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Leukemia burden delays lymphocyte and platelet recovery after allo-SCT for AML

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Abstract

Lymphocyte and platelet recovery may influence outcomes of allo-SCT for treatment of AML. It is not clear, however, if this impact is independent of patient and transplant characteristics. To investigate this question, we evaluated the influence of pre- or post transplant factors on day + 30 absolute lymphocyte count (ALC) and the speed of platelet engraftment. We studied 106 AML patients treated with fludarabine and melphalan reduced-intensity conditioning and allo-SCT. Twenty nine percent of patients were in CR at the initiation of the conditioning, 39% had active disease with circulating blasts and 32% had active disease without circulating blasts. The graft source was peripheral blood from a matched sibling donor in 55% and BM from a matched unrelated donor in 45%. Our data showed that the presence of circulating blasts before transplantation is significantly correlated with low post-SCT day + 30 ALC and slow platelet engraftment. This finding suggests that the impact of early ALC and platelet recovery on transplant outcome may not be independent of disease status at transplantation.

Keywords

AML; platelets; neutrophils; hematopoietic reconstitution; allogeneic transplantation

Introduction

In patients with AML, disease relapse and treatment related mortality are the major causes of treatment failure after allo-SCT using reduced-intensity conditioning regimens.[1] Improving leukemia-free survival in these patients depends, at least in part, on the

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identification of prognostic factors and biomarkers for treatment failure that would facilitate risk stratification and development of more efficacious therapies.

Several reports have evaluated the prognostic value of two biomarkers of early post transplant hematopoietic reconstitution, the absolute lymphocyte count (ALC) and/or platelet recovery[2-13] in various disease groups including AML. The presence of a low ALC and/or low platelet count evaluated at different time points has been consistently reported to be associated with poor outcomes. It is not clear, however, if this association is independent of patient and transplant characteristics, especially if it is independent of disease status at transplantation, which is the most significant prognostic factor in AML patients treated with reduced-intensity conditioning and SCT.[14,15]

We sought to test this hypothesis by systematically evaluating the impact of pre- and post transplantation factors, including graft composition, on post-SCT day + 30 ALC and on the speed of platelet engraftment in a relatively homogeneous cohort of AML patients treated uniformly at our institution with fludarabine and melphalan reduced-intensity conditioning and allo-SCT.[14,15] We limited the analysis to patients who were alive and in CR on post-SCT day + 30, as these represent the group of patients in whom identification of biomarkers to guide early interventions would be most relevant.

Materials and methods

Study population

All consecutive patients with AML treated at our institution with a fludarabine and melphalan-based conditioning regimen and SCT between August 1996 and June 2006 were included in the analysis (N = 181). Patients who underwent SCT before December 2003 were included in an earlier report[14] (n = 122/181). All patients provided written informed consent before being treated on protocols approved by the Institutional Review Board (IRB) or were treated under the compassionate investigational drug mechanism, which was also approved by the IRB. The IRB also granted approval to this retrospective analysis.

Conditioning regimen and GVHD prophylaxis

All patients had been prospectively accrued to one of four protocols involving the use of the fludarabine and melphalan preparative regimen during the study period. Details of these studies have been described previously.[16,17] Antithymocyte globulin was given to 39% of recipients of matched unrelated donor (MUD) transplants. GVHD prophylaxis consisted mainly (in 93% of patients) of tacrolimus (adjusted to maintain blood levels of 5–15 ng per 100 ml during the first 100 days and then tapered, as clinically indicated) and MTX (5 mg/m^2 i.v. on days 1, 3, 6 and 11 after transplantation). Ten recipients of MUD transplants were also given pentostatin.

Stem cell procurement

Standard mobilization protocols and apheresis techniques were used for the procurement of donor BM or G-CSF-primed PBSCs. BM from unrelated donors was obtained through the

National Marrow Donor Program according to the applicable guidelines. All donors provided written informed consent.

Supportive care

Infection prophylaxis consisted of levofloxacin, fluconazole and acyclovir or valacyclovir. Filgrastim at a dose of 5 μg/kg was administered subcutaneously daily beginning on post-SCT day + 7 and discontinued once the granulocyte count recovered to more than 1.5×10^9/l and remained at this level for 3 consecutive days. After recovery of the neutrophil count to more than 1.0×10^9/l, trimethoprim-sulfamethoxazole (given orally twice weekly) or pentamidine (given intravenously every 3 weeks) was used for prophylaxis against *Pneumocystis carinii* infection. CMV antigenemia surveillance consisted of twice weekly screening, with preemptive use of ganciclovir or foscarnet in the event of positive assay findings. Blood products were irradiated and filtered to remove leukocytes.

Definitions

Chimerism analysis was performed on post-SCT days + 30 and + 100 and every 3 months thereafter. Engraftment was defined as the first of 3 consecutive days with an ANC $>500 \times 10^6$/l. Failure to engraft by day + 30 was considered primary graft failure. Mixed chimerism was defined as the presence of any detectable (1% or greater) recipient DNA or cells in addition to donor-derived DNA or cells. The day of platelet engraftment was defined as the first of 7 consecutive days with a platelet count of >20 k/mm^3, without platelet transfusion support.

The CR before SCT was defined as a normocellular BM sample containing 100×10^9/l. The same criteria were used to define CR after transplantation, except for the platelet count and evidence of donor cell engraftment. Response to transplant was assessed on post-SCT day + 30 and every 4 months during the first 2 years. For patients with active disease before transplantation, disease status was categorized based on the presence or absence of circulating blasts. AML cytogenetic abnormalities were grouped according to the Southwestern Oncology Group published criteria.[18]

Statistical methods

Patients who were alive and in CR on post-SCT day + 30 were considered eligible for this study. We initially considered four biomarkers of hematopoietic reconstitution: time to ALC recovery to 500×10^6/l, time to platelet engraftment, post-SCT day + 30 ALC and post-SCT day + 30 platelet counts. Only two of these factors (post-SCT day + 30 ALC and the speed of platelet engraftment) were considered for the final analyses because we found a high correlation between the speed of platelet engraftment and the platelet count on post-SCT day + 30 onwards, and a lack of correlation between the speed of ALC recovery and post-SCT day + 30 ALC. The cutoff points for the post-SCT day +30 ALC were selected based on those reported in the literature[8,11,12] and included $<150 \times 10^6$/l, $<200 \times 10^6$/l and $<500 \times 10^6$/l. We considered only an ALC of $<500 \times 10^6$/l for the final analyses because of the small number of patients in our patient population with an ALC of $<200 = 10^6$/l (14%). The median time to platelet engraftment was used to define a slow platelet engraftment. The impact of patient and transplant characteristics on post-SCT day + 30 ALC and on the speed

of platelet engraftment was evaluated in univariate analyses and multivariate analyses (when possible) using logistic regression methods. The pre-transplantation factors considered included graft composition (numbers of CD3+, CD34+ and total nucleated cells infused), disease status at transplantation (categorized as described above), karyotype, patient age (categorized at the median of 55 years), patient sex, and the combination of donor and patient sex, donor and patient CMV serostatus at the time of transplantation, melphalan dose (100, 140 or 180 mg/m^2), and the use of gemtuzumab (Mylotarg) or antithymocyte globulin in the conditioning regimen. The post transplantation factors evaluated included the occurrence of grades II–IV acute GVHD and CMV reactivation before day +30. These events are referred to henceforth as early acute GVHD and early CMV reactivation, respectively. Statistical significance was set at 0.05. Analysis was performed using STATA 2001 software (StataCorp, College Station, TX, USA).

Results

Study population

There were 181 patients treated with a fludarabine and melphalan-based conditioning during the study period. Patient characteristics are listed in Table 1. Twenty-two of these patients were excluded for the analysis because of early death (n = 11), primary graft failure (n = 3) or failure to achieve CR by day + 30 (n = 8). We further restricted the study to the 125 patients who received a PBSC graft from a matched sibling donor (MSD) (n = 65) or a BM graft from a MUD (n = 60) because of a lack of meaningful numbers in the other graft categories (listed in Table 1). Donor chimerism was documented at the time of engraftment in 94% (118/125) of these patients. Myeloid and T-cell chimerism was 100% donor in 97% of patients for whom subset chimerism was available.

Nineteen patients were diagnosed with early grades II–IV acute GVHD (GVHD occurring before post-SCT day + 30) and had a significantly lower ALC (median, 320 vs 640 × 10^6/l, P = 0.005) and platelet count (median, 37 vs 67 k/mm^3, P = 0.004) on post-SCT day + 30, irrespective of the type of graft. Because of the small number of patients affected (n = 19) it was not possible to adjust for the effect of early acute GVHD on hematopoietic recovery in a multivariate analysis. Instead, we adjusted for this effect by excluding the 19 patients diagnosed with early acute GVHD from further analyses.

Among the remaining 106 patients, the median day + 30 ALC was 640 × 10^6/l (range, 0–3150 × 10^6/l). Lymphopenia (ALC <500 × 10^6/l) was noted in 37% (39/106) of patients.

Platelet engraftment occurred in 93/106 patients (88%) at a median of 18 days (range, 7–49 days) after transplantation. There was no difference in the proportion of patients who successfully engrafted among the recipients of PBSC/MSD grafts (51/58, 88%) and recipients of BM/MUD grafts (42/48, 87%). However, engraftment was faster in the former group, occurring at a median of 15 days (range, 7–46 days) vs 21 days (range, 9–49 days) in the latter group. The median platelet count on post-SCT day + 30 was 80 and 60 k/mm^3 in the two groups, respectively, and was highly correlated with the speed of platelet engraftment, irrespective of the graft type (data not shown).

Of note, the speed of platelet engraftment was also highly correlated with post-SCT day + 30 lymphopenia in that 72% of patients with ALC <500 × 10^6/l had a slow platelet engraftment in contrast to 49% of those with higher ALC (P = 0.03).

Impact of pre- and post transplant factors on lymphocyte recovery

Results were comparable in recipients of PBSC/MSD grafts and BM/MUD grafts and are presented in combination for both groups (Table 2).

Impact of patient and transplant characteristics on lymphocyte recovery—The presence of circulating blasts (n = 31) at the time of transplantation and the development of early CMV reactivation (n = 20) were the only significant correlates of day + 30 lymphopenia. In particular, the median day + 30 ALC was significantly lower in patients who had active disease with circulating blasts (470 × 10^6/l), than those who had active disease without blasts (700 × 10^6/l) or those who were in CR (760 × 10^6/l). Lymphopenia was significantly more prevalent in patients with circulating blasts (55%) compared with those without blasts (26%, odds ratio (OR) = 3.4, P = 0.02) or those who were in CR (32%, OR = 2.5, P = 0.06). The difference between the latter two groups was not significant (OR = 0.7, P = 0.6). A diagnosis of early CMV reactivation was associated with a significantly higher day +30 ALC (median 780 × 10^6 vs 590 × 10^6) and lymphopenia was less prevalent in these patients (15%, OR = 0.2, P = 0.03) than in those without CMV reactivation (42%). With regard to CMV serostatus, pairs in which the donor was seronegative and the patient seropositive showed a trend toward a higher prevalence of day +30 lymphopenia (48%; OR = 2.1, P = 0.08). There was also a trend toward a higher prevalence of lymphopenia in patients older than 55 years (45 vs 28%, OR = 2.1, P = 0.08) and in patients who received more than the median number of chemotherapy regimens before transplantation (47 vs 31%, OR = 2.0, P = 0.09). The median number of regimens was one in PBSC/MSD graft recipients and two regimens in BM/MUD graft recipients. The impact of pentostatin in GVHD prophylaxis could not be evaluated because only 5 of the 10^6 patients received the drug.

Disease status at transplantation, early CMV antigenemia, patient age, donor/patient CMV serostatus and the number of previous chemotherapy regimens were considered in a multivariate logistic model to determine their independent association with day +30 lymphopenia. Of these factors, only disease status and early CMV antigenemia remained significant in the final model, with effects similar to those obtained in the univariate analysis (Table 2).

Impact of graft composition on lymphocyte recovery—As expected, the numbers of CD3+, CD34+ and total nucleated cells infused differed significantly according to the type of graft. In PBSC/MSD graft recipients, the respective medians were 1.9 × 10^8/kg (range 0.42–5.6), 4.6 × 106/kg (range 1.7–9.1) and 6.7 × 10^8/kg (range 2.0–22) vs 0.22 × 10^8/kg (range 0.05–2.6), 3.6 × 10^6/kg (range 0.6–13) and 3.1 × 10^8/kg (range 0.7–17) in BM/MUD graft recipients. We found no association between the numbers of CD3+, CD34+ or total nucleated cells infused and day +30 lymphopenia when evaluated as continuous variables or when stratified into quartiles, irrespective of the graft type.

Impact of pre- and post transplant factors on platelet engraftment

Results were comparable in recipients of PBSC/MSD grafts and BM/MUD grafts and are presented in combination for both groups (Table 3).

Impact of patient and transplant characteristics on platelet engraftment— Disease status at transplantation was the most significant correlate of the speed of platelet engraftment, followed by patient CMV serostatus, use of low-dose melphalan treatment and patient sex. Specifically, the speed of engraftment was significantly slower in patients with circulating blasts at transplantation, 77% of whom recovered later than the median time to engraftment (OR = 5.6, $P = 0.002$), compared with 60% of patients who had active disease without blasts (OR = 2.5, $P = 0.05$) and 38% of those in CR (reference group). Although the number of CMV-seronegative patients was relatively small in this series ($n = 16$), patient CMV seropositivity was associated with a significantly slower platelet engraftment (OR = 4.8, $P = 0.01$). Similarly, platelet counts recovered more slowly in male patients than in female patients (OR = 0.4, $P = 0.04$). This effect was mostly attributed to a faster recovery when both the donor and patient were female (OR = 0.3, $P = 0.04$). Conditioning with low-dose melphalan (100 mg/m^2) was also associated with faster platelet recovery (OR = 0.3, $P = 0.03$). The impact of pentostatin in GVHD prophylaxis could not be evaluated because only 5 of the 106 patients received the drug.

Impact of graft composition on platelet engraftment—There was no significant association between numbers of CD3+, CD34+ or total nucleated cells infused and the speed of platelet engraftment when evaluated as continuous variables. However, a quartile analysis stratified by graft type revealed a significant correlation between the CD34+ cell dose infused and the speed of platelet engraftment in PBSC/MSD graft recipients but not MUD/BM graft recipients. In the former group, patients who received a CD34+ cell dose below the median (4.6×10^6/kg) showed a significantly slower engraftment than did those who received a dose above this ($P = 0.02$). CD3+ and total nucleated cell dose did not influence platelet engraftment, irrespective of graft type.

The pre- and post transplantation factors that were statistically significant or marginally significant on univariate analysis ($P \leq 0.06$) were considered for multivariate analysis. However, such analysis was not possible, because of sample size limitation, given the large number of significant correlates observed on univariate analysis. It is noteworthy to mention that the impact of pre- and post transplant factors remained comparable when the 20 patients who received the lowest dose of melphalan (100 mg/m^2) were excluded from the analysis.

Discussion

Our data show a previously unreported significant correlation between disease status at transplantation and hematopoietic reconstitution during the first month after allo-SCT. This was reflected in a significantly lower post-SCT day + 30 ALC and slower platelet engraftment in patients with active disease at the initiation of the conditioning regimen, and especially those who had peripheral blood circulating blasts. A potential explanation for this association is a persistent deleterious effect of the leukemia burden, and/or its treatment, on

the ability of the lymphoid and marrow microenvironments to support T cell and platelet reconstitution after SCT.

Our finding of a strong impact for disease status on lymphocyte and platelet recovery calls into question the independent prognostic value of post-SCT day + 30 ALC and platelet recovery in AML patients. We could not assess this question in this study because of sample size limitations. As suggested by previous reports,[2-14] this may be difficult to achieve in single-institution studies. Multi-institutional studies are warranted for this purpose, as they would provide the statistical power needed for proper adjustment of confounding.

We found no correlation between the numbers of infused graft cells and early hematopoietic reconstitution (except for an impact of CD34+ cell dose on the speed of platelet engraftment in recipients of a PBSC/MSD graft). This suggests that host- and disease-related factors may be a greater determinant of early hematopoietic reconstitution than the simple numbers of adoptively transferred graft cells. It is noteworthy that on univariate analysis, the use of PBSCs resulted in faster platelet engraftment, but did not impact post-SCT day +30 ALC. The prevalence of day + 30 lymphopenia was not significantly different between recipients of a BM/MUD and PBSC/MSD grafts. This is consistent with the notion that, in T-cell replete grafts, expanding natural killer cells may constitute the majority of lymphocytes early post-SCT, irrespective of the graft composition, as was reported recently in recipient of BM or PBSC grafts[19,20] as well as in recipients of umbilical cord blood transplants.[21]

Early CMV reactivation significantly increased post-SCT day +30 ALC in our study. This is in agreement with the studies by Heining *et al.*[19] and Dolstra *et al.*,[22] both of which showed that an expansion of CD3+ CD8+ cells occurs in the presence of CMV reactivation. It is important to note, however, that the increased ALC may not necessarily correlate with enhanced immune function, as we previously found that dysfunction of CMV-specific CD8+ T cells may underlie an increased risk of viral reactivation.[23]

We could not evaluate the impact of early CMV reactivation on the speed of platelet engraftment because reactivation most frequently occurred after platelet engraftment in our cohort. However, data from the study by Dominietto *et al.*[4] support a potential negative impact of CMV reactivation (or its treatment) on platelet recovery, in that day + 50 thrombocytopenia was more frequent in patients with high-level CMV antigenemia who received allo-SCTs for various hematologic malignancies. It is noteworthy that CMV seropositive patients had a significantly slower platelet recovery in our study. This may provide an explanation for the poor survival consistently found to be associated with CMV seropositivity. Our results highlight the need to adjust for early CMV reactivation in studies evaluating the impact of hematopoietic reconstitution on transplantation outcome.

Confirming previous reports,[2,4,6,10] we found that early grades II–IV acute GVHD is a dominant factor affecting hematopoietic reconstitution. We have adjusted for this factor by excluding patients who had developed early severe acute GVHD from analyses of correlates of hematopoietic reconstitution. Because severe acute GVHD occurred after platelet engraftment in most cases, we were not able to determine the correlation between acute GVHD and speed of platelet recovery.

In summary, our study highlights the fact that in the allogeneic setting hematopoietic reconstitution is a complex process that is affected by a number of pre- and post transplant factors, predominantly severe acute GVHD and the leukemia burden. The independent prognostic value of biomarkers of hematopoietic reconstitution remains to be validated in large cohort studies.

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Table 1

Patient characteristics

Median age, years (range)	55	(13–74)
Median number of previous chemotherapy regimens (range)	2	(0–8)
	No. of patients	*(%)*
Patient sex		
Male/female	108/73	60/40
Source of stem cells		
PB	96	53
BM	85	47
Donor type		
Matched related	92	51
Matched unrelated	89	49
Donor type/source of stem cells		
Matched related/PB	77	42
Matched related/BM	15	8
Matched unrelated/PB	19	10
Matched unrelated/BM	70	39
Disease status at transplantation		
CR	52	29
Active disease without circulating blasts	71	39
Active disease with circulating blasts	58	32
Karyotype risk group		
High	77	42
Intermediate	95	52
Low	5	3
Undetermined	4	2
Conditioning regimen		
Fludarabine/melpahalan±ATG[a]	164	91
Fludarabine/melpahalan/mylotarg±ATG[a]	17	9
GVHD prophylaxis		
Tacrolimus/MTX	168	93
Tacrolimus/MTX/pentostatin[a]	10	5
Tacrolimus±other	2	1
CYA/steroids	1	0.6
Response day +30 after transplantation[b]		
CR	159	95
Other	8	5

Abbreviations: ATG = antithymocyte globulin; PB = peripheral blood.

[a] ATG and pentostatin were added only in recipients of a graft from a matched unrelated donor.

[b] Evaluated in 167/181 patients who were alive and engrafted on post transplant day +30

Table 2

Correlates of day +30 lymphopenia (ALC less than 500×10^6/l) excluding patients with early grade II–IV acute GVHD

	No. of patients	*Median*	*%*	*Univariate analysis*			*Multivariate analysis*		
	N = 106	*ALC*	*Lymphopenic*	*OR*	*95% CI*	*P-value*	*OR*	*95% CI*	*P-value*
Graft type									
Matched unrelated donor/BM	48	580	42	1.5	0.7–3.2	0.3	NA		
Matched sibling donor/PB	58	745	33	1.0	NA		NA		
Disease status at transplantation									
Active disease with circulating blasts	31	470	55	1.0			NA		
Active disease without circulating blasts	38	700	26	0.3	0.1–0.8	0.02	NA		
CR	37	760	32	0.4	0.1–1.1	0.06	NA		
Active disease with circulating blasts vs all other				2.9	1.2–6.9	0.02	2.7	1.1–6.6	0.03
CMV reactivation before day +30									
Yes	20	780	15	0.2	0.1–0.9	0.03	0.3	0.1–0.96	0.04
No	85	590	42	1.0	NA		1.0		
Donor/patient CMV serostatus									
Non-reactive/non-reactive	10	890	30	1.0	NA		NA		
Reactive/non-reactive	6	580	33	1.0	NA		NA		
Reactive/reactive	48	735	29	1.0	NA		NA		
Non-reactive/reactive	38	545	47	2.1	0.9–4.9	0.08	NA		
Number of previous chemotherapy regimens									
At least the median	38	560	47	2.0	0.9–4.6	0.09	NA		
Less than the median	68	670	31	1.0	NA		NA		
Age, years									
At least 55	56	570	45	2.1	0.9–4.7	0.08	NA		
Less than 55	50	705	28	1.0	NA		NA		
Patient sex									
Female	42	680	36	0.9	0.4–2.1	0.8	NA		
Male	64	630	37	1.0	NA		NA		
Donor/patient sex match									
M/M	38	640	34	0.8	0.2–2.7	0.7	NA		
F/F	15	690	40	1.0	NA		NA		
M/F	27	670	33	0.7	0.2–2.8	0.7	NA		
F/M	25	580	44	1.2	0.3–4.3	0.8	NA		
Karyotype risk group									
High	40	625	35	0.8	0.4–1.9	0.7	NA		
Intermediate	59	630	39	1.0	NA		NA		
Low	4	705	25	NA	NA		NA		
Unknown	3	700		NA	NA		NA		

	No. of patients	*Median*	*%*	*Univariate analysis*			*Multivariate analysis*		
	N = 106	*ALC*	*Lymphopenic*	*OR*	*95% CI*	**P-*value***	*OR*	*95% CI*	**P-*value***
Dose of melphalan, mg/m²									
100	20	860	25	0.5	0.2–1.5	0.2	NA		
140/180	86	630	39	1.0	NA		NA		
Mylotarg									
Yes	10	750	40	1.2	0.3–4.4	0.8	NA		
No	96	640	36	1.0	NA		NA		
Use of ATG in conditioning[a]									
Yes	18	570	44	1.2	0.4–3.9	0.8	NA		
No	30	580	40	1.0	NA		NA		
Time to ALC 500 × 10⁶/l[b]									
Less than the median	40	785	32	1.1	0.5–2.6	0.8	NA		
At least the median	66	670	30	1.0	NA		NA		

Abbreviations: ATG = antithymocyte globulin; CI = confidence interval; F = female; M = male; NA = not applicable; OR = odds ratio; PB = peripheral blood.

Early acute GVHD refers to acute GVHD diagnosed before post transplant day +30.

Totals are less than 106 for some variables because of missing data.

[a] Among recipients of a BM graft.

[b] Evaluated among patients who reached an ALC of 500×10^6/l by post transplant day +30.

Table 3

Correlates of the speed of platelet engraftment excluding patients with early grade II–IV acute GVHD

	No. of patients	*Slow platelet engraftment*	*Univariate analysis*		
	N = 106	*(%)*	*OR*	*95% CI*	*P-value*
Disease status at transplantation					
Active disease with circulating blasts	31	77	5.6	1.9–16.4	0.002
Active disease without circulating blasts	38	60	2.5	0.99–6.4	0.05
CR	37	38	1.0	NA	
Donor/patient CMV serostatus					
Non-reactive/non-reactive	10	30	NA		
Reactive/non-reactive	6	17	NA		
Reactive/reactive	48	69	NA		
Non-reactive/reactive	38	53	NA		
Patient R/vs all other			4.8	1.4–16.2	0.01
Number of previous chemotherapy regimens					
At least the median	38	68	2.0	0.9–4.7	0.09
Less than the median	68	51	1.0	NA	
Age, years					
At least 55	56	66	2.1	0.96–4.6	0.06
Less than 55	50	48	1.0	NA	
Patient sex					
Female	42	45	0.4	0.2–0.96	0.04
Male	64	66	1.0	NA	
Donor/patient sex match					
M/M	38	63	1.0	NA	
F/F	15	33	0.3	0.1–0.96	0.04
M/F	27	52	1.0	NA	
F/M	25	72	1.0	NA	
Karyotype risk group					
High	40	62	1.4	0.6–3.2	0.4
Intermediate	59	54	1.0	NA	
Low	4	75			
Unknown	3	33			
Dose of melphalan, mg/m^2					
100	20	35	0.3	0.1–0.9	0.03
140/180	86	63	1.0	NA	
Mylotarg					
Yes	10	70	1.8	0.4–7.4	0.4
No	96	56	1.0	NA	
Use of ATG in conditioning[a]					
Yes	18	61	1.2	0.4–3.9	0.8
No	30	57	1.0	NA	

	No. of patients	*Slow platelet engraftment*	*Univariate analysis*		
	N = 106	***(%)***	***OR***	***95% CI***	**P-*value***
Post-SCT day +30 ALC					
Less than 500 × 10^6/l	39	72	2.6	1.1–6.1	0.03
At least 500 × 10^6/l	67	49	1.0		

Abbreviations: CI = confidence interval; F = female; M = male; MSD = matched sibling donor; MUD = matched unrelated donor; NA = not applicable; OR = odds ratio; PB = peripheral blood; R = reactive.

Early acute GVHD refers to acute GVHD diagnosed before post transplant day +30.

Slow platelet engraftment is defined as occurring at or after post-SCT day + 15 in recipients of a MSD/PB graft, and at or after day +21 in recipients of a BM/MUD graft.

Totals are less than 106 for some variables because of missing data.

[a] Among recipients of a BM graft.