Outcome of Second Allogeneic Hematopoietic Cell Transplantation after Relapse of Myeloid Malignancies following Allogeneic Hematopoietic Cell Transplantation: A Retrospective Cohort on Behalf of the Grupo Español de Trasplante Hematopoyetico

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A B S T R A C T

Allogeneic stem cell transplantation (allo-HCT) represents the most effective immunotherapy for acute myeloid leukemia (AML) and myeloid malignancies. However, disease relapse remains the most common cause of treatment failure. By performing a second allo-HCT, durable remission can be achieved in some patients. However, a second allo-HCT is of no benefit for the majority of patients, so this approach requires further understanding. We present a retrospective cohort of 116 patients diagnosed with AML, myelodysplastic syndromes, and myeloproliferative disorders who consecutively underwent a second allo-HCT for disease relapse. The median age was 38 years (range, 4 to 69 years). Sixty-three patients were alive at last follow-up. The median follow-up of the whole cohort was 193 days (range, 2 to 6724 days) and the median follow-up of survivors was 1628 days (range, 52 to 5518 days). Overall survival (OS) at 5 years was 32% (SE ± 4.7%). Multivariate analysis identified active disease status ($P < .001$) and second allo-HCT < 430 days (the median of the time to second transplantation) after the first transplantation ($P < .001$) as factors for poor prognosis, whereas the use of an HLA-identical sibling donor for the second allo-HCT was identified as a good prognostic factor ($P < .05$) for OS. The use of myeloablative conditioning ($P = .01$), active disease ($P = .02$), and a donor other than an HLA-identical sibling (others versus HLA-identical siblings) ($P = .009$) were factors statistically significant for nonrelapse mortality in multivariate analysis. Time to second transplantation was statistically significant ($P = .001$) in the relapse multivariate analysis, whereas multivariate analysis identified active disease status ($P < .001$) and time to second transplantation ($P < .001$) as poor prognosis factors for disease-free survival. This study confirms active disease and early relapse as dismal prognostic factors for a second allo-HCT. Using a different donor at second allo-HCT did not appear to change outcome, but using an HLA-identical sibling donor for a second transplantation appears to be associated with better survival. Further studies are warranted.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HCT) represents the most effective immunotherapy for acute myeloid leukemia (AML) and other myeloid malignancies. However, disease relapse is the most common cause of treatment failure after allo-HCT, which carries a poor prognosis [1,2]. Relapse rates in myeloid malignancies after allo-HCT have been reported up to 70% [3]. The therapeutic approach for this group of patients varies according to several factors [4,5] and the best treatment for these patients is yet to be determined.

At present, there are limited curative options for relapse of AML or myeloid malignancies occurring after an allo-HCT. Novel drugs tested in early phase clinical trials have been subsequently applied to patients relapsing after allo-HCT, and although responses have been reported [6], the majority of patients fail to achieve durable remission. On the other hand, enhancing the graft-versus-tumor (GVT) effect by means of donor lymphocyte infusions (DLI) has been accepted as a post–allo-HCT relapse approach [7-10] since its initial use [11]. However, DLI is only indicated in a limited number of patients. Its efficacy is variable and depends, among other causes, on the underlying disease or the tumor burden [12]. Thus, patients who relapse with high disease burden would not generally be considered for DLI. A second allo-HCT is an option for these patients.

A second allo-HCT allows the administration of further intensive chemotherapy and switching the donor immune system. It is assumed that by doing this, a different GVT may develop. However, despite improvements in transplantation-related mortality, performing a second allo-HCT still entails

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high rates of toxicity and relapse. Altogether, this is linked to poor outcome, with a 5-year overall survival (OS) of 25% [3,13]. Although randomized prospective trials have not been reported in this setting, retrospective data suggest that a second allo-HCT, albeit feasible, implies high nonrelapse mortality (NRM) rates. However, the donor to be chosen, the use of T cell depletion, or whether and which other prognostic factors apply remain open questions. The length of the remission after the first allo-HCT and the disease status at second allo-HCT appear to be 2 main independent prognostic factors for the outcome of a second allogeneic transplantation [13,14], as in the first allo-HCT.

To assist in the clinical decision of whether or not to perform a second allo-HCT in such high-risk patients, further understanding of the prognosis of this difficult scenario is required. We report a retrospective cohort of patients diagnosed with myeloid malignancies who relapsed after allo-HCT and underwent a second allogeneic transplantation.

PATIENTS AND METHODS

Patients who underwent a second allo-HCT for relapse of AML, high-risk myelodysplastic syndromes (MDS) and myeloproliferative disease (MPN) between 1979 and 2011 in 19 Spanish transplantation centers were included. Data were collected from center members of the Grupo Español de Trasplante Hematopoyetico that agreed to participate; this was followed by data query updates requested to the participating centers. Patients included in this study gave previous consent for their data to be used when they consented for an allo-HCT, and from 2003, for their data to be included in the European Bone Marrow Transplantation database (EBMT). The study was reviewed and approved by the Comite Etico de Investigacion Clinica of Bellvitge Hospital (Barcelona, Spain) and the Agencia Española de Medicamentos y Productos Sanitarios, Spain.

Patients who received a second allo-HCT after a relapse of AML, MDS, or MPN were included, and those who received a second allo-HCT for primary or secondary graft failure were not included. Response and relapse were assessed by morphology: molecular and cytogenetic tests were not used for response in this study. We used the World Health Organization and National Cancer Institute criteria to assess response in MDS and AML patients, respectively [15,16]. To assess the length of the remission, *time to relapse* was defined as the time from first allo-HCT to relapse. Because this variable had missing data, *time to second transplantation*, which measured the time between the first and second allo-HCT, was created to assess the outcome according to the length of remission. For statistical analysis, time to second transplantation was divided in 2 groups according to the median cut-off point. For the descriptive results analysis, acute and chronic graft-versus-host disease (GVHD) were graded according to the Keystone 1994 consensus criteria [17] and the historical criteria [18].

Endpoints

The primary endpoints were OS, NRM, and disease-free survival (DFS). The analysis included OS, DFS, relapse, and NRM. These variables were defined and codified following the Statistical Guidelines for EBMT.

Statistical Analysis

Patient and transplantation characteristics were described using frequency categorical variables and as mean (SD) or median (interquartile range) continuous variables. The estimate of NRM was calculated using cumulative incidence curves. *NRM* was defined as the date of transplantation to death from any cause other than relapse, with relapse being defined as a competitive risk in the estimate of NRM. NRM was a competitive risk in the estimation of relapse incidence and results were presented as subhazard ratios according to the model of Fine and Gray. The probabilities of OS and DFS were analyzed using Kaplan-Meier estimates. *DFS* was defined as time to relapse or death from any cause. Univariate and multivariate analysis used the Cox proportional hazards regression model. For multivariate analysis, we included all independent variables with a P value $< .10$ in the univariate analysis. The P value was set at $< .05$ for statistical significance. Statistical analyses were performed with the Statistical Package Stata ver.13 and SPSS ver.17.

RESULTS

A total of 116 consecutive patients with AML, MDS, and MPN were included. All 3 MPN patients had the second allo-HCT in active disease. The median follow-up of the whole cohort was 193 days (range, 2 to 6724 days) and the median follow-up of the surviving patients was 1628 days (range, 52 to 5518 days). Sixty-nine patients were male and 47 were female. Four patients were <14 years old. The median age at second transplantation was 38 years (range, 4 to 69 years).

Underlying diagnoses were as follows: 88 patients were diagnosed with AML (76%) and 28 (24%) patients were diagnosed with MDS/MPN, of which 3 patients were diagnosed with high-risk MPN. In terms of disease status, patients were divided in 2 main groups and distributed as follows: 80 (70%) patients had active disease and 34 (30%) were in complete remission (CR) (disease status was unknown in 2 patients). The source of cells for the second allo-HCT was peripheral blood in 99 patients, bone marrow in 11 patients, and cord blood (CB) in 5. Two patients had a previous autologous HCT before a first allo-HCT. Eighteen patients (25%) received total body irradiation–based conditioning, 42 (36%) received a myeloablative conditioning (MAC), and 67 (58%) received a nonmyeloablative allo-HCT. The donor who was used for the first transplantation was also used for the second allo-HCT in 93 patients, whereas 18 patients received their transplant from a different donor. Donor HLA matching was distributed as follows: HLA-identical siblings for 96 patients (82.7%) and other matching for 20 patients (17.3%), of which 13 (11.2%) were unrelated donor, 5 (4.3%) were a nonidentical relative, 2 (1.8%)were syngeneic. Of the patients who had a second allo-HCT from an HLA-identical sibling, 7 transplantations were done using a different donor. Further information of patient characteristics can be found in Table 1. The median interval between the first allo-HCT and the relapse (time to relapse) was 242 days (range, 37 to 3589 days) and median time to second transplantation was 430 days (range, 55 to 3791 days).

DFS

The 5-year DFS was 30% (SE ± 4.5%). Univariate analysis showed that that disease status at transplantation ($P < .001$) and length of the remission before the second allo-HCT (divided in 2 groups as time to second transplantation, setting the cut-off point in the median) ($P < .001$) were statistically significant variables. The multivariate analysis confirmed the statistically significant variables of the univariate: disease status (hazard ratio [HR], 2.83; 95% confidence interval [CI], 1.58 to 5.07; $P < .001$) and time to second transplantation (HR, 2.45; 95% CI, 1.55 to 3.86; $P < .001$).

Relapse

The 5-year cumulative incidence of relapse was 37.8% (95% CI, 28.7 to 46.7). Three variables were statistically significant in the relapse univariate analysis: CB as source of stem cells ($P < .001$), nonmyeloablative conditioning ($P = .021$), and time to second transplantation > 430 days ($P = .001$). Multivariate analysis confirmed time to second transplantation > 430 days as the only statistically significant variable (subhazard ratio [SHR], .37; 95% CI, .20 to .67; $P = .001$).

NRM

The 5-year NRM was 32% (95% CI, 23.4 to 40.9). Several factors were identified as statistically significant in univariate analysis: active disease ($P = .03$), CB ($P = .02$), conditioning regimen busulfan/cyclophosphamide ($P = .008$), MAC

Table 1
Patient Characteristics

	Number of Cases	Patients Analyzed, %
Sex		
Male	69	59.5
Female	47	40.5
Age		
<50 yr	83	71.6
≥50 yr	33	28.4
Transplantation Year		
<2004	51	44
≥2004	65	56
Disease		
AML	88	76
MDS	25	21
MPN	3	3
Disease status		
CR	34	30
Active disease	80	70
TBI		
TBI	18	25.3
Non-TBI	56	74.7
Donor sex		
Male	57	50
Female	57	50
Donor		
Same	96	85
New	17	15
Donor matching		
HLA-identical sibling	96	82.7
Unrelated	13	11.2
Nonidentical relative	5	4.3
Syngeneic	2	1.8
Immunosuppression		
CsA + MTX	33	28.4
CsA + MMF	19	16.4
CsA + other	14	12.1
Other	50	43.1
MAC versus NMA		
MAC	42	38.5
NMA	67	61.5
Conditioning		
Flu/Bu	30	25.9
Flu/Mel	9	7.7
Bu/Cy	8	6.9
TBI	18	15.6
Others	51	43.9
Cell source		
PB	100	86.2
BM	11	9.5
CB	5	4.3

TBI indicates total body irradiation; CsA, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil; NMA, nonmyeloablative; Flu, fludarabine; Bu, busulfan; Cy, cyclophosphamide; PB, peripheral blood; BM, bone marrow; CB, cord blood.

conditioning ($P = .01$), and a donor other than an HLA-identical sibling (HLA-identical siblings versus others, $P = .001$). Multivariate analysis confirmed 3 of these variables: use of MAC (SHR, 2.67; 95% CI, 1.32 to 5.4; $P = .01$), active disease (SHR, 2.57; 95% CI, 1.11 to 5.93; $P = .02$), and a donor other than an HLA-identical sibling (HLA-identical siblings versus others, SHR, 2.55; 95% CI; 1.26 to 5.17; $P = .009$).

OS

The 5-year OS was 32% (SE ± 4.7%) (Figure 1). Univariate analysis identified disease status at transplantation ($P < .001$), the length of the remission before second allo-HCT (using the variable time to second transplantation, which was divided in 2 groups, setting the median as the cut-off point) ($P < .001$), and conditioning regimen ($P = .001$) as statistically significant variables. The use of an HLA-identical sibling versus other donor showed a trend ($P = .056$) in log-rank analysis, being statistically significant ($P < .05$) in Tarone-Ware and Breslow analysis. Full details of OS univariate analysis are provided in Table 2. Variables with $P < .10$ in univariate analysis were included in multivariate analysis, which confirmed 3 variables: active disease (HR, 3.24; 95% CI, 1.73 to 6.05; $P < .001$), time to second transplantation < 430 days (HR, 2.42; 95% CI, 1.52 to 3.87; $P < .001$), and donor other than an HLA-identical sibling (HR, 1.92; 95% CI, 1.04 to 3.53; $P = .03$).

GVHD

In terms of GVHD, 54 (47%) patients developed acute GVHD. Of them, 12 (10.3%) developed grade I, 22 (19%) grade II, and 20 (20.3%) developed grades III and IV acute GVHD. In terms of chronic GVHD, 17 patients (14.7%) developed limited chronic GVHD and 20 (17.2%) were diagnosed with extensive chronic GVHD.

DISCUSSION

For patients diagnosed with AML, MDS, and MPN, relapse is still the main cause of treatment failure after allo-HCT. Although transplantation supportive care has dramatically improved over the last years, the only way to prolong survival is by achieving durable CR. A second allo-HCT may be a therapeutic alternative for a group of such patients. Therefore, better understanding of second allo-HCT prognostic factors is of interest. In this nationwide, multicenter, retrospective study, we contribute to the identification of prognostic factors by presenting what is, to our knowledge, 1 of the largest published cohorts of patients who underwent a second allo-HCT for myeloid malignancies. We identified, in line with previous papers [1,14,19,20], the following variables for poor prognosis: the length of the pre–allo-HCT remission and disease status disease. Sibling allo-HCT was identified as a good prognosis variable. Thus, according to our data, patients who received their second allo-HCT with active disease or those who had an early relapse are most unlikely to benefit from the procedure.

Eapen et al. [14] reported that in their cohort of 279 acute and chronic leukemia Center for International Blood and Marrow Transplant Research patients (including 125 AML patients) who received a second sibling allo-HCT for relapse, 5-year OS was 28%. In this study, the time from first allogeneic transplantation to relapse, or otherwise the duration of

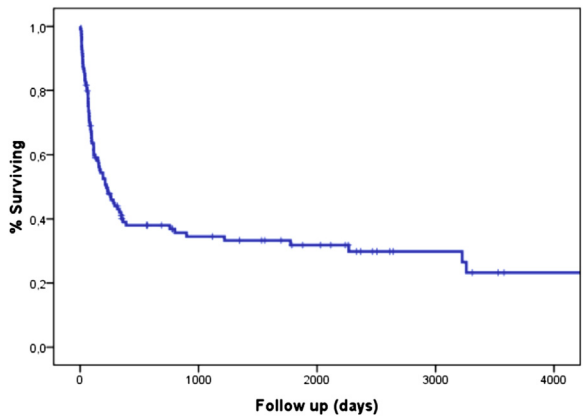

Figure 1. Overall survival (OS) of the total population.

Table 2
OS Univariate Analysis

	Patients	Events	Chi-Square	*P* Value
Disease status				
CR	34	12	15.75	<.001
Active disease	80	65		
Time to second transplantation				
<430 d	57	45	16.52	<.001
≥430 d	57	32		
Gender				
Male	69	47	.16	.687
Female	47	31		
Age				
<50 yr	83	56	.01	.933
≥50 yr	33	22		
Disease				
AML	86	59	.87	.647
MDS	25	16		
MPN	3	2		
Stem cell source				
PB	98	67	.26	.875
BM	11	7		
CB	5	3		
Type of donor				
HLA Id Sib	95	63	3.63	.056
Other	20	14		
Donor				
Same	93	68	3.68	.15
Other	18	11		
TBI				
Yes	19	10	3.17	.204
No	55	38		
Conditioning				
FluBu	30	17	19.3	0.001
TBI-based	18	10		
BuCy	9	9		
FluMel	8	8		
Others	49	33		
MAC				
Yes	65	42	1.0	.606
No	42	31		
TCD				
No	94	64	1.31	.251
Yes	19	12		
Immunosuppression				
CsA + MTX	33	19	3.03	.347
CsA + MMF	20	14		
CsA + Other	14	10		
Other	49	35		

HLA Id sib indicates HLA-identical sibling; TCD, T cell depleted.

remission, the conditioning regimen, and disease status at second allo-HCT were statistically significant variables. In terms of the previous length of remission, Eapen et al. [14] also found that patients relapsing < 6 months after allo-HCT had poorer outcomes than other patients. In line with this, Shaw et al. [13] set a similar cut-off point of 11 months. In our study, we set as cut-off point the median of the variable time to second transplantation, which clearly differentiated 2 cohorts. This approach was strong in terms of statistical power (data not shown). However, time is a continuous variable and the conclusion would, therefore, be that the shorter the length of remission, the poorer outcome.

As others have reported [13,14,21], we observed that disease status before second allo-HCT is a very strong poor prognostic factor, as it is for first allo-HCT. A survey of the EBMT Acute Leukemia Working Party (including 244 patients who had a second allo-HCT after an allogeneic transplant in CR1) found it statistically significant as well. A 2-year OS of 38% ± 7% was reported for patients in remission at the time of a second allo-HCT compared with 16% ± 4% for patients not in remission. The 5-year OS of our cohort was 32% and the 2-year OS for patients in CR and active disease were 64% ± 8.7% and 26.2% ± 5%, respectively. Of note, in this study, 70% of the patients received their second allo-HCT while in active disease. On the other hand, the question about the use of another donor for a second allo-HCT is of major relevance. Although, as previously published [22], switching donors does not appear to influence the outcome: the attempted enhancement of the GVT effect by switching donor might be affected by the toxicity that a second allo-HCT implies. In this study, we did not observe better OS when using a different donor for the second allo-HCT, although the use of a sibling at second transplantation appeared to be a good prognostic for OS. This might be due to the fact that the use of an HLA-identical sibling donor might entail less transplantation-related toxicity, as the NRM multivariate analysis points out. On the other hand, we can hypothesize from the NRM analysis that MAC conditioning may be more toxic in the second allo-HCT setting; however, this had no impact on OS. In addition, busulfan/cyclophosphamide conditioning was identified as worse prognostic factor in the NRM univariate analysis, but this was not confirmed in multivariate analysis. However, as this conditioning was used in less than the 7% of our population, conclusions should not be withdrawn from this result. In terms of the source of stem cell used, we found no difference on the use of graft source. In contrast, Shaw et al. [13] reported that peripheral blood as the source implies a better outcome in a reduced-intensity second allo-HCT cohort, whereas other authors found a significant benefit from other graft sources [3].

Strategies for treatment of hematological malignancies relapsing after allo-HCT need further research. Adapting the strategy to each individual patient might be the appropriate approach. Whether chemotherapy plus DLI is more effective than a second transplantation is still uncertain and only few such retrospective studies have been published [23]. Randomized trials are needed, but given the potential unavailability of donors, those studies would be highly complex. In clinical practice, physicians rely on factors such as the disease burden, the patient's performance status, or the availability of donors when choosing the best treatment for relapse after allo-HCT.

Attempts to improve the effectiveness of a second transplantation have been adopted, such as to performing a T cell–replete allo-HCT after a first TCD transplantation, which does not seem to prolong survival [24], or performing a reduced-intensity conditioned allo-HCT as second transplantation to reduce NRM rates [25]. None of these approaches appear to be superior to others.

We acknowledge some limitations of this study. Its retrospective nature limits the statistical power of the results; besides, it hampers an accurate analysis of some variables of complex collection. Further, missing data for the variable time to relapse became an issue for the multivariate analysis. Creating the variable time to second transplantation partially compensated for this. We analyzed survival using both variables, and outcomes did not differ (data not shown). This issue has occurred in other studies and has been compensated for similarly [14].

On the other hand, given that this study included transplantations performed more than 20 years ago, we created a time cut-off point in 2004 to assess whether the year of transplantation had an influence on outcome, and we did not find any difference. Regarding GVHD, there is a bias in GVHD grading as different grading systems were used according to the year of diagnosis.

Overall, the results reported here might specifically guide physicians treating patients diagnosed with AML who relapsed after allo-HCT. This study presents a large and homogeneous group of patients with high-risk myeloid malignancies and confirms, like others [26], that a second allo-HCT is feasible and of benefit for a group of patients without poor prognostic features. Prospective studies are warranted to confirm and better identify factors associated with a second transplantation.

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REFERENCES

1. Mrsíc M, Horowitz MM, Atkinson K, et al. Second HLA-identical sibling transplants for leukemia recurrence. *Bone Marrow Transplant*. 1992;9: 269-275.
2. Bishop MR, Alyea EP, Cairo MS, et al. National Cancer Institute's First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: summary and recommendations from the organizing committee. *Biol Blood Marrow Transplant*. 2011;17:443-454.
3. Bosi A, Laszlo D, Labopin M, et al. Acute Leukemia Working Party of the European Blood and Marrow Transplant Group. Second allogeneic bone marrow transplantation in acute leukemia: results of a survey by the European Cooperative Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2001;19:3675-3684.
4. Kumar L. Leukemia: management of relapse after allogeneic bone marrow transplantation. *J Clin Oncol*. 1994;12:1710-1717.
5. Burnett A, Wetzler M, Löwenberg B. Therapeutic advances in acute myeloid leukemia. *J Clin Oncol*. 2011;29:487-494.
6. Czibere A, Bruns I, Kröger N, et al. 5-Azacytidine for the treatment of patients with acute myeloid leukemia or myelodysplastic syndrome who relapse after allo-SCT: a retrospective analysis. *Bone Marrow Transplant*. 2010;45:872-876.
7. Drobyski WR, Keever CA, Roth MS, et al. Salvage immunotherapy using donor leukocyte infusions as treatment for relapsed chronic myelogenous leukemia after allogeneic bone marrow transplantation: efficacy and toxicity of a defined T-cell dose. *Blood*. 1993; 82:2310-2318.
8. Deol A, Lum LG. Role of donor lymphocyte infusions in relapsed hematological malignancies after stem cell transplantation revisited. *Cancer Treat Rev*. 2010;36:528-538.
9. Roddie C, Peggs KS. Donor lymphocyte infusion following allogeneic hematopoietic stem cell transplantation. *Expert Opin Biol Ther*. 2011;11: 473-487.
10. Lübbert M, Bertz H, Wäsch R, et al. Efficacy of a 3-day, low-dose treatment with 5-azacytidine followed by donor lymphocyte infusions in older patients with acute myeloid leukemia or chronic myelomonocytic leukemia relapsed after allografting. *Bone Marrow Transplant*. 2010;45:627-632.
11. Kolb HJ, Mittermüller J, Clemm C, et al. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. *Blood*. 1990;76:2462-2465.
12. Schmid C, Labopin M, Nagler A, et al. EBMT Acute Leukemia Working Party. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. *J Clin Oncol*. 2007;25:4938-4945.
13. Shaw BE, Mufti GJ, Mackinnon S, et al. Outcome of second allogeneic transplants using reduced-intensity conditioning following relapse of haematological malignancy after an initial allogeneic transplant. *Bone Marrow Transplant*. 2008;42:783-789.
14. Eapen M, Giralt SA, Horowitz MM, et al. Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. *Bone Marrow Transplant*. 2004;34:721-727.
15. Cheson BD, Bennett JM, Kantarjian H, et al. World Health Organization (WHO) international working group. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood*. 2000;96:3671-3674.
16. Cheson BD, Cassileth PA, Head DR, et al. Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. *J Clin Oncol*. 1990;8:813-819.
17. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD. *Bone Marrow Transplant*. 1995;15:825-828.
18. Atkinson K. Chronic graft-versus-host disease. *Bone Marrow Transplant*. 1990;5:69-82.
19. Bosi A, Bacci S, Miniero R, et al. Second allogeneic bone marrow transplantation in acute leukemia: a multicenter study from the Gruppo Italiano Trapianto Di Midollo Osseo (GITMO). *Leukemia*. 1997; 11:420-424.
20. Radich JP, Sanders JE, Buckner CD, et al. Second allogeneic marrow transplantation for patients with recurrent leukemia after initial transplant with total-body irradiation-containing regimens. *J Clin Oncol*. 1993;11:304-313.
21. Ruutu T, de Wreede LC, van Biezen A, et al. Second allogeneic transplantation for relapse of malignant disease: retrospective analysis of outcome and predictive factors by the EBMT. *Bone Marrow Transplant*. 2015;50:1542-1550.
22. Christopeit M, Kuss O, Finke J, et al. Second allograft for hematologic relapse of acute leukemia after first allogeneic stem-cell transplantation from related and unrelated donors: the role of donor change. *J Clin Oncol*. 2013;31:3259-3271.
23. Thanarajasingam G, Kim HT, Cutler C, et al. Outcome and prognostic factors for patients who relapse after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2013;19: 1713-1718.
24. McIver ZA, Yin F, Hughes T, et al. Second hematopoietic SCT for leukemia relapsing after myeloablative T cell-depleted transplants does not prolong survival. *Bone Marrow Transplant*. 2013;48: 1192-1197.
25. Bay JO, Cabrespine A, Faucher C, et al. Société Française de Greffe de Moelle et de Thérapie Cellulaire. Double reduced-intensity allogeneic hematopoietic stem cell transplantation: a retrospective study from the SFGM-TC. *Biol Blood Marrow Transplant*. 2012;18:250-256.
26. Michallet M, Tanguy ML, Socié G, et al. Second allogeneic haematopoietic stem cell transplantation in relapsed acute and chronic leukaemias for patients who underwent a first allogeneic bone marrow transplantation: a survey of the Société Française de Greffe de moelle (SFGM). *Br J Haematol*. 2000;108:400-407.