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Research paper

Hematopoietic stem cell transplantation for pediatric acute myeloid leukemia patients with *KMT2A* rearrangement; A nationwide retrospective analysis in Japan

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ABSTRACT

Objective: Pediatric acute myeloid leukemia (AML) with *KMT2A* rearrangement is detected in 15–20% of all pediatric AML patients and is associated with adverse outcomes even after allogeneic hematopoietic stem cell transplantation (HSCT). To investigate outcomes and prognostic factors, we investigated 90 pediatric AML patients with *KMT2A* rearrangement after allogeneic HSCT.

Methods: We retrospectively analyzed Japanese registration data for patients who had received allogeneic HSCT between 1988 and 2011. Median age was 3 years (range, 0–15 years), and no gender difference was evident. Median observation period was 119 months.

Results: The 3-year overall survival (OS) rate of *KMT2A*-rearranged AML was 52.1% (95% confidence interval (CI), 42.4–64%, n = 90), and the 3-year disease-free survival (DFS) rate was 46.7% (95%CI, 36.8–58.2%). The 3-year DFS of *KMT2A*-rearranged AML was not significantly poorer than that of other AML ($P = 0.09$), and no significant difference was also seen in 3-year OS rate ($P = 0.21$). Multivariate analysis showed disease status (complete remission) at HSCT was associated with better outcomes. A significant difference in treatment-related mortality (TRM) was apparent between HSCT from a HLA full-matched related donor and that from a haploi-

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dentical donor ($P = 0.001$).
Discussion: HSCT is a curative option for pediatric AML with *KMT2A* rearrangement. Pretransplant status was the most significant prognostic indicator for relapse and survival. Enhancing supportive therapy to reduce TRM will further improve treatment outcomes of *KMT2A*-rearranged pediatric AML.

1. Introduction

Cytogenetic abnormalities are a significant prognostic factor in pediatric acute myeloid leukemia (AML) and can help decide treatment strategies [1–3]. Recently, although the prognosis of pediatric AML has improved, 30–40% of cases have failed to achieve long-term remission despite intensive therapy [4]. Pediatric AML is a heterogeneous disease showing variability in morphology, cytogenetic abnormalities, and treatment response. Investigation of the prognosis of AML in association with various chromosomal abnormalities is extremely important for determining treatment strategies.

Cytogenetic abnormalities in 11q23 involving lysine-specific methyltransferase 2A (KMT2A), previously called mixed-lineage leukemia (MLL) gene rearrangements, have been detected in 3–4% of adult AML cases and 15–20% of pediatric AML cases [5]. Recent studies have shown that *KMT2A*-rearranged AML itself is genetically and clinically heterogeneous, as many different translocation partners with differences in prognosis have been described [6,7]. The presence of *KMT2A* rearrangement has been associated with adverse outcomes even after allogeneic hematopoietic stem cell transplantation (HSCT) [1].

To identify the clinical significance of AML with *KMT2A* rearrangement, we should investigate various factors, such as translocation partners, additional cytogenetic aberrations, donor sources, preconditioning regimens, status before HSCT, and so on. This study retrospectively investigated the outcomes and prognostic factors of AML with *KMT2A* rearrangement treated with allogeneic HSCT using a Japanese nationwide database maintained by the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT).

2. Materials and methods

2.1. Patients

We collected clinical data from the Japanese Society of Hematopoietic Cell Transplantation and the JDCHCT using the Transplant Registry Unified Management Program (TRUMP) [8–10]. We selected pediatric AML patients with *KMT2A* rearrangement who received allogeneic HSCT between January 1988 and December 2011. AML with *KMT2A* rearrangement was diagnosed by the presence of 11q23 abnormalities on G-banding analysis and/or *KMT2A* fusion gene detected by PCR (polymerase chain reaction) analysis.

Myeloablative conditioning (MAC) regimens were defined according to the criteria of the Center for International Blood and Marrow Transplant Research, which included a regimen containing either total body irradiation ≥8 Gy, oral busulfan dose ≥9 mg/kg, or intravenous busulfan dose ≥7.2 mg/kg. All other conditioning regimens were defined as reduced-intensity conditioning (RIC) [11].

2.2. Statistical analysis

Overall survival (OS) was defined as the time between diagnosis and death from any cause, and disease-free survival (DFS) was defined as the time from diagnosis to first event, defined as the relapse at any site, death from any cause, or development of a second malignancy. For patients who did not experience an event, DFS was defined as the time from diagnosis to last follow-up. Survival probabilities and 95% confidence intervals (CIs) were estimated by the Kaplan-Meir method. Survival curves were compared by means of log-rank testing. All *P*-values were two-tailed, and the level of statistical significance was $P < 0.05$.

All statistical analyses were performed using 'R' version 3.5.2 statistical software (2018-12-20; The R Foundation for Statistical

Table 1
Patients characteristics.

Characteristic	Value
Number of patients	90
Age at HSCT (year)	
< 10 year, n	66
≥10 years, n	24
Gender	
male, n	49
Female, n	41
FAB classification	
M0, n	1
M1, n	6
M2, n	8
M3, n	0
M4, n	18
M5, n	55
M6, n	0
M7, n	2
Chromosomal abnormalities	
KMT2A/ MLLT3 or t(911), n	14
KMT2A/ MLLT1 or t(1119), n	9
KMT2A/ MLLT11 or t(111), n	3
KMT2A/ MLLT4 or t(611), n	4
KMT2A/ MLLT10 or t(1011), n	4
KMT2A/ AFF1 or t(411), n	2
t(511), n	2
t(711), n	1
t(811), n	1
other *KMT2A* rearrangements, n	50
Etiology	
De novo AML, n	85
Secondary AML, n	5
Year of HSCT	
1988-2005, n	48
2006-2011, n	42
Donor source	
related BM, n	27
matched, n	17
haploidentical, n	10
unrelated BM, n	19
related PB, n	8
matched, n	2
haploidentical, n	6
cord blood, n	36
Conditioning regimen	
RIC, n	11
MAC, n	79
Prognosis	
death, n	50
alive, n	40

HSCT; hematopoietic stem cell transplantation, FAB; French-American-British Classification, BM; bone marrow, PB; peripheral blood, RIC; reduced intensity conditioning, MAC; Myeloablative conditiong.

Computing Platform).

This study was approved by the institutional review board of the Osaka University Graduate School of Medicine.

3. Results

3.1. Patient characteristics

In our study, a total of 102 patients showing AML with *KMTA2* rearrangement were registered to the JHSCT, of whom we analyzed all 90 patients who received allogeneic HSCT. The characteristics of patients and transplant information are described in Table 1. Age at HSCT ranged from 0 to 15 years (median, 3.0 years; average, 5.5 years) and median observation period was 119 months (25–291 months).

No significant difference was seen in sex (male, n = 49; female, n = 41). French-American-British (FAB) classification was as follows: M0, n = 1; M1, n = 6; M2, n = 8; M3, n = 0; M4, n = 18; M5, n = 55; M6, n = 0; and M7, n = 2 Morphologically, FAB classifications M4 and M5 were the most frequent. The 90 patients showed the following *KMT2A* rearrangements: *KMT2A/MLLT3* or t(9,11) in 14 patients; *KMT2A/MLLT1* or t(11,19) in 9 patients; *KMT2A/MLLT11* or t(1,11) in 3 patients; t(6,11) or *KMT2A/MLLT4* in 4 patients; t(10,11) or *KMT2A/MLLT10* in 4 patients; t(4,11) or *KMT2A/AFF1* in 2 patients; t(7,11) in 2 patients; t(5,11) in 1 patient; t(8,11) in 1 patient; and other *KMT2A* rearrangements in 50 patients.

The type of donor sources varied. We classified HSCT according to stem cell sources, as related bone marrow transplantation (RBMT), unrelated BMT (UBMT), related peripheral blood stem cell transplantation (RPBSCT), and cord blood stem cell transplantation (CBSCT). In our survey, 46 patients received BMT, comprising UBMT in 19 patients and RBMT in 27 patients. Ten of these patients received the transplant from a haploidentical related donor. Eight patients received RPBSCT, of whom 2 patients received the transplant from a matched sibling donor. Thirty-four patients received RCBSCT, of whom 2 patients received the transplant from a matched sibling donor. No significant difference in the frequency of treatment-related mortality (TRM) according to donor source was apparent (related HSCT, n = 10; unrelated HSCT, n = 6; CBSCT, n = 10).

Disease status at transplantation was judged as complete remission (CR) in 54 patients, relapse in 26 patients, and inability to achieve CR (i.e., induction failure) in 9 patients.

Five patients were considered to show secondary leukemia. Previous malignancies in each patient were retinoblastoma, osteosarcoma, neuroblastoma, anaplastic large-cell lymphoma, and Epstein-Barr virus-associated lymphoproliferative disorders.

3.2. Outcome of KMT2A-rearranged AML

The 3-year OS rate of *KMT2A*-rearranged AML was 52.1% (95%CI, 42.4–64% n = 102), and the 3-year DFS was 46.3% (95%CI, 36.8–58.2% n = 102), respectively (Fig. 1). The 3-year OS and DFS rates of other AML patients were 57.1% (95%CI, 54.6–59.7%, n = 1521) and 51.7% (95%CI, 49.7–54.3%, n = 1521), respectively. The 3-year DFS of *KMT2A*-rearranged AML was not significantly poorer than that of other AML ($P = 0.09$), and no significant difference was also seen in 3-year OS rate ($P = 0.21$) (Fig. 2).

Forty-four *KMT2A*-rearranged AML patients died in our cohort, due to disease progression in 17 patients, treatment-related toxicity (TRT) in 26 patients and secondary cancer in 1 patient. Details of TRT were as follows: interstitial pneumonia, n = 11; multi-organ failure, n = 5; hemorrhage, n = 2; acute graft-versus-host disease (GVHD), n = 5; chronic GVHD, n = 1; graft failure, n = 1; and sinusoidal obstruction syndrome, n = 1. Acute GVHD grade 2–4 was detected in 38 patients (42.2%). No significant difference in 3-year OS was seen, irrespective of the presence or absence of acute GVHD (P = 0.23) or chronic GVHD (P = 0.56).

3.3. Prognostic factors for KMT2A-rearranged AML

The 3-year OS rate for non-CR patients at transplantation was 24.1% (95%CI, 11.3–51.7%, n = 23), much poorer than those in patients with first CR (CR1) or second CR (CR2) at transplantation, who showed rates of 71.2% (95%CI, 58.6–86.5%, n = 54) and 38.9% (95%CI, 19–79.8%, n = 15), respectively (P < 0.01 each) (Fig. 3).

OS and DFS rates were also analyzed according to donor source. The 3-year OS rates of RBMT (n = 27), RPBSCT (n = 8), UBMT (n = 19), and CBSCT (n = 36) were 57.5% (95%CI, 41.2–80.2%), 25% (95%CI, 7.5–83%), 44.1% (95%CI, 25.7–75.7%), and 58% (95%CI, 43.2–77.9%), respectively. The 3-year DFS rates of RBMT, RPBSCT, UBMT, and CBSCT were 54.1% (95%CI, 38–77.1%), 25% (95%CI,

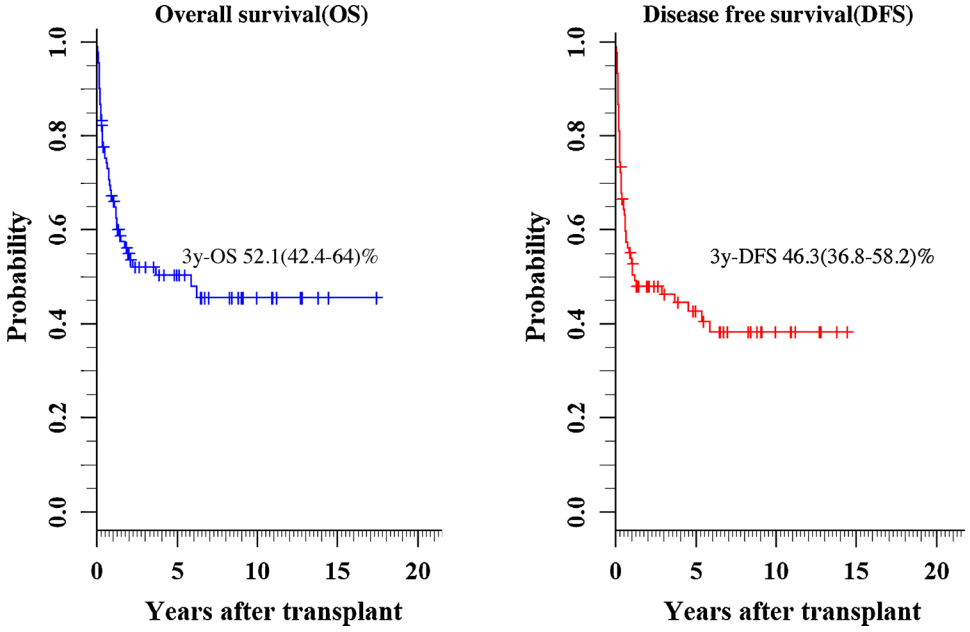

Fig. 1. Overall and disease-free survival rates of pediatric AML with *KMT2A* rearrangement.

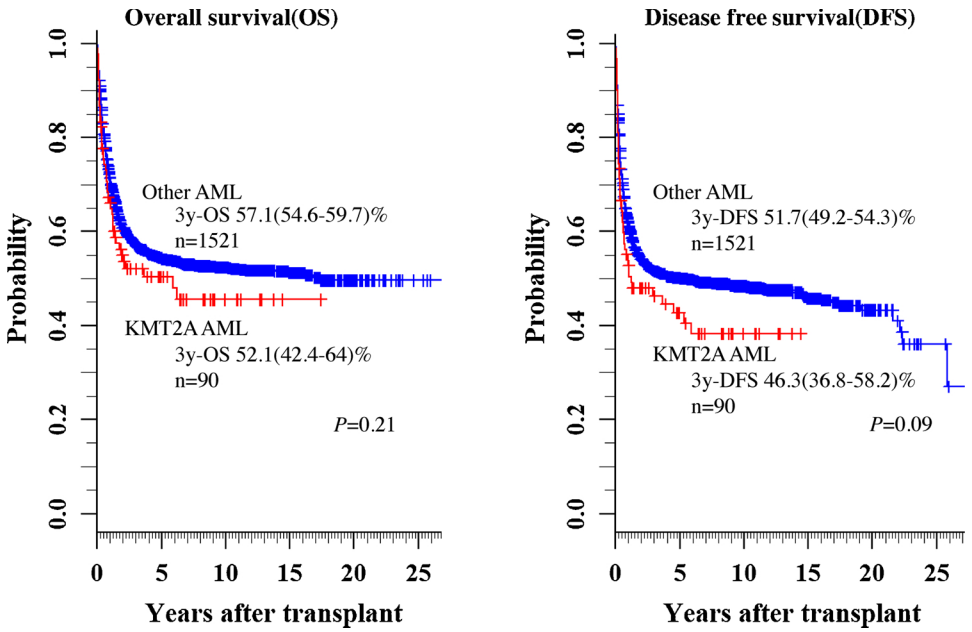

Fig. 2. Overall and disease-free survival rates of pediatric *KMT2A*-rearranged AML and other pediatric AML.

7.5–83%), 36.8% (95%CI, 20.4–66.4%), and 50.6% (95%CI, 35.9–71.2%), respectively. There was no significant difference by donor source.

The type of *KMT2A* fusion partner was not a significant prognostic factor in our cohort. *KMT2A* rearrangements were diagnosed by G-banding analysis or RT-PCR analysis at each institution and registered in our study. Detailed data, such as the partner gene of *KMT2A* or the results of chromosomal analysis, were unavailable for some patients, who have been categorized as "other *KMT2A* rearrangements" in Table 1.

The 3-year OS rate was not significantly difference between the patients who received HSCT by MAC regimen and RIC regimen (RIC: n = 11, 3-year OS 71.6% (95%CI, 48.8–100%); MAC: n = 79, 3-year OS 49.5% (95%CI, 39.3–62.4%, $P = 0.23$). In addition, the 3-year DFS of patients who received RIC regimen was 63.5% (95%CI, 40.7–99.5%), and that of patients who received MAC regimen was 43.7% (95%CI, 33.7–56.6%; $P = 0.26$) (Fig. 4). No significant differences were detected according to the conditioning regimen.

According to the analysis of related HSCT, a significant difference in TRM was seen between HSCT from HLA full matched related donors and haploidentical related donors *(P = 0.001)*, while no difference in leukemia-related mortality was evident (Fig. 5). The cumulative incidence of TRM at 5 years in patients who received HLA full matched HSCT was 0% (n = 16), while that with haploidentical HSCT was 49.0% (n = 19; *P = 0.001)* (Fig. 5a). The cumulative incidence of relapse at 5 years in patients who received HLA full matched HSCT was 25.0% (n = 16), while that with haploidentical HSCT was 22.7% (n = 19; *P = 0.496)* (Fig. 5b).

Multivariate analysis identified non-CR at HSCT as a poor prognostic factor for both OS and DFS rates.

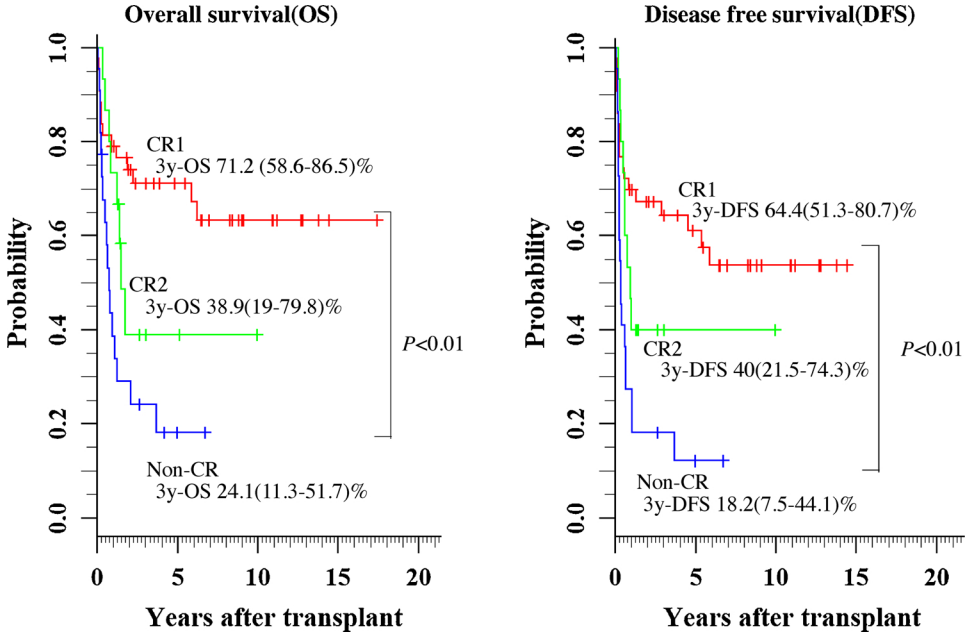

Fig. 3. Overall and disease-free survival rates according to disease status at hematopoietic stem cell transplantation.

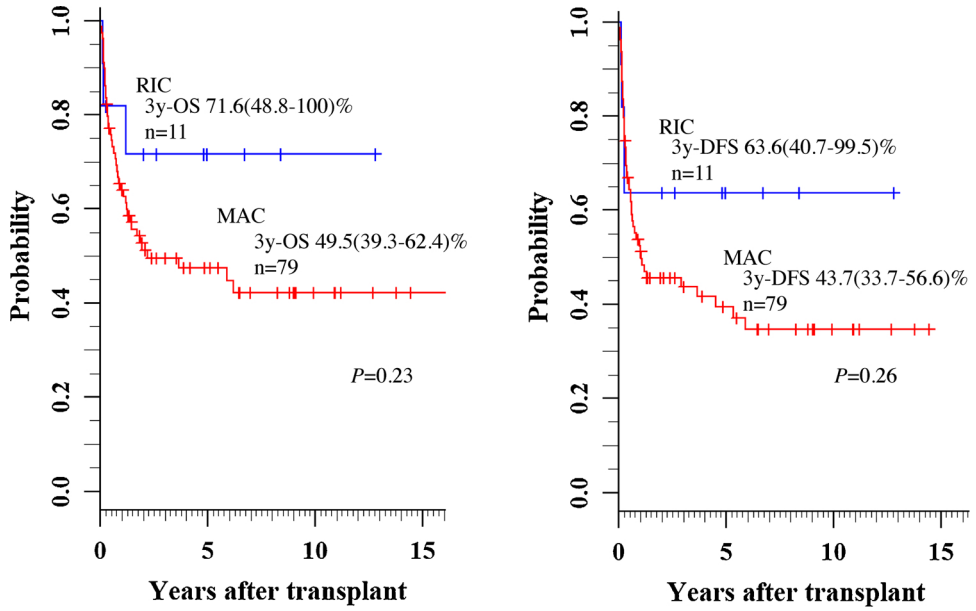

Fig. 4. Overall and disease-free survival rates according to conditioning regimen.

4. Discussion

This study aimed to identify the outcomes and prognostic factors of pediatric AML with *KMT2A* rearrangement who had received HSCT between 1988 and 2011 in Japan. We identified disease status at HSCT as one of the significant prognostic factors. The method of achieving remission before transplantation has thus long been known as an important issue. Not only achieving remission, but also achieving deeper remission (i.e., negative minimal residual disease (MRD) status) is considered important [13–15]. Monitoring of MRD status has been reported as useful to determine the treatment strategy in adult AML [12,13]. Even though having a lower level of MRD prior to transplantation may prove important, achieving a lower level of MRD is actually not easy.

The most common translocation partners in pediatric AML with *KMT2A* rearrangement have been reported as *AF9* in t(9,11), *AF10* in t(10,11), and *ENL* in t(11,19) [16]. Previous reports have indicated that outcomes of pediatric AML with *KMT2A* rearrangement differ significantly according to translocation partners [6,17]. Some reports have demonstrated that AML with t(9,11) was associated with better prognosis, and *AF6* in t(6,11) and *AF10* in t(10,11) were associated with poor prognosis [6]. In our study, although patients with t(9,11) were the most frequently encountered (n = 14), prognosis did not differ significantly from that of other 11q23 abnormalities. There could be various reasons for this. Since our study was a retrospective analysis of *KMT2A*-rearranged pediatric AML patients selected to receive HSCT for some reason, selection bias may have contributed to the lack of difference in transplantation results. No patients with t(6,11) remained alive in CR in our study, and only 1 patient with t(10,11) remained alive in CR.

Although most translocations in this study would fall into the intermediate category according to the modern definition of *KMT2A* rearrangements in AML [18,19], there seemed to be various reasons to perform HSCT. First, 31 patients were non-CR before HSCT (relapse, n = 22; induction failure, n = 9). Since these patients were predicted to experience poor outcomes, they received HSCT. Second, 5 patients

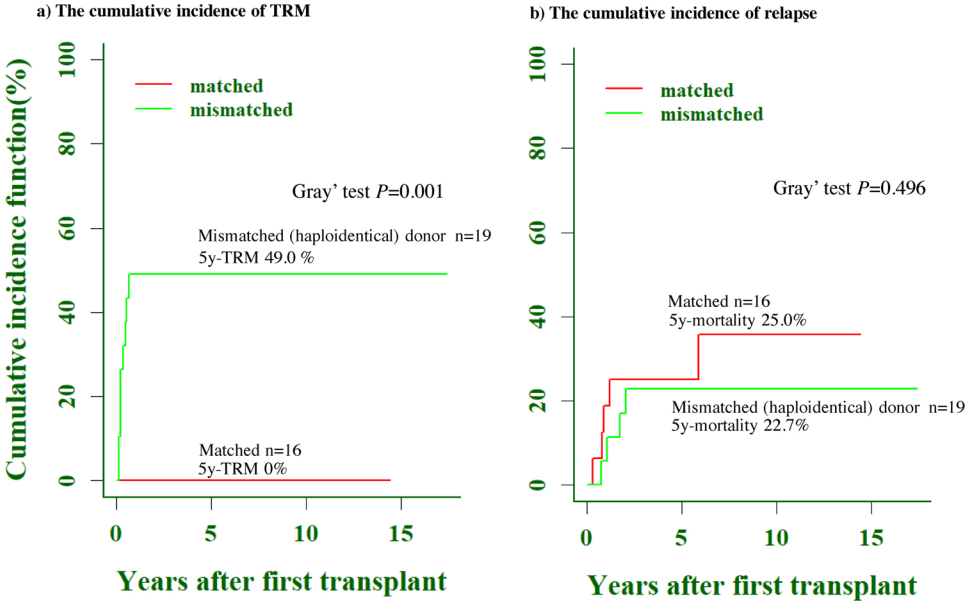

Fig. 5. Cumulative incidence of TRM and relapse in HLA-matched related HSCT and HLA-mismatched related HSCT.
a) Cumulative incidence of TRM.
A significant difference in TRM is evident between HSCT from HLA full matched related donors and from haploidentical related donors. The 5-year TRM with HLA-mismatched HSCT was 49.0% (n = 19), and that with HLA full matched HSCT was 0% (n = 16; P = 0.001).
b) Cumulative incidence of relapse.
No difference in leukemia-related mortality is apparent. The 5-year leukemia-related mortality of patients who received HLA full matched HSCT was 25.0% (n = 16), and that with haploidentical HSCT was 22.7% (n = 19; P = 0.496).

diagnosed with secondary leukemia were also predicted to show poor outcomes. A retrospective European Group for Blood and Marrow Transplantation (EBMT) study demonstrated a 3-year OS of 31% for individuals with secondary AML [20]. Secondary AML is frequently considered to represent an indication for allogeneic HSCT. Third, the prognostic significance of the partner gene of *KMT2A* was established in the 2000s. In the 1980s, allogeneic HSCT was widely recommended for patients with newly diagnosed AML who had a matched sibling donor. In the 1990s, several reports suggested that allogeneic HSCT should not be recommended for low-risk patients, defined as those with APL, ML-DS, t(8,21), or inv (16). However, indications for allogeneic HSCT differed significantly between study groups for the remaining patients [21–25], with some previous reports suggesting dismal prognosis for patients with *KMT2A*/11q23 rearrangements. Other recent reports have suggested that the prognostic significance of the partner gene of *KMT2A* was established around 2000s [26]. In total, 32 patients who received transplants in the 1980s–1990s in our study might be considered to have met the indications for HSCT. Such factors might be meaningful when considering future treatment strategies.

Considering the difficulty of establishing novel treatment strategies to achieve higher remission rates, treatment strategies to reduce TRM may well contribute to the improvement of treatment outcomes.

This study has several limitations that must be considered. First, we had no information about somatic mutation data such as *KIT, FLT3-ITD*, or *MECOM*, which have sometimes of establishing with *KMT2A* mutations [27–31]. Second, we had no data on MRD status. Third, *KMT2A* partial tandem duplications (*KMT2A*-PTD) were not evaluated in this study. This consists of an in-frame repetition of *KMT2A* exons [32]. *KMT2A*-PTD has reportedly been detected in pediatric AML with both normal karyotype and 11q23 abnormalities [33]. Pediatric *KMT2A*-rearranged AML presents with a distinct expression profile as compared with *KMT2A*-PTD [29,34].

In conclusion, HSCT is a curative option for pediatric AML with *KMT2A* rearrangement. Pretransplant status was the most significant prognostic indicator for relapse and survival. Enhancing supportive therapy to reduce TRM and considering the donor source according to risk factors might be useful for improving treatment outcomes of pediatric *KMT2A* rearranged AML.

Contributors

TM: study design, data interpretation, critical revision, and final approval of the manuscript; KK, HI, DT, TT, DH, SA: study design, critical revision; KT: statistical analysis; HG, AH, MI, NF, HN: collection and management of patient data; YO: chair of JDCHCT-AML-WG.

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Declaration of Competing Interest

There are no conflicts to interest to declare.

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