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Extramedullary Relapse of Acute Myelogenous Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

The clinical significance of extramedullary relapse (EMR) of acute myelogenous leukemia (AML) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains poorly defined. Here we report the clinical outcomes of patients who underwent allo-HSCT for AML at our institution between 2000 and 2012. A total of 293 patients with AML who underwent allo-HSCT were included. The median duration of follow-up in survivors was 1840 days. Disease status at the time of allo-HSCT was complete remission in 192 patients and nonremission in 101 patients. A total of 110 patients experienced AML relapse after allo-HSCT, including 18 with EMR only, 83 with bone marrow relapse (BMR) only, and 9 with both EMR and BMR. The 5-year cumulative incidence of EMR after allo-HSCT was 9.5%, whereas that of BMR only was 28.9%. In multivariate analysis, peripheral blood stem cell transplantation was associated with an increased risk of EMR. The 2-year overall survival after post-transplantation relapse was 7.5% in patients with BMR only, 11.1% in those with both EMR and BMR, and 27.5% in those with EMR only ($P < .05$). Although the short-term survival was better in patients with EMR only, they rarely achieved long-term survival. Appropriate strategies for both post-transplantation EMR and BMR are needed.

INTRODUCTION

The prognosis of patients who have undergone allogeneic hematopoietic stem cell transplantation (allo-HSCT) has improved over the past few decades, largely due to a lower risk of transplantation-related mortality (TRM) [1,2]. With the significant decrease in the risk of TRM, relapse after allo-HSCT has now become one of the most crucial factors determining post-transplantation outcomes. The risk of relapse of acute myelogenous leukemia (AML) after allo-HSCT was shown to vary according to groups defined by the presence of various cytogenetic and molecular markers: 20% to 25% in the intermediate-risk group, 30% to 40% in the poor-risk group, and 40% to 50% in the very-poor-risk group [3]. Patients with relapsed AML may experience either bone marrow relapse (BMR) or extramedullary relapse (EMR). How the clinical significance of EMR of AML after allo-HSCT compares to that of BMR remains unclear.

Several retrospective studies have investigated EMR of AML after allo-HSCT [4-12]. In these studies, the incidence of EMR varied markedly, ranging from 1% to 30% [4-10]. Some studies showed that the prognosis of patients with EMR was better than those with BMR [4-6,8], whereas others demonstrated that the pattern of relapse was not a significant prognostic factor [9,10]. Most of the studies did not describe risk factors for EMR owing to small sample sizes [4-7,13,14].

Detailed clinical data on patients with EMR after allo-HSCT would be helpful to facilitate the detection of EMR in high-risk patients and establish approaches to the preemptive management of post-transplantation relapse. Here we analyzed differences in incidence and risk factors between EMR and BMR in a cohort of patients with AML.

METHODS

Patients who underwent their first allo-HSCT for AML at the National Cancer Center Hospital between 2000 and 2012 were included in this study. The exclusion criteria were primary graft failure, death before engraftment, and nonremission at the first evaluation of AML after allo-HSCT.

Clinical data were collected from medical records, including patient characteristics, transplantation characteristics, and clinical outcomes after allo-HSCT. HLA disparities were assessed in 8 loci, including HLA-A, -B, -C, and -DRB1. Cytogenetic risk was evaluated based on National Comprehensive Cancer Network classification. We evaluated the cumulative incidences of BMR and EMR after allo-HSCT, as well as survival rates after post-transplantation BMR and EMR. We also analyzed the risk factors for each pattern of relapse. BMR was defined as hematologic relapse proven by bone marrow examination. EMR was confirmed by tumor biopsy. Patients who received donor lymphocyte infusion or the WT-1 peptide vaccine at the time of molecular or cytogenetic relapse were treated as censored.

The cumulative incidence of relapse was determined by death before any pattern of relapse, which was treated as a competing risk, and was

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estimated by the Gray method [15]. The association between clinical variables and relapse was analyzed using the Fine-Gray proportional hazards model, excluding patients with post-transplantation relapse or death within 100 days or less. Variables with $P < .1$ in the univariate analysis were subjected to multivariate analysis. Overall survival after post-transplantation relapse was estimated by the Kaplan-Meier method from the date of relapse to the date of death from any cause. All analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria) [16].

This study was conducted in accordance with the provisions of the Declaration of Helsinki. The Institutional Review Board of the National Cancer Center approved this study protocol.

Table 1
Patient Characteristics (N = 293)

Characteristic	Value
Age, yr, median (range)	47 (1-69)
Sex, n (%)	
Male	177 (60)
Female	116 (40)
FAB classification	
M0	22 (7)
M1	31 (11)
M2	130 (44)
M3	11 (4)
M4	40 (14)
M5	29 (10)
M6	7 (2)
M7	3 (1)
Myeloid sarcoma	6 (2)
Unknown	14 (5)
WHO classification	
AML with recurrent genetic abnormalities	52 (18)
AML with MRC	78 (26)
Therapy-related myeloid neoplasms	17 (6)
AML, NOS	140 (48)
Myeloid sarcoma	6 (2)
Cytogenetic risk group based on NCCN	
Favorable	50 (17)
Intermediate	162 (55)
Poor	61 (21)
Unknown	20 (7)
Extramedullary infiltration before allo-HSCT	
Yes	43 (15)
No	250 (85)
Disease status before allo-HSCT	
CR1	108 (37)
CR2	75 (26)
CR3	9 (3)
NR	101 (34)
HCT-CI	
0	215 (74)
1-2	48 (16)
≥3	
Donor/stem cell source	30 (10)
Related BM	12 (4)
Related PBSCs	117 (40)
Unrelated BM	148 (51)
Unrelated PBSCs	1 (0)
Cord blood	15 (5)
HLA disparity	
Matched	220
1 locus mismatched	54
2 loci mismatched	12
Haploidentical	7
Conditioning regimen	
RIC	112 (38)
MAC	181 (62)
TBI	
Yes	138 (47)
No	155 (53)

FAB indicates French-American-British; WHO, World Health Organization; NCCN, National Comprehensive Cancer Network; HCT-CI, hematopoietic cell transplantation comorbidity index; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation.

RESULTS

Patient Characteristics

Between January 2000 and December 2012, 329 patients with AML underwent their first allo-HSCT. Excluding 36 patients (persistent refractory AML after allo-HSCT, n = 22; death before engraftment, n = 6; primary graft failure, n = 8), 293 patients, with a median age of 47 years (range, 1 to 69 years), were included in further analyses. Patient characteristics are summarized in Table 1. Forty-three patients (14.6%) had a history of extramedullary lesions before allo-HSCT. Disease status at the time of allo-HSCT was first complete remission (CR1) in 108 patients, second complete remission (CR2) in 75, third complete remission (CR3) in 9, and nonremission in 101. Bone marrow grafts were used in most cases of unrelated donor transplantation, and peripheral blood stem cell transplantation (PBSCT) was performed in most cases of related donor transplantation, including 1 haploidentical donor HSCT. HLA-matched related HSCT was performed using cyclosporin-based graft-versus-host disease (GVHD) prophylaxis and HSCT with other types of donors was performed using tacrolimus-based prophylaxis. Ten patients received antithymocyte globulin as GVHD prophylaxis. Short-term methotrexate was added to calcineurin inhibitors, except in cases of cord blood transplantation. Post-transplantation cyclophosphamide was administered to 2 of the patients with haploidentical donor HSCT transplantation.

Cumulative Incidence of Relapse

Among 293 patients, 110 patients had relapsed AML after allo-HSCT, including 18 with EMR only, 83 with BMR only, and 9 with both EMR and BMR at diagnosis of relapse. The median follow-up period of survivors was 1840 days (range, 71 to 5025 days). The most common sites of EMR were skin and bone (Table 2). The 5-year cumulative incidence of EMR, including EMR concurrent with BMR after allo-HSCT, was 9.5% (95% confidence interval [CI], 6.4% to 13.4%) (Figure 1A). The 5-year cumulative incidence of BMR only after allo-HSCT was 28.7% (95% CI, 23.7% to 34.2%) (Figure 1B). The median interval from allo-HSCT to post-transplantation relapse was 210 days (range, 31 to 1847 days) in EMR with or without BMR and 159 days (range, 32 to 2748 days) in BMR only ($P = .30$). In multivariate analysis, PBSCT was identified as an independent risk factor for EMR, whereas absence of chronic GVHD, nonremission at the time of allo-HSCT, and intermediate or poor cytogenetic risk were identified as risk factors for BMR (Table 3).

Survival

The median duration of follow-up after post-transplantation relapse was 414 days (range, 5 to 3296 days). The survival

Table 2
Sites of EMR (N = 27)

Site	Number (%)
Any site	27
1 site	18 (67)
More than 1 site	9 (33)
Skin	8 (30)
Bone	8 (30)
Central nervous system	6 (22)
Epidural space	5 (19)
Lymph nodes	4 (15)
Muscle	2 (7)
Breast	1 (4)
Pancreas	1 (4)
Pulmonary effusion	1 (4)
Dissemination	1 (4)
Unknown	1 (4)

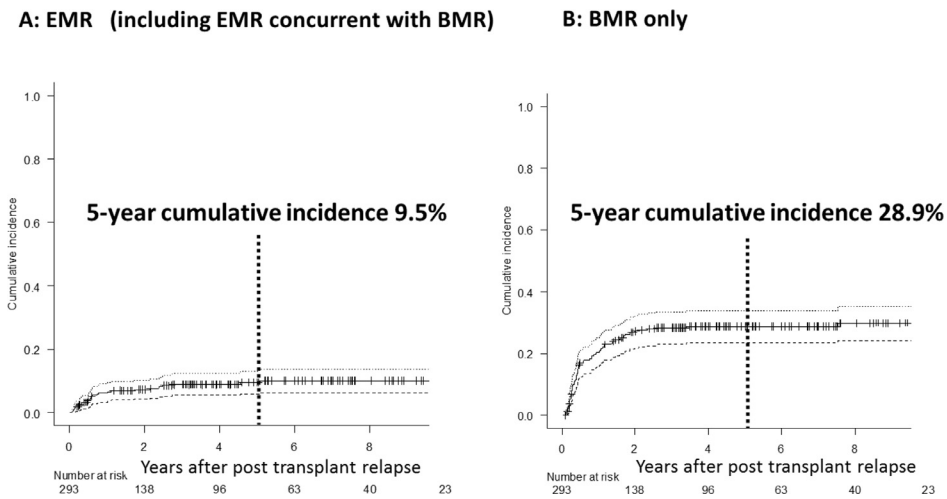

Figure 1. Cumulative incidence of post-transplantation relapse EMR concurrent with BMR (A) and BMR only (B). Numbers in parentheses indicate numbers of patients with events per cohort.

Table 3
Risk Factors for EMR or BMR Only

Variable	N	EMR						BMR only					
		Univariate Analysis			Multivariate Analysis			Univariate			Multivariate		
		HR	95% CI	*P* value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Acute GVHD													
Grade 0–I	178	1.00			1.00			1.00					
Grade II–IV	115	.37	.12-1.11	.08	.36	.12-1.08	.07	.95	.57-1.59	.85	-	-	-
Chronic GVHD													
No	155	1.00						1.00			1.00		
Yes	138	1.10	.44-2.71	.84	-	-	-	.38	.22-.65	<.05	.34	.20-.57	<.05
Conditioning regimen													
TBI-MAC	94	1.00						1.00					
non-TBI-MAC	87	2.32	.72-7.44	.16	-	-	-	.94	.48-1.82	.85	-	-	-
RIC	112	1.25	.35-4.45	.73	-	-	-	1.13	.61-2.09	.69	-	-	-
Extramedullary lesions before allo-HSCT													
No	250	1.00						1.00					
Yes	43	1.77	.57-5.43	.32	-	-	-	.70	.30-1.63	.41	-	-	-
FAB classification													
M0-2, 6, 7, unknown MS	213	1.00						1.00					
M3-5	80	1.26	.48-3.30	.63	-	-	-	1.09	.62-1.91	.77	-	-	-
GVHD prophylaxis													
CSP-based	141	1.00						1.00					
TAC-based	152	.73	.29-1.88	.52	-	-	-	1.12	.67-1.87	.66	-	-	-
HCT-CI													
0	251	1.00						1.00					
≥1	42	1.87	.74-4.70	.18	-	-	-	.66	.35-1.26	.21	-	-	-
HLA disparity													
Matched	220	1.00						1.00					
Mismatched	73	.60	.18-2.09	.43	-	-	-	.72	.37-1.38	.32	-	-	-
Cytogenetic risk group													
Favorable	50	1.00						1.00			1.00		
Intermediate/poor	243	.46	.18-1.21	.12	-	-	-	2.53	1.01-6.34	<.05	2.60	1.02–6.66	< 0.05
Sex													
Male	177	1.00						1.00					
Female	116	1.03	.42-2.53	.96	-	-	-	1.29	.78-2.16	.32	-	-	-
Stem cell source													
BM	160	1.00			1.00			1.00					
PBSCs	118	2.68	1.00-7.13	<.05	2.77	1.04-7.34	<.05	.86	.51-1.45	.57	-	-	-
CB	15	2.40	.30-19.03	.41	2.39	.27-20.89	.43	.36	.05-2.37	.29	-	-	-
Disease status at allo-HSCT													
Any CR	192	1.00						1.00			1.00		
Non-CR	101	1.51	.60-3.80	.39	-	-	-	2.03	1.21-3.39	<.05	2.14	1.27-3.59	<.05

TBI-MAC, total body irradiation-containing myeloablative conditioning; CSP, cyclosporine; TAC, tacrolimus.

rates after post-transplantation relapse at 2 years were 7.5% (95% CI, 2.7% to 15.8%) in patients with BMR only, 11.1% (95% CI, .6% to 38.8%) in those with both EMR and BMR, and 27.5% (95% CI, 8.9% to 50.2%) in those with EMR only ($P < .05$) (Figure 2). Although short-term survival was better in patients with EMR compared with those with BMR, long-term survival was dismal, with only 1 of 18 patients still alive at 5 years. Of the patients with EMR only, 12 died of AML.

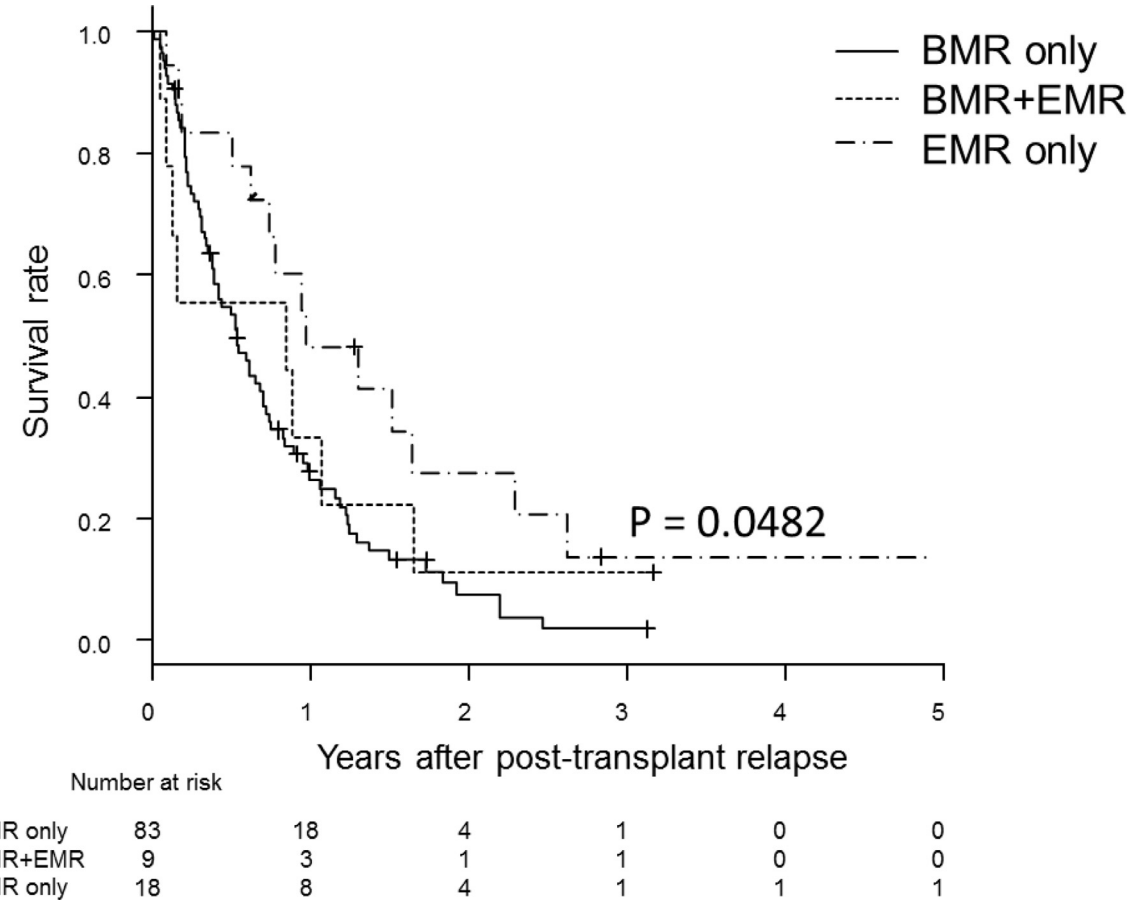

Figure 2. Kaplan-Meier curves overall survival after post-transplantation relapse. Numbers in parentheses indicate numbers of patients with events per cohort.

Treatment Strategy after Post-Transplantation Relapse

The initial treatment strategy differed by the type of post-transplantation relapse (Table 4), although strategic withdrawal of immunosuppressive agents was performed in most of the patients with BMR and/or EMR. In patients with EMR only who received treatment for post-transplantation relapse (n = 18), the median survival of patients who underwent radiotherapy and/or intrathecal therapy (n = 12) did not differ from that of patients who received systemic therapy (n = 6) (346 days [range, 60 to 839 days] versus 455 days [range, 184 to 958 days]; $P = .89$) (Figure 3). Nevertheless, most of the patients who initially achieved control of EMR using local therapy proceeded to subsequent systemic therapy owing to the systemic disease. Overall, 22 patients underwent second allo-HSCT, including 16 with BMR only, 3 with EMR only, and 3 with both EMR and BMR. The CR rate before second allo-HSCT was approximately 30% in each cohort, and there was no significant difference between BMR and EMR. The 1-year survival rates after second allo-HSCT were 20.4% (95% CI, 3.5% to 46.9%) in patients with BMR only, 0% in patients with EMR only, and 66.7% (95% CI, 5.4% to 94.5%) in those with EMR and BMR ($P = .341$). The main cause of death after second allo-HSCT was progressive AML, in 7 patients with BMR only, 1 patient with EMR only, and 2 patients in those with both EMR and BMR.

DISCUSSION

There is a paucity of clinical data on EMR after allo-HSCT compared with that on BMR. In this study, EMR was uncommon after allo-HSCT and was associated with poor clinical outcomes. The cumulative incidence of EMR in the 5 years after allo-HSCT was 9.5% at a median follow-up of 1840 days, similar to the values reported in some previous studies [4,5,17]. The majority of studies with a median follow-up of >5 years after allo-HSCT showed an incidence of EMR of approximately 10% [4,5,17], whereas studies with a shorter follow-up tended to report a lower incidence of EMR after allo-HSCT [6,7,9]. In studies

Table 4
Initial Treatment Strategy after Post-Transplantation Relapse

Treatment	BMR Only (N = 83)	EMR Only (N = 18)	BMR and EMR (N = 9)
Systemic chemotherapy, n	47	6	4
Second HSCT, n	7	0	1
RT, n	0	9	1
IT, n	0	1	0
RT + IT, n	0	2	0
BSC, n	7	0	1
Unknown, n	22	0	2

BSC indicates best supportive care; IT, intrathecal therapy; RT, radiotherapy.

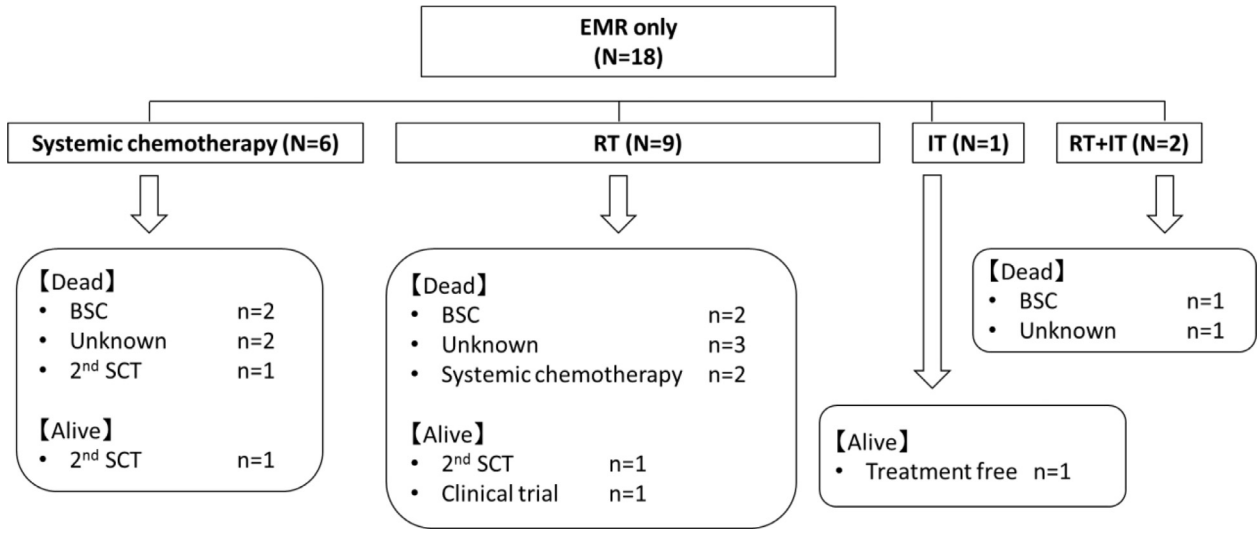

Figure 3. Treatment strategy after post-transplantation EMR only (n = 18). RT, radiotherapy; IT, intrathecal therapy; BSC, best supportive care.

evaluating long-term follow-up after allo-HSCT, EMR occurred later than BMR [5,6,8,9,13,17,18]. These findings support the idea that EMR after allo-HSCT is an uncommon event, but it is crucial to monitor its possible emergence over an extended period.

In this study, PBSCT was the sole risk factor for EMR identified in multivariate analysis, whereas risk factors for BMR included absence of chronic GVHD, intermediate or poor cytogenetic risk, and nonremission at the time of allo-HSCT. In previous reports on EMR after allo-HSCT, extramedullary lesions before allo-HSCT [5,7], chronic GVHD [4,8,19], French-American-British classification 4 or 5 [5], nonremission at allo-HSCT [5,7,13], non-total body irradiation-containing conditioning regimen [7,14,20], reduced-intensity conditioning regimen [21], poor cytogenetic risk [5,6,13], and male sex [12] were identified as risk factors for EMR, although they were not significant risk factors in our study. The difference in donor sources between our study and others might have affected the identification of EMR risk factors; almost all the PBSC donors for the patients with EMR were HLA-matched or 1 HLA locus-mismatched related donors. We also identified poor cytogenetic risk and nonremission before allo-HSCT as risk factors for EMR in patients with a non-total body irradiation-containing conditioning regimen (data not shown). In a retrospective analysis with a median follow-up of 17 months, PBSCT was a risk factor for EMR of acute lymphocytic leukemia after allo-HSCT and was possibly associated with a higher incidence of chronic GVHD [7]. In our study, the rate of chronic GVHD incidence was higher after PBSCT than after bone marrow transplantation (BMT) (60.1% versus 38.8%). Taking these data into account, we assume that the presence of chronic GVHD may be protective for BMR but not for EMR. Our retrospective study did not directly demonstrate an association between the risk of EMR and chronic GVHD, EMR might not be controllable with graft-versus-leukemia (GVL) effects, in contrast to BMR [5,7,8,18,19,22-24].

Although patients with EMR only had better outcomes compared with patients with BMR only or with BMR concurrent with EMR, the survival rate with long-term follow-up was low even in patients with EMR only at first relapse. Previous studies with large numbers of patients also have reported dismal findings on clinical courses after EMR. Harris et al [5] and Curley et al [9] reported a median overall survival after EMR of <1 year, but a longer median time to EMR after HSCT compared with that of BMR (≥1 year versus 4 months). This is because most of the patients with EMR died due to the disease progression to BMR during or soon after the treatment for EMR. Some reports have noted the effectiveness of systemic chemotherapy against EMR [4,5,8,24]. In our study, localized therapy appeared to be an acceptable strategy for patients with EMR only in the short term, even though most of them developed systemic disease and required subsequent chemotherapy. Thus, systemic disease control in combination with local control of EMR might be necessary in patients with EMR only at first relapse after allo-HSCT.

It is essential to establish treatment strategies for EMR and BMR, including monitoring minimal residual disease in combination with the detection of local EMR. Several studies on minimal residual disease have shown the utility of monitoring WT-1 levels in peripheral blood [25,26]. Elevation of WT-1 levels in peripheral blood in patients without BMR may be an appropriate indicator to screen for EMR with ^{18}F-fluorodexyglucose positron emission tomography (FDG-PET) [27-29]. Early screening with FDG-PET might allow for treatment with localized therapy only [24]. Two case series of EMR have investigated the efficacy of hypomethylating agents instead of intensive chemotherapy [30,31]. Emerging immunotherapies, such as immune checkpoint inhibitors [32], might be a promising treatment in patients with EMR.

This study has several limitations inherent to its retrospective nature and selection bias. Patient backgrounds and treatments for AML and GVHD were heterogeneous. Because the number of the patients with EMR was rather small, it was difficult to statistically evaluate risk factors for EMR and survival after a second allo-HSCT. We performed multivariate analyses to compensate for these limitations, but our findings require confirmation. Lack of the data on molecular profile, such as FLT3, NPM1, and others, by polymerase chain reaction is an additional limitation. This information is vital in the management of patients with AML, especially in the upcoming era of molecular targeted therapy.

In conclusion, the incidence of EMR in patients with AML after allo-HSCT was rather high in this long-term follow-up study. Long-term prognosis was dismal regardless of the pattern of post-

transplant relapse. Taking into consideration the fact that GVL effects might not sufficiently prevent EMR, careful observation in patients at high risk of EMR, such as those undergoing PBSCT, is warranted. Further research on preventive and treatment strategies for post-transplantation relapse of AML is needed.

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