News Release

Title

Elucidation of poor prognostic factors in acute myeloid leukemia

- Expected to develop new treatment strategy and improve prognosis -

Key Points

・This study revealed many additional genetic alterations in CBF-AML.

・*KIT* exon 17 mutation is a poor prognostic factor in AML patients with *RUNX1-RUNX1T1*, but not those with *CBFB-MYH11*.

・*NRAS* mutation is a poor prognostic factor in AML patients with CBFB-MYH11.

Summary 1

Hitoshi Kiyoi, Yuichi Ishikawa and Naomi Kawashima at Department of Hematology and Oncology, Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu) demonstrated the clinical significance of *KIT* mutation in core binding factor-acute myeloid leukemia（CBF-AML）patients in collaboration with Japan Adult Leukemia Study Groupe (JALSG).

CBF-AML comprises AML with *RUNX1-RUNX1T1* or *CBFB-MYH11* fusion transcripts and accounts for 20% of AML cases. It is considered as a favorable risk group with a higher remission rate and better overall survival. However, relapse occurs in approximately 40% of patients and the establishment of risk stratification and risk-adapted therapy in CBF-AML is required. To clarify the prognostic factors in CBF-AML, we analyzed mutations in 56 genes and evaluated minimal residual disease (MRD) in 199 newly diagnosed *de novo* CBF-AML patients who were registered into JALSG CBF-AML209-KIT study.

This study identified many additional genetic alterations in CBF-AML patients, and AML with *RUNX1-RUNX1T1* and *CBFB-MYH11* revealed different characteristics in co-existing gene mutations. Relapse-free survival (RFS) in *KIT*-mutated patients was inferior than in unmutated patients in all patients. Subgroup analysis showed that prognostic impact of the *KIT* mutation was observed in patients with *RUNX1-RUNX1T1* and only exon 17 mutation had worth prognostic impact. Multivariate analysis showed that the *KIT* exon 17 mutation in patients with *RUNX1-RUNX1T1*, and *NRAS* mutation in patients with *CBFB-MYH11* were poor prognostic factor for RFS. Moreover, the presence of the MRD was associated with worse RFS in the patients with *CBFB-MYH11*, but not in those with *RUNX1-RUNX1T1*. These results indicate that it is necessary to evaluate separately the prognosis of AML with *RUNX1-RUNX1T1* and *CBFB-MYH11* according to appropriate prognostic factors.

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Summary 2

Core binding factor-acute myeloid leukemia（CBF-AML）is categorized into a favorable risk group with a higher remission rate and better overall survival, however, relapse occurs in approximately 40% of patients. To clarify the prognostic factors in CBF-AML, we analyzed gene mutations and evaluated minimal residual disease (MRD) in 199 newly diagnosed CBF-AML patients who were registered into JALSG CBF-AML209-KIT study. In this study, Relapse-free survival (RFS) in *KIT*-mutated patients was inferior than in unmutated patients in all patients. Subgroup analysis showed that prognostic impact of the *KIT* mutation was observed only in patients with *RUNX1-RUNX1T1*. Multivariate analysis showed that the *KIT* exon 17 mutation in patients with *RUNX1-RUNX1T1*, and *NRAS* mutation the presence of MRD in patients with *CBFB-MYH11* were poor prognostic factor for RFS.

Research Background

Core binding factor-acute myeloid leukemia（CBF-AML）comprises AML with *RUNX1-RUNX1T1* or *CBFB-MYH11* fusion transcripts and accounts for 20% of AML cases and is considered as a favorable risk group with a higher remission rate and better overall survival. However, relapse occurs in approximately 40% of patients and the establishment of risk stratification and risk-adapted therapy in CBF-AML is necessary. Although activating mutations of receptor tyrosine kinase *KIT* are identified in about 30% of CBF-AML patients, prognostic impact of *KIT* mutation on CBF-AML remains controversial. Therefore, a prospective multicenter cooperative study (JALSG CBF-AML209-KIT) was conducted to evaluate the prognostic impact of *KIT* mutation on AML patients with *RUNX1-RUNX1T1* or *CBFB-MYH11*. Furthermore, we evaluated the incidence and clinical relevance of the other gene mutations and prognostic impact of minimal residual disease (MRD).

Research Results

KIT mutation was the most frequently identified, followed by *NRAS, FLT3* and *ASXL2* mutations in AML with *RUNX1-RUNX1T1* and *CBFB-MYH11*; however, the mutation status was different between AML with *RUNX1-RUNX1T1* and *CBFB-MYH11* (Figure 1). *ASXL2, ASXL1, RAD21* and *ZBTB7A* mutations were more frequent in AML with *RUNX1-RUNX1T1* than in that with *CBFB-MYH11*. In contrast, *NRAS, KRAS* and *FLT3*-TKD mutations were more frequent in AML with *CBFB-MYH11* than in that with *RUNX1-RUNX1T1*. Relapse-free

survival (RFS) in *KIT*-mutated patients was inferior than in unmutated patients in all patients. Subgroup analysis showed that prognostic impact of the *KIT* mutation was observed in patients with *RUNX1-RUNX1T1*, but not in those with *CBFB-MYH11*, and only exon 17 mutation had worth prognostic impact (Figure 2). Multivariate analysis showed that the *KIT* exon 17 mutation in patients with *RUNX1-RUNX1T1*, and *NRAS* mutation in patients with *CBFB-MYH11* were poor prognostic factor for RFS (Figure 3). Moreover, the presence of the MRD was associated with worse RFS in the patients with *CBFB-MYH11*, but not in those with *RUNX1-RUNX1T1*. These results indicate that it is necessary to evaluate separately the prognosis of AML with *RUNX1-RUNX1T1* and *CBFB-MYH11* according to appropriate prognostic factors.

Figure 1. Landscape of Gene mutations in CBF-AML

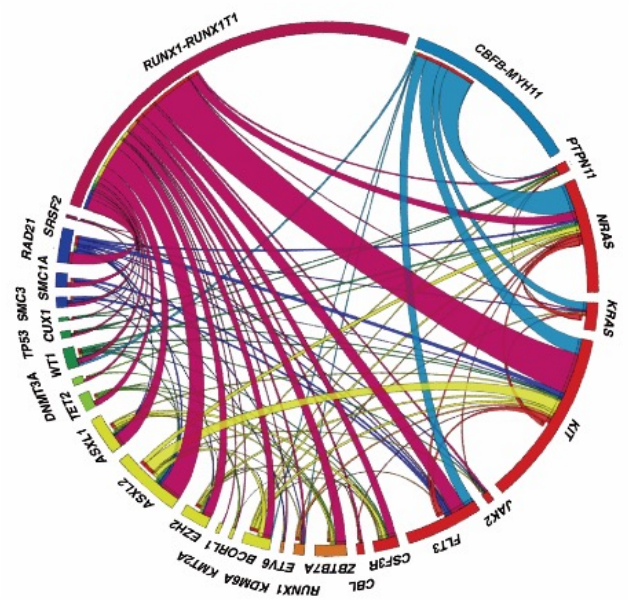
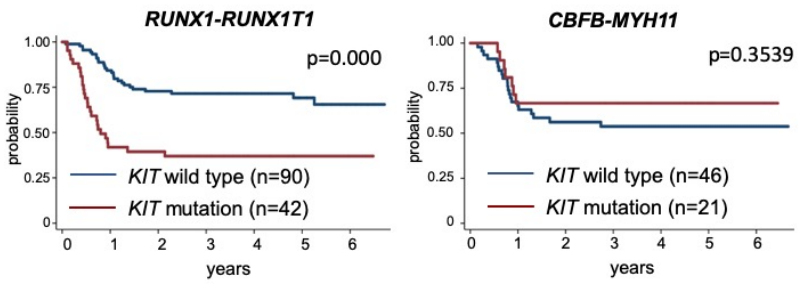
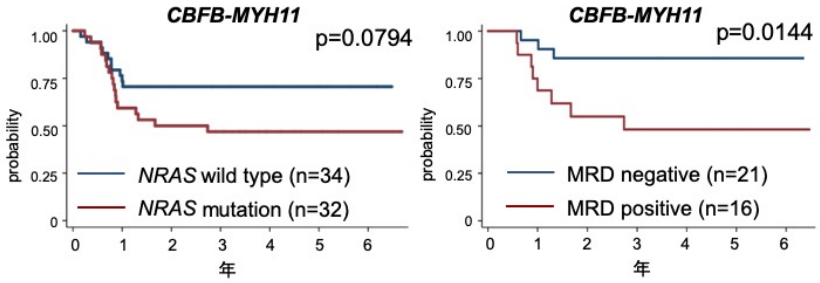


Figure 2. Relapse-free survival according to *KIT* mutation in CBF-AML



		RFS at 2yr. (%)	95% CI
RUNX1-RUNX1T1	KIT wild type	72.8	62.2-80.9
	KIT mutation	39.5	24.7-53.9
CBFB-MYH11	KIT wild type	56.2	40.7-69.1
	KIT mutation	66.7	42.5-82.5

Figure 3. Prognostic factors for relapse-free survival in AML with *CBFB-MYH11*



Multivariate analysis in AML with *CBFB-MYH11*

	Hazard Ratio	95% CI	P value
NRAS mutation	3.93	1.03-15.0	0.05
MRD positive	5.49	1.43-21.0	0.01

Research Summary and Future Perspective

We clarified the prognostic impacts of *KIT* mutation and MRD status in adult AML patients with *RUNX1-RUNX1T1* or *CBFB-MYH11.* The molecular risk presented in this study provides a basis for future clinical trials and research investigations to improve the clinical outcomes of AML.

Publication

Yuichi Ishikawa*, Naomi Kawashima*, Yoshiko Atsuta, Isamu Sugiura, Masashi Sawa, Nobuaki Dobashi, Hisayuki Yokoyama, Noriko Doki, Akihiro Tomita, Toru Kiguchi, Shiro Koh, Heiwa Kanamori, Noriyoshi Iriyama, Akio Kohno, Yukiyoshi Moriuchi, Noboru Asada, Daiki Hirano, Kazuto Togitani, Toru Sakura, Maki Hagihara, Tatsuki Tomikawa, Yasuhisa Yokoyama, Norio Asou, Shigeki Ohtake, Itaru Matsumura, Yasushi Miyazaki, Tomoki Naoe and Hitoshi Kiyoi, for the Japan Adult Leukemia Study Group (*These authors contributed equally to this work), Prospective evaluation of prognostic impact of KIT mutations on acute myeloid leukemia Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan; [3]Division of Hematology and Oncology, Toyohashi Municipal Hospital, Toyohashi, Japan; [4]Department of Hematology and Oncology, Anjo Kosei Hospital, Anjo, Japan; [5]Division of Clinical Oncology and Hematology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [6]Department of Hematology, National Hospital Organization Sendai Medical Center, Sendai, Japan; [7]Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan; [8]Department of Hematology, Fujita Health University School of Medicine, Toyoake, Japan; [9]Department of Hematology, Chugoku Central Hospital, Fukuyama, Japan; [10]Department of Hematology, Fuchu Hospital, Izumi, Japan; [11]Department of Hematology, Kanagawa Cancer Center, Yokohama, Japan; [12]Division of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo,

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Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Blo_Adv_200123.pdf