Bone Marrow Versus Mobilized Peripheral Blood Stem Cells in Haploidentical Transplants Using Posttransplantation Cyclophosphamide

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Abstract: Incidence of graft-versus-host disease (GVHD) in haploidentical bone marrow (BM) transplants using posttransplantation cyclophosphamide (PT-Cy) is low, whereas GVHD using mobilized peripheral blood stem cells (PBSC) ranges between 30% and 40%. METHODS: To evaluate the effect of stem cell source in haploidentical transplantation with PT-Cy, we analyzed 451 patients transplanted for acute myeloid leukemia or acute lymphoblastic leukemia reported to the European Society for Blood and Marrow Transplantation. RESULTS: BM was used in 260 patients, and PBSC were used in 191 patients. The median follow-up was 21 months. Engraftment was lower in BM (92% vs 95%, $P < 0.001$). BM was associated with a lower incidence of stage II-IV and stage III-IV acute GVHD (21% vs 38%, $P \leq .01$; and 4% vs 14%, $P < .01$, respectively). No difference in chronic GVHD, relapse, or nonrelapse mortality were found for PBSC or BM. The 2-year overall survival (OS) was 55% versus 56% (P 5 .57) and leukemia-free survival (LFS) was 49% versus 54% (P 5 .74) for BM and PBSC, respectively. On multivariate analysis, PBSC were associated with an increased risk of stage II-IV (hazard ratio [HR], 2.1; $P < .001$) and stage III-IV acute GVHD (HR, 3.8; $P < .001$). For LFS and OS, reduced intensity conditioning was the only factor associated with treatment failure (LFS: HR, 1.40; P 5 .04) and relapse (HR, 1.62; P 5 .02). CONCLUSION: In patients with acute leukemia in first or second remission receiving haploidentical transplantation with PT-Cy, the use of PBSC increases the risk of acute GVHD, whereas survival outcomes are comparable.

KEYWORDS: haploidentical transplantation, posttransplantation cyclophosphamide, stem cell source, acute leukemia, acute graft-versus-host disease.

INTRODUCTION

The role of stem cell source in the setting of related or unrelated donor transplant (hematopoietic stem cell transplantation [HSCT]) and a myeloablative conditioning (MAC) regimen has been evaluated in randomized trials, showing an excess of chronic graft-versus-host disease (GVHD) with peripheral blood stem cells (PBSC) as the stem cell source, with no differences in disease-free and overall survival.[1] Subsequently, Eapen et al[2] did not confirm an increased risk of chronic GVHD with PBSC grafts in a registry-based study analyzing HSCT with a reduced intensity conditioning (RIC) regimen from unrelated donors.

The number of unmanipulated haploidentical stem cell transplantations (haplo-SCT) in adult patients with hematological malignancies such as acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) is increasing constantly.[3] Haplo-SCT is performed with a different conditioning regimen and GVHD prophylaxis,[4] with comparable results to HSCT from unrelated donors.[5,6]

Historically, Luznik et al[7] pioneered the use of posttransplantion cyclophosphamide (PT-Cy) in the setting of RIC using bone marrow (BM) as stem cell source. This protocol is associated with a low incidence of acute and chronic

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GVHD and low transplantation-related mortality for older patients, although disease recurrence is rather high, partially because of the high risk of disease in most patients.[8]

To overcome the high incidence of relapse with RIC haplo-SCT, some authors effectively reported the application of BM and PT-Cy with myeloablative regimes (MAC)[9] and also with the use of PBSC[10] as a stem cell source. The incidence of GVHD in haploidentical transplantations using PBSC grafts ranges from 30% to 40% in single-center reports.[11]

Recently, O'Donnell et al[12] reported comparable results in recipients of BM versus PBSC grafts in the nonablative setting in a matched paired analysis on patients who received transplants for several hematological malignancies.

The effect of stem cell source in recipients of haploidentical transplants has been reported by Bashey et al[13] in a series of 681 patients with hematologic malignancy receiving PT-Cy as GVHD prophylaxis.

The goal of this study was to investigate the effects of stem cell source in non–T-cell–depleted haploidentical transplantation using PT-Cy. We analyzed patients who received transplants for AML or ALL who were in first or second complete remission (CR) and reported to the European Society for Blood and Marrow Transplantation (EBMT) registry from 2010 to 2014.

METHODS

Study Design

This is a retrospective registry-based analysis on behalf of the Acute Leukaemia Working Party (ALWP) of the EBMT.

The EBMT is a voluntary working group of more than 500 transplantation centers that are required to report all consecutive stem cell transplantations and follow-up once a year. Audits are routinely performed to determine the accuracy of the data.

All adults (age >18 years) with ALL or AML in first or second CR (CR1 or CR2) at transplantation, reported to Promise-EBMT, who underwent haplo-SCT using PT-Cy as first allogeneic HSCT between 2010 and 2014 were analyzed. Haplo was defined as recipient-donor number of human leukocyte antigen (HLA) mismatches >2.

A total of 451 patients were reported from 99 transplantation centers, including 260 patients receiving BM and 191 patients receiving PBSC as a stem cell source.

This study was approved by the ALWP of the EBMT institutional review board. It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients or legal guardians provided written informed consent authorizing the use of clinical information for research purposes.

Endpoints and Definitions

The primary endpoint was leukemia-free survival (LFS). Secondary endpoints were neutrophil engraftment, acute GVHD (aGVHD) and chronic GVHD (cGVHD), relapse incidence, nonrelapse mortality (NRM), GVHD-free and relapse-free survival (GRFS), and overall survival (OS). Refined GRFS[14] was defined as survival without the following events: stage III-IV aGVHD, severe cGVHD, disease relapse, or death from any cause after haplo-SCT. LFS was calculated until the date of first relapse, death from any cause or the last follow-up for patients in CR. Relapse was defined as disease recurrence and appearance of blasts in the peripheral blood or BM (>5%) after CR. NRM was defined as death from any cause other than relapse. Acute GVHD was staged according to the modified Seattle Glucksberg criteria[15] and cGVHD according to the revised Seattle criteria.[16] Neutrophil engraftment was defined as first of 3 consecutive days with a neutrophil count of at least 0.5×10^9/L.

MAC was defined as a regimen containing either total body irradiation with a dose greater than 6 Gray, a total dose of oral busulfan greater than 8 mg/kg, or a total dose of intravenous busulfan >6.4 mg/kg or melphalan at doses >140 mg/m^2. In addition, regimens containing 2 alkylating agents were considered as MAC. All other regimens were defined as RIC.

Statistical Analysis

GRFS, LFS, and OS were estimated using the Kaplan-Meier method. Cumulative incidence functions were used to estimate neutrophil engraftment, aGVHD, cGVHD, relapse incidence, and NRM. Competing risks were death for relapse incidence, relapse for NRM, relapse or death for aGVHD and cGVHD. Univariate analyses were done using the log-rank test for GRFS, OS and LFS, and Gray's test for cumulative incidence.

For univariate analysis, comparisons were made by using chi-squared tests for categorical and Mann-Whitney tests for continuous variables. Multivariate analyses were performed using the Cox proportional hazard model.

Stem cell source, diagnosis, disease status, age at transplantation, transplantation year, cytomegalovirus serostatus (donor and recipient negative vs other

TABLE 1. Patient and Transplantation Characteristics

Characteristic	BM (n 5 260)	PBSC (n 5 191)	P[a]
Follow-up, mo, median (range)	22.8 (2.4-62.4)	18.3 (1.6-50.5)	.42
Patient age, y, median (range)	46.5 (18.4-74.8)	44.4 (18.2-74.9)	.88
Time from diagnosis to transplantation, mo, median (range)	7.7 (2-100.3)	8.1 (2-237.9)	.56
Year of transplantation, median (range)	2013 (2010-2014)	2013 (2010-2014)	.15
AML, n (%)	195 (75)	136 (71)	.36
ALL, n (%)	65 (25)	55 (29)	
CR1, n (%)	174 (67)	131 (69)	.70
CR2, n (%)	86 (33)	60 (31)	
De novo AL, n (%)	225 (87)	155 (81)	.12
Secondary AL, n (%)	35 (13)	36 (19)	
CMV D2/R2, n (%)	25 (10)	18 (9)	.04
CMV D1/R1, n (%)	153 (60)	132 (70)	
MAC, n (%)	159 (61)	93 (49)	.008
RIC, n (%)	101 (39)	98 (51)	
No ATG, n (%)	247 (95)	178 (93)	.41
ATG, n (%)	13 (5)	13 (7)	

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; BM, bone marrow; CMV, cytomegalovirus; CR, complete response; MAC, myeloablative conditioning; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioning.
[a] Significant *P* values are presented in boldface type.

combination), conditioning regimen and center experience were included in the final model. To test for center effect, we introduced a random effect or frailty for each center into the model.

The significance level was fixed at .05, and *P* values were 2-sided. Statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY) and R version 3.2.3 (R Development Core Team, Vienna, Austria) software packages.

RESULTS

Patient and Transplantation Characteristics

Table 1 summarizes the main patient and transplantation characteristics. A total of 451 patients were reported, 260 of whom received BM and 191 of whom received PBSC as a stem cell source. The majority of the patients in both groups underwent transplantation for AML (73%) in CR1 (67%). The median age at transplantation was 45 years (range, 18-76 years).

Median follow-up was longer for patients receiving BM (22.8 vs 18.3 months) and those patients were more likely transplanted with MAC (61% vs 49% [$P = .008$]). The combination of thiotepa, busulfan, and fludarabine or FluCy and low-dose total body irradiation were the most common conditioning regimen used in MAC and RIC setting, respectively.

All patients received PT-Cy as GVHD prophylaxis, mainly in combination with calcineurin inhibitor and mycophenolate mofetil, according to the transplantation center's policy. The use of antithymocyte globulin (ATG) use was not different for the 2 groups (5% vs 7% [$P = .41$]).

The median CD341 was 2.8×10^6/kg and 6.8×10^6/kg for BM and PBSC, respectively ($P < .001$).

Neutrophil Engraftment and GVHD

The cumulative incidence of neutrophil engraftment was 92% and 95% for patients receiving BM and PBSC, respectively ($P < .001$). The time to neutrophil engraftment was longer in the BM group (18 vs 17 days [$P < .001$]).

The cumulative incidence of day 100 stage II-IV aGVHD and 1-year cGVHD were 28% and 35%, respectively.

On univariate analysis (Table 2), patients who underwent transplantation with BM had a lower incidence of stage II-IV and stage III-IV aGVHD (21% vs 38% [$P \leq .01$] and 4% vs 14% [$P \leq 0.01$], respectively) (Fig. 1a). On adjusted multivariate analysis (Table 3), PBSC were independently associated with increased risk of stage II-IV aGVHD (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.46-3.0; $P < .001$) and stage III-IV aGVHD (HR, 3.8; 95% CI, 1.7-8.2; $P < .001$).

No difference in cGVHD (36% vs 32% [$P = .28$]) was observed in recipients of BM versus PBSC grafts (Fig. 1b). Similarly, type of stem cell (PBSC vs BM) was not associated with cGVHD (HR, 1.0; 95% CI, 0.58-1.9; $P = .88$) on multivariate analysis (Table 3).

Relapse and NRM

At 2 years, the cumulative incidence of relapse was 25% with no difference according to the stem cell source (BM 26% vs PBSC 22% [$P = .38$]) (Fig. 1c). The cumulative incidence of relapse was 22.4% for AML and 30.8% for

TABLE 2. Univariate Analysis

	Relapse	NRM	LFS	OS	GRFS	aGVHD Stage II-IV	aGVHD Stage III-IV	cGVHD	ext. cGVHD
BM	26.8 (21.2-32.6)	23.5 (18.1-29.3)	49.4 (42.7-56.1)	55.5 (48.7-62.3)	44 (37.5-50.5)	21.6 (16.7-26.9)	4 (2-6.9)	36.4 (30-42.8)	12.3 (8.3-17.1)
PBSC	21.9 (15.9-28.6)	23.5 (17.5-30)	54.4 (46.8-62.1)	55.6 (47.8-63.5)	43.2 (35.7-50.7)	38.3 (31.2-45.3)	13.8 (9.3-19.3)	32.1 (24.8-39.6)	10.3 (6.1-15.7)
P	.38	.60	.74	.57	.39	.0004	.0001	.28	.48
Age <45 y	28.2 (22-34.6)	22 (16.5-28)	49.4 (42.3-56.5)	56.9 (49.6-64.1)	39.2 (32.3-46)	29.8 (23.8-36)	10.7 (7-15.2)	33.7 (26.9-40.6)	11.4 (7.3-16.6)
Age ≥45 y	21.1 (15.8-27)	25.3 (19.3-31.7)	53.5 (46.3-60.7)	54 (46.6-61.4)	48 (41-55)	27.3 (21.5-33.4)	5.5 (3-9.1)	35.6 (28.8-42.5)	11.4 (7.4-16.4)
P	.13	.40	.54	.54	.10	.48	.04	.68	.99
Interval from diagnosis to haplo-Tx <8 mo	22.7 (17.1-28.7)	21 (15.5-27.1)	55.9 (48.8-63.1)	59.5 (52.2-66.8)	47.7 (40.7-54.6)	26.5 (20.8-32.6)	8.8 (5.5-13.1)	39.7 (32.6-46.7)	12.6 (8.3-17.8)
Interval from diagnosis to haplo-Tx ≤8 mo	26.6 (20.6-32.9)	26.3 (20.3-32.6)	47 (39.9-54.1)	51.5 (44.2-58.8)	39.7 (32.9-46.6)	30.6 (24.5-36.8)	7.3 (4.4-11.3)	29.5 (23.1-36.3)	10.2 (6.4-15.1)
P	.44	.27	.10	.07	.17	.50	.56	.02	.45
Year <2013	31.7 (24.1-39.6)	19.7 (13.5-26.8)	48.1 (39.7-56.5)	53.7 (45.3-62.1)	38.8 (30.6-47)	23.8 (17.1-31.2)	7.2 (3.7-12.3)	38.6 (30.3-46.7)	14.8 (9.4-21.4)
Year ≥2013	20.7 (16-25.8)	25.8 (20.5-31.4)	53.4 (47.1-59.7)	56.8 (50.3-63.3)	46.4 (40.3-52.5)	30.8 (25.6-36.2)	8.5 (5.7-12.1)	32.7 (26.7-38.8)	9.6 (6.2-13.8)
P	.02	.16	.43	.60	.28	.15	.65	.15	.11
AML	22.4 (17.8-27.4)	24.4 (19.6-29.5)	53 (47.2-58.9)	56 (50-62)	44.7 (38.9-50.4)	26 (21.3-31)	7.6 (5-10.9)	33 (27.5-38.6)	11.6 (8.2-15.8)
ALL	30.8 (22.2-39.9)	21.5 (14.1-29.9)	47.1 (37.2-57)	53.8 (43.7-64)	40.6 (31.2-50)	35.5 (26.9-44.3)	9.5 (5-15.7)	39.3 (29.5-49)	10.9 (5.7-17.9)
P	.04	.38	.31	.79	.23	.04	.50	.22	.96
CR1	22.2 (17.4-27.4)	24.4 (19.3-29.8)	53.1 (46.9-59.4)	57.7 (51.4-64)	46.5 (40.6-52.5)	24.7 (19.9-29.7)	8.9 (6-12.5)	33.8 (27.9-39.7)	10.2 (6.9-14.4)
CR2	29.6 (22-37.5)	22.2 (15.5-29.7)	48 (39.3-56.6)	51.1 (42.1-60.1)	37.9 (29.5-46.3)	36.7 (28.7-44.7)	6.4 (3.2-11.3)	36.2 (27.8-44.6)	13.6 (8.3-20.3)
P	.08	.50	.36	.33	.32	.02	.38	.75	.38
De novo AL	25 (20.4-29.7)	23.6 (19.1-28.4)	51.2 (45.7-56.7)	55.7 (50-61.4)	43 (37.7-48.4)	29.5 (24.9-34.3)	8.8 (6.2-12)	36.2 (30.9-41.6)	12.4 (9-16.4)
Secondary AL	23 (13.5-33.9)	23.9 (14.4-34.7)	52.8 (40.5-65)	53.9 (41.3-66.6)	47.1 (34.9-59.3)	23.5 (14.2-34.2)	4.4 (1.2-11.3)	26.6 (15.9-38.5)	6.3 (2-14.3)
P	.79	.38	.64	.20	.69	.35	.22	.11	.18
No F->M	24.1 (19.4-29.1)	23.4 (18.8-28.4)	52.2 (46.5-58)	56 (50.1-61.9)	45.7 (40.1-51.4)	28.6 (23.8-33.6)	8.5 (5.8-11.8)	31.9 (26.5-37.4)	9.5 (6.4-13.2)
F->M	26.2 (17.9-35.4)	24.4 (16-33.7)	49.1 (38.7-59.5)	53.6 (42.9-64.4)	37.4 (27.8-47.1)	28.3 (19.9-37.3)	6.8 (3-12.8)	42.9 (32.3-53)	17.4 (10.4-25.9)
P	.84	.76	.78	.96	.26	.97	.60	.10	.04
CMV D2/R2	28 (14.9-42.6)	34.3 (18.8-50.5)	37.7 (21.3-54.1)	38 (20.5-55.5)	30 (15.4-44.6)	31 (17.2-45.9)	7.7 (1.9-18.8)	26.4 (13.4-41.3)	13.5 (4.8-26.7)
CMV D1/R2	20.6 (7.9-37.4)	19.6 (7.7-35.5)	59.8 (41.7-77.8)	65.9 (48.5-83.3)	52.7 (35-70.3)	29 (14.3-45.6)	6.5 (1.1-18.9)	39.6 (21.3-57.5)	14.3 (4.3-29.9)
CMV D2/R1	32.7 (22.1-43.6)	14.2 (7.1-23.5)	52.7 (40.9-64.5)	55.1 (43-67.2)	48 (36.4-59.7)	14.3 (7.5-23.1)	3.8 (1-9.9)	38.1 (25.9-50.3)	7.2 (2.6-15)
CMV D1/R1							9.8 (6.7-13.7)		

TABLE 2. *Continued*

	Relapse	NRM	LFS	OS	GRFS	aGVHD Stage II-IV	aGVHD Stage III-IV	cGVHD	ext. cGVHD
	22.8 (17.8-28.2)	25 (19.8-30.4)	52 (45.6-58.3)	56.9 (50.5-63.4)	43.1 (36.9-49.3)	32.9 (27.3-38.5)		33.5 (27.5-39.7)	11.6 (7.8-16.1)
P	.36	.11	.48	.57	.35	.01	.38	.65	.64
MAC							9.9 (6.5-14)		
	22.8 (17.4-28.6)	21.3 (16.1-27.1)	55.7 (48.8-62.5)	63.8 (57.1-70.5)	45 (38.4-51.6)	29.7 (24.1-35.5)		37.4 (30.7-44.2)	13.5 (9.2-18.6)
RIC							5.8 (3.1-9.8)		
	27 (20.7-33.6)	26.4 (20.2-33)	46.3 (38.9-53.7)	45.1 (37.3-52.9)	41.9 (34.7-49.2)	27.1 (20.9-33.6)		31.4 (24.5-38.5)	8.8 (5.1-13.7)
P	.12	.10	.004	.0002	.25	.43	.11	.48	.17
No ATG							8.4 (5.9-11.3)		
	25.1 (20.8-29.5)	23 (18.8-27.4)	51.7 (46.5-56.9)	55.9 (50.5-61.2)	44.6 (39.5-49.6)	28.4 (24.1-32.9)		33.7 (28.8-38.7)	10.7 (7.8-14.3)
ATG							3.8 (0.3-16.8)	NA (NA-NA)	
	18 (5.2-37)	32.2 (14.9-51)	49.7 (29.2-70.3)	48.7 (25.8-71.5)	30.5 (12-49)	30.8 (14.3-49)			21.3 (7.4-39.8)
P	.30	.13	.84	.45	.52	.76	.42	.27	.11

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; BM, bone marrow; CMV, cytomegalovirus; CR, complete response; F->M, female to male; haplo-Tx, haploidentical transplantation; MAC, myeloablative conditioning; NA, not available; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioning.
Data are in percent (%) and are presented as the hazard ratio (95% confidence interval).

ALL (*P* 5 .04) and 22.2% and 29.6% for patients who underwent transplantation in CR1 and CR2 (*P* 5 .08), respectively (Table 2).

aGVHD and cGVHD were not associated with relapse incidence in a time-dependent fashion model (data not shown). The overall 2-year NRM was 23%, with no difference for BM or PBSC recipients (23% vs 23% [*P* 5 .61]) (Table 2) (Fig. 1d). The main causes of death were disease recurrence (BM, 33%; PBSC, 39%), infection (BM, 39%; PBSC, 33%), and GVHD (BM, 14%; PBSC, 17%).

On multivariate analysis (Table 3), the type of stem cell graft (PBSC vs BM) was not associated with relapse (HR, 0.8; 95% CI, 0.51-1.15; *P* 5 .21) or NRM (HR, 0.81; 95% CI, 0.49-1.32; *P* 5 .4). RIC regimen was the only factor associated with an increased risk of relapse (HR, 1.62; 95% CI, 1.07-2.44; *P* 5 .02).

OS, LFS, and GRFS

OS, LFS, and GRFS at 2 years were 55%, 51%, and 44%, respectively. According to stem cell source, OS was 55% versus 56% (*P* 5 .57), LFS was 49% versus 54% (*P* 5 .74), and GRFS was 44% and 43% (*P* 5 .39) for BM and PBSC, respectively (Fig. 2). LFS was 53% for patients who underwent transplantation for AML and 47% for those with ALL (*P* 5 .32), and it was 56% and 46% (*P* 5

TABLE 3. Multivariate Analysis

	HR	95% CI	*P*[a]
aGVHD stage II-IV			
PBSC vs BM	2.09	1.45-3.01	.0007
Age per 10 years	1.03	0.91-1.18	.57
Year of Tx	1.23	1.02-1.47	.02
ALL vs AML	1.58	1.06-2.35	.02
CR2 vs CR1	1.71	1.17-2.49	.005
CMV D2/R2 vs other	1.00	0.54-1.84	.98
RIC vs MAC	0.79	0.54-1.16	.23
Center (frailty)			.92
cGVHD			
PBSC vs BM	1.04	0.57-1.90	.87
Age per 10 years	0.98	0.84-1.14	.84
Year of Tx	0.90	0.75-1.08	.26
ALL vs AML	1.21	0.79-1.87	.36
CR2 vs CR1	1.01	0.67-1.50	.95
CMV D2/R2 vs other	0.83	0.40-1.71	.62
RIC vs MAC	1.40	0.88-2.24	.14
Center (frailty)			.0003
Relapse			
PBSC vs BM	0.76	0.51-1.15	.21
Age per 10 years	0.93	0.81-1.08	.38
Year of Tx	0.91	0.76-1.09	.32
ALL vs AML	1.50	0.97-2.31	.06
CR2 vs CR1	1.29	0.85-1.94	.22
CMV D2/R2 vs other	1.14	0.60-2.17	.68
RIC vs MAC	1.61	1.06-2.44	.02
Center (frailty)			.31

TABLE 3. *Continued*

	HR	95% CI	P^a
NRM			
PBSC vs BM	0.80	0.49-1.32	.40
Age per 10 years	1.14	0.98-1.34	[illegible]
Year of Tx	1.04	0.85-1.28	.66
ALL vs AML	1.02	0.61-1.70	.93
CR2 vs CR1	0.81	0.51-1.29	[illegible]
CMV D2/R2 vs other	1.57	0.82-2.99	.17
RIC vs MAC	1.25	0.79-1.99	.33
Center (frailty)			.04
LFS			
PBSC vs BM	0.73	0.51-1.04	.08
Age per 10 years	1.03	0.93-1.15	.53
Year of Tx	0.95	0.83-1.09	.54
ALL vs AML	1.28	0.92-1.80	.14
CR2 vs CR1	1.03	0.75-1.40	.84
CMV D2/R2 vs other	1.29	0.81-2.05	.27
RIC vs MAC	1.39	1.01-1.93	.04
Center (frailty)			.06
OS			
PBSC vs BM	0.79	0.54-1.15	.23
Age per 10 years	1.11	0.99-1.24	.06
Year of Tx	0.95	0.82-1.10	.54
ALL vs AML	1.24	0.86-1.79	.24
CR2 vs CR1	1.07	0.77-1.49	.65
CMV D2/R2 vs other	1.21	0.74-1.98	.43
RIC vs MAC	1.51	1.06-2.13	.01
Center (frailty)			.01
GRFS			
PBSC vs BM	0.96	0.69-1.33	.82
Age per 10 years	1.01	0.92-1.12	.72
Year of Tx	0.95	0.84-1.08	.44
ALL vs AML	1.23	0.90-1.67	.18
CR2 vs CR1	1.03	0.78-1.37	.81
CMV D2/R2 vs other	1.36	0.89-2.09	.15
RIC vs MAC	1.05	0.78-1.42	.72
Center (frailty)			.05

Abbreviations: aGVHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; CR, complete response; GRFS, GVHD-free and relapse-free survival; LFS, leukemia-free survival; MAC, myeloablative conditioning; NRM, nonrelapse mortality; OS, overall survival; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioning; Tx, transplantation.

[a] Significant *P* values are presented in boldface type.

.004) for MAC versus RIC recipients, respectively (Table 2). On multivariate analysis (Table 3), the use of BM or PBSC was not associated with GRFS (HR, 0.96; 95% CI 0.69-1.33; *P* 5 .82), LFS (HR, 0.74; 95% CI, 0.52-1.04; *P* 5 .08) and OS (HR, 0.79; 95% CI, 0.54-1.15; *P* 5 .23). For LFS and OS, the use of RIC regimen was the only factor associated with higher risk of treatment failure (LFS: HR, 1.40; 95% CI, 1.01-1.93; *P* 5 .04; OS: HR, 1.5; 95% CI, 1.07-2.14; *P* 5 .02). Center effect, which was entered as a frailty variable in a multivariate model, was significant for NRM, LFS, GRFS, OS, and cGVHD (Table 3).

DISCUSSION

The number of transplantations from an HLA partially matched related donor[17] has increased in recent years due to the use of novel strategies without ex vivo T cell depletion. Non–T-cell–depleted approaches are attractive because they require no expertise in graft manipulation or CD34[1] cell selection and are affordable for most transplantation centers. In addition, familiar donors are easily available and the procedure may be organized quickly, minimizing delay. The attractiveness of haplo-SCT should be verified by a detailed analysis of the results, because the potential advantages may be counterbalanced by increased risk of immune-related complications. Despite short follow-up, several studies have reported comparable outcomes after haplo-SCT and HLA-matched sibling and unrelated donors.[18-20]

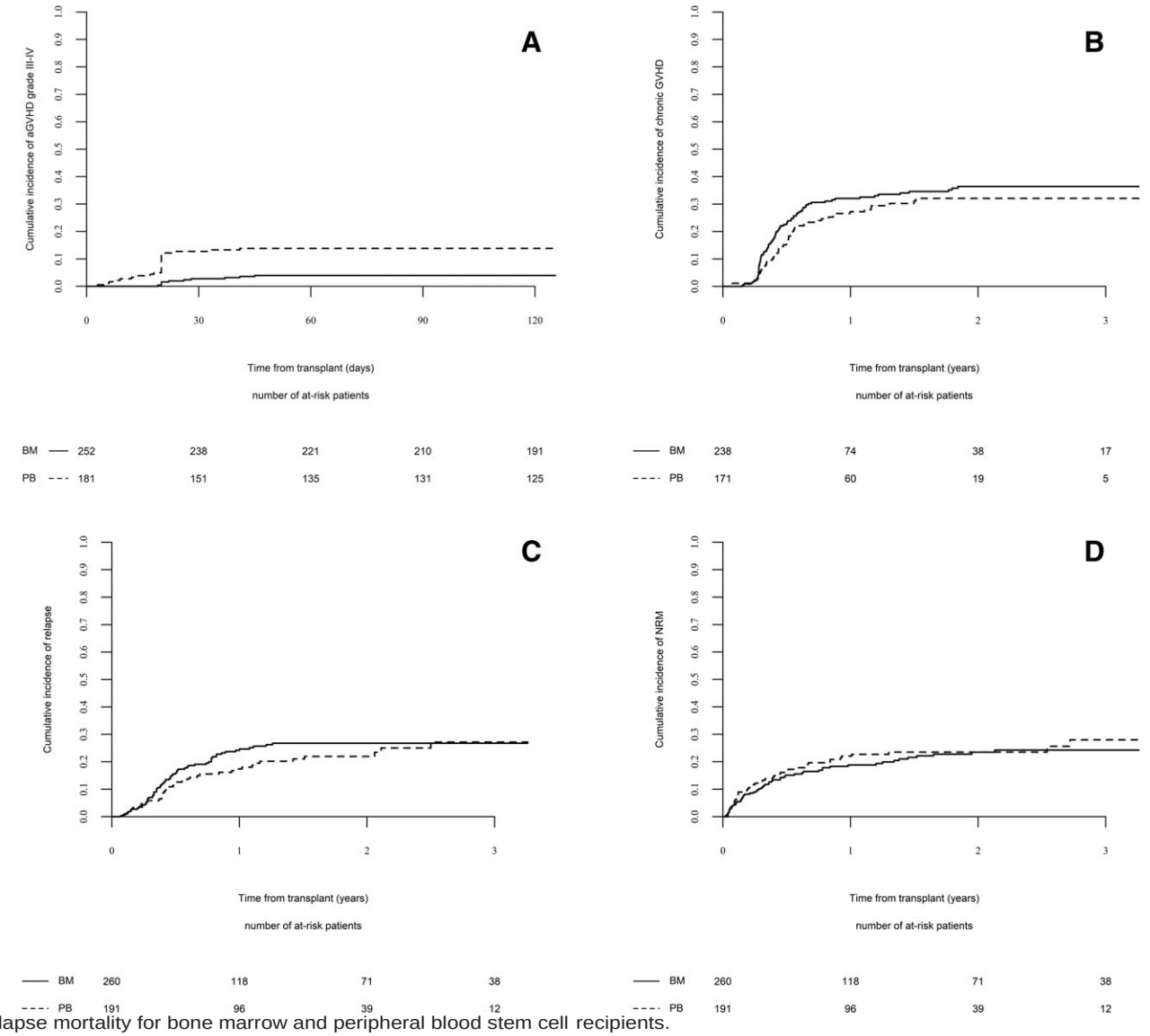
The application of unmanipulated haploidentical transplantation to adults with different hematological diseases has led to investigations of the feasibility of using different stem cell sources in this setting. The first reports using BM, mainly in a non-myeloablative setting with low-dose total body irradiation, were associated with low incidence of both aGVHD and cGVHD, counterbalanced by an excess in disease recurrence.[21] This prompted some investigators to assess the use of PBSC in this setting, facing the risk of severe GVHD.[11] With the aim of analyzing the effect of stem cell sources in patients with acute leukemia, we compared the transplantation outcomes with BM versus PBSC from a haploidentical donor by using data reported to the ALWP-EBMT registry.

In our study, OS and LFS were not different using BM versus PBSC grafts, consistent with data of prospective and retrospective studies using MAC or RIC in sibling and unrelated donors.[22,23] Engraftment of myeloid cells was higher with PBSC grafts compared with BM grafts. This finding is in agreement with many previous reports indicating faster engraftment with PBSC versus BM grafts in different transplantation settings.[1]

In the haploidentical setting, retrospective studies comparing the type of stem cell source using PT-Cy were published, showing no difference in the incidence of GVHD and survival.[12,24,25] These analyses included RIC transplants and patients with heterogeneous myeloid and lymphoid malignancies.

Interestingly, an advantage in survival and progression-free survival of PBSC over BM has been recently reported in 62 patients receiving a haploidentical transplant for advanced Hodgkin disease.[26] The biology of this disease and its sensitivity to the immunological

Figure 1. (A) Acute graft-versus-host disease stage III-IV. (B) Chronic graft-versus-host disease. (C) Relapse incidence. (D) Nonrelapse mortality for bone marrow and peripheral blood stem cell recipients.



effect mediated by the haploidentical cells, may in part explain this finding.

Bashey et al[13] reported comparable OS and mortality between BM and PBSC recipients in a large series of patients with lymphoid and myeloid malignancies. In this report, despite the increased risk of aGVHD using PBSC, there was a reduced risk of relapse compared with BM. Importantly in this series, the BM group received a high proportion of RIC regimen using low-dose total body irradiation, which could partly explain the difference in our results, in which the graft source did not influence the relapse risk. In our population, given the different techniques developed in Europe in the haploidentical transplantation setting, there was a higher proportion of MAC in the BM group, and there was no interaction between the source of stem cells and conditioning intensity for all endpoints evaluated.

Consistent with the CIBMTR study, we observed significant differences in incidence of severe aGVHD comparing PBSC and BM grafts in a homogenous group of patients with leukemia. In accordance, BM with PT-Cy was reported to be associated with a low incidence of GVHD in different single-center reports.[7,27] The action of PT-Cy in preventing GVHD after BM graft has been

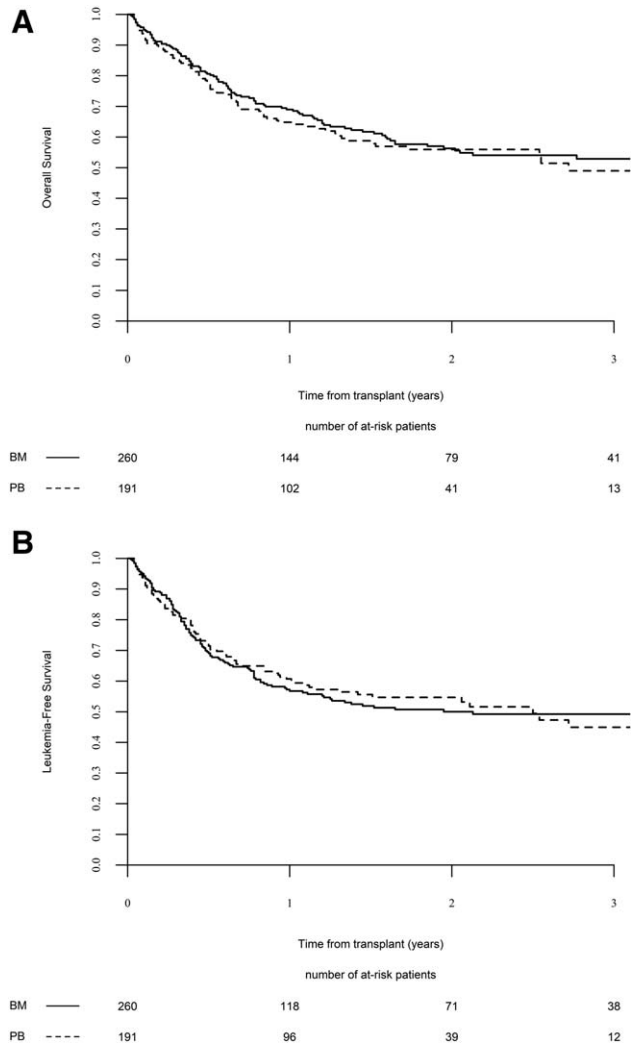


Figure 2. (A) Overall survival. (B) Leukemia-free survival for bone marrow and peripheral blood stem cell recipients.

elucidated, mediating selective in vivo destruction of alloreactive T cells, induction of tolerance, and intrathymic clonal deletion of alloreactive T lymphocytes.[28]

One could argue that the lymphocyte count infused with the unmanipulated PBSC graft in the setting of a full haplotype mismatch could be responsible for an increase of aGVHD; however, one of the limitations of our registry-based study is the lack of CD31 cell number infused with the graft.

We did not find a difference in cGVHD according to stem cell source. This finding is consistent with reports in unrelated[2] and haploidentical[12] settings using RIC regimens.

Of note, in our study the difference in aGVHD was not reflected by an excess of NRM, nor were GRFS, LFS, and OS. This may also be due to the substantial improvements in supportive care after allogeneic transplantation over the years, allowing better survival and reduction of treatment-related toxicities. There is a learning curve associated with the procedure, and transplantation centers are using it more frequently for the management of haploidentical transplantation complications.

Therefore, we have adjusted the comparison of BM versus PBSC using a random effect for each center that could reflect the variability between centers due to all factors, some of which may not be reported in such a retrospective study. We confirm that the center experience is not a confounding factor for the comparison between the 2 sources of stem cells in our study as the 2 types of centers are rather well balanced between the use of BM and PBSC.

The type of conditioning regimen was an independent factor associated with relapse and LFS and OS, with RIC associated with treatment failure. RIC regimens are

associated with a greater risk of disease relapse. Large registry studies have shown that the use of an RIC regimen was associated with a higher risk of relapse but also a lower incidence of NRM, translating to similar OS and LFS.[29,30]

Other investigators have not detected differences in outcomes with RIC versus MAC in unmanipulated haploidentical transplantation; however, this series included a quite heterogeneous population of patients with different disease status and several platforms of GVHD prophylaxis.[31]

We are aware that there may be unmeasured factors that have not been considered in our study, which is a limitation when conducting any retrospective study.

With the available data, our study indicates that in patients with acute leukemia in CR1 or CR2 who underwent haploidentical transplantation with PT-Cy, the use of PBSC significantly increased the risk of aGVHD, whereas survival outcomes were comparable. Importantly, with a follow-up of 2 years, cGVHD, which is a major contributor to long-term morbidity and mortality, is similar using PBSC or BM grafts.

The ultimate choice of graft source depends on the design of the full transplantation package based on transplantation center experience. Our results suggest that a prospective comparative trial of PBSC versus BM in PT-Cy haploidentical transplantation could help establish a standard in the field.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Annalisa Ruggeri, Myriam Labopin, Arnon Nagler: designed the study. Annalisa Ruggeri, Myriam Labopin: performed statistical analysis. Annalisa Ruggeri: wrote the manuscript. Andrea Bacigalupo, Zafer Gülbas, Yener Koc, Didier Blaise, Benedetto Bruno, Giuseppe Irrera, Johanna Tischer, Jose Luiz Diez-Martin, Luca Castagna, Fabio Ciceri, Mohamad Mohty: provided cases for the study. All authors edited and approved the manuscript.

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