Pathol. Oncol. Res. (2012) 18:1003–1008
DOI 10.1007/s12253-012-9535-7

RESEARCH

Second Allogeneic Transplantation for Relapsed Acute Leukemia after Initial Allogeneic Hematopoietic Stem Cell Transplantation

Ryo Hanajiri · Kazuteru Ohashi · Yuka Hirashima · Kazuhiko Kakihana · Takeshi Kobayashi · Takuya Yamashita · Hisashi Sakamaki · Hideki Akiyama

Received: 10 February 2011 / Accepted: 12 April 2012 / Published online: 29 April 2012

Abstract We retrospectively reviewed the medical records of 45 patients with relapsed acute leukemia after initial allogeneic hematopoietic stem ell transplantation (allo-HSCT). Among 45 patients, a total of 11 patients eventually underwent second allo-HSCT (HSCT-2). Median survival after relapse was 294 days (range, 135–942 days) for HSCT-2. Multivariate analysis showed significantly better survival for recipients of second allo-HSCT than for other patients (hazard ratio, 4.38; 95 % confidence interval, 1.45–13.2; P=0.009). Although outcomes for patients with relapsed leukemia were generally poor, our results suggest that second HSCT could offer a survival advantage over other conventional salvage strategies.

Keywords Second allogeneic hematopoietic stem cell transplantation · Acute leukemia · Relapse · Salvage treatment

R. Hanajiri · K. Ohashi (✉) · K. Kakihana · T. Kobayashi · T. Yamashita · H. Sakamaki · H. Akiyama
Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan
e-mail: k.ohashi@cick.jp

Y. Hirashima
Pharmacy Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

Introduction

The management of early post-transplant relapse is extremely difficult. Immunotherapies such as donor lymphocyte infusion (DLI) or second allogeneic hematopoietic stem cell transplantation (allo-HSCT) can be viable therapeutic options when a hematological malignancy relapses after the initial allo-HSCT [1–7]. However, patients with gross hematological relapses show poor response to immunotherapy alone. Chemotherapy may be required to reduce the relapsed clone to a level that can be effectively handled by immunotherapy. A second allo-HSCT together with adequate doses of myeloablative agents can thus be advantageous and the only therapy that induces sustained remission in patients with gross hematological relapses. Moreover, many years of clinical evaluations have supported these basic principles. Nevertheless, mortality rates associated with preparative regimen-related toxicity are extremely high, with death typically occurring early post-second transplant and with half of patients dying before 100 days [8–13]. In particular, patients who relapse within 1 year after initial HSCT show dire outcomes [13]. Non-myeloablative conditioning has recently been shown to be effective for reducing transplant-related early mortality, but little information is available for the setting of second transplantation [14, 15]. To evaluate the clinical impact of second allo-HSCT, particularly in terms of survival advantage over other conventional treatment options, we retrospectively analyzed the clinical outcomes of 45 patients with relapsed leukemia after initial allo-HSCT, including 11 patients who underwent second allogeneic HSCT.

Patients and Methods

Patients

Between January 2004 and December 2009, a total of 186 adult patients (≥16 years old) with acute leukemia underwent first allo-HSCT. Data from 176 of these patients for whom post-transplant outcomes were available were included in the present study. Clinical characteristics of these 176 patients (101 men, 75 women) are summarized in Table 1. Median age was 42 years (range, 16–64 years). Underlying disease was acute myeloid leukemia in 117 patients and acute lymphoblastic leukemia in 59 patients. At the time of transplantation, 116 patients were in complete remission (CR) and 60 patients had active disease. A total of 161 patients received a myeloablative conditioning regimen, and the remaining received a reduced-intensity conditioning regimen. Stem cell sources included bone marrow in 130 patients, peripheral blood in 21 patients, and cord blood in 25 patients. Median duration of follow-up for survivors was 982 days (range, 152–2,279 days).

Definition of Relapse and CR

Relapse was defined as a reappearance of leukemic blasts in peripheral blood or more than 5 % blasts in bone marrow by morphologic examination after the initial CR had been obtained. Molecular, cytogenetic or flow cytometric relapse were all excluded. Extramedullary relapse including central nervous system were also excluded. In contrast, CR was defined by the presence of less than 5 % blasts in the bone marrow and absence of extramedullary leukemia. Peripheral blood counts recovered with a neutrophil count of at least 1×10^9/L and a platelet count of at least 100×10^9/L. A bone marrow examination was routinely performed on day 14 and day 28 after transplantation.

Statistical Analysis

Descriptive statistics were provided for baseline patient characteristics. Patient-, disease-, and transplant-related variables were compared, using the χ^2 test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Overall survival (OS) was calculated using Kaplan-Meier methods and compared with the log-rank test. OS was calculated from the first relapse after first allo-HSCT to the time of death or the last follow-up. Associations between post-relapse treatment and outcomes were evaluated by multivariate analysis, performed using a Cox proportional hazards model. The following covariates were included in multivariate analysis: age; sex; primary diagnosis; disease status; stem cell source; donor type; conditioning regimen; graft-versus-host disease (GVHD) prophylaxis; post-relapse treatment; interval between transplantation and relapse; and

Table 1 Patient characteristics

Leukemic relapse	Yes	No	*P-value*
Total	45	131	
Age, median (range)	43 (17–62)	42 (16–64)	0.73
Sex, Male/Female	27/18	74/57	0.68
Diagnosis AML	39	78	0.001
ALL	6	53	
Type of transplant			
syngenic	0	0	
related	11	34	
unrelated	34	97	0.84
Stem cell source			
BM	34	96	
PB	4	17	
CB	7	18	0.75
HLA disparity			
full match	34	86	
1 locus mismatch	8	25	
>2 loci mismatch	3	20	0.51
Preparative regimen			
myeloablative	41	114	
non myeloablative	4	17	0.78
GVHD prophylaxis			
CyA / MTX	30	66	
FK506 / MTX	15	65	0.58
Disease status before transplant			
in remission	14	102	
on disease	31	29	<0.001
Number of chemotherapy before transplant, median (range)	4 (0–11)	4 (0–14)	0.95
Extramedullary lesions beforetransplant			
Yes/No	4/41	10/121	0.79
Development of acute GVHD			
grade 0–I	26	86	0.34
grade II–IV	19	45	
Development of chronic GVHD			
No	36	96	0.36
Yes (any type)	8	32	
no data	1	3	

* Abbreviations: *ALL* acute lymphoid leukemia; *AML* acute myeloid leukemia; *BM* bone marrow transplantation; *PB* peripheral stem cell transplantation; *CB* cord blood stem cell transplantation; *BU* busulfan; *CY* cyclophosphamide; *MEL* melphalan; *CA* cytarabine; *TBI* total body irradiation; *FLU* fludarabine; *GVHD* graftversus-host disease; *CyA* cyclosporine; *MTX* methotrexate; *FK506* tacrolimus

CR after intervention except for second transplantation. All P values were 2-sided. Values of $P<0.05$ were considered statistically significant. All analyses were performed using SPSS software (SPSS, Chicago, IL).

Results

Leukemic Relapse after Allo-HSCT

A total of 45 patients (26 %) eventually relapsed at a median of 110 days (range, 17–910 days) after allo-HSCT. Clinical characteristics of these 45 patients are summarized in Tables 1 and 2. Intervals from HSCT to relapse were <100 days for 18 patients, 100–300 days for 19 patients, and >300 days for 8 patients. With regard to risk analysis for relapse of leukemia, active disease at transplantation was a significant risk (hazard ratio, 6.9; 95 % confidence interval, 3.2–14.5; $P<0.001$). In our small cohort, development of acute GVHD and chronic GVHD did not reduce the risk of relapse. According to Kaplan-Meier product-limit estimates, 1-year OS was 22 % and median OS was 112 days (range, 7–942 days). Relapse within 100 days after transplantation showed a dismal prognosis. One-year OS estimates among patients with relapsed leukemia <100 days and ≥100 days from allo-HSCT were 13 % and 33 %, respectively (Fig. 1).

Clinical Outcomes Based on Treatment Options for Relapsed Leukemia

Although all relapsing patients were considered eligible for second transplant if general condition was good enough, only 11 patients (24 %) ultimately received second courses of allo-HSCT. Since no specific eligibility criteria existed for second transplantation, the final decision about second transplantation was made at the discretion of the senior attending physicians. Figure 2 shows details of treatment options actually adopted in our cohort of 45 patients with relapsed leukemia. In consideration of the number and severity of comorbidities, 11 patients (24 %) were allocated only to receive best supportive care. The remaining 34 patients without apparent GVHD underwent rapid withdrawal of immunosuppressants as the first action commonly taken in such cases. After excluding 4 patients with poor performance status, 30 patients then underwent second-line treatments; i.e., re-induction chemotherapy ($n=26$), DLI ($n=3$), or second HSCT ($n=1$).

Second allo-HSCT was performed in a total of 11 patients (24 %). The characteristics of patients who underwent second allo-HSCT are shown in Table 3. Nine patients (82 %) obtained CR after second allo-HSCT and the median OS was 294 days (range, 135–942 days).

Factors Associated with Better OS after Leukemic Relapse

We examined which variables were associated with better OS. Uni- and multivariate analyses of risk factors are shown in Table 2. According to univariate analysis, donor type, second allo-HSCT, and time to hematological relapse after initial transplantation were associated with superior outcomes, whereas age, sex, primary diagnosis, and type of transplant did not reach statistical significance. Multivariate analysis with logistic regression identified only second allo-HSCT as significantly associated with better survival.

Table 2 Univariate and multivariate analysis of adverse factors for overall survival

	Univariate P^a	HR (95 % CI)	Multivariate P^b	HR (95 % CI)
Age (≥43 years / <43 years)	0.65	1.16 (0.61–3.11)		
Sex (female / male)	0.60	1.20 (0.61–2.37)		
Diagnosis (ALL / AML)	0.21	0.51 (0.18–1.46)		
Disease status at the initial transplantation (on disease / remission)	0.12	1.74 (0.86–3.49)		
Stem cell source (PBSC or CBSC / BM)	0.71	0.86 (0.39–1.92)		
Donor type (unrelated / related)	0.04	2.50 (1.03–6.09)	0.81	1.14 (0.39–3.30)
Conditioning regimen (non myeloablative / myeloablative)	0.27	1.82 (0.62–5.33)		
GVHD prophylaxis (FK / CyA)	0.33	1.42 (0.70–2.88)		
Second transplantation (no / yes)	0.001	4.88 (1.88–12.7)	0.02	3.92 (1.27–12.1)
Time to hematological relapse after the initial transplantation (<100 days / ≥100 days)	0.01	2.47 (1.24–4.92)	0.27	1.51 (0.73–3.14)
CR after intervention except for second transplantation (non CR / CR)	0.08	2.58 (0.91–7.36)	0.12	2.55 (0.78–8.17)

Abbreviations: *HR* hazard ratio; *CI* confidence interval; *ALL* acute lymphoid leukemia; *AML* acute myeloid leukemia; *PBSC* peripheral blood stem cell; *CBSC* cord blood stem cell; *BM* bone marrow; *GVHD* graft-versus-host disease; *CyA* cyclosporine; *FK* tacrolimus; *CR* complete remission

[a] Univariate analysis with the $\chi 2$ test for categorical variables and the nonparametric Mann–Whitney U test for continuous variables, and [b] multivariate analysis with the multiple logistic regression analysis for appropriate variables to evaluate the risk. Statistical significance was determined at the .05 level. All P values were 2 sided

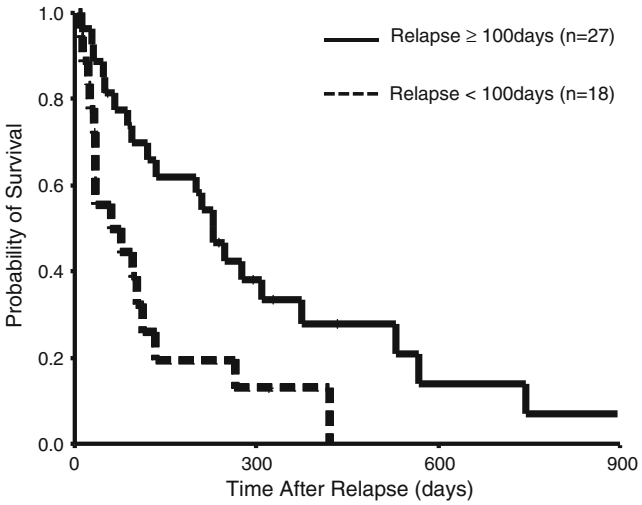

Fig. 1 Overall survival among patients with relapsed leukemia <100 days and ≥100 days from allo-HSCT

Discussion

Optimum management of relapse after first allo-HSCT, including DLI and second allo-HSCT, remains contentious [16–18]. Despite several recent reports on the use of DLI in the treatment of relapsed acute leukemia after transplantation that demonstrated disease control through immune-mediated graft-versus-leukemia effects, the clinical efficacy of DLI in acute leukemia is still controversial and sustained eradication of leukemia is rare. Other therapeutic options such as second transplantation thus seem likely to represent the more encouraging strategy for managing relapsed leukemia. In the context of rapid disease kinetics of relapsed leukemia, clear advantages exist to the use of mega-doses of myeloablative agents and radiotherapy followed by second allogeneic transplantation rather than DLI alone, in that this approach can provide rapid hematopoietic reconstitution and restoration of complete donor chimerism. However, treatment-related mortality rates associated with this approach have been shown to be extremely high, and very few patients become long-term survivors. Moreover, early death due to regimen-related toxicity within 100 days has been reported in up to 50 % of second HSCT recipients [8–13].

The present study retrospectively reviewed 176 medical records for allogeneic transplantations performed over the last 6 years in our institution, showing 45 patients (26 %) who had faced apparent leukemic relapse. Intervals from first HSCT to subsequent relapse were <100 days in 18 patients and ≥100 days in 27 patients. In our series, as many as 15 patients (33 %) could only received supportive care or withdrawal of immunosuppressive agents alone, and none

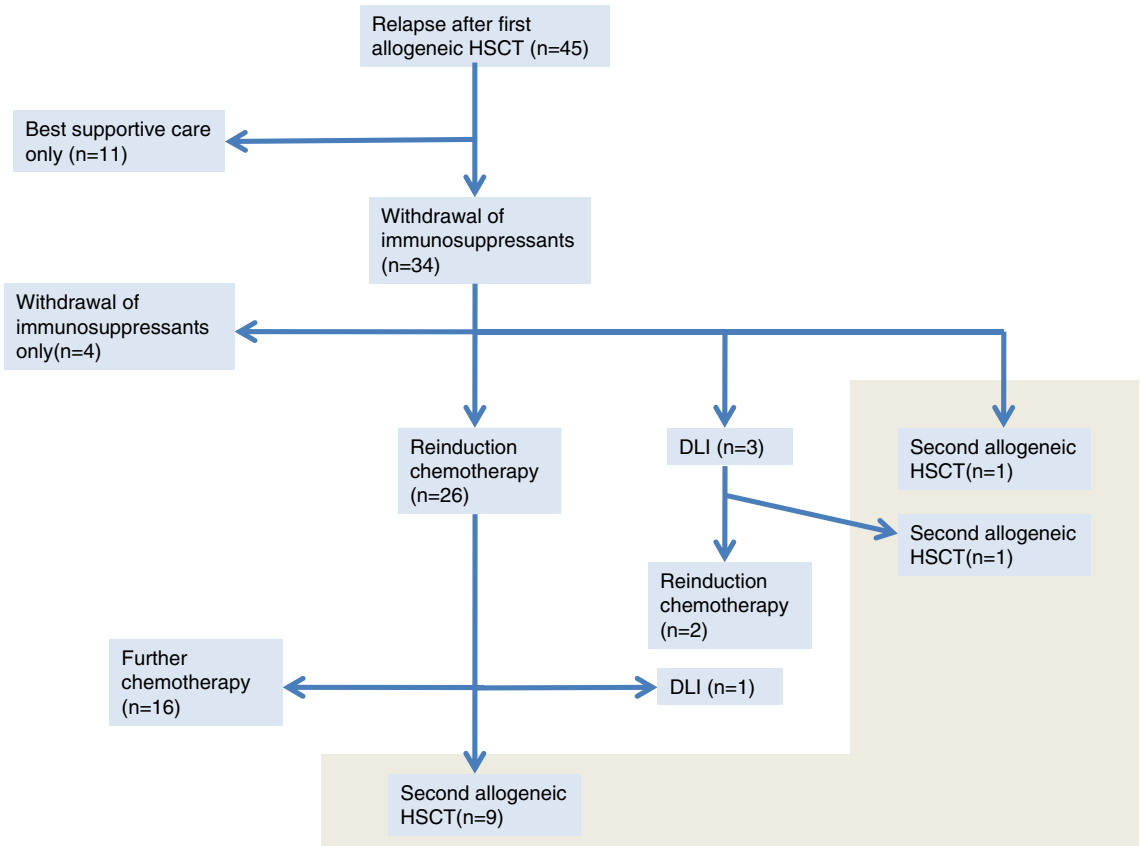

Fig. 2 Summary of interventions after relapse

Table 3 Characteristics of second transplantation

Characteristics	No. of patients
Total	11
Age, median (range)	39 (27–59)
Sex, Male/Female	6/5
Diagnosis	
AML	8
ALL	3
Time from first transplantation to relapse	
<100 days	1
>100 days	10
Disease status before second transplantation	
in remission	4
on disease	7
Donor for first and second transplantation	
same	3
different	8
Conditioning for first and second transplantation	
myeloablative-myeloablative	8
myeloablative-RIC	2
RIC-RIC	1
Stem cell source	
BM	6
PB	4
CB	1

Abbreviations: *AML* acute myeloid leukemia; *ALL* acute lymphoid leukemia; *RIC* reduced-intensity conditioning; *BM* bone marrow transplantation; *PB* peripheral stem cell transplantation; *CB* cord blood cell transplantation

of these patients achieved CR. In terms of the salvage chemotherapy applied in 26 patients, a variety of regimens were chosen, mainly based on the general condition of the patient, and only 6 patients (23 %) achieved CR. Details of regimens that induced CR were as follows: MEC (n=1); FLAG (n=2); GO (n=1); and hyper-CVAD (n=2). No hematological responses were observed in patients treated with CAG or CA and high-dose cytarabine regimens, suggesting that the dose intensity of cytarabine may not play a pivotal role in obtaining CR in this setting. Four of the 6 patients who achieved hematological remission underwent second allo-HSCT. In addition to these 4 patients, 7 patients who did not achieve CR after re-induction chemotherapy (N=5), withdrawal of immunosuppressants only (n=1), or DLI following rapid withdrawal of immunosuppressants (n=1) proceeded to second allo-HSCT. A total of 11 patients ultimately received second transplantation. These 11 patients enjoyed significantly longer survival (median, 294 days; range, 135–942 days), but 6 patients eventually died. Causes of death were cyclophosphamide-induced cardiomyopathy (n=1), hepatic veno-occlusive disease (n=2), acute GVHD (n=1) and bacterial pneumonia (n=2). No deaths attributed to second relapse were observed. In multivariate analysis, recipients of second allo-HSCT had significantly better survival than patients treated with other therapeutic options (hazard ratio, 4.38; 95 % confidence interval, 1.45–13.2; P=0.009). These results confirm a recent report finding that remission status, use of re-induction chemotherapy, longer interval (≥100 days) from HSCT to relapse, and second HSCT were associated with improved OS [19]. Another retrospective study showed that all long-term survivors received second HSCT as a part of their salvage therapy after relapse [20]. Other findings in our cohort were also in line with previous reports. Active disease at transplantation was the major risk factor of relapsing leukemia in our cohorts. Arellano *et al.* also reported that active disease at transplantation, unfavorable cytogenetics, and related donor was associated with relapse on multivariate analysis [21]. Duration from first HSCT to relapse <100 days was also associated with poor OS in univariate analysis. Prior reports have demonstrated that shorter time to relapse is associated with increased risk of overall mortality [22].

The present study showed several limitations. Given the retrospective nature of the study, some patients with early hematological relapse may have been missed, despite the detailed database and extensive chart review. Actually, the leukemic relapse rate in our cohort seems slightly lower than the 32–35 % reported elsewhere [21, 22]. Moreover, the small size of our cohorts represents a flaw to this study. Nevertheless, since large-scaled prospective randomized clinical trials will not be available for relapsed acute leukemia after HSCT, retrospective data provide useful information for this disease condition. Although our results suggest that second allo-HSCT could offer survival advantages, various undefined clinical problems seem to remain. Regarding suitable salvage chemotherapy and subsequent conditioning regimen for second allo-HSCT, optimal treatment approaches remain largely undefined, particularly in cases of relapse shortly after the initial transplant following myeloablative conditioning. Although further study is warranted, our data should provide useful insights into this disease condition.

Acknowledgments This study was supported in part by a grant for clinical cancer research from the Ministry of Health, Labor and Welfare of Japan. The authors would like to thank the nursing staff at Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, for their excellent patient care.

References

1. Greinix HT (2002) DLI or second transplant. Ann Hematol 81 (Suppl 2):S34–S35
2. Mehta J, Powles R, Kulkarni S et al (1997) Induction of graft-versus-host disease as immunotherapy of leukemia relapsing after

allogeneic transplantation: single-center experience of 32 adult patients. Bone Marrow Transplant 20:129–135
3. Locatelli F (1998) The role of repeat transplantation of haemopoietic stem cells and adoptive immunotherapy in treatment of leukaemia relapsing following allogeneic transplantation. Br J Haematol 102:633–638
4. Wolff SN (2002) Second hematopoietic stem cell transplantation for the treatment of graft failure, graft rejection or relapse after allogeneic transplantation. Bone Marrow Transplant 29:545–552
5. Kono N, Ohashi K, Sasaki E et al (2001) Second allogeneic peripheral blood stem cell transplantation with fludarabine-based low-intensity conditioning regimen for relapsed myelodysplastic syndrome after allogeneic bone marrow transplantation. Int J Hematol 73:122–125
6. Kono N, Ohashi K, Okuyama Y et al (2001) Treatment of relapsing Ph+ acute lymphoblastic leukemia with donor leukocyte infusion followed by quantitative monitoring of residual disease. Hematology 6:261–265
7. Schmid C, Labopin M, Nagler A et al (2007) 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 25:4938–4945
8. Mehta J, Powles R, Treleaven J et al (1997) Outcome of acute leukemia relapsing after bone marrow transplantation: utility of second transplants and adoptive immunotherapy. Bone Marrow Transplant 19:709–719
9. Mrsic M, Horowitz MM, Atkinson K et al (1992) Second HLA-identical sibling transplants for leukemia recurrence. Bone Marrow Transplant 9:269–275
10. Bosi A, Laszlo D, Labopin M et al (2001) 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 16:3675–3684
11. Barrett AJ, Locatelli F, Treleaven JG et al (1991) Second transplants for leukaemic relapse after bone marrow transplantation: high early mortality but favorable effect of chronic GVHD on continued remission. A report by the EBMT Leukaemia Working Party. Br J Haematol 79:567–574
12. Michallet M, Tanguy ML, Socie G et al (2000) 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 Societe Francaise de Greffe de moelle (SFGM). Br J Haematol 108:400–407
13. Kishi K, Takahashi S, Gondo H et al (1997) Second allogeneic bone marrow transplantation for post-transplant leukemia relapse: results of a survey of 66 cases in 24 Japanese institutes. Bone Marrow Transplant 19:461–466
14. Pawson R, Potter MN, Theocharous P et al (2001) Treatment of relapse after allogeneic bone marrow transplantation with reduced intensity conditioning (FLAG +/− Ida) and second allogeneic stem cell transplant. Br J Haematol 115:622–629
15. Cheng H, Ohashi K, Kurosawa S et al (2005) Busulfan and melphalan as a conditioning regimen for second peripheral blood stem cell transplantation in relapsed acute lymphoblastic leukemia after initial transplantation with total-body irradiation. Haema 8:83–90
16. Giralt SA, Champlin RE (1994) Leukemia relapse after allogeneic bone marrow transplantation: a review. Blood 84:3603–3612
17. Kumar L (1994) Leukemia: management of relapse after allogeneic bone marrow transplantation. J Clin Oncol 12:1710–1717
18. Savani BN, Mielke S, Reddy N et al (2009) Management of relapse after allo-SCT for AML and the role of second transplantation. Bone Marrow Transplant 44:769–777
19. Kurosawa S, Fukuda T, Tajima K et al (2009) Outcome of 93 patients with relapse or progression following allogeneic hematopoietic cell transplantation. Am J Hematol 84:815–820
20. Oran B, Giralt S, Couriel D et al (2007) Treatment of AML and MDS relapsing after reduced-intensity conditioning and allogeneic hematopoietic stem cell transplantation. Leukemia 21:2540–2544
21. Arellano ML, Langston A, Winton E et al (2007) Treatment of relapsed acute leukemia after allogeneic transplantation: a single center experience. Biol Blood Marrow Transplant 13:116–123
22. Mielcarek M, Storer BE, Flowers ME et al (2007) Outcomes among patients with recurrent high-risk hematologic malignancies after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 13:1160–1168