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Comparison of Unrelated Cord Blood and Peripheral Blood Stem Cell Transplantation in Adults with Myelodysplastic Syndrome after Reduced-Intensity Conditioning Regimen: A Collaborative Study from Eurocord (Cord blood Committee of Cellular Therapy & Immunobiology Working Party of EBMT) and Chronic Malignancies Working Party

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A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment in patients with higher risk myelodysplastic syndrome (MDS), but the choice of the optimal alternative stem cell source is still a subject of debate in patients lacking an HLA-matched sibling donor. Here, we report on a large series of patients with MDS (N = 631) transplanted either with mobilized peripheral stem cells (PBs) from unrelated donors (n = 502) or with umbilical cord blood transplant (UCB, n = 129) as alternative grafts after reduced-intensity conditioning. Neutrophil engraftment was higher after PB (98% versus 78%, $P < .0001$). Acute graft-versus-host disease (GVHD) was similar after PB (31%) and UCB (29%), and chronic GVHD incidence was higher after PB (41% versus 23%). Two-year nonrelapse mortality was lower after PB (31% versus 42% $P = .03$). There was a better overall survival (OS) and disease-free survival (DFS) after PB (49% ± 2% versus 30% ± 4%, $P < .0001$ and 44% ± 2% versus 28% ± 4%, $P < .0001$). Multivariate analysis confirmed the advantage of PB for treatment-related mortality, OS, and DFS, whereas relative risk of chronic GVHD was similar. A multivariate analysis comparing PB from a 10/10 HLA-matched donor, PB from a 9/10 HLA-matched donor, and UCB

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showed an advantage on treatment-related mortality, DFS, and OS only in 10/10 PB. We conclude that in MDS patients lacking an HLA-matched sibling donor, PB from a 10/10 HLA-matched unrelated donor is the preferred source of hematopoietic stem cells. HLA-mismatched unrelated donor or cord blood seem to give similar inferior results except for neutrophil engraftment, which is delayed after UCB.

INTRODUCTION

Myelodysplastic syndrome (MDS) is a hematological malignancy resulting in ineffective hematopoietic transplantation and leading to acute leukemia in a substantial proportion of patients. Patients with MDS have an expected survival that ranges from a few months to more than 10 years depending on prognostic factors. In particular cytogenetics, cytopenia and blast count are used to calculate the International Prognostic Scoring System (IPSS) [1]. According to the IPSS, for patients with higher risk MDS (intermediate-2 or high), life expectancy is lower than 3 years, and allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option [2]. Because these patients are in median older than 60 years, a reduced-intensity conditioning regimen (RIC) has been increasingly used, resulting in long-term survival in approximately one third of them, with relapses remaining the primary cause of treatment failure followed by toxicity and infection [3-5].

For patients who need an HSCT and lack a suitable HLA-matched sibling donor, alternative donor graft sources such as an unrelated donor or unrelated umbilical cord blood (UCB) can be considered [6]. Transplantation from an unrelated donor is limited by HLA matching and donor availability, whereas UCB is more easily available with less HLA barrier, increasing probability to identify 1 or 2 suitable cord blood units.

Furthermore, graft-versus-host disease (GVHD) incidence has been reported to be lower after UCB than after use of an unrelated donor. This can be particularly important for long-term quality of life. We reported encouraging results in 108 MDS patients transplanted with UCB with a decreased non-relapse mortality (NRM) in patients receiving RIC and a 2-year overall survival (OS) rate of 35% [7]. Currently, there is no report comparing results of transplantation using unrelated donor and cord blood in MDS patients. We report here the outcome of a large cohort of MDS patients who received HSCT after a RIC using as graft source either granulocyte colony-stimulating factor peripheral blood (PB) from an unrelated donor or UCB.

METHODS

Data Collection

Data were obtained from the European Group for Blood and Marrow Transplantation (EBMT) or Eurocord registries. The MDS subcommittee of the Chronic Malignancies Working Party and Eurocord both approved this study, which was performed according to the Declaration of Helsinki.

All patients gave written consent for their data registration. Data were extracted by the EBMT office from PROMISE and Eurocord, and a questionnaire was sent to transplant centers to confirm HLA typing and request for the last follow-up status.

Patient Selection

This study included adult patients (age $\geq$ 18 years) with a diagnosis of MDS (de novo or secondary) according to the World Health Organization definition who received a RIC according to the EBMT definition from January 2005 to December 2011. Patients received an allograft from either unrelated donor PB or unrelated unmanipulated single- or double-unit UCB. Only patients with sufficient information of HLA typing were included: 10 antigens HLA-A, -B, -C, -DRB1, and -DQB1 at the allele level for PB stem cell or HLA-A and -B at the antigen level and -DRB1 at the allele level for UCB. Patients who received haploidentical grafts were excluded. Cytogenetics at time of transplant were also available.

Definitions of Outcome

Neutrophil recovery was defined as achieving an absolute neutrophil count $>.5 \times 10^9$/L on 3 consecutive days. Grades of acute and chronic GVHD were assigned using standard criteria [8,9], because data to determine National Institutes of Health chronic GVHD classifications were not available for most patients. NRM was defined as death occurring in the absence of MDS relapse. MDS relapse was defined by cytological morphological evidence.

Statistical Analysis

Primary endpoints were disease-free survival (DFS), relapse incidence (RI), NRM, and OS. Secondary endpoints were engraftment and acute and chronic GVHD. DFS was defined as survival with no evidence of relapse or progression. NRM was defined as death without evidence of relapse or progression. OS was defined as the time from HSCT to death, regardless of the cause.

Patient-, disease-, and transplant-related variables were compared between the 2 groups receiving PB or UCB using the chi-square statistic for categorical variables and the Mann-Whitney test for continuous variables. Variables considered were source of stem cells; cytogenetics categorized as good (reference), intermediate, poor, or acute myelogenous leukemia (AML; patients with MDS transformed into AML were not classified by IPSS); patient gender and age; time from diagnosis to transplantation; type of conditioning regimen (total body irradiation [TBI] versus non TBI); and previous autologous transplantation.

Probabilities of DFS and OS were calculated using the Kaplan-Meier estimates. Cumulative incidence functions were used to estimate RI and NRM in a competing risks setting, because death and relapse compete with each other. To study engraftment and chronic GVHD, we considered death to be a competing event. Univariate analyses were performed using Gray's test for cumulative incidence functions and the log-rank test for DFS and OS. Associations of patient and graft characteristics with outcomes were evaluated in multivariate analysis, using logistic regression for acute GVHD and Cox proportional hazards model for other endpoints.

All factors that differed significantly between the 2 groups with $P < .05$ were included in the final models. All tests were 2-sided. The Type I error rate was fixed at .05 for determination of factors associated with time to event outcomes. Statistical analyses were performed with SPSS 19 (SPSS Inc./IBM, Armonk, NY) and R 3.0.1 (R Development Core Team, Vienna, Austria).

RESULTS

Patients

Among the 631 recipients, 502 received PB and 129 UCB as the source of stem cells. Among the 129 patients who received UCB, 80 received 2 units and 49 a single unit according to each center policy. Baseline patient characteristics according to the source of stem cells are shown in Table 1. Patients transplanted with PB were older (60 versus 57 years, $P < .0001$) and were less often transformed into AML at the time of transplantation (64% versus 71%, $P = .04$). MDS World Health Organization classification was refractory anemia in 37, refractory cytopenia with multilineage dysplasia in 31, refractory anemia with excess blasts-1 in 50 and refractory anemia with excess blasts-2 in 87, and unclassified in 10 patients. Considering only patients who were not transformed into AML, the cytogenetic score according to IPSS was good in 96, intermediate in 57, and poor in 65 patients. Approximately half of the patients with MDS who transformed into AML were in complete remission at

Table 1
Patients and Transplantation Characteristics

Characteristics	PB Group	UCB Group	*P*
Total number of patients	502	129	
Median age, yr (range)	60 (20-76)	57 (20-72)	<.0001
Number of men	308 (61)	59 (47)	.003
Female donor-to-male recipient			<.0001
Yes	74 (15)	39 (34)	
Missing	6 (1)	13 (10)	
Transformation into AML before the transplantation	321 (64)	92 (71)	.04
Cytogenetic according to IPSS in patients with MDS at time of transplantation			.04
Good	86 (48)	10 (27)	
Intermediate	42 (23)	15 (41)	
Poor	53 (29)	12 (32)	
Time from diagnosis to transplantation, days (range)	310 (40-6300)	322 (71-6838)	.08
Year of transplantation	2010	2009	.08
CMV positive serology	310 (62)	80 (69)	.16
T cell depletion in vivo	417 (83)	47 (40)	<.0001
Antithymocyte globulin in conditioning regimen	304	46	
Alemtuzumab	113	1	
Missing	1	11 (8)	
Low-dose TBI in conditioning regimen	110 (22)	90 (70)	<.0001
Conditioning regimen			<.0001
Fludarabine and melphalan	125 (25)	7 (6)	
Fludarabine and busulfan	213 (42)	1 (1)	
Fludarabine and TBI	62 (12)	1 (1)	
Fludarabine and TBI 2 Gy and cyclophosphamide	39 (8)	79 (65)	
Other	63 (13)	41 (28)	
GVHD prophylaxis			<.0001
Cyclosporine and mycophenolate mofetil ± other	237 (48)	97 (75)	
Cyclosporine and methotrexate ± other	98 (18)	5 (4)	
Cyclosporine alone or with steroids	124 (25)	11 (9)	
Other	43 (9)	16 (12)	
Previous autologous transplantation	22 (4)	12 (9)	.03

CMV indicates cytomegalovirus.
Values are number of cases with percents in parentheses, unless otherwise indicated.

time of transplantation (170 [54%] for PB and 44 [48%] for UCB).

Among the PB recipients, HLA matching with the recipient was 10/10 in 379 (75%), 9/10 in 107 (21%), and less than 9/10 in 16 (3%) patients. Baseline characteristics of patients receiving PB according to the HLA matching are shown in Table 2. Most UCB (n = 126, 98%) recipients had at least 1 HLA mismatch on 6 antigens (HLA-A and -B antigen level and

Table 2
Characteristics of Patients Receiving Either PB 10/10 HLA-Matched Donor or 9/10 HLA-Matched Donor

Characteristics	PB 10/10 HLA-Matched Donor	PB 9/10 HLA-Matched Donor	*P*
Total number of patients	379	107	
Median age, yr (range)	60 (24-76)	61 (20-74)	.77
Number of men	232 (61)	69 (65)	.47
Female donor-to-male recipient	57 (15)	14 (14)	.67
Transformation into AML before the transplantation	242 (64)	68 (64)	.95
Cytogenetic according to IPSS in patients with MDS at time of transplantation			.29
Good	61 (44)	22 (56)	
Intermediate	31 (23)	9 (23)	
Poor	45 (33)	8 (21)	
Time from diagnosis to transplantation, days (range)	312 (40-6300)	302 (48-4249)	.66
Year of transplantation	2010	2009	.24
CMV positive serology	234 (62)	66 (62)	.98
T cell depletion in vivo	309 (82)	93 (87)	.21
Antithymocyte globulin in conditioning regimen	230	64	
Alemtuzumab	79	29	
Low-dose TBI in conditioning regimen	85 (22)	21 (20)	.54
Conditioning regimen			.67
Fludarabine and melphalan	89 (23)	30 (28)	
Fludarabine and busulfan	161 (42)	48 (45)	
Fludarabine and TBI	48 (13)	11 (10)	
Fludarabine and TBI 2 Gy and cyclophosphamide	30 (8)	8 (8)	
Other	51 (14)	10 (9)	
GVHD prophylaxis			.31
Cyclosporine and mycophenolate mofetil ± other	171 (45)	56 (52)	
Cyclosporine and methotrexate ± other	82 (22)	15 (14)	
Cyclosporine alone or with steroids	93 (24)	28 (26)	
Other	33 (9)	8 (8)	
Previous autologous transplantation	18 (5)	3 (3)	.38

Values are number of cases with percents in parentheses, unless otherwise indicated.

Table 3
Outcome Estimation According to the Type of Donor: Unrelated Donor HLA 10/10, Unrelated Donor HLA 9/10, or UCB

Groups	Neutrophil Recovery Incidence (95% CI)	Chronic GVHD Incidence (95% CI)	OS (95% CI)	DFS (95% CI)	RI (95% CI)	Non-RI (95% CI)
HLA 10/10	97 (96-98)	44 (41-47)	50 (47-53)	45 (42-48)	23 (21-25)	32 (30-34)
HLA 9/10	97 (95-99)	37 (31-43)	43 (38-48)	36 (30-42)	28 (23-33)	36 (31-41)
UCB	78 (74-82)	23 (19-27)	30 (26-34)	28 (24-32)	30 (24-34)	42 (38-46)
Overall *P*	<.0001	.004	<.0001	<.0001	.47	.04
P value for						
HLA 10/10 vs. CB	<.0001	.002	<.0001	<.0001	.1	.02
HLA 9/10 vs. CB	<.0001	.03	.05	.03	.32	.33

-DRB1 allelic level) tested, 41 (32%) had 1 HLA mismatch, and 85 (66%) had 2 HLA mismatches. Median nucleated cell number at collection was 9.6×10^8/kg (range, 1.5 to 33.20) for PB and 4.58×10^7/kg (range, 1.4 to 13) for UCB.

Conditioning regimen characteristics are summarized in Table 1. The most commonly used regimens were the combination of fludarabine and busulfan in PB recipients (42%) and 2-Gy TBI, cyclophosphamide and fludarabine for UCB recipients (65%). Antithymocyte globulin was more frequently used in the PB group (83 versus 40%, $P < .0001$), whereas TBI was less frequently used (22 versus 70%, $P < .0001$). Cyclosporine-based GVHD prophylaxis was the more often used associated with mycophenolate mofetil in 237 of 502 recipients (48%) of PB transplants and 97 of 129 (75%) recipients of UCB transplants (Table 1). The period of transplantation was not significantly different between PB and UCB transplants (median year of transplantation: 2010 for PB and 2009 for CB).

Engraftment and GVHD

The cumulative incidence of neutrophil recovery was significantly improved with PB (98%; 95% confidence interval [CI], 97 to 99) than with UCB (78%; 95% CI, 74 to 82, $P < .0001$) (Table 3). The cumulative incidence of engraftment did not differ for patients receiving single or double UCB (77% versus 79%, $P = .18$) and for patients receiving total nucleated cells $>4.58 \times 10^7$/kg (median) (76% versus 78%, $P = .87$). The delay for neutrophil recovery was shorter after PB (16 days [range, 3 to 60] versus 20 days [range, 6 to 72], $P < .0001$).

The cumulative incidence of day 100 grades II to IV acute GVHD incidence was similar in both groups (PB, 29%; UCB, 31%). In a multivariate analysis, after adjustment for differences, stem cell source remained not significantly associated with the risk of acute GVHD. The cumulative incidence of 2-year chronic GVHD was significantly lower after UCB transplants (23% ± 4%) compared with PB transplants (41% ± 2%) (Table 3). Chronic GVHD was extensive in 11 of 25 UCB recipients (44%) and in 56 of 131 PB recipients (43%). After adjustment, patients transplanted with PB or UCB have a similar risk to develop chronic GVHD. When comparing chronic GVHD in patients receiving 10/10 PB, 9/10 PB, and UCB, patients were at the highest risk for development of chronic GVHD after 9/10 PB (44% ± 3%, 37% ± 6%, versus 23% ± 4%, respectively). Chronic GVHD had no impact on RI (hazard ratio [HR], .88; 95% CI, .55 to 1.41; $P = .59$) in a time-dependent fashion.

Mortality

After a median follow-up of 25 and 24 months for the recipients of PB and UCB transplants, respectively, 346 of 631 patients died: 52% in the PB group and 68% in the CB group. The most frequent cause of death was relapse (33% in PB and 37.5% in UCB) followed by infections (17% for PB versus 21% in UCB). GVHD was a more frequent cause of death in the PB group (18% versus 10%, not significant [ns]), whereas organ failure was less common in the PB group (6% versus 19%, ns). Second malignancy was a cause of death in 2% of patients from the PB group and 2% of patients from the UCB group. Causes of death were missing in 46 patients (18%) from the PB group and in 4 patients (4.5%) from the UCB group.

Two-year NRM was lower in the PB group than in the UCB group (31% ± 2% versus 42% ± 5%, $P = .03$) (Table 3). After adjusting for other variables, NRM risk remained significantly lower in the PB than in the UCB group (HR, 1.68; 95% CI, 1.16 to 2.43; $P = .006$), and no other factor significantly impacted the NRM risk (Table 3). For the group of patients transplanted with PB from either an HLA 9/10 or 10/10 matched unrelated donor, NRM was 36% ± 5% and 32% ± 2%, respectively, and was significant lower using 10/10 matched grafts as compared with UCB (10/10 versus UCB, $P = .02$; 9/10 versus UCB, $P = .33$; Figure 1). In multivariate analysis comparing UCB, 9/10 PB, and 10/10 PB, the NRM risk was higher when comparing 10/10 PB to UCB (HR, .57; 95% CI, .39 to 0.83; $P = .003$) and similar between 9/10 PB and UCB (HR, .71; 95% CI, .44 to 1.15; $P = .16$).

Relapse and Progression

Overall, 162 patients relapsed or progressed after the transplantation, 122 in the PB and 40 in UCB group. Of note, only 273 of 631 patients (43%) in the whole series were

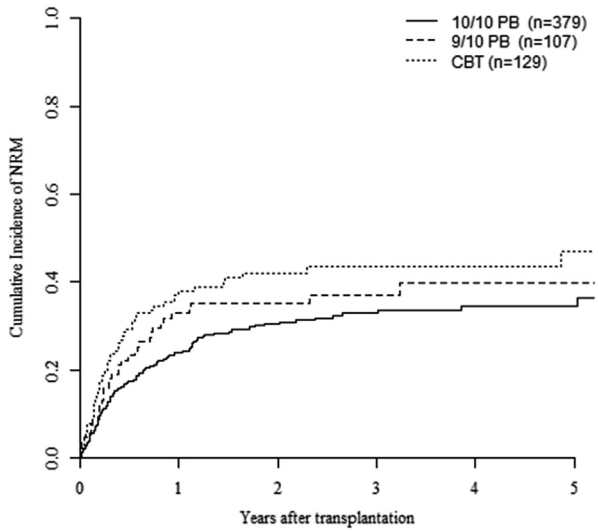

Figure 1. NRM according to the source of stem cells: PB HLA 10/10, PB HLA 9/10, and UCB (CBT).

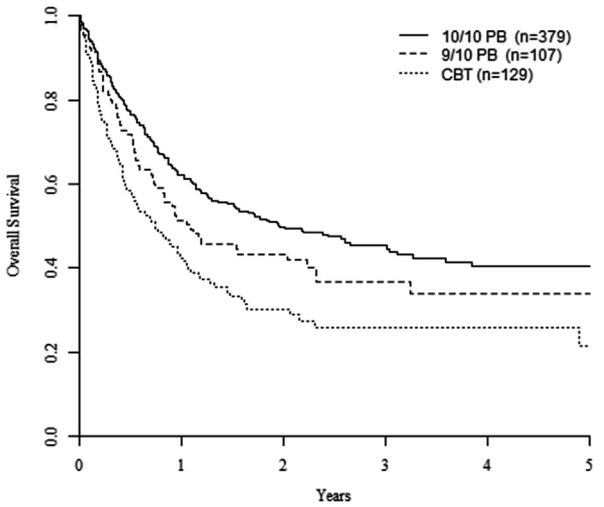

Figure 2. OS in patients according to the 3 groups: PB HLA 10/10, PB HLA 9/10, and UCB (CBT).

transplanted in remission and 413 of 631 patients (65%) were transformed into AML at time of transplantation. The cumulative incidence of relapse was similar in both groups (PB, 25% ± 2%; UCB, 30% ± 4%; $P = .1$; Table 3). In a multivariate analysis, risk of relapse was lower in the PB group as compared with the UCB group (HR, 1.74; 95% CI, 1.12 to 2.70; $P = .01$), and a poor cytogenetic score also increased the risk of relapse (HR, 2.39; 95% CI, 1.31 to 4.35; $P = .004$) (Table 3). In the subgroup of patients who received PB from a 9/10 mismatched donor, RI was 28% ± 5%; RI was 23% ± 2% in the group of patients transplanted with 10/10 PB (10/10 versus UCB, $P = .4$, 9/10 versus UCB, $P = .32$). When comparing the 3 groups, 10/10 PB, 9/10 PB, and UCB, adjusted to other covariates, there was a higher risk of relapse in UCB as compared with 10/10 PB and a similar risk of relapse between 9/10 and UCB (10/10 versus UCB: HR, .57; 95% CI, .37 to .90; $P = .02$; 9/10 versus UCB: HR, .70; 95% CI, .39 to 1.23; $P = .21$).

Survival Rates

Two-year OS and DFS were better after PB transplantation compared with UCB transplantation (49% ± 2% versus 30% ± 4%, $P < .0001$ and 44% ± 2% versus 28% ± 4%, respectively; $P < .0001$). Of note, there was no statistical difference for OS and DFS in patients who received a single (n = 49) or a double UCB transplant (n = 80): OS and DFS were 39% ± 7% and 24% ± 5% versus 35% ± 7% and 23% ± 5%, respectively. In the multivariate analysis OS was lower after UCB compared with PB transplantation (HR, 1.72; 95% CI, 1.29 to 2.30; $P = .0003$) along with a poor cytogenetic score (HR, 1.37; 95% CI, 1.08 to 2.59; $P = .02$), whereas female recipients had a better OS (HR, .77; 95% CI, .62 to 0.97; $P = .02$). DFS was also influenced by stem cell source and was decreased with UCB (HR, 1.70; 95% CI, 1.28 to 2.25; $P = .0002$).

The type of conditioning regimen (comparing TBI plus fludarabine ± cyclophosphamide with others) had no impact on DFS (for PB, 46% versus 42%; for CB, 25% versus 25%). Patients who received PB from a 9/10 HLA-mismatched donor had 2-year OS and DFS rates of 43% ± 5% and 36% ± 6%, whereas those who received PB from a 10/10 HLA-matched donor had OS and DFS rates of 50% ± 3% and 45% ± 3% (Figure 2). Adjusted analysis within the 3 groups showed no significant difference between 9/10 PB transplant and UCB transplant for OS (HR, .73; 95% CI, .50 to 1.06; $P = .10$), whereas there was a trend to an improved adjusted DFS for 9/10 PB compared with UCB transplants (HR, .70; 95% CI, .49 to 1.01; $P = .06$) (Table 4).

Table 4
Multivariate Analysis for Outcome Comparing Source of Hematopoietic Stem Cell

	Characteristics	*P*	HR	95% CI	
OS	UCB (reference)		1.00		
	UD 10/10 vs. UCB	.0001	.56	.41	.75
	UD 9/10 vs. UCB	.10	.73	.50	1.06
	Cytogenetics				
	Good (reference)		1.00		
	Intermediate	.52	1.17	.72	1.90
	Poor	.01	1.75	1.12	2.74
	sAML	.07	1.37	.98	1.93
	Patient gender (female vs. male)	.02	.76	.60	.95
	Age > median	.21	1.15	.92	1.45
	Time from diagnosis to transplant > median	.22	.87	.70	1.09
	TBI in conditioning regimen	.34	1.14	.87	1.48
	Previous autograft	.55	1.15	.73	1.80
DFS	UCB (reference)		1.00		
	UD 10/10 vs. UCB	.0002	.57	.43	.76
	UD 9/10 vs. UCB	.06	.70	.49	1.01
	Cytogenetics				
	Good (reference)		1.00		
	Intermediate	.91	1.03	.65	1.63
	Poor	.01	1.73	1.13	2.64
	sAML	.17	1.25	.91	1.72
	Patient gender (female vs. male)	.04	.79	.63	.98
	Age > median	.29	1.12	.91	1.40
	Time from diagnosis to transplant > median	.40	.91	.74	1.13
	TBI in conditioning regimen	.41	1.11	.86	1.44
	Previous autograft	.74	1.08	.69	1.68
RI	UCB (reference)		1.00		
	UD 10/10 vs. UCB	.02	.57	.37	.90
	UD 9/10 vs. UCB	.21	.70	.39	1.23
	Cytogenetics				
	Good (reference)		1.00		
	Intermediate	.38	.70	.32	1.55
	Poor	.005	2.38	1.31	4.34
	sAML	.47	1.20	.74	1.94
	Patient gender (female vs. male)	.27	.83	.59	1.15
	Age > median	.80	1.04	.75	1.45
	Time from diagnosis to transplant > median	.90	1.02	.74	1.41
	TBI in conditioning regimen	.86	1.04	.70	1.55
	Previous autograft	.20	1.47	.82	2.64
NRM	CB (reference)		1.00		
	UD 10/10 vs. UCB	.003	.57	.39	.83
	UD 9/10 vs. UCB	.16	.71	.44	1.15
	Cytogenetics				
	Good (reference)		1.00		
	Intermediate	.40	1.28	.72	2.29
	Poor	.50	1.24	.67	2.28
	sAML	.23	1.29	.85	1.97
	Patient gender (female vs. male)	.07	.76	.57	1.02
	Age > median	.24	1.19	.89	1.58
	Time from diagnosis to transplant > median	.23	.84	.64	1.12
	TBI in conditioning regimen	.33	1.18	.85	1.65
	Previous autograft	.45	.77	.38	1.53

UD indicates unrelated donor; sAML, MDS transformed into AML.

DISCUSSION

This study reports on outcomes in MDS patients who received allogeneic HSCT after RIC from donors other than HLA-matched sibling. The outcomes after unrelated PB stem cell grafts and UCB were compared. Engraftment, OS, DFS, and NRM were significantly better with PB than with UCB.

When the UCB group was compared with the 9/10 mismatched PB group, outcomes were not significantly different but the statistical power decreased with the 3-subset analysis (10/10, 9/10, and UCB), and results should be taken with caution.

Outcomes after UCB has been only rarely reported in MDS patients, whereas there are many reports on other hematological malignancies [10-12]. The largest study of MDS patients transplanted with UCB is reported by the EBMT registry showing that OS rates can reach 46% in patients with favorable prognostic factors [7]. In this previous study, outcome was significantly influenced by conditioning regimen, with a higher NRM (>60%) after myeloablative conditioning. In the present study and comparing with the previous EBMT study, patients transplanted with UCB seemed to have worse prognostic features: they were older (57 versus 43 years) and transformation to AML was present in more than half. Nevertheless, OS among these patients was around 30% at 2 years, quite similar to the previous EBMT study.

Curiously, the results were poorer than after unrelated PB transplant in this cohort, whereas many other studies reported the outcome between UCB and PB transplant to be quite similar, particularly in acute leukemia or lymphoma [13-16]. Brunstein et al. [13] reported the outcome of patients with acute myeloblastic or lymphoblastic leukemia who received a RIC, which was not significantly different in those receiving PB from an 8/8 or 7/8 HLA-matched donor and those receiving UCB. A strong prognostic factor in the Brunstein study, which we failed to find in the present study, was the type of conditioning regimen before UCB, with poorer results in patients not receiving fludarabine–cyclophosphamide–low-dose TBI (TCF). Brunstein et al. [13] reported that NRM was even lower in patients receiving UCB after TCF than in patients receiving PB from a 7/8 HLA-mismatched donor. In addition, a collaborative multicenter study reported similar outcomes using UCB or PB in AML patients transplanted after RIC [14]. In this latter study, all patients transplanted with UCB received TCF, and all patients (n = 197) were transplanted in only 3 experienced centers with homogeneous comparable policy for transplant management. In contrast, in this EBMT study, conditioning regimen, donor choice, transplant indication, and general management differed between 124 centers, which can be considered a weakness but was required to lead this study to a large number of patients. For these reasons, conclusions should be taken with caution, even if endpoints were adjusted for all possible confounders.

HLA matching seems to impact results in this study, and large studies have already described an impact of HLA mismatch, including in MDS patients [17-20]. A recent study analyzed the outcome of MDS patients transplanted either with a matched related donor, an 8/8 HLA-matched unrelated donor (n = 413), or a 7/8 mismatched unrelated donor (n = 112) [20]. Three-year OS rates were 45% for the 8/8 HLA-matched unrelated donor group and 10% less for the 7/8 mismatched unrelated donor group [20], which is close to our results showing 2-year OS rates of 50% for the 10/10 group (n = 379) and 7% less for the 9/10 group (n = 107). OS after UCB transplant was also 13% less than after 9/10 PB transplant.

The multivariate analysis for OS is not in favor of a significant advantage of 9/10 PB over the UCB transplant, but the power of the analysis was not optimal because of the relative low number of patients. Concerning DFS, there was a trend to poorer outcomes after use of UCB as compared with use of 9/10 PB. In fact, HLA studies need very large cohorts to conclude firmly on potential impact. This is why in the present study, which was initially not designed for an HLA study, we did not study impact of each HLA antigen on survival rates. Larger, well-defined cohorts are needed to compare outcomes of patients receiving 9/10 unrelated donor and UCB. However, this study reports results that seem to be comparable.

Overall, these data suggest that in MDS patients lacking an HLA-matched sibling, HLA-matched unrelated donor is the best choice. When no HLA-matched donor is available, UCB and HLA-mismatched 9/10 PB should both be considered. Given the fact that UCB is more easily available and associated with a lower risk of chronic GVHD, this source of stem cells appears to be a valuable option, particularly if conducted with validated strategies that include a sufficient number of cells and a TCF conditioning regimen and when a transplant is urgently needed.

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