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44th Sysmex Scientific Seminar

Explanatory Material for Lectures

Blood Disease: Weaving Tomorrow's Healthcare Through Diagnosis

June 4th, 2022(Sat)

Objective of the Seminar

The advancement of various innovative technologies has led to continuous breakthrough in the diagnosis, treatment, and pathophysiology of many diseases. Blood is composed of blood cells and plasma, and not only plays an important role in maintaining homeostasis of the human body, but also helps grasp its health condition. Therefore, it is not an overstatement to say that blood test is the most used test in daily medical practice. In recent years, blood-based molecular diagnostics are becoming more important as the molecular abnormalities involved in the onset and progression of many diseases have been clarified.

Particularly in hematological diseases, a large number of molecular abnormalities have been identified besides malignancies. Therefore, it is the most advanced disease area for practical application in not only diagnostics, but also other daily medical practices including prognosis prediction, evaluation of therapeutic effect, and early prediction of recurrence. Among the various hematological diseases, this seminar will focus on genome medicine in hematopoietic tumors, minimal residual tumor cells, liquid biopsy, and hemostatic monitoring. We hope this serves as an opportunity to share the tomorrow of blood disease practice that innovative diagnostic technologies "weave" for us.

Prof. **Hitoshi Kiyoi**, Planner of the 44th Sysmex Scientific Seminar

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(titles omitted)

Lecture 1

Tokyo

10 :05 ～11 :10 (15-minute Q&A session) *JST

Future Direction of Genome Medicine in Hematologic Malignancies

Keisuke Kataoka M.D., Ph.D.

Professor, Division of Hematology, Department of Medicine, Keio University School of Medicine

Chief, Division of Molecular Oncology, National Cancer Center Research Institute

Summary

Although the healthcare system for cancer precision medicine has been established in Japan for the past few years, it mainly focuses on solid cancers. In hematologic malignancies, such as leukemia and lymphoma, driver genes targeted by somatic alterations are different from those in solid cancers. Clinical sequencing has been performed mainly for identifying therapeutic targets in solid cancers. Besides this purpose, it is useful in diagnosis and prognostic prediction for hematologic malignancies. Therefore, different strategy and next-generation sequencing (NGS) panel are needed for precision medicine in hematologic malignancies. In this presentation, I summarize the clinical relevance of somatic alterations and the underlying scientific basis in hematologic malignancies.

Explanatory material

Cancer genomic medicine: precision medicine

"Cancer genomic medicine" refers to medicine that provides "personalized care" suited to individual patients' constitutions and disease states, capitalizing on their "genomic information" identified by next-generation sequencing and other measures. To be specific, results of quality- and reliability-assured genomic testing and other various health information are used as a basis to establish a diagnosis, to select the most promising preventive and treatment strategies, and to estimate the disease onset for each individual. Taking an example of the epidermal growth factor receptor (EGFR) inhibitor gefitinib, public health insurance coverage was first approved in the treatment of inoperable nonsmall cell lung cancer, but the response rate remained 20%–30%. This drug was later found to be effective only in treating nonsmall cell lung cancer with *EGFR* gene mutation, and the indication was changed accordingly. The response rate then increased up to approximately 70%–80%. This episode indicates that selection and stratification of probable responders among patients based on their genomic information can lead to the avoidance of medical therapy to poor responders and therefore higher drug effectiveness. Examination for single gene abnormalities had been possible using companion diagnostics; recently, the advent of next-generation sequencing has enabled simultaneous assessment of numerous cancer-related genes.

Genomic abnormalities in malignancies

All malignancies, including hematopoietic tumors, arise through the acquisition of somatic cell abnormality that causes a functional change in genes related to cancer development and progression. Large-scale comprehensive genome sequencing has been done lately in the projects by The Cancer Genome Atlas of the United States, the International Cancer Genome Consortium comprising cancer research institutes worldwide, and others. In Japan, we have mainly focused our genetic analysis on adult T-cell leukemia/lymphoma, a common malignancy among Japanese, and have identified various new genomic abnormalities. These efforts together have led to the accumulation of genomic analysis data from several hundreds of thousands of cases regarding malignancies of over 100 different histologic types, and the collection of such data is continuously expanding. With the use of these data, the whole picture of genomic abnormalities (e.g., genetic variants, copy number variants, chromosomal rearrangements) is being uncovered, and the biological process that leads to tumorigenesis is being unraveled. Additionally, several potential therapeutic targets and biomarkers that affect treatment responses and outcomes have been identified.

Clinical significance of genomic medicine in hematological malignancies

Regarding genomic testing for solid cancers, the "Clinical practice guidance for next-generation sequencing in cancer diagnosis and treatment (Edition 1.0)" was jointly released in 2017 by the Japanese Society of Medical Oncology, Japanese Society of Clinical Oncology, and Japanese Cancer Association. In 2018, the Japanese Society of Hematology (JSH) issued separate guidelines for hematopoietic tumors, the "Guidelines for genomic testing for tumors of hematopoietic and lymphoid tissues" (http://www.jshem.or.jp/genomgl/), on the basis of their standpoint on genomic testing for hematological malignancies, which differed from that reflected in the above solid tumor guidelines. The JSH guidelines provide not only clinically significant gene mutations in hematopoietic tumors selected on the basis of the latest published evidence and information that constitutes the basis of gene panel testing-based genomic medicine but also detailed descriptions of its clinical utility. Gene panel testing in hematopoietic tumors is especially distinct from that in solid tumors in its usefulness in "diagnosing," "selecting treatment," and "predicting prognosis." These clinical utilities have been demonstrated in various prospective studies. It is awaited that gene panel testing for hematopoietic tumors will be applied in clinical practice in Japan as well.

【Reference】 As of Nov. 30, 2021

- Koya J, Saito Y, Kataoka K (corresponding), et al. Single-cell analysis of the multicellular ecosystem in viral carcinogenesis by HTLV-1. Blood Cancer Discov. 2021; 2(5): 450-467.
- Saito Y, Koya J, Kataoka K (corresponding), et al. Landscape and function of multiple mutations within individual oncogenes. Nature. 2020; 582(7810): 95-99.
- Watatani Y, Sato Y, Kataoka K (corresponding), et al. Molecular heterogeneity in peripheral T-cell lymphoma, not otherwise specified revealed by comprehensive genetic profiling. Leukemia. 2019; 33(12): 2867-2883.
- Kataoka K, Shiraishi Y, Ogawa S, et al. Aberrant PD-L1 expression through 3'-UTR disruption in multiple cancers. Nature. 2016; 534(7607): 402-406.
- Kataoka K, Nagata Y, Ogawa S, et al. Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet. 2015; 47(11): 1304-1315.

Lecture 2

Kobe
11 :10 ～12 :15 (15-minute Q&A session)*JST

Minimal Residual Disease in Pediatric Leukemia

Takashi Taga M.D., Ph.D.
Clinical Professor, Department of Pediatrics, Shiga University of Medical Science

Summary

The prognosis for pediatric leukemia, especially for acute lymphoblastic leukemia (ALL), which is most popular in pediatric leukemia, has improved, and many patients are expected to be cured. On the other hand, there are not a few refractory and relapsed patients predicted poor prognosis, so it is important to find risk factors for prognosis at an early stage and treat according to these risk factors. As risk stratification, treatment response in addition to the phenotype and genotype of leukemic blasts has been used. Recently, much attention has been focused on minimal residual disease (MRD) as treatment response and prognostic factor. The MRD means detection of "deepness of complete remission" and the detection of MRD involves searching for chimeric transcripts, or specific gene abnormalities by polymerase chain reaction (PCR) and/or specific surface antigens by flow cytometry (FCM) of residual leukemic cells at morphological remission. In this lecture, current status and future directions of MRD study for pediatric leukemia with history of clinical trials is presented.

Explanatory material

Minimal residual disease in leukemia

A healthy human is said to have 10^{12} cells in the bone marrow. Almost all these cells have been replaced with leukemic cells at the time of the initial diagnosis of this disease. Response to leukemia treatment is evaluated by observing the peripheral blood and bone marrow smears using a light microscope. When a sufficient decrease in leukemic cells in number and restoration of normal hematopoiesis are achieved, this condition is called hematological complete remission (CR). In acute lymphoblastic leukemia (ALL), however, it is considered that there are still 10^{10} leukemic cells remaining even at the time of hematological CR following the initial remission–induction therapy. With a light microscope's detection limit for leukemic cells being approximately 10^{-2} (one malignant cell in 100 normal cells), a microscopic assay is not sensitive enough to assess cases where leukemic cells have decreased to fewer than 10^{10}. This disease state remaining at the time of hematological CR is referred to as minimal residual disease (MRD). Recently, the use of the term "measurable residual disease (MRD)" is recommended. The MRD status with the absence of detectable levels of leukemic cells at higher sensitivity is called immunophenotypic CR or molecular CR; this new definition of CR is gaining acceptance.

How to measure MRD

1) Flow cytometry–MRD

As the term indicates, this is a method to measure MRD using flow cytometry (FCM). Leukemic cells are detected using multiparametric FCM on the basis of the phenotype of the leukemic cell surface antigen. This is a widely used method that is capable of analysis within short periods of time but also has shortcomings: not all leukemic cells present abnormal phenotypes; shifts occur between diagnostic phenotypes and relapse/progression phenotypes; the sensitivity is inferior compared with that of the polymerase chain reaction (PCR) assay; and expertise and experience are required to use this method. The measurement sensitivity of the analysis with a ≤6-color flow cytometer is less than 10^{-3}–10^{-4} and that of the EuroFlow Consortium-developed protocol with an eight-color multidimensional flow cytometer is 10^{-4}–10^{-5}.

2) Molecular MRD

A PCR assay is applied to detect and measure DNA or chimeric mRNA specific to leukemic cells. In ALL, a

widely used MRD measurement method is to identify gene sequences specific to T-cell receptor (TCR) or immunoglobulin (Ig) gene rearrangements from the gene sequences of diagnostic leukemic cells (i.e., screening for rearrangement) and based on the results to prepare clone-specific (allele-specific oligonucleotide, ASO) primers and then measure MRD in post-therapy samples using real-time quantitative PCR (RQ-PCR). For the screening for rearrangement, the PCR assay is done for *IgH, Igk, TCRδ, TCRγ, TCRβ,* and *TAL1* genes, which have been established by the European international joint research company, Biomedical Solutions. By analyzing these genes, 90%–95% of the entire ALL cases can be covered. The RQ-PCR analysis and interpretation of its results are closely specified in the guidelines by EuroMRD (Berlin–Frankfurt–Münster Group's MRD research institution) and standardized. The detection sensitivity is reported to be 10^{-4} at minimum and 10^{-5} at maximum. This method's drawbacks are complicated techniques involved in the procedure and being time consuming for analysis. In Japan, molecular MRD was categorized as a public health insurance-covered procedure in 2019 and can be performed on two occasions except for the initial consultation. A recently developed high-throughput sequencing (HTS)-based MRD detection method is also available. HTS has enabled exhaustive analysis of base sequences of Ig or TCR gene fragments and identification of all clonally rearranged genes that contain ALL-specific sequences and thereupon detection of MRD based on the base sequences in post-therapy samples. The detection sensitivity reaches 10^{-6}; besides, simultaneous detection of all rearranged leukemic cells overcomes the weakness of the conventional assays, i.e., MRD false negativity due to clonal evolution that can occur during the post-treatment monitoring period. Moreover, designing ASO primers is not needed. With these advantages, molecular MRD has the potential to replace current methods for MRD measurement.

In acute myeloid leukemia (AML), mutation of a nucleolar protein nucleophosmin (NPM1) is seen in 25%–30% of all cases and 45%–60% of cases with the normal karyotype. RQ-PCR assessment of mutated *NPM1* transcripts is utilized as MRD measurement. Quantitative assay of *WT1* gene mRNA, although nonspecific, is also applied to MRD analysis since this assay is an insured method and has broad use.

Chimeric fusion genes may be targets for MRD detection, for example, *BCR-ABL* in Philadelphia chromosome-positive cases and *MLL-AF4* in infants for ALL, core-binding factors *RUNX1-RUNX1T1* and *CBFB-MYH11* for AML, and *PML-RARA* for acute promyelocytic leukemia. This methodology is advantageous in terms of cost, techniques, and time required for analysis, with high sensitivity at 10^{-4}–10^{-6}. Its disadvantages are instability due to the use of RNA, careful handling required to avoid possible contaminations, and absence of standardization, resulting in variable sensitivities depending on testing companies, although testing for many of these targets is an insured procedure and can be outsourced to testing companies.

【Reference】 As of Nov. 30, 2021

・ [Japanese] Takashi Taga. MRD in Acute Leukemia, Nippon Rinsho. 2020; 78(3): 447-451.

Lecture 3

Tokyo

13 :30 ～14 :35 (15-minute Q&A session) *JST

Utilization of Liquid Biopsy in Clinical Practice of Hematological Diseases

Akihiro Tomita, M.D., Ph.D.

Senior Professor, Department of Hematology, Fujita Health University School of Medicine

Summary

Advances in next generation sequencing have revealed many genetic alterations in malignant lymphoma (ML). The importance of genetic analysis is being recognized not only in molecular diagnosis but also in the selection of targeted therapy. Tumor biopsy is essential for genetic analysis of ML, but there are some cases in which the tumor biopsy is difficult. In this issue, I would like to outline the current status of "liquid biopsy", a genetic analysis strategy using body fluids of patients, and discuss the usefulness in the clinical setting of ML.

Explanatory material

Genetic abnormalities in malignant lymphomas

It has become known that the accumulation of genetic abnormalities in mature lymphocytes can lead to the onset of malignant lymphoma and that differences in the mature stage of the affected lymphocytes, sites where abnormalities occurred, and types of abnormalities result in different types of the disease. Diffuse large B-cell lymphoma (DLBCL) is the most common form of adult malignant lymphoma, occupying approximately 50% of malignant lymphomas reported in Japan. On the basis of profiles of gene expression and protein expression in tumor cells, DLBCL is currently classified into germinal center B-cell-like DLBCL (GCB type) and activated B-cell-like DLBCL (ABC or non-GCB type).[1] These subgroups are related to clinical symptoms and prognosis and therefore have been considered important in clinical settings. Recent exhaustive genetic mutation studies have revealed the presence of characteristic genetic abnormalities behind respective individual mutations.[2)3)] Evaluation of these abnormalities can lead to pathological diagnosis and further detailed subgrouping of the disease. Moreover, with the recent development of molecular targeting drugs, selection of targeting therapies suited to individual patients' genetic abnormalities and personalized medicine is advancing toward reality.

Liquid biopsy

In the genetic analysis of malignant lymphoma, tumor tissue biopsy is usually essential. Nevertheless, in practice, isolating genes from biopsy specimens is often difficult in cases where lymphomas are situated in hard-to-reach sites, such as the peritoneal cavity and the central nerve, or when tumors are not formed as in cases of intravascular large B-cell lymphoma (IVLBCL). This is where liquid biopsy (LB) comes into play. LB is a new method for tumor biopsy, in which tumor-derived material in the patient's body fluid is isolated and analyzed.[4] In the peripheral blood, the presence of multiple materials has been confirmed that include circulating tumor cells, circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), free RNA, microRNAs, and extracellular vesicles. cfDNA refers to all fragmented DNA in the fluid and includes DNA derived from normal tissue, besides tumor-derived DNA (i.e., ctDNA). Tumor-derived DNA is present not only in plasma but also in saliva, stool, urine, cerebrospinal fluid (CSF), and in other body fluids, such as pleural and ascitic fluids. LB is thus drawing attention as a minimally invasive method to obtain tumor-derived materials.

Use of LB in malignant lymphoma treatment

At our laboratory, we have assessed LB for its effectiveness in the diagnosis of malignant lymphoma and evaluation of post-therapy minimal residual disease. A

study of cfDNA isolated from peripheral blood (plasma) of patients with IVLBCL[5] revealed significantly higher cfDNA concentrations in the patients than in the healthy control subjects and the presence of correlation between cfDNA levels and serum lactate dehydrogenase levels, indicating the potential utility of cfDNA as a biomarker reflecting tumor amount. Additionally, the whole-exome sequencing was possible using cfDNA, with a finding of greater accumulation of tumor-derived DNA in cfDNA samples from patients with IVLBCL and successful profiling of IVLBCL-specific genetic abnormalities. Given those results, we are currently conducting a prospective study on patients with a clinically suspected malignant lymphoma that is hard to diagnose by a regular biopsy to see if it is possible to detect genetic abnormalities characteristic of malignant lymphoma by cfDNA-based gene analysis and if this approach will contribute to diagnosing lymphoma. We have performed another mutation analysis using CSF and have confirmed its potential utility in assisting with detection and diagnosis of lymphoma of the central nervous system, for which biopsy is difficult to perform, via detection of genetic mutations specific to this disease.[6]

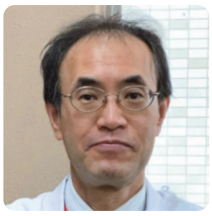
Genetic mutation analysis using LB is likely to be useful in clinical practice as a minimally invasive aid for lymphoma diagnosis. Further accumulation of data is desired regarding forms of lymphoma that are diagnosable by LB and mutation detection sensitivity and specificity, among others.

【Reference】 As of Nov. 30, 2021

1) Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000; 403(6769): 503-511.
2) Wright GW, Huang DW, Phelan JD, et al. A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications. Cancer Cell. 2020; 37(4): 551-568 e514.
3) [Japanese] Akihiro Tomita. Genetic Mutations in Malignant Lymphoma: Clinical Significance and Application in Therapy Development. Jpn J Clin Hematol 2013; 54(10): 1788-1798.
4) [Japanese] Akihiro Tomita. The Present and Future of Liquid Biopsy in Malignant Lymphoma. Hematology. 2020; 81(2): 266-272.
5) Shimada K, Yoshida K, Suzuki Y, et al. Frequent genetic alterations in immune checkpoint-related genes in intravascular large B-cell lymphoma. Blood. 2021; 137(11): 1491-1502.
6) Iriyama C, Murate K, Iba S, et al. Detection of circulating tumor DNA in cerebrospinal fluid prior to diagnosis of spinal cord lymphoma by flow cytometric and cytologic analyses. Ann Hematol. 2021.

Lecture 4

Kobe
14 :55～16 :00(15-minute Q&A session)*JST



Advances and Innovations in Diagnosis and Hemostasis Monitoring on Hemophilia

Keiji Nogami, M.D., Ph. D.
Professor, Department of Pediatrics, Nara Medical University

Summary

Hemophilia A and B is diagnosed, based on the coagulation factor (F)VIII and IX activity, respectively. This disorder is classified into three groups, severe (<1 IU/dL), moderate (1-<5 IU/dL), and mild type (5-<40 IU/dL), since FVIII or FIX activity correlates with the clinical severity. Although this activity is measured by conventional one-stage clotting assay based on activated partial thromboplastin time (aPTT), we often experience cases where the severity of the disease based on the activity level does not correlate with the clinical symptoms. Also, it is difficult to monitor hemostasis potentials when alloantibodies (inhibitors) have appeared, which is one of the serious unmet needs in hemophilia therapy. In addition, although innovative advances have been made in terms of hemostatic products for hemophilia, there are limitations to conventional aPTT-base hemostatic monitoring, as it is not always possible to accurately measure coagulation potential depending on the products. To solve these issues, comprehensive coagulation function measurement has been developed to evaluate hemostatic coagulation function. In particular, coagulation waveform analysis (CWA) can monitor the changes of permeability in plasma sample during fibrin formation in the prothrombin time (PT) and aPTT measurement systems, and depict the entire coagulation process as coagulation waveforms. Computer analysis of the data enables quantitative evaluation of the dynamic process of coagulation and fibrinolysis from this waveform and the obtained parameters. Innovations in coagulation measurement devices have made it possible to more accurately reflect the coagulation assessment of patients with hemophilia, and are now leading to improvements in hemophilia treatment care.

Explanatory material

Hemophilia

Hemophilia is a quantitative and qualitative disorder caused by genetic abnormalities of blood coagulation factor VIII (FVIII, hemophilia A) or factor IX (hemophilia B) and is the most common among the hereditary coagulation disorders. Impaired factor X (FX) activity in the intrinsic FX-activating complex in the coagulation response mechanism results in serious bleeding symptoms, mainly deep bleeding (intra-articular and intramuscular). Repeated intra-articular hemorrhages can lead to the onset of chronic synovitis and eventually irreversible hemophilic arthropathy. Advancement in the antihemophilic drug development and treatment of this disorder has enabled routine factor replacement therapy with the appropriate factor drug to be initiated in childhood for bleeding prophylaxis, reducing the onset risk of arthropathy and thereby contributing greatly to a better quality of life of patients with hemophilia.

Paradigm shift in the treatment

The following issues remain unmet needs in hemophilia treatment: the need for frequent intravenous injections of factor drugs because of their shot half-lives in blood, securing access to a blood vessel, and formation of alloantibodies. To overcome these issues, many drugs with extended half-lives have been commercialized, including a bispecific antibody—a nonclotting factor drug—that mimics the cofactor function of activated FVIII. Additionally, clinical trials for gene therapy are currently underway. There is a paradigm shift ongoing in hemophilia treatment.[1)]

Comprehensive coagulation function testing

In hemophilia, the factor activity level and clinical severity are correlated. By the one-stage clotting assay, the severity of hemophilia is defined on the basis of

factor activity levels as follows: <1 IU/dL, severe; 1–<5 IU/dL, moderate; and 5–<40 IU/dL, mild. In clinical settings, we often encounter severe cases with very mild bleeding symptoms and mild cases with heavy hemorrhagic symptoms.[2] One of the causes of this inconsistency between the factor activity and clinical severity lies in the limitations of the assay. Since the one-stage clotting assay is based on activated partial thromboplastin time (APTT) measured under nonphysiological conditions, there is a limit to assessing the patient's total hemostatic capacity using factor activity levels obtained from this assay alone. Additionally, other clotting factors may affect the clinical severity. Frequent factor drug injections can cause the emergence of alloantibodies (inhibitors), which neutralize the hemostatic effect of the factor replacement therapy. Bypass hemostatic agents are then used to control hemostasis. In this case, because of the difficulty of assessing clotting capacity based on factor activity levels, comprehensive coagulation function testing needs to be performed, which has been handled only at specialized laboratories. In recent years, advances have been made in comprehensive coagulation function tests, including thromboelastography, clot waveform analysis (CWA), and thrombin generation assay.[3] The clotting potential measurement methods have been computerized, enabling qualitative and quantitative evaluation of the coagulation process using various calculation parameters.

Clot waveform analysis

Conventional assays are usually based on prothrombin time (PT) or APTT, both of which only cover the precoagulation phase, i.e., from the addition of calcium till clotting initiation. For higher accuracy, the entire clotting process should be assessed since a clotting reaction proceeds after clotting initiation throughout the coagulation phase, where fibrins are formed at a constant rate, to the postcoagulation phase. CWA is used to monitor changes in the light transmittance rate for the plasma sample during the fibrin formation process in the PT or APTT measurement reaction system and to generate coagulation waveforms for the entire coagulation process.[4] Resulting data are analyzed by the computer; the first and the second derivatives of the coagulation waveform represent the velocity and acceleration of clot formation, respectively, and the maximum value of the first and second derivatives is obtained as an indicator of the maximum velocity (Min1) and the maximum acceleration (Min2) of coagulation, respectively. These coagulation waveforms and parameters allow us to grasp and quantitatively assess the dynamic process of coagulation.

Current status and future prospects

The combination of factor activity measurement and comprehensive coagulation function testing can promote a more accurate understanding of the blood clotting and hemostatic capacity of each patient with hemophilia, and this approach has been introduced and applied in clinical practice.[5] It is now possible to predict hemorrhagic severity and to formulate hemostasis control strategies and, further, long-term hemostasis control strategies for individual patients. We intend to continue to accumulate relevant case data and, on the basis of them, demonstrate the higher utility of comprehensive coagulation capacity testing in clinical settings.

【Reference】 As of Nov. 30, 2021

1) [Japanese] Keiji Nogami. Therapeutic Strategy for Hemophilia A Patients. J. Pediatr. Hematol. Oncol. 2019: 56(3): 282-286.
2) Nogami K, et al. Phenotypic heterogeneity of hemostasis in severe hemophilia. Semin Thromb Hemost. 2015; 41: 826-831.
3) [Japanese] Keiji Nogami. Recent advance in hemophilia practice utilizing the comprehensive coagulation function evaluation. Jpn J Thromb Hemost. 2017; 28(4): 451-459.
4) Shima M, et al. The utility of activated partial thromboplastin time (aPTT) clot waveform analysis in the investigation of hemophilia A patients with very low levels of factor VIII activity (FVIII:C). Thromb Haemost. 2002; 87(3): 436-441.
5) Matsumoto T, et al. A combined approach using global coagulation assays quickly differentiates coagulation disorders with prolonged aPTT and low levels of FVIII activity. Int J Hematol. 2017; 105(2): 174-183.

Program (Each lecture is followed by a 15-minute Q&A session.)

*All times are JST

Kobe 10:00 ▼ 10:05

Opening Address

Yutaka Yatomi Chairman of Sysmex Scientific Seminar planning committee

Tokyo 10:05 ▼ 11:10

Future Direction of Genome Medicine in Hematologic Malignancies

Keisuke Kataoka, M.D., Ph. D.
Professor, Division of Hematology, Department of Medicine, Keio University School of Medicine /
Chief, Division of Molecular Oncology, National Cancer Center Research Institute

Kobe 11:10 ▼ 12:15

Minimal Residual Disease in Pediatric Leukemia

Takashi Taga, M.D., Ph. D.
Clinical Professor, Department of Pediatrics, Shiga University of Medical Science

12:15 – 13:30 Break

Tokyo 13:30 ▼ 14:35

Utilization of Liquid Biopsy in Clinical Practice of Hematological Diseases

Akihiro Tomita, M.D., Ph. D.
Senior Professor, Department of Hematology, Fujita Health University School of Medicine

14:35 – 14:55 Break

Kobe 14:55 ▼ 16:00

Advances and Innovations in Diagnosis and Hemostasis Monitoring on Hemophilia

Keiji Nogami, M.D., Ph. D.
Professor, Department of Pediatrics, Nara Medical University

Kobe 16:00 ▼ 16:05

Closing Address

Hitoshi Kiyoi (Planner of the 44th Sysmex Scientific Seminar)
Professor, Graduate School of Medicine, Nagoya University

Chairpersons

Kobe : Hitoshi Kiyoi, Professor, Graduate School of Medicine, Nagoya University
Tokyo: Tomoki Naoe, Honorary Director, National Hospital Organization Nagoya Medical Center

For registration or details on the 44th Sysmex Scientific Seminar, please contact your local Sysmex office.