대한 3상 임상시험에서, 이 약을 하루에 두 번 400mg 을 투여한 환자의 6.9%, 하루에 두 번 300mg을 투여한 환자의 7.2%에서 3등급의 혈당 증가가 관찰되었다. 이 약으로 치료하기 전 혈당 수치가 평가되어야 하며, 치료 중 당뇨병 징후가 있는 경우 혈당 모니터링이 권고된다. 혈당 감시 결과 치료가 필요한 경우, 의료진은 국내 표준 진료지침에 따라 치료해야 한다. 8) 새롭게 진단된 만성골수성 백혈병 환자를 대상으로 한 무작위 3상 닐로티닙 시험에서 보고되었고 시판 후 조사에서 선행군에 시간의 관찰되었다. 환자에게 선행군에 시간의 급성 징후나 증상이 발생하면 즉시 의사의 치료를 받도록 조언해야 한다. 이 약으로 치료하는 중에는 표준치침에 따라서 환자의 심혈관계 상태가 평가되어야 할 뿐 아니라, 심혈관계 위험요소가 모니터되고 적극적으로 관리되어야 한다. 9) 새로 진단된 CML 환자를 대상으로 한 3상 임상시험에서 흉막삼출, 폐부종, 심낭삼출과 같은 약물관련 체액저류의 심각한 형태가 흔히지 않게(0.1-1%) 관찰되었다. 시판 후 보고에서도 유사한 사건들이 관찰되었다. 예상치 못한 급격한 체중의 증가는 주의 깊게 조사되어야 한다. 이 약으로 치료하는 동안 심각한 체액저류의 징후가 나타나면 병인을 평가하고, 환자를 이에 따라 치료해야 한다. 10) BCR-ABL 티로신 키나아제 억제제를 투여 받은 B형 간염 바이러스의 보균자에서 B형 간염 재활성화가 나타났다. 일부 사례는 급성 간 부전 또는 간 이식에나 저장적인 결과로 이어지는 드라성 간염을 야기하였다. 환자들은 이 약의 치료를 시작하기 전에 B형 간염 바이러스(HBV) 감염 검사를 받아야 한다. B형 간염 혈청 검사에서 양성인 환자(활성 상태인 환자 포함)는 치료를 시작하기 전에 B형 간염 치료 전문가와 상담해야 하고 이 약의 치료 중 실시된 HBV 감염 검사에서 양성인 환자 또한 전문가와 상담해야 한다. 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. 11) 급은 분자학적 반응 유지 시 투여 중단 전략적인 BCR-ABL유전자의 전사체, e1a2/b2a2 또는 e14a2/b3a2를 발현하는 것으로 확인되고 이 약의 투여중단 기준에 적합한 환자들에서 투약 중단이 고려될 수 있다. 환자들은 반드시 BCR-ABL수준을 정량할 수 있는 전문적인 BCR-ABL 전사 및 같은 분자학적 반응 평가를 받아야 하고, 이 약의 치료 중단 후 분자학적 검해 소실에 대해 평가 받아야 한다. 치료 중단에 적합한 환자들에서 투약 중단이 고려될 수 있다. 분자학적 반응(MR4.5)을 유지하면서 최소 3년간 투약하였고, 투약중단 직전까지 최소 1년간 분자학적 반응(MR4.0 이상)을 유지한 만성기의 Ph+CML 환자에서 이 약의 투여 중단이 고려될 수 있다. 이 약의 투여 중단은 만성 골수성 백혈병 환자에 대한 치료 경험이 있는 의사의 감독 하에서 이뤄져야 한다. 치료 중단 기간에 적합한 환자들에서 투약 중단이 고려될 수 있다. 이 약의 투여 중단은 만성 골수성 백혈병 환자에 대한 치료 경험이 있는 의사의 감독 하에서 이뤄져야 한다. 치료 중단 기간에 적합한 환자들에서 투약 중단이 고려될 수 있다. 분자학적 반응 재발은 무치료관찰기간 동안 빈번한 주기로 분자학적 반응 (MR4.5)을 유지하였을 때 투약 중단 이 약을 1일 2회, 1회 300mg으로 최소 3년간 투약하였고, 투약중단 직전까지 최소 1년간 분자학적 반응(MR^{4}, BCR-ABL/ABL ≤0.0032% IS)을 유지한 만성기의 Ph+CML 환자에서 이 약의 투여 중단이 고려될 수 있다. 이 약의 투여 중단은 만성 골수성 백혈병 환자에 대한 치료 경험이 있는 의사의 감독 하에서 이뤄져야 한다. 치료 중단 기간에 적합한 환자들은 반드시 첫 번째 해에는 매 달마다, 그리고 주요 분자학적 반응(MMR) 도달 이후에는 12주 마다 BCR-ABL 전사수준을 모니터링 하여야 한다. ② 이전에 선행요법 이후 이 약을 투여한 만성기의 필라델피아 염색체 양성 만성 골수성 백혈병 환자에 대한 치료경험이 있는 의사의 감독 하에 이뤄져야 한다. 치료 중단 기간에 적합한 환자들은 반드시 첫 번째 해에는 매 달마다, 두 번째 해에는 6주 마다, 그 후에는 12주 간격으로 BCR-ABL 전사수준검사 및 감염을 포함한 전혈구 검사 모니터링을 실시해야 한다. 무치료관찰기간 동안 분자학적반응(MMR)이 다시 회복될 때까지 매달, 그리고 주요 분자학적 반응(MMR) 도달 이후에는 12주 마다 BCR-ABL 전사수준을 모니터링 하여야 한다. 이 약의 투여를 재시작한 환자는 주요 분자학적 반응(MMR)이 다시 회복될 때까지 매달, 그리고 주요 분자학적 반응(MMR) 도달 이후에는 12주 마다 BCR-ABL 전사수준을 모니터링 하여야 한다. 처방하시기 전, 제품정보전문을 참조하시기 바랍니다.

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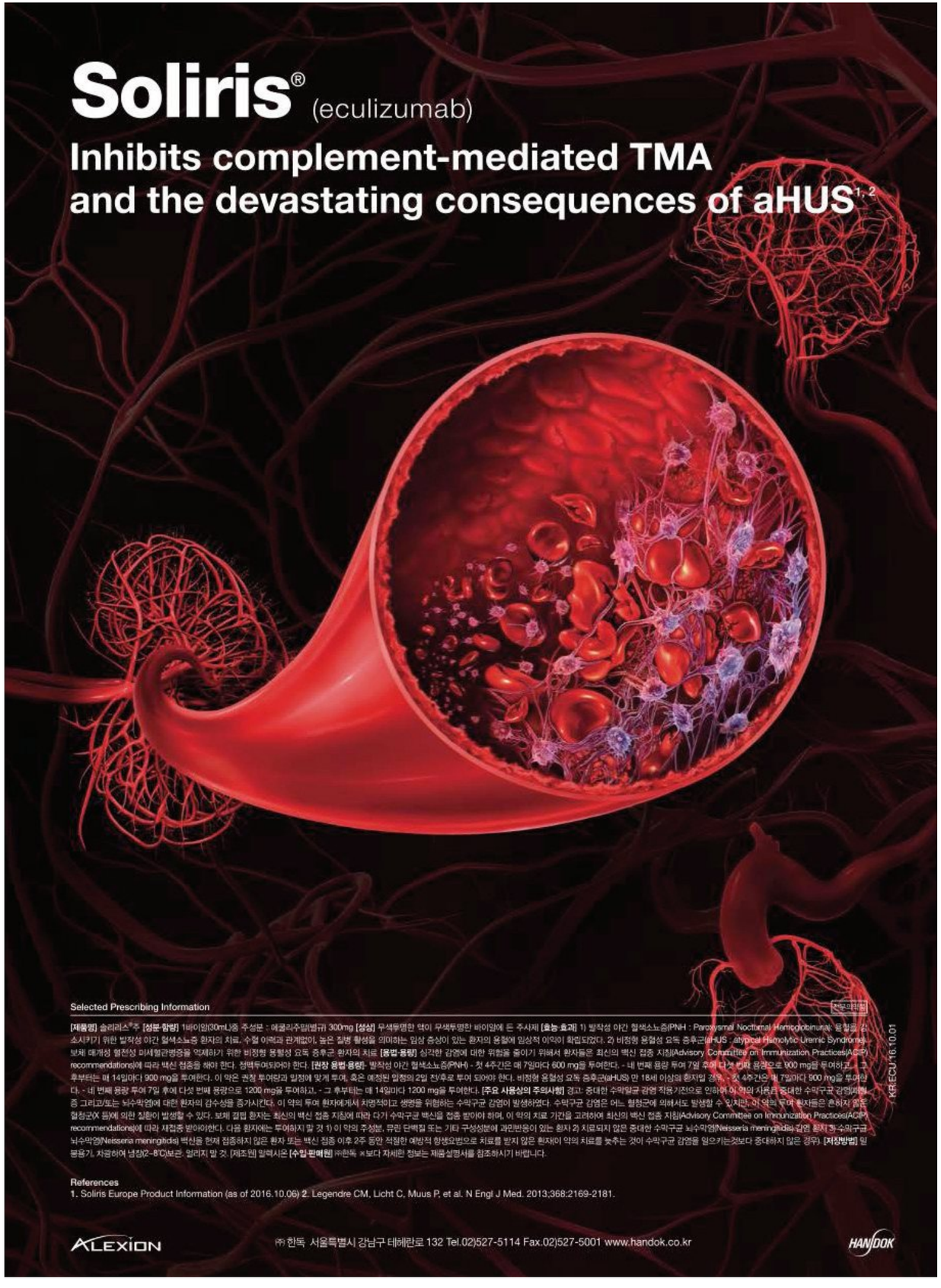
Inhibits complement-mediated TMA and the devastating consequences of aHUS[1,2]



Selected Prescribing Information

전문의약품

[제품명] 솔리리스®주 **[성분·함량]** 1바이알(30mL)중 주성분 : 에쿨리주맙(범규위 300mg **[성상]** 무색투명한 액이 무색투명한 바이알에 든 주사제 **[효능·효과]** 1) 발작성 야간 혈색소뇨증(PNH : Paroxysmal Nocturnal Hemoglobinuria) 용혈을 동반한 증상 소시키기 위한 발작성 야간 혈색소뇨증 환자의 치료. 수혈 이력과 관계없이, 높은 질병 활성을 의미하는 임상 증상이 있는 환자의 용혈에 임상적 이익이 확립되었다. 2) 비정형 용혈성 요독 증후군(aHUS : atypical Hemolytic Uremic Syndrome) 보체 매개성 혈전성 미세혈관병증을 억제하기 위한 비정형 용혈성 요독 증후군 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. 적절투여되어야 한다. **[권장 용법·용량]** 발작성 야간 혈색소뇨증(PNH) - 첫 4주간은 매 7일마다 600 mg을 투여한다. - 그 후부터는 매 14일마다 900 mg을 투여한다. 비정형 용혈성 요독 증후군(aHUS) 만 18세 이상의 환자일 경우, - 첫 4주간은 매 7일마다 600 mg을 투여한다. - 그 후부터는 매 14일마다 900 mg을 투여한다. 이 약은 권장 투여량과 밀청에 맞게 투여, 혹은 예정된 일정의 2일 전/후로 투여 되어야 한다. 비정형 용혈성 요독 증후군(aHUS) 만 18세 이상의 환자일 경우, - 첫 4주간은 매 7일마다 600 mg을 투여한다. - 네 번째 용량 투여 7일 후에 다섯 번째 용량으로 1200 mg을 투여하고, - 그 후부터는 매 14일마다 1200 mg을 투여한다. **[주요 사용상의 주의사항]** 경고: 중대한 수막알균 감염 작용 기전으로 인하여 이 약의 치료를 중대한 수막구균 감염(패혈증 그리고/또는 뇌수막염)에 대한 환자의 감수성을 증가시킨다. 이 약의 투여 환자에게서 처명적이고 생명을 위협하는 수막구균 감염이 발생하였다. 수막구균 감염은 어느 혈청군에 의해서도 발생할 수 있지만, 이 약의 투여 환자들은 흔히지 않은 혈청군(W 등)에 의한 질환이 발생할 수 있다. 보체 결합 환자는 최신의 백신 접종 지침에 따라 다기 수막구균 백신을 접종 받아야 하며, 이 약의 치료 가간을 고려하여 최신의 백신 접종 지침(Advisory Committee on Immunization Practices(ACIP) recommendations)에 따라 새접종 받아야한다. 다음 환자에는 투여하지 말 것 1) 이 약의 주성분, 뮤린 단백질 또는 기타 구성성분에 과민반응이 있는 환자 2) 치료되지 않은 중대한 수막구균 뇌수막염(Neisseria meningitidis)감염 환자 3) 수막구균 뇌수막염(Neisseria meningitidis) 백신을 현재 접종하지 않은 환자 또는 백신 접종 이후 2주 동안 적절한 예방적 항생요법으로 치료를 받지 않은 환자(이 약의 치료를 늦추는 것이 수막구균 감염을 일으키는것보다 중대하지 않은 경우). **[저장방법]** 밀봉용기, 차광하여 냉장(2-8℃)보관. 얼리지 말 것. [제조원] 알렉시온 **[수입·판매원]** ㈜한독 ※보다 자세한 정보는 제품설명서를 참조하시기 바랍니다.

References
1. Soliris Europe Product Information (as of 2016.10.06) 2. Legendre CM, Licht C, Muus P, et al. N Engl J Med. 2013;368:2169-2181.

ALEXION

㈜한독 서울특별시 강남구 테헤란로 132 Tel.02)527-5114 Fax.02)527-5001 www.handok.co.kr

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Early, deep and durable response[1,2]

Known and manageable safety profile[1]

Convenience to improve adherence[3]

References 1. Jabbour E, Kantarjian HM, Saglio G, et al. Blood 2014;123(4):494-500. **2.** Shah NP, Guilhot F, Cortes JE, et al. Blood 2014;123(15):2317-24. **3.** Sprycel® (dasatinib) prescribing information.

스프라이셀 정 20mg, 50mg, 70mg, 80mg, 100mg(다사티닙)

[효능·효과 및 용법·용량] 1) 새로이 진단받은 만성기 필라델피아 염색체 양성 만성골수성백혈병(Ph+ CML) 성인환자의 치료. 1일 1회 100mg 경구 투여 2) 이매티닙을 포함한 선행요법에 저항성 또는 불내성을 보이는 만성기의 만성골수성백혈병(Ph+ CML) 성인환자의 치료. 1일 1회 100mg 경구 투여 3) 이매티닙을 포함한 선행요법에 저항성 또는 불내성을 보이는 가속기, 또는 골수성이나 림프구성 모구성위기의 만성골수성백혈병(Ph+ CML) 성인환자의치료. 1일 1회 140mg 경구 투여 4) 선행요법에 저항성 또는 불내성을 보이는 필라델피아 염색체 양성 급성 림프구성 백혈병(Ph+ ALL) 성인환자의 치료. 1일 1회 140mg 경구 투여. 이 약은 복용 시 질병 투수기나 치료시 있고, 그외로 심부 복용하여야 한다. 이 약은 시시의 관계없이 아침이나 저녁에 복용할 수 있다. **[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 성분분에 과민증 환자 2) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성galactose intolerant, Lapp 유당분해효소 결핍증Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애glucose-galactosemalabsorption) 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 QT- 연장증환이 있거나 기능성이 있는 환자에게 주의하여 투여되어야 한다. 여기에는 저칼륨혈증 또는 저마그네슘혈증 환자, 선천성 연장 QT 증후군을 가진 환자, 항부정맥약물 복용중인 환자, 또는 QT 연장을 유도할 수 있는 다른 약물을 복용하고 있는 환자, 그리고 축적성 고용량 안트라사이클린 요법을 받고 있는 환자가 포함된다. 여기에는 저칼륨혈증 또는 저마그네슘혈증 환자, 선천성 연장 QT 증후군을 가진 환자, 항부정맥약물 복용중인 환자, 또는 QT 연장을 유도할 수 있는 다른 약물을 복용하고 있는 환자, 그리고 축적성 고용량 안트라사이클린 요법을 받고 있는 환자가 포함된다. 저칼륨혈증 또는 저마그네슘혈증은 이 약 투여 전에 교정되어 있어야 한다. 3) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 4) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 4) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 5) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 6) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 7) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 8) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 9) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 10) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 11) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 12) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 13) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 14) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 15) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 16) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 17) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 18) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 19) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 20) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 21) 이 약은 간 또는 신장 기능이 손상된 환자에게 투여하여야 한다. 22) 이 약은 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Bristol-Myers Squibb

Neulasta®
(pegfilgrastim)

FN Prophylaxis through every cycle

Neulasta® used first and every cycle
helps reduce the incidence of
febrile neutropenia

전 문 의 약 품

원료의약품 및 분량 1시린지(0.6밀리리터)중 (주성분) 페그필그라스틴(별규) … 6mg, (첨가제) 빙초산(글라시알아세틱에시드), 수산화나트륨, 소르비톨(30mg), 폴리소르베이트20(0.02mg), 주사용수 성상 무색의 용액이 충진 된 주사침이 달린 투명한 유리프리필드시린지 주사제 효능효과 악성종양에 대한 세포독성 화학요법을 투여 받는 환자의 발열성 호중구 감소증의 발생과 호중구 감소증의 기간 감소(만성골수성 백혈병과 골수이형성증후군은 제외함) **용법용량** 이 약 6mg을 항암화학요법 이후 약 24시간 후에 피하주사 *소아에 대한 사용 제한 *말기 신장애 환자를 포함한 신장애 환자에게 용량 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) 겸상적혈구질환 환자가 필그라스팀, 페그필그라스팀을 투여 받는 경우 중증, 때때로 치명적인 겸상적혈구발증이 발생할 수 있음 5) 폐그필그라스팀과 필그라스팀이 작용하는 G-CSF수용체가 암세포에서 발견됨, 폐그필그라스팀이 골수성 암과 골수이형성증을 포함한 암 종류를 증가시키는 요소로 작용할 수 있음 **2. 다음 환자에는 투여하지 말 것** 대장균으로부터 유래된 단백질, 페그필그라스팀, 필그라스팀 등에 과민증이 알려진 환자 **3. 다음 환자에는 신중히 투여할 것** 1) 악물 과민증의 병력이 있는 환자 2) 알레르기 소인이 있는 환자 **포장기한** 1시린지/박스 **저장방법** 냉장보관(2-8℃). 진탕금지 동결금지, 차광보관, 밀봉용기 **사용기한** 외부포장재에 표시된 사용기한 내에 사용 *제품에 대한 자세한 정보는 제품설명서를 참조해주시기를 바라며, 홈페이지(www.kyowa-kirin-korea.com)에서 확인하실 수 있습니다. [수입판매원] 한국교와하코기린(주)

KYOWA KIRIN
한국교와하코기린(주)
서울특별시 강남구 논현동 430(역삼동), 11층(아세아 타워빌딩) 우)06223
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723NK189PE0003/Jan2018

For Ph-negative relapsed/refractory B-cell precursor ALL

REACH BEYOND REMISSION.
EXTEND SURVIVAL.

Significantly extend OVERALL SURVIVAL vs. chemotherapy
with the power of a bispecific T-cell engaging immunotherapy

Of evaluable Ph-negative relapsed/refractory B-precursor ALL patients who received BLINCYTO® (n=271/405),

Median Overall Survival

- **7.7 months** vs. 4.0 months in the chemotherapy group
  (HR 0.71; 95% CI, 0.55-0.93; *P* = 0.01)[1]
- **11.1 months** vs. 5.3 months in the chemotherapy group at **1st salvage-treatment phase**
  (HR 0.60; 95% CI, 0.39-0.91)

Remission Rate within 12 Weeks after Treatment Initiation

- **CR/CRh/CRi**
  43.9% vs 24.6% in the chemotherapy group
  [Treatment difference 19.3 (95% CI, 9.9-28.7; *P* <0.001)][1]
- **MRD negative status among the patients who had CR/CRh/CRi**
  76% vs 48% in the chemotherapy group
  [Treatment difference 28 (95% CI, 9-47)]

CR/CRh/CRi = complete remission with full, partial, or incomplete hematologic recovery

CR was defined as 5% or less bone marrow blasts and no evidence of disease and was further characterized as follows: CR with full recovery (platelet count of >100,000/μL and ANC of >1000/μL), CR with partial recovery (platelet count of >50,000/μL and ANC of >500/μL), or CR with incomplete recovery (platelet count of >100,000/μL or ANC of >1000/μL).

ANC, absolute neutrophil count

§which crossed the prespecified stopping boundary

Reference Kantarjian H, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 2017;376:836-47.

블린사이토®주 제품요약정보

제품명: 블린사이토®주350마이크로그램(블린사투모맙,유전자재조합), **효능효과:** 필라델피아 염색체 음성인 재발 또는 불응성 전구 B세포 급성 림프모구성 백혈병의 치료. **용법용량:** 이 약 치료 단회 주기는 28일간의 지속적인 정맥 투여와 이후의 14일간의 치료 휴지 기간으로 이루어져 있다(총 42일). 체중 45kg 이상 환자의 경우 고정된 용량을 투여하고 (주기 1의 1~7일차: 9㎍/일, 주기 1의 8~28일차 및 이후 주기의 1~28일차: 28㎍/일), 45kg 미만 환자는 환자의 체표면적을 고려하여 용량을 설정한다. (주기 1의 1~7일차: 5㎍/㎡/일, 주기 1의 8~28일차 및 이후 주기의 1~28일차: 15㎍/㎡/일) 이 약은 24시간 동안 10mL/시간의 속도로 주입, 또는 48시간 동안 5mL/시간의 속도로 주입하며, 일정한 속도로 총 240mL이 주입된다. **경고:** 사이토카인 방출 증후군, 신경학적 독성, **다음 환자에게는 투여하지 말 것:** 이 약의 주성분 또는 다른 성분에 과민반응이 있는 환자, **약물이상반응:** 가장 빈번하게 발생한 약물이상반응(≥ 20%)은 발열, 두통, 구역, 부종, 저혈압혈증, 빈혈, 열성 호중구감소증, 호중구감소증, 혈소판감소증, 복통. 가장 빈번하게 발생한 중증 이상반응 (≥ 2%)은 체중 45kg 이상 환자의 경우: 열성 호중구감소증, 발열, 폐렴증, 폐렴, 기구 관련 감염, 호중구감소증, 진전, 과량투여, 뇌병증, 감염, 혼돈, 두통, 45kg 미만 환자의 경우: 발열, 열성 호중구감소증, 사이토카인 방출 증후군, 경련, 기구 관련 감염, 저산소증, 패혈증, 과량투여, **일반적 주의:** 감염증, 중앙응해증후군, 호중구감소증, 열성 호중구감소증, 온전 및 기계조작 능력에 대한 영향, 간 효소 증가, 췌장염, 백질뇌증, 조제 및 투여 실수, 예방접종, **임부 및 수유부:** 비임상 연구에서 임신한 생쥐에게 투여된 설치류 대리 분자는 태반 장벽을 통과하였다. 임신부에게 태아에 대한 잠재적인 위험성을 알려야 한다. 해당 모집단에서 주요 출생 결함과 유산의 발생률은 알려지지 않았다. 유즙 중 이 약의 존재 여부, 수유 시 영아에 미치는 영향, 유즙 생성에 미치는 영향에 대한 정보는 없으나 이 약으로 인해 수유중인 영아에서 B 세포 림프구감소증과 같은 중증 약물이상반응 발생 가능성이 있으므로, 이 약으로 치료 중이거나 치료 후 최소 48시간까지는 수유하지 않도록 권고해야 한다. **보관 및 취급상의 주의사항:** 차광 냉장 (2~8°C) 보관. 적응상의 주의—**주입을 위한 약액 재구성 및 조제: 투약 오류 (과량 투여와 소량 투여를 포함)를 최소화하기 위해서 제품에 첨부된 제품설명서의 조제(혼합)와 투여에 대한 설명을 엄격하게 지키는 것이 중요하다. 수입판매원:** 암젠코리아유한회사 (서울특별시 강남구 테헤란로 203, 서울인터내셔널타워 14층). **제품을 처방하시기 전 상세 제품설명서를 참고하여주시기 바랍니다.**

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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 who are 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 (375mg/m²). MabThera 1400mg is allowed for Non-Hodgkin's lymphoma (NHL). MabThera 1400 mg subcutaneous formulation should be administered as subcutaneous injection only, over approximately 5 minutes. Premedication consisting of an anti-pyretic and an antihistaminic, 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/Rituxan SC should be injected subcutaneously into the abdominal wall and never into 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 subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of 1400 mg irrespective 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 formulation 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 8cycles. 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. In 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 patient. **Special warnings** The use of MabThera subcutaneous formulation as monotherapy in patients with stage III-IV follicular lymphoma who are chemoresistant or 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 symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated. If any doubt exists, 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, stabilisation 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 infusion/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. This 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 with 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 characterised 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, hyperphosphatemia, 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 which 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 or ruled out. Patients who treated after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome. Like Chronic lymphocytic leukemia, Patients with a high tumor burden or with a high number (≥ 25 x 10⁹/L) of circulating malignant cells, who may be at 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 x 10⁹/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 for 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 bronchospasm in 10 % 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 bronchodilators, 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 pruritus, rash and injections 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 formulation 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 resuscitation 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 reversible thrombocytopenia. Since hypotension may occur during MabThera administration, withholding anti-hypertensive medicines 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 < 1.5 x 10⁹/L and/or platelet counts < 75 x 10⁹/L as clinical experience in this population is limited. The MabThera intravenous formulation has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable 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 hemptitis** 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. 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.These 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 NHL and CLL. The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. **Immunisation** The safety of immunisation 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 had been reported from specific group of patients who had administrated MabThera, which had fatal outcome. These reactions occured after 1 to 13 weeks after beginning of treatment. Patients with these reactions should discontinue MabThera and examinned immediately. Skin biopsy is useful to distinguish with other skin reaction and make decision for the sequential treatment. Adverse events reported as mucocutaneous reaction include paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichen dermatitis, Blister 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 an event, with suspected relationship to MabThera, treatment should be permanently discontinued. **Precautions for use** Patients with Infection. Patients with History of cardiac disease, Patients with Lung infiltration, Pulmonary insufficiency or history of pulmonary insufficiency. Patients with Severe myelosuppression or marrow infiltration in cancer cell. Patients administrating anti-hypertensive medicines. Patients with history of drug-hypersensitivity. Patients who has lymphocyte count <1.5 X 10⁹ and/or platelet count <7.5 x 10⁹

MabThera SC–2018-03-07–2.0

For more detailed product information and/or reporting product-related adverse events, Please contact Roche Korea(02-3451-3600)
For the latest product information, please refer to Roche Korea website (www.roche.co.kr)
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CD30 TARGETED
PROVEN EFFECTIVE[1-4]

In relapsed or refractory sALCL[3,6]

86% ORR

59% CR

55.1 MONTHS MEDIAN OS
(95% CI, 21.3 – not estimable)

In relapsed or refractory Hodgkin lymphoma with prior ASCT[1,5]

75% ORR

34% CR

40.5 MONTHS MEDIAN OS
(95% CI, 28.7 – not estimable)

7

보험 급여 기준	비호지킨림프종에 brentuximab 단독요법 (2차 이상)
	호지킨림프종에 brentuximab 단독요법 (3차 이상)
보험 약가	3,262,400원/바이알

PRESCRIBING INFORMATION

[원료약품 및 그 분량] 1. 바이알 중 주성분 브렌툭시맙 베도틴(벌규) 50mg **[효능효과]** 1. 자가조혈모세포이식(Autologous Stem Cell Transplant, ASCT)을 실패하거나 자가조혈모세포이식 비대상 환자에서의 최소 두 가지 이상의 이전 복합 화학요법에 실패한 호지킨 림프종 환자의 치료 2. 최소 한가지 이상의 이전 복합 화학요법에 실패한 전신역형성대세포림프종(systemic Anaplastic Large Cell Lymphoma, sALCL) 환자의 치료 3. 자가조혈모세포이식 이후 재발 또는 진행의 위험이 높은(1차 치료에 불응성이거나 1차 치료 후 1년 이내에 재발한 경우 혹은 자가조혈모세포 이식 전 림프절 이외의 부분에 종양 발생) 호지킨 림프종 환자의 치료 **[용법용량]** 이 약은 항암제 사용에 숙련된 의사의 감독 하에 투여해야 한다. 1. 용량 및 용량 조절 1) 용량: 이 약은 1.8mg/kg을 3주마다 30분에 걸쳐 정맥 내 주입으로 투여한다. 신장애 및 간장애 환자는 다음에 주의하여 사용한다. 중증 신장애 환자에서의 권장 시작 용량은 1.2mg/kg으로 3주마다 30분에 걸쳐 정맥 내 주입으로 투여한다. 신장애가 있는 환자는 유해사례에 대해 면밀히 모니터링해야 한다. 간장애 환자에서의 권장 시작 용량은 1.2mg/kg으로 3주마다 30분에 걸쳐 정맥 내 주입으로 투여한다. 간장애가 있는 환자는 유해사례에 대해 면밀히 모니터링해야 한다. 환자의 체중이 100kg을 초과한다면, 체중 100kg에 해당하는 용량을 사용해야 한다. 안정적인 질병 또는 그보다 양호한 상태에 도달한 환자는 최소 8주기 그리고 최대 16주기(약 1년)를 받아야 한다. 자가조혈모세포이식 이후에 재발 또는 진행의 위험이 높은 호지킨 림프종 환자들은 의학적 진단에 근거하여 ASCT 후 회복 후에 치료를 시작해야 한다. 이 환자들은 16주기까지의 치료를 받아야 한다. 이전에 이 약의 투여시 효과가 있었던 재발 또는 불응성의 호지킨림프종 혹은 전신역형성대세포림프종환자에게 재투여(retreatment)시의 권장시작 용량은 1.8mg/kg으로 3주마다 30분에 걸쳐 정맥 내 주입으로 투여한다. 대신에 최종내약용량으로 투여를 시작해도 좋다. 2) 용량 조절: 호중구 감소증: 치료 도중 호중구 감소증이 발생한다면 투여를 연기하여 호중구 감소증을 관리해야 한다. 말초 신경병증: 치료 도중 말초 감각 또는 운동 신경병증이 나타나거나 악화되는 경우 적절한 투여 권고사항을 참조하여 관리해야 한다. 2. 투여방법: 이 약은 30분에 걸쳐 정맥 내 주입한다. 이 약은 정맥 내 급속 또는 일시로 투여해서는 안 된다. 이 약은 전용 정맥 내 라인을 통해 투여해야 하며 다른 의약품과 섞으면 안 된다. **[사용상의 주의사항]** 1. 경고: 1) 진행성 다초점 백질뇌병증 (Progressive multifocal leukoencephalopathy, PML): 이 약으로 치료받은 환자에서 진행성 다초점백질뇌병증(PML) 및 사망을 초래하는 John Cunningham virus(JCV) 재활성화가 발생할 수 있다. PML은 이러 이전 화학요법을 받은 후 이 치료를 받은 환자에서 보고되었다. 2) 췌장염: 이 약으로 치료받은 환자에서 급성 췌장염이 관찰되었다. 치명적 결과가 보고되었다. 급성 췌장염을 시사하는 것일 수 있는 새로운 또는 악화되는 복부 통증에 대해 환자를 면밀히 모니터링해야 한다. 3) 폐독성: 이 약을 투여받은 환자에서 폐독성 사례가 보고되었다. 이 약과의 상관관계는 확립되지 않았으나 폐독성의 위험은 배제될수 없다. 새로운 또는 악화되는 폐증상(예. 기침, 호흡곤란)이 나타날 경우에는 즉각적인 진단평가가 행해져야 하며 환자는 적절하게 치료되어야만 한다. 4) 중대한 감염 및 기회감염: 이 약으로 치료받은 환자에서 폐렴, 포도알균혈증, 패혈증/패혈성 쇼크(치명적결과 포함) 및 대상포진과 같은 중대한 감염, 그리고 사람 패로자충 폐렴 및 구강 칸디다증과 같은 기회감염이 보고되었다. 5) 주입 관련 반응: 2상에서는 11%, 3상에서는 15%가 보고되었으며, 두통, 발진, 요통, 구토, 오한, 오심, 호흡곤란 및 가려움증, 그리고 기침 이었다. 6) 종양 용해 증후군 : 이 약 사용 시 종양용해 증후군(Tumour lysis syndrome)이 보고되었다. 급속하게 증식하는 종양 및 높은 종양 부담이 있는 환자는 종양 용해 증후군의 위험이 있다. 7) 말초 신경 병증: 이 약치료는 주로 감각 말초 신경병증을 유발할 수 있다. 말초 운동 신경병증의 사례도 보고 되었다. 이 약으로 유발된 말초 신경병증은 이 약에 대한 누적 노출의 영향인 것이 일반적이며 대부분의 경우 가역적이다. 2상 임상시험에서, 최종 평가 시점에 환자의 대다수가(62%) 말초 신경병증 증상이 개선 또는 해소되었다. 8) 혈액학적 독성: 이 약 사용시 3등급 또는 4등급 빈혈, 혈소판 감소증 및 호중구(ANC) 3등급 또는 4등급 호중구 감소증이 발생할 수 있다. 9) 발열성 호중구 감소증: 이 약 치료 시 발열성 호중구 감소증(절대 호중구 수 <1.0 x 10⁹/L, 열 38.5℃)을 동반하면서 임상적으로 또는 미생물학적으로 기록된 감염이 없는 기원 불명의 열이 보고되었다. 10) 스티븐스-존슨 증후군, 독성표피괴사용해: 이 약 사용 시 스티븐스-존슨 증후군(Stevens-Johnson syndrome)과 독성표피괴사용해(toxic epidermal necrolysis)가 보고되었다. 치명적 결과가 보고되었다. 스티븐스-존슨 증후군 또는 독성표피괴사용해가 발생하면 이 약치료를 중단해야 하며 적절한 의학적 요법을 실시해야 한다. 2. 금기: 1) 이 약의 주성분이나 부형제에 과민반응이 있는 환자 2) 블레오마이신(Bleomycin)과 이 약의 병용은 폐독성을 유발한다. 3. 신중 투여: 1) 간기능: ALT(alanine aminotransferase), AST(aspartate aminotransferase)의 상승이 보고되었다. 2) 고혈당증 환자 : 당뇨병의 병력이 있거나 또는 없으며 체질량지수(BMI)가 상승한 환자의 임상시험 도중 고혈당증이 보고되었다. 3) 신장애 및 간장애 환자 : 신장애 및 간장애가 있는 환자들의 사용 경험은 제한적이다. 이용 가능한 자료에 의하면 MMAE(monomethyl auristatin E) 청소율은 중등 간장애와 간장애에 의해, 그리고 낮은 혈청 알부민 농도에 의해 영향을 받을 수 있는 것으로 나타났다. 4. 이상반응: 1) 안전성 프로파일의 요약, 이 약의 안전성 프로파일은 이용 가능한 임상시험 자료, Named Patient Program(NPP)* 및 지금까지의 시판 후 사용 경험을 기반으로 하고 있다. 다음의 내용 및 허가사항 내 표에 기재된 이상반응의 빈도는 임상시험으로부터 생성된 자료를 기반으로 결정되었다. 이 약은 재발 및 불응성의 호지킨림프종 환자 219명과 재발한 전신역형성대세포림프종 환자 89명에게 반복투여되었다.(retreatment) (SGN35-006) 투여횟수의 중간값은 7이었다. (투여횟수의 범위 2 – 37)이 약은 무작위, 위약대조 3상 임상시험(SGN35-005)에서 자가조혈모세포 이식 후 재발 또는 진행의 위험이 있는 환자 329명 중 167명에게 단독요법으로 투여되었다. 대조군 및 시험군에서 투여횟수의 중간값은 15였다. 이 약물로 치료받은 환자에서 중대한 감염 및 기회감염이 보고되었다. 환자의 16%가 감염을 나타내는 이상반응이 보고되었다. 중대한 이상약물반응은 다음과 같았다 : 폐렴, 급성 호흡곤란 증후군, 두통, 호중구 감소증, 혈소판 감소증, 빈血, 설사, 구토, 오심, 열, 말초 운동 신경병증 및 말초 감각 신경병증, 고혈당증, 탈수초 다발성 신경병증, 중앙 용해 증후군 및 스티븐스-존슨 증후군. 가장 빈번하게 관찰된 이상반응은 다음과 같았다 : 말초 감각 신경병증, 피로, 오심, 설사, 호중구 감소증, 구토, 열 및 상기도 감염, 기침. 추가적으로 2상에서는 구토, 열, 3상에서는 말초 운동 신경병증이 빈번하게 관찰된 이상반응이었다.(20%이상). 이 약을 투여받은 환자의 중 2상에서 23%, 3상에서 32%가 이상반응으로 치료를 중단했다. 두명 이상의 호지킨림프종(HL) 또는 전신역형성대세포림프종(sALCL) 환자들에서 치료 중단을 초래한 중대한 이상반응은 말초 감각 (6%) 및 말초 운동 신경병증(2%), 감각이상, 구토, 급성호흡곤란증후군이었다. 5. 일반적 주의: 1)부형제의 나트륨 함유: 이 약은 투여당 단 나트륨을 최대 2.1mmol(또는 47mg)을 함유한다. 나트륨 식이 통제 중인 환자의 경우 고려해야 한다. 2) 운전 및 기계사용 능력에 대한 영향: 이 약은 운전 및 기계사용 능력에 가벼운 영향을 미칠 수 있다. 6. 상호작용: 1)CYP3A4 경로를 통해 대사되는 약약품과의 상호작용(CYP3A4 억제제/유도제): 강력한 CYP3A4 및 P-gp 억제제인 케토코나졸과 이 약의 병용은 항-미세소관제인 MMAE에 대한 노출을 약 73% 증가시켰으며, 이 약에 대한 혈장 노출을 변화시키지 않았다. *Named Patient Program : 품목허가 전 환자의 요청에 의한 사용 **[보장단위]** 바이알/병 **[저장방법]** 밀봉 용기, 2~8℃에서 보관 **[수입자]** 한국다케다제약주식회사 서울특별시 강남구 테헤란로 98길 8, 12층 (대치동) 전화 : (02)3484-0800 **[제조원]** : Takeda Austria GmbH, St. Peter-Straße 25, A-4020 Linz, Austria **[라벨 및 포장제조원]** : 1) Takeda Italia Farmaceutici S.P.A./ Via Crosa, 86, Cerano, 28065, Italy 2) Takeda Austria GmbH, St. Peter-Straße 25, A-4020 Linz, Austria *더 자세한 제품정보는 식품의약품안전처 홈페이지 (http://ezdrugs.mfds.go.kr/kfda2)의 제품 허가사항을 참조하시기 바랍니다.

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Takeda
한국다케다제약주식회사
서울특별시 강남구 테헤란로 98길 8 (대치동 945-10 KT&G 대치타워) 12층
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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.[2]

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]

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카프롤리스™주 제품요약정보

제품명: 카프롤리스주60밀리그램, 30밀리그램(카르필조밉). **효능효과:** 이전에 한 가지 이상의 치료를 받은 다발성골수종 환자의 치료에 레날리도마이드 및 덱사메타손과의 병용요법 **용법용량:** 3주 동안 매주 2일 연속으로 투여 후 12일간 휴약하여 총 28일을 1 치료주기로 한다. 첫 번째 주기의 1일, 2일에 20mg/m²의 시작용량으로 투여한다. **[레날리도마이드 및 덱사메타손과의 병용요법]** 10분 동안 정맥내 주입으로 투여. 시작 용량 투여 후, 첫 번째 주기의 8일에 목표 용량 27mg/m²로 증량한다. 13주기부터는 8일과 9일에 투여하지 않으며 18 주기 이후에는 투여를 중단한다. 레날리도마이드는 1-21일에 25mg을 경구 투여하고, 덱사메타손은 28일 주기의 1일, 8일, 15일, 22일에 40mg을 경구 또는 정맥투여한다. **[덱사메타손과의 병용요법]** 30분동안 정맥내 주입으로 투여. 시작용량 투여 후, 첫 번째 주기의 8일에 목표용량 56mg/m²로 증량한다. 매 28일 주기의 1, 2, 8, 9, 15, 16, 22, 23일에 덱사메타손 20mg을 경구 또는 정맥투여 한다. **다음 환자에게는 투여하지 말 것:** 이 약의 주성분 또는 다른 성분에 과민반응이 있는 환자. **이상반응:** [레날리도마이드 및 덱사메타손과의 병용요법] 임상시험에서 10% 이상 보고된 이상반응은 빈혈, 호중구감소증, 혈소판감소증, 설사, 변비, 구역, 피로, 발열, 말초부종, 무력증, 상기도감염, 비인두염, 기관지염, 폐렴, 저칼륨혈증, 저칼슘혈증, 고혈당증, 근육경련, 기타 미분류 말초신경병증, 불면증, 기침, 호흡곤란, 발진, 정맥색전증 및 혈전증, 고혈압이었고, 10% 이상 보고된 3-4등급 임상검사치 이상은 림프구, 절대호중구수, 인, 혈소판, 총 백혈구수, 헤모글로빈, 칼륨 감소이었다. [덱사메타손과의 병용요법] 임상시험에서 10% 이상 보고된 이상반응은 빈혈, 혈소판감소증, 설사, 구역, 변비, 구토, 피로, 발열, 말초부종, 무력증, 상기도감염, 기관지염, 비인두염, 근육경련, 요통, 두통, 말초신경병증, 불면증, 호흡곤란, 기침, 고혈압이었고, 10% 이상 보고된 3-4등급 임상검사치 이상은 림프구수, 헤모글로빈, 혈소판, 인, 크레아티닌 청소율 감소 및 요산, 칼륨증가이었다. 시판 후 용혈요독증후군 (HUS), 위장관 천공, 심낭염이 자발보고 되었다. **일반적 주의:** 심장독성, 급성신부전, 종양용해증후군, 폐독성, 폐동맥고혈압, 호흡곤란, 고혈압, 정맥혈전증, 주입반응, 출혈, 혈소판감소증, 간독성 및 간부전, 혈전성 미세혈관병증, 가역성 후두부 뇌병증 증후군(PRES), 배태자독성이 발생할 수 있으므로 모니터링, 용량감량, 투여중지, 중단 등의 필요한 의학적 조치를 취하여야 한다. **임부 및 수유부:** 작용기전과 동물시험 결과로 볼 때, 태아독성을 야기할수 있으므로 적절한 피임 조치를 해야 한다. 임신 중 사용하거나 환자가 투약 중에 임신하게 되면, 환자에게 태아에 위험이 있음을 알려야 한다. **보관 및 취급상의 주의사항:** 차광 냉장 (2-8℃) 보관. **정맥 투여를 위한 재구성 및 조제방법:** 과량투여를 막기위해 투여량 계산에 주의해야 하며, 재구성하기 전 조제방법을 숙지하여야 한다. **수입판매원:** 암젠코리아유한회사 (서울특별시 강남구 테헤란로 203, 서울인터내셔널타워 14층). **제품을 처방하시기 전 상세 제품설명서를 참고하여주시기 바랍니다.**

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