Allogeneic hematopoietic stem cell transplantation (allo-HSCT) in acute myeloblastic leukemia (AML): A single center experience

Akut myeloblastik lösemide (AML) allojeneik hematopoetik kök hücre transplantasyonu (Allo-HKHT): Tek merkez deneyimi

Osman İlhan, Pervin Topçuoğlu, Mutlu Arat, Ender A. Soydan, Meltem K. Yüksel, Önder Arslan, Muhit Özcan, Günhan Gürman, Taner Demirer, Hamdi Akan, Nahide Konuk, Akın Uysal

Department of Hematology, Stem Cell Transplantation Unit, Ankara University Faculty of Medicine, Ankara, Turkey

Abstract

Objective: We retrospectively analyzed the impact of pre- and post-transplant variables on the outcome of transplantation in 145 consecutive patients with acute myeloblastic leukemia (AML) allografted from their HLA-identical siblings in our single center cohort.

Results: The stem cell source used was bone marrow (BM) (36.6%) or peripheral blood (PB) (63.4%). Both neutrophil and platelet engraftments were observed on the median 14th day. Engraftment was faster in the PB group than in the BM group ($p<0.0001$). Severe acute graft versus host disease (aGvHD) was observed in 27.9% of the patients while chronic (c)GvHD developed in 61.2%. The use of PB was associated with more severe aGvHD. Estimated leukemia-free survival (LFS) and overall survival (OS) at 10 years were 43.4%±5.2% and 52.7%±4.6%, respectively.

Conclusion: Both in univariate and multivariate analyses for LFS and OS, remission status at transplant and the presence of aGvHD were independent risk factors. *(Turk J Hematol 2008; 25: 87-93)*

Key words: Allogeneic transplantation, AML, HLA-identical sibling donor, stem cell source, graft versus host disease.

Özet

Amaç: AML tanısı ile HLA-özdeş kardeş vericiden allojeneik transplantasyon yapılan 145 hastada transplantasyon öncesi ve sonrası değişkenlerin transplantasyon sonuçlarına etkisini geriye dönük olarak değerlendirdik.

Bulgular: Kullanılan kök hücre kaynağı kemik iliği (Kİ) (% 36.6) veya periferik kan (PK) (% 63.4)' dı. Nötrofil ve trombosit engraftmanı ortanca 14.günlerdeydi. PK grubunda engraftman Kİ grubuna göre daha kısa sürede oldu ($p<0.0001$). Ciddi akut graft versus host hastalığı (aGvHH) hastaların % 27,9'unda gözlenirken, kronik(k) GvHH % 61,2'inde gelişti. PK kullanımı daha ciddi aGvHH gelişimine neden oldu. On yıllık lösemisiz sağkalım (LSK) ve genel sağkalım (GSK) olasılığı sırayla % 43,4±% 5,2 and % 52,7±% 4.6 idi.

Sonuç: Hem tek hem de çok değişkenli istatistiksel analizde transplantasyondaki hastalık durumu ve akut GvHH gelişimi hem LSK hem de GSK üzerine etkileyen bağımsız risk faktörleri olduğu saptandı. *(Turk J Hematol 2008; 25: 87-93)*

Anahtar kelimeler: Allojeneik transplantasyon, AML, HLA-özdeş kardeş verici, kök hücre kaynağı, graft versus host hastalığı

Address for Correspondence: Dr. Osman İlhan, Department of Hematology, Stem Cell Transplantation Unit, Ankara University Faculty of Medicine, Ankara, Turkey
Tel: +90 312 595 70 99 E-mail: oilhan@superonline.com

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) cures many patients with standard- or high-risk acute myeloblastic leukemia (AML) [1-8]. Large single and multi-institutional studies have demonstrated that long-term leukemia-free survival (LFS) was achieved in 45% to 50% of individuals less than 50 years of age in whom transplantation was performed in the first complete remission (CR), and in a lower percentage of patients who have more advanced disease [1-6]. Since in adults with cytogenetically good-risk AML, chemotherapy alone can lead to sustained CR and cure, allo-HSCT is usually indicated either in patients with standard and poor-risk cytogenetic first CR or relapse and/or refractory disease [9-11]. However, relapse after transplantation remains the most important cause of treatment failure in this setting and has in general a poor outcome. The most important predictor of leukemia relapse after transplantation is disease status in the

Table 1. Pre-transplantation characteristics of the recipients and the donors

Variables (n=145)	
Median recipient age, years (range)	30 (14-63)
Median donor age, years (range)	29 (9-62)
FAB classification, n (%)	
De novo AML	139 (95.9%)
M3	9 (6.5%)
Other	130 (93.5%)
MDS secondary AML	6 (4.1%)
Status at Transplant	
CR1	98 (67.6%)
Not-CR1	47 (32.4%)
2nd CR	15 (31.9%)
3rd CR	3 (6.4%)
Refractory	29 (61.7%)
Conditioning regimen	
Ablative, n (%)	137 (94.5%))
Bu-Cy / Cy-TBI / Ida-Bu-Cy	126 (92.0%) / 7 (5.1%) / 4 (2.9%)
Reduced intensity, n (%)	8 (5.5%)
FAMP + ARAC-ATG /+ Bu-ATG /2 (25.0%) / 2 (25.0%) / 2 (25.0%)/	
+ Mel-ATG/Mel/Bu	1 (12.5%) / 1 (12.5%)
The donor - recipient pairs, n (%)	
Male → Male/Female → Female	52 (35.9%) / 30 (20.7%)
Male → Female/Female→ Male	30 (20.7%) / 33 (22.8%)
ABO and Rh-compatible, n (%)	84 (57.9%)
ABO and Rh-incompatible, n (%)	61 (42.1%)
Major ABO-mismatched, n (%)	21 (34.4%)
Minor ABO-mismatched, n (%)	27 (44.3%)
Bidirectional ABO-mismatched, n (%)	5 (8.2%)
Only Rh-mismatched, n (%)	8 (13.1%)
Stem cell source	
Peripheral Blood vs Bone Marrow	92 (63.4%) / 53 (36.6%)
GvHD prophylaxis	
CsA-short-term Mtx	72 (49.7%)
CsA-long-term Mtx	64 (44.1%)
ECP-CsA-long-term Mtx	4 (2.8%)
CsA-MMF	5 (3.4%)

FAB: French, American, British. CR: Complete remission. Bu: Busulfan. Cy: Cyclophosphamide. TBI: Total body irradiation. FAMP: Fludarabine monophosphate. ARAC: Cytosine arabinoside. ATG: Antithymocyte globulin. Mel: Melphalan. CsA: Cyclosporin A. ECP: Extracorporeal photopheresis. Mtx: Methotrexate.

pre-transplantation period [12-14]. Relapse rates are two or three times higher in patients not in remission at the time of transplantation as compared with rates in those in remission.

There has been a recent increase in the use of peripheral blood (PB) as a source of HSCs [15-24]. Many studies being done either retrospectively or prospectively have compared the outcome of patients receiving allograft with bone marrow (BM) versus PB, using an HLA-identical sibling donor [18-24]. In most studies, the incidence and severity of acute graft versus host disease (aGvHD) have been similar with BM and PB. On the other hand, PB has been associated with more chronic GvHD (cGvHD) than BM. However, the outcome with PB, in terms of LFS and overall survival (OS), has been identical to BM and sometimes superior [24].

Until recently, a myeloablative conditioning regimen has been considered a prerequisite for successful allo-HSCT both because of its anti-tumor activity and also its perceived role in securing sustained graft function. Allo-HSCT has been limited to young patients due to increased risk of regimen-related toxicity. Therefore, in contrast to a standard-dose myeloablative regimen, the use of a reduced intensity conditioning (RIC) in allo-HSCT appears to be well tolerated by high-risk patients of advanced age or with associated comorbidities [25-28]. Furthermore, there are accumulating data that the donor-derived immune systems exert a potent antileukemic effect after a RIC allo-HSCT.

In this descriptive study, we retrospectively analyzed the impacts of pre- and post-transplant variables on the transplantation outcome in 145 consecutive patients with de novo or secondary AML who received allo-HSCT in our center.

Materials and Methods

Patients

Between November 1989 and November 2004, a total of 148 allo-HSCT procedures were performed on 145 patients (85 M, 60 F) with de novo (n=139) or secondary AML (n=6) from their HLA-identical sibling donors at the Stem Cell Transplantation Unit, Department of Hematology, Ankara University School of Medicine. Three out of 145 patients underwent a second allo-HSCT due to post-transplant relapse. The median age was 30 years (14-63 years). Pre-transplantation characteristics of the recipients and their donors are shown in Table 1.

Preparative Regimen, Stem Cell Source and GvHD Prophylaxis

One hundred and thirty-seven patients received an ablative conditioning regimen including standard dose busulfan (peroral or intravenous) and cyclophosphamide (Cy) (n=126) and/or idarubicin (n=4) or total body irradiation (TBI) plus Cy (n=7). The remaining patients (n=8) received a fludarabine monophosphate (FAMP)-based RIC regimen as shown in Table 1. Infused stem cell sources were either granulocyte colony-stimulating factor (G-CSF) mobilized PB (63.4%) or BM (36.1%). Most of the patients (n=136) received the combination of cyclosporin A (CsA) and short- or long-term methotrexate (Mtx) (n=72 or n=64, respectively) for GvHD prophylaxis. While 4 out of the remaining 9 patients received pretransplantation extracorporeal photopheresis plus posttransplant-CsA and long-term Mtx, 5 patients conditioned by a RIC regimen received CsA plus mycophenolate mofetil (MMF) for immune prophylaxis.

Engraftment, GvHD, Relapse and Disease End-Points

Time to neutrophil engraftment was defined as the first of 3 consecutive days in which the absolute neutrophil count exceeded $0.5x10^9$/L. Platelet recovery was also defined as the platelet count exceeding $20x10^9$/L without platelet transfusion within 7 days.

Both aGvHD and cGvHD were diagnosed on the basis of clinical symptoms and/or verified by biopsy of involved tissue. aGvHD was graded on a scale from 0 (absent) to IV (severe) according to Seattle criteria [29]. The presence of severe aGvHD was accepted in patients with grade II to grade IV aGvHD. Patients surviving 100 days or longer were monitored for cGvHD. The severity of cGvHD was defined as limited or extensive according to the consensus criteria [30].

Relapse was defined as the appearances of either hematological or molecular signs of the disease after engraftment with full donor chimerism.

LFS was defined as the length of time from the date of transplantation to the relapse or death at last contact. OS was defined as the interval from the date of transplantation to the date of death from any cause at last follow-up. Patients still alive at the time of the analysis were entered according to the date of the last follow-up.

Statistical Analysis

Mann-Whitney U test was used for comparison of continuous variables. Categorical variables were compared using the X2 test. Results were expressed as probabilities (%) with 95% confidence intervals (CI). The predictive factors for the risks of acute and cGvHD were evaluated by univariate analysis. Actuarial OS and LFS were calculated by the method of Kaplan and Meier [31]. Significance of differences between survival curves was estimated by the log-rank test [32]. The analyses were performed in patients whose follow-ups were at least 6 months. Cox proportional hazards regression model was used in multivariate analysis to identify possible risk factors of LFS and OS [33]. Significance level for all analyses was $p< 0.05$. All data was computed using SPSS 10.0 package program software (SPSS, Inc, Chicago, IL).

Results

Engraftment occurred in 138 of 145 patients. Both neutrophil and platelet engraftments were observed on the median 14th day of stem cell infusion. Hematopoietic recovery in the allo-PB group was faster than in the allo-BM group ($p<0.0001$) (Table 2). We observed hemorrhagic cystitis in 30 (20.6%) out of all patients and non-severe veno-occlusive disease in only 9 (6.2%) patients.

Severe aGvHD was observed in 27.9% of the patients, while cGvHD developed in 61.1% of those surviving at day 100 post-transplantation. At median 74.5 months (range, 0.23-185 months) follow-up, 41 patients (28.3%) experienced a relapse and/or progression of the underlying disease. Seventeen patients received donor lymphocyte infusion because of hema-

tological relapse or loss of donor chimerism. The 10-year cumulative incidence of LFS and OS were estimated as 43.4%±5.2% and 52.7%±4.6% by Kaplan-Meier survival curve, respectively (Figure 1).

Variables Related to Transplant Outcome

Stem Cell Source

We observed a statistically significant difference in frequency of aGvHD according to stem cell source, with aGvHD more frequent in the PB group than in the BM group (p=0.059). The incidence of severe aGvHD (≥grade II-IV) was higher in the PB group (p=0.005, Table 2). Additionally and as expected, the frequency of cGvHD was also significantly higher in the PB group than in the BM group (p<0.0001). However, we were unable to show any impact of stem cell source on either early-transplant related mortality (TRM) or the probability of LFS and OS (Table 2, Figure 2).

Status at Transplant

The patients were divided into two groups according to their pre-transplantation disease status as: the first CR (n=98) and non-CR1, including the patients with ≥2 CR and partial remission and refractory disease (n=47). There was no difference between the two groups in the frequencies of either acute or cGvHD. The incidence of TRM in the CR1 group was lower than in the non-CR1 group (p=0.002). In addition, the probabilities of LFS and OS in the CR1 group were also significantly better than in the others (Table 2, Figure 3).

Graft versus Host Disease

Factors including the gender of recipients and donors, age of the recipients, infused stem cell source (PB vs BM), gender- and ABO-mismatch between the donor and recipient, ablative versus RIC regimen, pre-transplantation disease status (CR1 vs non-CR1), use of G-CSF in the post-transplantation period, and the year of transplantation (<1998 vs ≥1998) were evaluated by univariate analysis to determine their impact, if any, on the development of severe acute (grade ≥II) and cGvHD. We observed that the use of PB as HSCs had a negative effect on severe aGvHD (Grade II-IV) (RR: 2.575 [95% CI: 1.1225-5.410], p=0.006) (Table 3). In addition, patients with a female donor had an increased incidence of cGvHD (RR:1.401 [95% CI:1.059-1.853], p=0.020) (Table 3).

Leukemia Free-Survival and Overall Survival

Estimated LFS and OS at 10 years were 43.4% ± 5.2% and 52.7% ± 4.6%, respectively. Univariate analysis showed that the status at transplant (non-CR1), use of a RIC regimen and the presence of severe aGvHD were independent risk factors for LFS. On the other hand, only pretransplant disease status and severe aGvHD had a negative effect on LFS using Cox-regression for multivariate analysis (Table 4).

Discussion

Patients receiving standard myeloablative allo-HSCT at CR1 had 50% to 65% of LFS, 20% relapse rates and less than 20% TRM rates in long-term follow-up [2,6,8]. In a Southwest Oncology Group (SWOG) study, statistically significant differences were observed between AML patients allografted in 2nd CR and those allografted in untreated- or refractory-relapse [10]. Significantly inferior results were shown in those transplanted at a more advanced stage because of increased rates of both TRM and relapse. In our analyses, non-CR1 had significantly shortened LFS and OS, as expected. Since cytogenetic and/or molecular statuses at diagnosis in most of the patients were not clearly defined, we could not evaluate whether favorable cytogenetics had any effect on the transplant outcome especially in patients with CR1.

Many studies, either retrospective or prospective, have compared BM with PB as an alternative stem cell source for allo-HSCT using HLA-identical siblings [18-24]. Results obtained from these studies have emphasized that PB is associated with faster engraftment, similar or higher incidence of aGvHD, and constantly a significantly higher incidence of cGvHD. However, both LFS and OS have been shown to be similar or even better in the PB group according to recent published experience in high-risk and refractory AML patients. We observed that PB use facilitated the engraftment, but led to an increased incidence of both acute and cGvHD compared to BM. These findings were similar and in line with many published studies [18-24]. Although aGvHD shortened both the LFS and OS as shown in Table 4, we could not show that PB use had an adverse effect on the incidence of relapse and survival. The observation that PB-derived HSC use had a similar effect on LFS and OS could be explained by the increase of GvHD incidence in the PB group, which may offset the development of graft versus leukemia (GvL) effect mediated by alloreactive donor T-cells and may be an important contribution in the control of leukemia.

Sex-mismatched transplant, especially female donor to male recipient, is a major predictor for acute and cGvHD [34-36]. We detected that transplantation from a female donor was an independent risk factor associated with cGvHD, but not aGvHD.

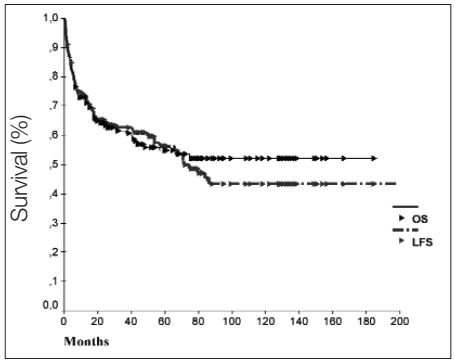

Figure 1. Kaplan-Meier estimate of LFS and OS after allo-HSCT for all patients with AML

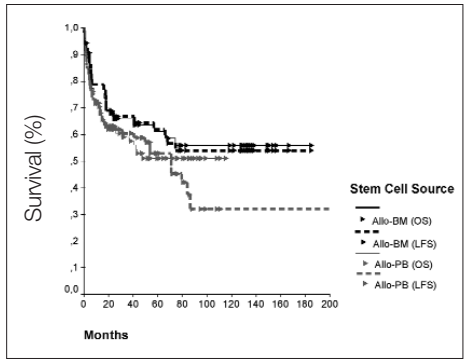

Figure 2. Kaplan-Meier estimate of LFS and OS after allo-HSCT for all patients with AML ccording to stem cell source infused

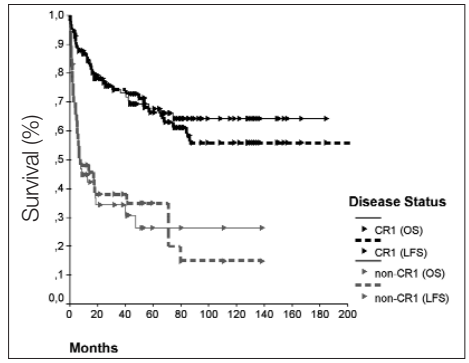

Figure 3. Kaplan-Meier estimate of LFS and OS after allo-HSCT for all patients with AML according to pretransplant disease status

Myeloablative allo-HSCT is a well-established therapy for adult patients with AML. However, because of the high incidence of regimen-related toxicity, this procedure is often limited to younger patients in good medical condition. In an attempt to reduce procedure-related toxicity in the elderly or in patients with comorbidities precluding the use of myeloablative preparative regimens, RIC regimens have been shown to have lower regimen-related toxicity [25-28]. Accumulating evidence that the donor-derived immune system exerts a potent antileukemic effect after allograft has led to the development of RIC regimens that are designed to produce durable donor engraftment of allogeneic stem cells and provide a platform for an immunologically mediated GvL effect with less attendant toxicity. The factors playing a role in our center's policy for using a RIC regimen in patients with AML were: advanced age of the recipient, comorbidity conditions precluding a conventional myeloablative regimen, and pre-transplant

Table 2. Hematopoietic reconstitution in neutrophil and platelets, incidence of acute and cGvHD, and probability of cumulative LFS or OS in AML patients receiving BM vs PB or with CR1 vs non-CR1 pretransplantation status

	Allo-BM (n=53)	Allo-PB (n=94)	p	CR1 (n=98)	Non-CR1 (n=47)	P
Status at transplant (CR1), n (%)	40 (75.5%)	59 (62.8%)	0.115			
Engraftment (Absent), n (%)	3/53 (56.7%)	7/94 (74.5%)	0.483	4/98 (40.8%)	6/47 (12.7%)	0.126
Median neurophil engraftment, days (range)	21 (13 - 26)	13.5 (8 - 23)	<.0001	13 (8-26)	14.5 (9-25)	0.222
Median platelet engraftment, days (range)	20 (18 - 64)	12 (8 - 43)	<.0001	12 (9-64)	14 (8-43)	0.902
aGvHD						
Absent (Grade 0-I)	43 (86.0%)	55 (64.0%)		70 (74.5%)	28 (66.7%)	
Severe (Grade II-IV)	7 (14.0%)	31 (36.0%)	0.006	24 (25.5%)	14 (33.3%)	0.481
cGvHD						
Absent	32 (69.6%)	15 (20.0%)		35 (38.9%)	12(38.7%)	
Limited	7 (15.2%)	34 (45.3%)		33 (36.7%)	8 (25.8)	
Extensive	7 (15.2%)	26 (34.7%)	<.0001	22 (24.4%)	11 (35.5)	0.400
Early transplant-related mortality (First day 100 after transplantation)	5/53 (9.4%)	14/92 (15.2%)	0.320	7/98 (7.1%)	12/47 (25.5%)	0.002
Probability of cumulative LFS at 10 years	53.9%±7.4%	32.0%±8.1%	0.142	55.8%±6.3%	14.9%±7.3%	<.00001
Probability of cumulative OS at 10 years	55.8%±7.3%	51.1% ± 5.7%	0.429	64.1%±5.4%	26.5%±7.4%	<.00001

BM: Bone marrow; PB: Peripheral blood. CR: Complete remission. LFS: Leukemia-free survival. OS: Overall survival. aGvHD: Acute graft versus host disease. cGvHD: Chronic graft versus host disease.

Table 3. The efficacy of various factors on the incidence of severe aGvHD and cGvHD

	Acute GvHD		Chronic GvHD	
Factors	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**
Recipient's gender (Female vs Male)	1.018 (0.674-1.986)	0.599	1.024 (0.768-1.364)	0.873
Donor's gender (Female vs Male)	1.140 (0.665-1.955)	0.634	1.401 (1.059-1.853)	0.020
Recipient's age (>30 yrs vs ≤30 yrs)	0.843 (0.487-1.459)	0.539	1.137 (0.857-1.508	0.376
Stem cell source (PB vs BM)	2.575 (1.225-5.410)	0.006	2.629 (1.674-4.128)	<.0001
Sex mismatch (Mismatched vs Matched)	0.894 (0.517-1.547)	0.688	0.978 (0.733-1.303)	0.877
ABO mismatch (Mismatched vs Matched)	1.196 (0.692-2.067)	0.525	1.104 (0.829-1.471)	0.507
Conditioning regimen (Ablative vs RIC)	0.977(0.293-3.255)	0.970	0.602 (0.520-0.697)	0.162
Pretransplant disease status (CR1 vs >CR1)	0.766 (0.442-1.327)	0.349	0.997 (0.721-1.380)	0.986
Posttransplant G-CSF use (Present vs Absent)	0.296 (0.458-1.382)	0.378	0.857 (0.646-1.137)	0.276
Transplant period (<1998 vs ≥ 1998)	0.794 (0.441-1.430)	0.435	0.853 (0.628-1.159)	0.237

aGvHD: Acute graft versus host disease. cGvHD: Chronic graft versus host disease. PB: Peripheral blood. BM: Bone marrow. RIC: Reduced intensity regimen. CR: Complete remission. G-CSF: Granulocyte colony-stimulating factor. RR: Relative risk. CI: Confidence interval.

Table 4. The efficacy of various factors on the probability of LFS and OS

	LFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
Factors	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Recipient's gender (Female vs Male)	1.220 (0.752-1.980)	0.420			1.031 (0.624-1.704)	0.905		
Donor's gender (Female vs Male)	0.833 (0.511-1.358)	0.465			0.857 (0.513-1.407)	0.527		
Recipient's age (> 30 ys vs < =30 ys)	1.013 (0.626-1.637)	0.959			0.981 (0.597-1.613)	0.940		
Stem cell source (PB vs BM)	1.468 (0.877-2.457)	0.142			1.233 (0.734-2.074)	0.429		
Sex (Mismatched vs Matched)	1.069 (0.661-1.728)	0.785			1.009 (0.604-1.685)	0.973		
ABO mismatched (Mismatched vs Matched)	1.170 (0.716-1.913)	0.532			1.032 (0.623-1.708)	0.903		
Conditioning regimen (RIC vs Ablative)	3.376 (1.447-7.879)	0.005			3.416 (1.455-8.020)	0.005		
Status at transplant (>CR1 vs CR1)	3.438 (2.111-5.598)	<.0001	2.957 (1.575-5.539)	0.001	3.698 (2.231-6.131)	<.0001	3.774 (1.985-7.101)	<.0001
Posttransplant G-CSF use (Present vs Absent)	0.794 (0.479-1.318)	0.372			0.808 (0.479-1.362)	0.423		
Transplant period (<1998 vs ≥1998)	0.920 (0.556-1.522)	0.744			1.023 (0.616-1.697)	0.931		
Severe aGvHD (Present vs Absent)	1.736 (1.015-2.969)	0.044	1.936 (1.069-3.505)	0.029	1.925 (1.107-3.347)	0.020	2.113 (1.162-3.846)	0.014
cGvHD (Present vs Absent)	0.741 (0.411-1.334)	0.317			0.700 (0.373-1.315)	0.268		

LFS: Leukemia-free survival. OS: Overall survival. PB: Peripheral blood. BM: Bone marrow. RIC: Reduced intensity regimen. CR: Complete remission. aGvHD: Acute graft versus host disease. cGvHD: Chronic graft versus host disease. RR: Relative risk. CI: Confidence interval.

disease status. Due to the small number of patients in the RIC group in our series, the impact of RIC on outcome cannot be evaluated in this analysis; therefore, prospective randomized comparative clinical studies comparing ablative regimen with RIC are urgently needed.

In conclusion, in our single center cohort, G-CSF mobilized PB use in AML patients for allo-transplantation increased the incidence of both acute and cGvHD, but had no effect on the relapse risk and survival in standard-risk AML. Considering all patients in this series, our data suggest that pretransplant control of the leukemic status and severe aGvHD are independent risk factors for both LFS and OS.

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