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Original Article

Survival disparities in patients with relapsed core-binding factor acute myeloid leukemia following allogeneic hematopoietic stem cell transplantation

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Abstract: Relapse rate of core-binding factor (CBF) acute myeloid leukemia (AML) is higher than expected. In attempts to investigate the role of hematopoietic stem cell transplantation (HSCT) as post-remission therapy for relapsed CBF-AML patients in second remission (CR2), we have conducted this study. This was a single-center retrospective study of relapsed *de novo* CBF-AML patients over 18 years old undergoing HSCT at CR2 between January 2000 and December 2015. Forty-two patients were divided into 2 groups according to their cytogenetics: 24 in t(8;21) group and 18 in inv(16)/t(16;16) group. When cytogenetic profiles at relapse were compared to those at diagnosis, changes in chromosomal/karyotype abnormalities were observed in 66.7% and 25% of patients with t(8;21) and inv(16)/t(16;16) (P = 0.002). t(8;21) patient relapsed more often compared to inv(16)/t(16;16) patients (P = 0.007) and this translated into shorter overall survival for t(8;21) patients with 30.6% 3-year survival rate after HSCT, compared to inv(16)/t(16;16) patients with 3-year survival rate at 64.5% (P = 0.041). The initial cytogenetics and first remission duration were identified as prognostic factors affecting survival. Among relapsed CBF-AML patients undergoing HSCT, those with t(8;21) are associated with worse prognosis compared to those with inv(16)/t(16;16) and this has to do with failure to achieve durable response with HSCT.

Keywords: Core-binding factor, acute myeloid leukemia, hematopoietic stem cell transplantation, relapse, survival

Introduction

Core binding factor acute myeloid leukemia (CBF-AML) has traditionally been associated with favorable prognosis [1-3]. Such being the case, current consensus does not support benefits of allogeneic hematopoietic stem cell transplantation (HSCT) in first remission (CR_1) for CBF-AML patients [4, 5]. However, recent studies suggested higher than believed relapse rates ranging from 25 to 58% [6, 7] with heterogeneous prognosis according to distinct cytogenetic groups [8]. In a meta-analysis of several German AML trials, Schlenk et al. [9] showed patients with t(8;21) do worse than those with inv(16)/t(16;16) after relapse due to differences in response to salvage treatment. Considerably fewer patients with t(8;21) achieved complete remission (CR) after re-induction compared to those with inv(16)/t(16;16), leading to fewer patients receiving intensive consolidation therapy and this phenomenon translated into significantly inferior survival outcomes for patients with t(8;21). There have been studies reporting these patients with t(8;21) can gain a survival benefit from allogeneic HSCT [7]. However, there lack detailed reports on the role of HSCT as post-remission therapy for relapsed CBF-AML patients in second remission (CR2). To tackle this issue and subsequently establish risk-adaptive therapeutic strategies by characterizing high-risk groups, we have conducted retrospective analyses of relapsed CBF-AML patients undergoing HSCT.

Material and methods

Study design and subjects

This was a retrospective longitudinal cohort study carried out at Seoul National University Hospital. Adult patients over 18 years of age

Table 1. Characteristics of enrolled patients. Differences between groups were assessed using a Student's t-test or one-way analysis of variance for continuous variables, and Pearson chi-square test for categorical variables, as appropriate

	Total (%)	t(8;21) (%)	inv(16) (%)	*p* Value
Baseline characteristics				
N	42	24 (57.1)	18 (42.9)	NA
Male (%)	23 (54.8)	12 (50.0)	11 (61.1)	0.474
FAB				
M0	5 (11.9)	5 (20.8)	0	NA
M1	1 (2.4)	1 (4.2)	0	
M2	12 (28.6)	10 (41.7)	2 (11.1)	
M4	23 (54.8)	8 (33.3)	15 (83.3)	
M5	1 (2.4)	0	1 (5.6)	
At diagnosis				
Age (years)[a]	37 (18-63)	39 (18-63)	34 (19-59)	0.578
BM blast (%)[b]	53.1 (27.2)	46.6 (23.7)	61.7 (29.7)	0.075
WBC count (10^9/L)[b]	30.3 (44.7)	14.2 (12.8)	51.8 (61.2)	0.006
Platelet count (10^9/L)[b]	44.7 (22.2)	40.5 (22.1)	50.2 (21.8)	0.178
Cytogenetics at diagnosis				
Sole	21 (50.0)	11 (54.8)	10 (55.6)	0.533
Combined	21 (50.0)	13 (54.2)	8 (44.4)	
At relapse				
Age (years)[a]	38 (19-64)	40 (19-64)	36 (20-60)	0.642
BM blast (%)[b]	56.1 (28.6)	59.6 (30.0)	52.6 (27.0)	0.482
WBC count (10^9/L)[b]	8.1 (13.6)	8.5 (14.4)	7.6 (12.7)	0.830
Platelet count (10^9/L)[b]	61.6 (53.5)	57.3 (32.6)	67.2 (73.6)	0.560
Cytogenetics at relapse				
Same	23 (54.8)	8 (33.3)	15 (83.3)	0.002
Different	19 (45.2)	16 (66.7)	3 (16.7)	
Increased[c]	10 (52.6)	9 (56.3)	1 (33.3)	
Decreased[c]	9 (47.4)	7 (43.8)	2 (66.7)	

NA, not applicable; FAB, French-American-British classification; BM, bone marrow; WBC, white blood cell. [a]values are presented as median (range); [b]values are presented as mean (± standard deviation); [c]percentage is out of the total number in respective "Different" row.

Table 2. Additional chromosomal aberration

Type	t(8;21) (N = 24)		Type	inv(16) (N = 18)	
	N	%		N	%
As sole	11	45.8	As sole	10	55.6
-Y	5	20.8	Trisomy 22	4	22.2
-X	5	20.8	Trisomy 8	0	0
Others	3	12.5	Others	4	22.2

with *de novo* CBF-AML patients who experienced relapse after being treated with consolidative chemotherapy only after CR_1 and underwent HSCT between January 2000 and December 2015 were included. During the study period, a total of 298 AML patients received HSCT at our institution. Among them, 52 were identified as CBF-AML patients. After excluding 10 patients, 7 for undergoing upfront HSCT and 3 for secondary AML, 42 patients were included for evaluation. These 42 patients were divided into 2 groups according to their cytogenetics, t(8;21) and inv(16)/t(16;16) respectively. This study was conducted according to the Declaration of Helsinki and was approved by the institutional review board at Seoul National University (IRB No. H-1510029-708).

Cytogenetic analyses

The diagnosis of AML was made according to the World Health Organization Classification of Hematopoietic Neoplasms, which requires identification of 20% or more leukemic blasts in the bone marrow [10]. The French-American-British (FAB) classification was used to classify AML phenotypically [11]. All cytogenetic studies were performed at our center, whose satisfactory performance was monitored by a national external quality assurance scheme. Bone marrow cells were cultured for 24 hours then karyotype was analyzed using the standard G-banding technique. The karyotypes were constructed and chromosomal abnormalities were reported in accordance with the International System for Human Cytogenetic Nomenclature [12]. The cytogenetics at relapse was compared to the cytogenetics at AML diagnosis and then was triaged into "same" group or "different" group. The "different" group was further categorized into "increase in chromosomal abnormalities" and "decrease in chromosomal abnormalities" for subgroup analyses.

Table 3. Parameters related to hematopoietic stem cell transplantation. Differences between groups were assessed using a Student's t-test or one-way analysis of variance for continuous variables, and Pearson chi-square test for categorical variables, as appropriate

	Total (%)	t(8;21) (%)	inv(16) (%)	*p* Value
CR_1 to relapse interval[a]	9 (1-49)	8 (1-49)	11 (1-23)	0.866
Relapse to HSCT interval[a]	3 (0-55)	3 (0-8)	4 (2-55)	0.152
Donor				
Matched related	21 (50.0)	11 (45.8)	10 (55.6)	0.772
Matched unrelated	19 (45.2)	12 (50.0)	7 (38.9)	
Others	2 (4.8)	1 (4.2)	1 (5.6)	
Conditioning				
Myeloablative	19 (45.2)	12 (50.0)	7 (38.9)	0.474
Reduced intensity	23 (54.8)	12 (50.0)	11 (61.1)	
Relapse after HSCT	24 (57.1)	18 (75)	6 (33.3)	0.007

CR_1, first remission; HSCT, hematopoietic stem cell transplantation. [a]values are presented as median (range).

Statistical analysis

The overall survival after HSCT (OS) and leukemia free survival after HSCT (LFS) curves were estimated using the Kaplan-Meier method. OSwas defined as the time from the date of HSCT to death of any cause while LFS was derived from the date of HSCT to that of relapse. If patients survived without relapse after HSCT or did not expire, parameters were censored on the latest date of follow-up when no relapse or death was confirmed. Cox proportional hazards model and logistic regression were used to identify significant prognostic indicators for survival. Differences between groups were assessed using a Student's t-test or one-way analysis of variance for continuous variables, and Pearson chi-square test for categorical variables, as appropriate. All data were analyzed using the Statistical Package for the Social Sciences software (IBM® SPSS® Statistics, version 22.0). A *p* value <0.05 was considered to be statistically significant.

Results

Patient characteristics

Table 1 shows the characteristics of 42 relapsed CBF-AML patients included in this study at baseline and at relapse. Cytogenetic abnormalities generally matched morphologic classification by FAB. The patients with t(8;21) tended to be a little older than those with inv(16)/t(16;16) both at diagnosis and at relapse, but the difference did not show statistical significance. The white blood cell (WBC) count was significantly lower in t(8;21) group compared to inv(16)/t(16;16) group at diagnosis (P = 0.006) but the gap disappeared at relapse (P = 0.830). There were no differences regarding bone marrow (BM) blast count and platelet count at diagnosis and relapse between two groups. At diagnosis, 50% of all patients were associated with additional chromosomal aberration (**Table 2**). Loss of sex chromosome (LOS) was the most common abnormalities in t(8;21) group, while trisomy 22 was most common in inv(16)/t(16;16) group. When cytogenetic profiles at relapse were compared to those at diagnosis, changes in cytogenetics were observed in 66.7% and 16.7% of patients with t(8;21) and inv(16)/t(16;16), respectively.

Hematopoietic stem cell transplantation

For patients with t(8;21), the median CR_1 duration was 8 months (range 1-49) and the interval from relapse to HSCT was 3 months (range 0-8) (**Table 3**). As for the source of hematopoietic stem cells, HLA-matched unrelated donors (12, 50.0%) contributed the most, and one patient underwent related haplo-transplantation. For patients with inv(16), the median CR_1 duration was 11 months (range 1-23) and the interval from relapse to HSCT was 4 months (range 2-55 months) (**Table 3**). HLA-matched related donors (11, 55%) were the most common source of hematopoietic stem cells in this group, and one patient underwent related haplo-transplantation.

There were no significant differences between two groups with regards to donors, conditioning regimen, and the interval from relapse to HSCT. The proportion of patients with CR_1 duration less than 6 months was higher in t(8;21), but the difference did not reach statistical significance (25.0% vs. 11.1%, P = 0.054, data not shown). Patients with t(8;21) seemed to relapse more often compared with patients with inv(16)/t(16;16) (P = 0.007).

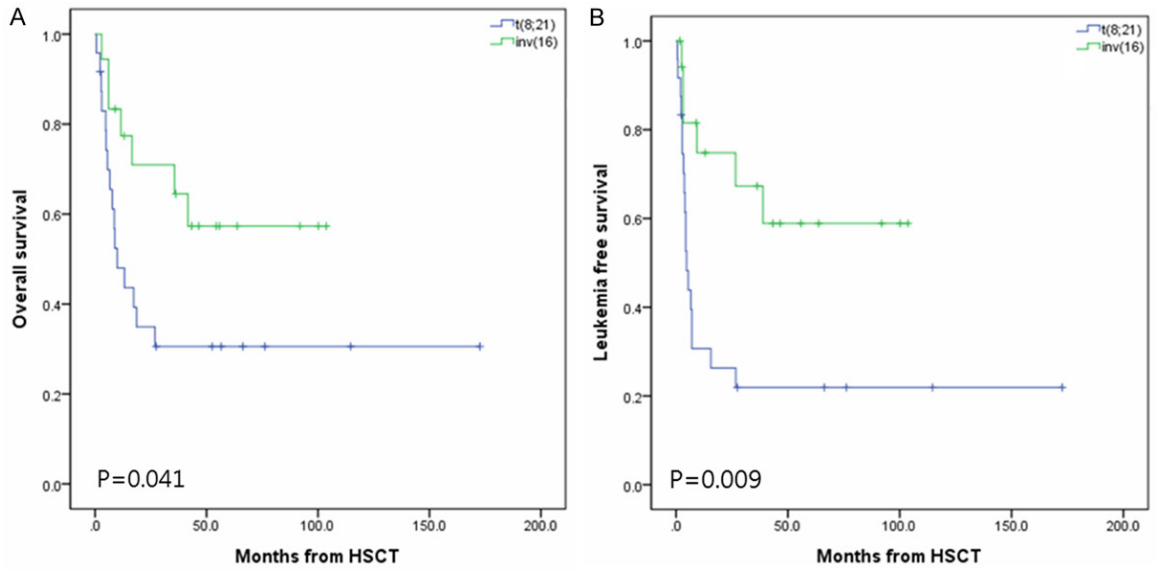

Figure 1. Kaplan-Meier curves for overall survival (OS) and leukemia free survival (LFS) after hematopoietic stem cell transplantation (HSCT). A: OS according to cytogenetics groups (P = 0.041). B: LFS according to cytogenetics groups (P = 0.009).

Survival analysis

The median follow-up duration was 21.3 months from relapse and estimated 2-year OS was 30.6% for t(8;21) patients and 67.7% for inv(16)/t(16;16) patients (P = 0.041, **Figure 1**). During the follow-up period, 23 patients died. The most common cause of death was sepsis (7, 30.4%), followed by graft-versus-host disease and related problems (5, 21.7%) and relapse or AML progression (5, 21.7%), then treatment-related mortality (TRM) (2, 8.7%). The cause of death was unknown in 4 (17.3%) patients.

Patients with t(8;21) were associated with worse prognosis than those with inv(16)/t(16;16), with shorter OS and LFS as shown in **Figure 1**. The median OS of t(8;21) was 10 months while that of inv(16) had not been reached. Further analysis showed in t(8;21), patients with LOS did worse than those without LOS (P = 0.001, **Figure 3A**). Also, higher WBC count at relapse was associated with shorter OS (P = 0.011, **Figure 2B**). Age and initial WBC count were not relevant to OS (data not shown). In inv(16)/t(16;16) group, neither the presence of trisomy 22 nor the WBC count at relapse affected OS (**Figure 4**). The median LFS of t(8;21) was 4.7 months while that of inv(16) had not been reached (P = 0.009, **Figure 1B**).

Prognostic factors affecting survival after HSCT

Table 4 shows the univariate analysis to identify prognostic variables for overall survival after HSCT. The cytogenetics at diagnosis and CR_1 duration were associated with overall outcomes. Patients with t(8;21) were associated with worse outcomes than inv(16)/t(16;16) (HR 2.458, 95% CI 1.007-5.999). Likewise, patients with CR_1 duration shorter than 6 months were associated with poor prognosis (HR 2.463, 95% CI 1.035-5.859). Although higher WBC count at relapse seems to be related to worse prognosis, the results did not reach statistical significance. In light of small sample size, multivariate analysis was not carried out.

In patients with t(8;21), univariate analysis identified higher WBC at relapse (P = 0.016, HR 3.685, 95% CI 1.270-10.692) and LOS (P = 0.003, HR 4.977, 95% CI 1.724-14.135) as factors associated with survival. On the other hand, in patients with inv(16)/t(16;16), only CR_1 duration (P = 0.041, HR 5.920, 95% CI 1.071-32.709) was identified as prognostic variable (data not shown).

Discussion

Higher than expected relapse rate of CBF-AML has fueled scientific interest in this particular

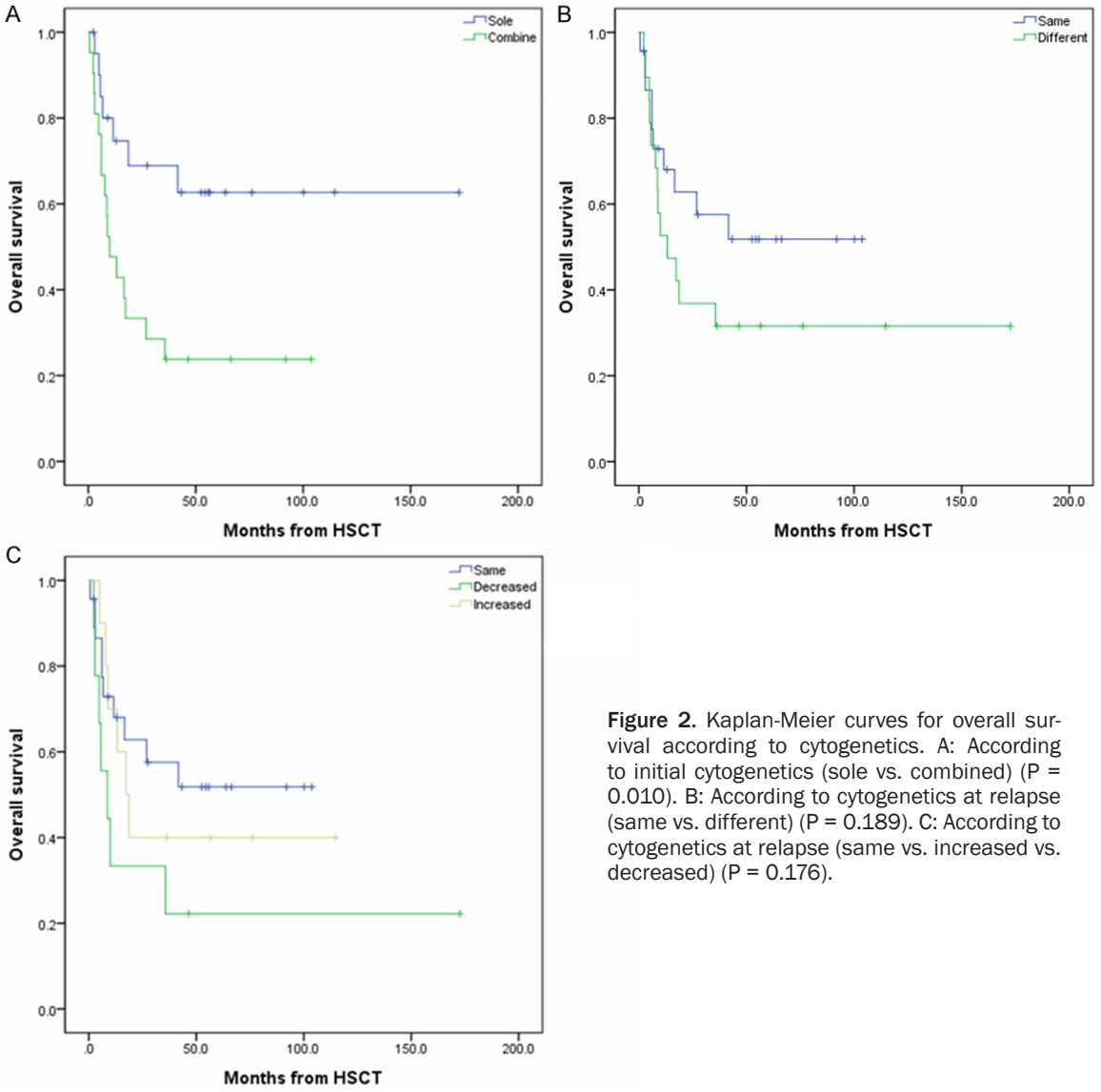

Figure 2. Kaplan-Meier curves for overall survival according to cytogenetics. A: According to initial cytogenetics (sole vs. combined) (P = 0.010). B: According to cytogenetics at relapse (same vs. different) (P = 0.189). C: According to cytogenetics at relapse (same vs. increased vs. decreased) (P = 0.176).

AML subgroup, and several groups have suggested relapsed CBF-AML is, in fact, a heterogeneous disease entity with different clinical outcomes and prognostic factors [9, 13, 14]. Although these reports have consistently shown that relapsed t(8;21) patients have worse prognosis than inv(16)/t(16;16) patients, they did not agree on the prognostic factors and more importantly, the standard of care for relapsed CBF-AML patients remain undetermined. The aim of this study was to assess the outcomes of CBF-AML patients in CR2 to evaluate the place of allogeneic HSCT in relapsed settings, and to identify high-risk groups. We found that about half of all relapsed CBF-AML patients achieved durable response with allogeneic HSCT at CR2. We also found that cytogenetics at initial diagnosis is important for overall survival. Patients with t(8;21) do worse than those with inv(16)/t(16;16), and those with additional chromosomal aberration were associated with poorer prognosis.

The overall 3-year survival after HSCT was 44.8% in our study, which is comparable to previous Japanese study [7] who reported OS at 3 years of 48.0%. Taking into account that the reported OS for relapsed non-M3 AML is only 30% [15], we hypothesized a favorable therapeutic role of HSCT for relapsed CBF-AML patients at CR2. From univariate analysis, we found that longer CR_1 duration and harboring

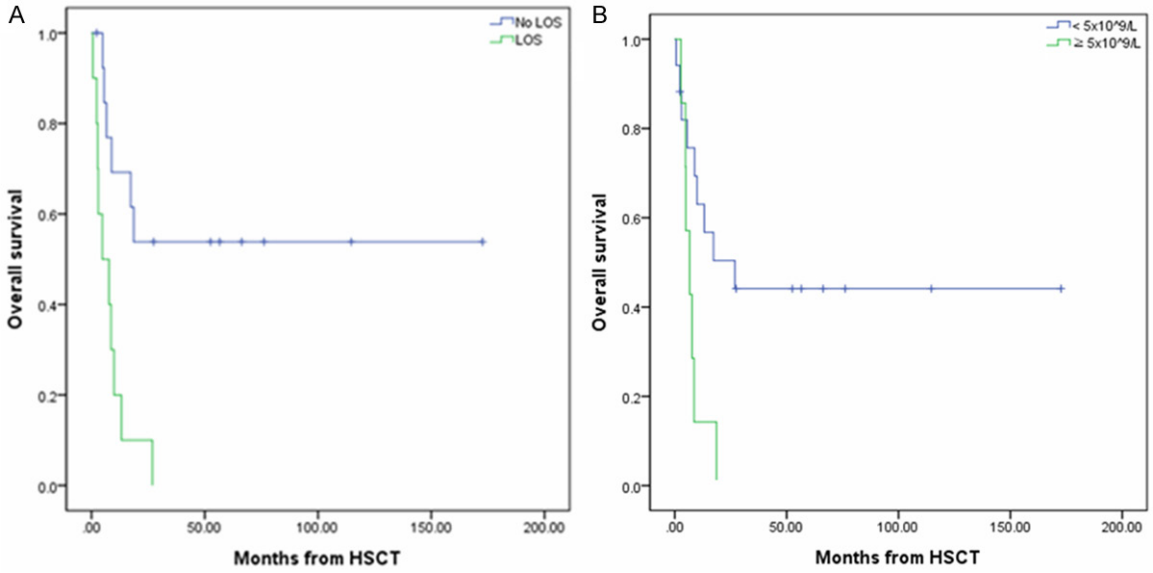

Figure 3. Kaplan-Meier curves for overall survival for t(8;21) patients. A: Grouped by loss of sex chromosome (LOS) (P = 0.001). B: Grouped by the white blood cell count at relapse (P = 0.011).

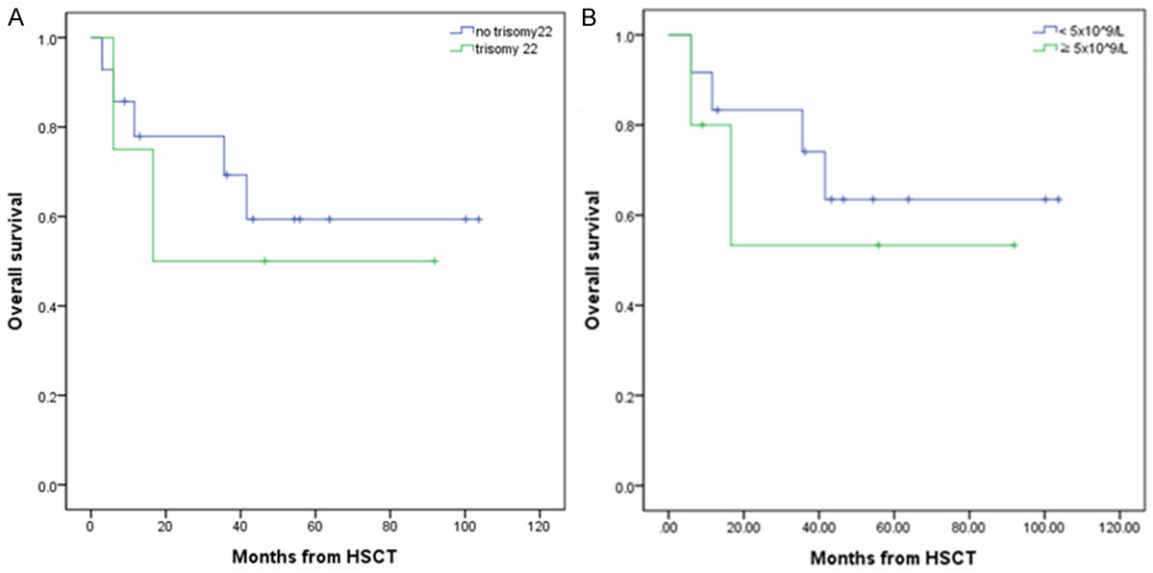

Figure 4. Kaplan-Meier curves for overall survival for inv(16)/t(16;16) patients. A: Grouped by the presence of trisomy 22 (P = 0.687). B: Grouped by the white blood cell count at relapse (P = 0.599).

inv(16)/t(16;16) were associated with better survival outcomes. Accordingly, patients with inv(16)/t(16;16) showed considerably better 3-year survival rate at 64.5% compared to patients with t(8;21) with 3-year survival rate at 30.6% (P = 0.041). There were 2 patients (4.8%) who expired due to TRM in our cohort, and both were in t(8;21) group. Although the careful interpretation of results is required, based on our findings, we, with some confidence, surmised that patients with inv(16)/t(16;16) can benefit more from allogeneic HSCT when relapsed.

Since patients with t(8;21) were associated with shorter OS and higher relapse rate after HSCT, we sought to identify high-risk subset within this cytogenetic group. As results, we found that high WBC count at relapse (P = 0.011) and loss of sex chromosome (P = 0.010) were associated with poor prognosis (**Figure 3**). Interestingly, contrary to previous reports [7, 9,

Table 4. Factors associated with survival after hematopoietic stem cell transplantation. Cox proportional hazards model and logistic regression were used to identify significant prognostic indicators for survival

	Univariate	
	HR (95% CI)	*p* Value
Sex		
Male	1	0.587
Female	0.795 (0.347-1.189)	
Age		
<50 years old	1	0.980
≥50 years old	0.986 (0.335-2.904)	
CR_1 duration 6 months		
>6 months	1	0.042
≤6 months	2.463 (1.035-5.859)	
WBC count at relapse 5×10^9/L		
$<5\times10^9$/L	1	0.051
$\geq5\times10^9$/L	2.342 (0.997-5.502)	
Cytogenetics at diagnosis		
inv(16)	1	0.048
t(8;21)	2.458 (1.007-5.999)	
Cytogenetics at relapse		
Same	1	0.196
Different	1.766 (0.755-3.943)	
Donor		
Matched related	1	0.568
Others	1.269 (0.559-2.881)	
Conditioning regimen		
Myeloablative	1	0.316
Reduced intensity	1.547 (0.659-3.629)	

HR, hazard ratio; CR_1, first remission; WBC, white blood cell.

14], age did not affect the outcomes of HSCT (P = 0.955, data not shown). WBC count at initial AML diagnosis was not associated with HSCT outcomes, either (P = 0.425, data not shown).

Interestingly, t(8;21) patients showed more chromosomal changes at relapse (P = 0.002). Sixteen (66.7%) patients in t(8;21) group showed changed cytogenetics at relapse compared to 3 (16.7%) patients in inv(16)/t(16;16). Patients with changed cytogenetics seem to be associated with worse prognosis (**Figure 2B**), but the difference did not reach statistical difference probably due to small sample size. When the changes in cytogenetics were further divided into "decreased" and "increased", decreased cytogenetics group was associated with the worst prognosis, but this too did not reach statistical significance (**Figure 2C**). The impact of changes in cytogenetics should be evaluated in more detail in a larger number of patients.

One of the major pitfalls of our study is the small sample number. Because the prevalence of CBF-AML is less than 10% of all AML [16], our cohort is not small for a single center. However, the absolute size of the sample is unarguably small, leading to diminished statistical power. Another limitation is the lack of data on c-*KIT* mutation status. The prognostic implication of c-*KIT* mutation is well known [17-19], and almost all guidelines recommend checking for c-*KIT* mutational status in CBF-AML patients. Unfortunately from our cohort, c-*KIT* mutation status data solid enough for evaluation was available in only 3 patients (7.1%) due to reimbursement and technical issues. Likewise, there have been studies reporting the presence of *FLT3* internal tandem duplication (ITD) as a main bad prognosis factor in relapsed CBF-AML patients [20]. In our study, *FLT3*-ITD data was available in 20 (47.6%) patients, but it was positive in only 1 patient. Thus, the impact of *FLT3*-ITD was not evaluated. More comprehensive study with a larger sample size and detailed molecular data should ensue to corroborate our results.

In conclusion, CBF-AML patients at CR2 show divergent clinical outcomes after allogeneic HSCT according to their initial cytogenetic abnormalities. For patients with inv(16)/t(16;16), allogeneic HSCT seems like a good salvage option, while for patients with t(8;21) more stratified approaches are needed. All in all, about half of CBF-AML patients can still acquire durable response with allogeneic HSCT at first relapse.

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Disclosure of conflict of interest

None.

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