Full Length Article
Haploidentical

Bone Marrow versus Peripheral Blood Grafts for Haploidentical Hematopoietic Cell Transplantation with Post-Transplantation Cyclophosphamide

Rohtesh S. Mehta[1],*, Rima M. Saliba[1], Leonard C. Alsfeld[1], Jeffrey L. Jorgensen[2], Sa A. Wang[2], Paolo Anderlini[1], Gheath Al-Atrash[1], Qaiser Bashir[1], Stefan O. Ciurea[3], Chitra M. Hosing[1], Jin S. Im[1], Partow Kebriaei[1], Issa Khouri[1], David Marin[1], Yago Nieto[1], Amanda Olson[1], Betul Oran[1], Uday R. Popat[1], Muzaffar H. Qazilbash[1], Jeremy Ramdial[1], Gabriela Rondon[1], Neeraj Saini[1], Samer A. Srour[1], Katayoun Rezvani[1], Elizabeth J. Shpall[1], Richard E. Champlin[1], Amin M. Alousi[1]

[1] Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[2] Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[3] University of California, Irvine, California

A B S T R A C T

In the coronavirus disease 19 (COVID-19) pandemic era, the number of haploidentical hematopoietic cell trans-plantations (HCTs) with peripheral blood (PB) grafts increased significantly compared with HCTs with bone mar-row (BM) grafts, which may be associated with adverse outcomes. We compared outcomes of HCT in BM graft and PB graft recipients age $\geq$18 years with hematologic malignancies who underwent T cell- replete haploidenti-cal HCT and received graft-versus-host disease (GVHD) prophylaxis with post-transplantation cyclophosphamide, tacrolimus, and mycophenolate mofetil. Among the 264 patients, 180 (68%) received a BM graft and 84 (32%) received a PB graft. The median patient age was 50 years in both groups. The majority (n = 199; 75%) received reduced-intensity conditioning. The rate of acute leukemia or myelodysplastic syndrome was higher in the BM graft recipients compared with the PB graft recipients (85% [n = 152] versus 55% [n = 46]; $P < .01$). The median times to neutrophil and platelet engraftment and the incidence of grade II-IV and grade III-IV acute GVHD (aGVHD) were comparable in the 2 groups. Among the patients with grade II-IV aGVHD, the rate of steroid-refractory aGVHD was 9% (95% confidence interval [CI], 5% to 18%) in the BM group versus 32% (95% CI, 19% to 54%) in the PB group (hazard ratio [HR], 3.7, 95% CI, 1.5 to 9.3; $P = .006$). At 1 year post-HCT, the rate of chronic GVHD (cGVHD) was 8% (95% CI, 4% to 13%) in the BM group versus 22% (95% CI, 14% to 36%) in the PB group (HR, 3.0; 95% CI, 1.4-6.6; $P = .005$), and the rate of systemic therapy-requiring cGVHD was 2.5% (95% CI, 1% to 7%) versus 14% (95% CI, 7% to 27%), respectively (HR, 5.6; 95% CI, 1.7 to 18; $P = .004$). The PB group had a significantly higher risk of bacterial and viral infections, with no appreciable advantage in the duration of hospitalization, immune reconstitution, relapse, nonrelapse mortality, or survival. Our data suggest a benefit of the use of BM grafts over PB grafts for haplo-HCT.
© 2021 The American Society for Transplantation and Cellular Therapy. Published by Elsevier Inc. All rights reserved.

INTRODUCTION

In the setting of haploidentical hematopoietic stem cell transplantation (HCT) with post-transplantation cyclophosphamide (PTCy) for graft-versus-host disease (GVHD) prophylaxis, the use of granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood (PB) grafts has increased dramatically and has now surpassed that of bone marrow (BM) grafts [1]. The utilization of PB graft increased further during the coronavirus disease 19 (COVID-19) pandemic era when the National Marrow Donor Program mandated cryopreservation of unrelated donor (URD) grafts before initiating conditioning [2]. This trend also translated to an increased use of PB grafts in the haploidentical (haplo) HCT setting. With this practice change, we anecdotally noted higher risks of acute GVHD (aGVHD) and chronic GVHD (cGVHD) that led us to conduct this study.

In the absence of a randomized prospective trial, registry studies have assessed the differences in outcomes of haplo-HCT with either BM or PB grafts using PTCy prophylaxis and

Table 1
Recipient and Donor Characteristics

Characteristic	BM Group (N = 180)	PB Group (N = 84)	P Value
Age, yr, median [IQR] (range)			
Recipient	50 [36-60] (18-72)	50 [36-61] (20-72)	.9
Donor	34 [25-42] (12-66)	31 [22-43] (11-67)	.3
Sex, donor/recipient, n (%)			
Female/male	33 (18)	25 (30)	.04
Female/female	24 (13)	16 (19)	.2
Male/male	84 (47)	32 (38)	.2
Male/female	39 (22)	11 (13)	.1
Donor relation, n (%)			.7
Child	94 (52)	46 (55)	
Sibling	72 (40)	30 (36)	
Parent	12 (7)	7 (8)	
Other relative	2 (1)	1 (1)	
Donor sex/age, n (%)			
Female/>30 yr	35 (19)	18 (21)	.7
Disease, n (%)			<.001
AML/MDS	115 (64)	36 (43)	
ALL	37 (21)	10 (12)	
Chronic lymphoid malignancies*	23 (13)	22 (26)	
Chronic myeloid malignancies*	5 (3)	16 (19)	
Conditioning intensity, n (%)			
MAC	46 (26)	19 (23)	
RIC	134 (74)	65 (77)	
MAC regimens, n (%)			
Bu/Flu + Thio/Clo	40 (22)	19 (23)	.2
Flu/TBI	6 (3)	0	
RIC regimens, n (%)			
Flu/Mel100 + TBI/Thio	69 (38)	42 (50)	.07
Flu/Mel140 + TBI/Thio	64 (36)	22 (26)	.1
Flu/Cy/TBI	1 (1)	1 (1)	.6
HCT-CI			
≥3, n (%)	95 (53)	41 (49)	.5
Median, [IQR] (range)	3 [1-4] (0-9)	2 [1-4] (0-8)	.8
DRI, n (%)			.08
Low/intermediate	109 (61)	54 (65)	
High/very high	71 (39)	21 (28)	
Missing	0	9 (11)	
Karnofsky Performance Status, n (%)			.3
<90	57 (32)	30 (36)	
≥90	99 (55)	38 (45)	
Missing	24 (13)	16 (19)	
CMV serostatus (recipient/donor), n (%)			.2
Positive/positive	90 (50)	35 (42)	
Positive/negative	63 (35)	25 (30)	
Negative/negative	15 (8)	13 (15)	
Negative/positive	11 (6)	6 (7)	
Missing	1 (1)	5 (6)	
ABO mismatch, n (%)			.3
None	124 (69)	51 (61)	
Major	27 (15)	19 (23)	
Minor	29 (16)	14 (17)	
Graft dose, median [IQR]			
TNC × 10^8/kg	3 [2-4]	8 [6-11]	
CD34 × 10^6/kg	2.8 [2.2-3.9]	5.8 [4.8-6.6]	
CD3 × 10^8/kg	0.30 [0.23-0.37]	2.62 [1.68-3.85]	
HCT year, n (%)			<.001
2015	41 (23)	2 (2)	

Table 1 (*Continued*)

Characteristic	BM Group (N = 180)	PB Group (N = 84)	P Value
2016-2017	72 (40)	22 (27)	
2018-2019	58 (32)	25 (30)	
2020	9 (5)	35 (42)	
Follow-up, mo, median (range)	25 (2-65)	9 (2-54)	

AML indicates acute myelogenous leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; Bu, busulfan; Flu, fludarabine; Thio, thiotepa; Clo, clofarabine; TBI, total body irradiation; Mel, Melphalan.

　* Chronic lymphoid malignancies include chronic lymphocytic leukemia (6 versus 3), Hodgkin disease (6 versus 5), non-Hodgkin lymphoma (10 versus 14), and multiple myeloma (1 each) in the BM versus PB groups, respectively, and chronic myeloid malignancies include chronic myelogenous leukemia/myeloproliferative disorders.

Table 2
Engraftment

Parameter	BM Group (N = 180)	PB Group (N = 84)	P Value
Neutrophil engraftment, d, median [IQR] (range)*			
All patients	19 [17-22] (12-41)	18 [16-21] (12-31)	.07
MAC	19 [17-21] (12-39)	18 [16-22] (13-26)	.8
RIC	20 [17-22] (13-41)	18 [16-20] (12-31)	.02
Platelet engraftment (20K), d, median [IQR] (range)			
All patients	28 [23, 36] (12-529)	26 [20, 35] (9-105)	.3
MAC	28 [24, 37] (13-529)	27 [17, 44] (13-105)	.8
RIC	28 [22, 35] (12-285)	26 [20, 31] (9-103)	.3
Platelet engraftment (50K), d, median [IQR] (range)			
All patients	35 [28-45] (20-453)	30 [26-41] (15-129)	.06
MAC	38 [30-49] (20-296)	29 [23-46] (15-129)	.6
RIC	35 [27-45] (20-453)	31 [27-40] (15-105)	.1

　* Among those who engrafted. Seven patients had graft failure (6 BM and 1 PB); 6 patients received Flu/Mel RIC and 1 received Bu/Flu MAC, with either a child (n = 6) or a sibling (n = 1) donor. Among 6 BM graft failures, 2 patients had donor-specific antibodies (DSAs): 1 with anti-HLA class I antibody and 1 with anti-HLA class I and class II antibodies. Of the remaining 4 patients without DSAs, the median TNC dose in the graft was 1.8×10^8/kg (range, 1.53 to 2.1×10^8/kg), which was lower than the median TNC dose (3×10^8/kg) in the overall BM group. One patient in the PB group with graft failure had anti-HLA class I and class II DSAs.

have yielded controversial results [3−6]. One reason for these conflicting outcomes may be related to the inclusion of patients across centers, which introduces biases that are difficult to control in a retrospective analysis. For instance, practice disparities exist among centers in terms of immunosuppression taper, GVHD management, and post-HCT complications. Moreover, data are lacking on other significant outcomes, such as steroid-refractory (SR) aGVHD, systemic therapy-requiring cGVHD, differences in immune reconstitution, and quality of life (QoL) after haploidentical BM grafts versus PB grafts.

　Here we report the outcomes of patients treated at the MD Anderson Cancer Center who underwent T cell-replete haploidentical HCT with either BM or G-CSF-mobilized cryopreserved PB grafts and a uniform GVHD prophylaxis regimen with PTCy, tacrolimus, and mycophenolate mofetil (MMF) (PTCy/Tac/MMF). We hypothesized that PB grafts would be associated with higher risks of aGVHD and cGVHD compared with BM grafts.

METHODS

　We included adult patients age ≥18 years with any hematologic malignancy who underwent haplo-HCT between January 2015 and July 2020 with any conditioning regimen and PTCy/Tac/MMF GVHD prophylaxis. Patients who received a manipulated graft (T cell depletion or ex vivo engineered T cells) were excluded. The primary objective was to compare the rates of aGVHD (grade II-IV, grade III-IV, SR) and cGVHD (overall, extensive, systemic therapy-requiring) between the BM and PB groups. Secondary outcomes were to compare neutrophil and platelet engraftment, chimerism, nonrelapse mortality (NRM), relapse, progression-free survival (PFS), overall survival (OS), GVHD-free relapse-free survival (GRFS), immune reconstitution, rates of infections, and differences in quality of life (QoL) in the 2 groups. Data on all important outcomes post-HCT, including infections, are routinely prospectively collected and entered into a database by a dedicated team at our institution. We routinely monitor for bacterial infections by blood cultures once weekly and

for viral infections, such as adenovirus, cytomegalovirus (CMV), and Epstein-Barr virus (EBV), by polymerase chain reaction (PCR) assay weekly at least until day +100 post-HCT, or longer depending on the clinical situation.

　For immune reconstitution, cell subsets in PB samples were analyzed by multicolor flow cytometry for CD3, CD4, CD8, CD19, CD25, CD27, CD45, CD45RO, CD56, CD62L, CD127, and IgM. The absolute numbers of T cells, B cells, regulatory T cells (Tregs), and natural killer (NK) cells, as well as their subsets, were calculated as cells/μL based on their frequency in a lymphoid-mononuclear cell-gated population. Chimerism analysis was performed at day +30, day +100, 6 months, and 12 months post-HCT using a PCR assay with primer sets flanking microsatellite repeats.

　QoL assessment was done using the Functional Assessment of Cancer Therapy−Bone Marrow Transplant (FACT-BMT) scale, version 4 [7]. This scale includes 5 subscales that capture physical, social/family, emotional, and functional well-being, along with a bone marrow transplantation (BMT) subscale. An aggregate global score and total scores for each subscale were calculated as suggested previously [7]. All patients who were alive in remission and had at least 1-year of follow-up were selected for QoL assessment and contacted by phone to confirm email addresses, and the survey was then distributed electronically.

Definitions

　Acute GVHD was staged and graded according to the consensus criteria [8], and cGVHD was staged and graded according to standard criteria [9,10]. SR-aGVHD was defined as (1) failure to respond after 7 days of treatment with corticosteroids (generally prednisone 2 mg/kg/day or an equivalent dose of methylprednisolone) or (2) progression after 72 hours. Neutrophil engraftment was defined as an absolute neutrophil count of >500 × 10^6/L for 3 consecutive days. Platelet engraftment (20K) was defined as a platelet count >20 × 10^9/L for 7 days without transfusion. Platelet engraftment (50K) was defined as a platelet count >50 × 10^9/L for 7 days without transfusion. Relapse or progression was defined as the time to recurrence or progression of the underlying malignancy, with death without relapse or progression (NRM) treated as a competing risk. PFS was defined as the time from HCT to relapse or progression or death. OS was defined as the time from HCT to death from any cause. GRFS was defined as the absence of grade III-IV aGVHD, systemic therapy-requiring
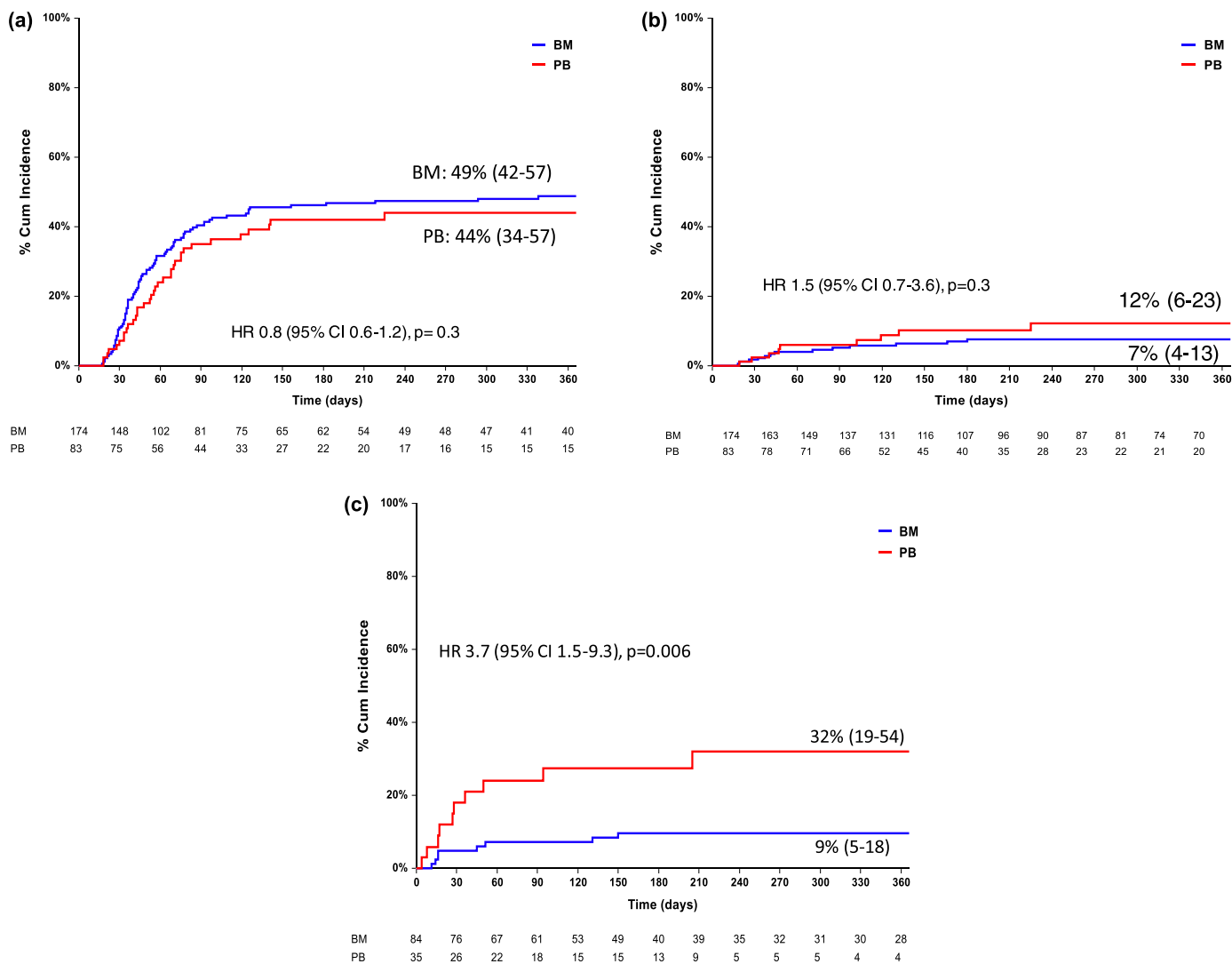
Figure 1. Cumulative incidence of acute GVHD grade II-IV (A), grade III-IV (B), and SR (C) in recipients of BM grafts (blue) and PB grafts (red).

cGVHD, relapse, or death. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional Investigational Review Board (MDACC 2021-0103).

Statistical Analysis

Descriptive analyses were performed to summarize clinical and demographic characteristics. Categorical variables were compared between treatment arms using Fisher's exact test, and continuous variables were compared using the Wilcoxon rank-sum test. Engraftment data were analyzed considering death before engraftment as a competing risk. The rate of NRM was estimated in a competing-risks framework with relapse as the competing risk. aGVHD and cGVHD were assessed with competing risks of relapse and death. aGVHD events included both classical (before day +100) and late aGVHD (aGVHD occurring beyond day +100). Kaplan-Meier curves were used to estimate OS, PFS, and GRFS, and the log-rank test was used to test differences by graft source. The Mann-Whitney U test was used to compare QoL data. Statistical analyses were performed primarily with STATA 14 (StataCorp, College Station, TX).

RESULTS

Of the 264 patients, 180 (68%) received BM grafts and 84 (32%) received PB grafts. Recipient age at HCT (median, 50 years) and donor age (median 34 years for BM and 31 years for PB) were similar in the 2 groups. More patients in the BM group than in the PB group had acute myelogenous leukemia/myelodysplastic syndrome (64% versus 43%) and acute lymphoblastic leukemia (21% versus 12%) ($P < .001$). Approximately three-quarters of the patients in both groups received reduced-intensity conditioning (RIC) with a fludarabine and melphalan-based regimen (74% versus 76%). Busulfan (with pharmacokinetic dose monitoring) and fludarabine-based myeloablative conditioning (MAC) was used in 22% and 23%. Approximately one-half of the patients had an HCT-Comorbidity Index (HCT-CI) of ≥3 (53% versus 49%; $P = .5$). Haploidentical children were the most common donors (52% versus 55%), followed by siblings (40% versus 36%). More male patients in the PB group than in the BM group received grafts from female donors (30% versus 18%; $P = .04$). As expected, there were significant differences in the graft composition, with a significantly lower total nucleated cell dose (median, 3×10^8/kg versus 8×10^8/kg), CD34 dose (median, 2.8×10^6/kg versus 5.8×10^6/kg), and CD3 dose (median, 0.3×10^8/kg versus 2.62×10^8/kg) in the BM group compared with the PB group (Table 1).

Engraftment and Chimerism

Primary graft failure occurred in 6 of 180 patients (3.33%) in the BM group and in 1 of 84 (1.19%) in the PB group. The median time to neutrophil engraftment was 19 days (interquartile range [IQR], 17 to 22 days) in the BM group and 18 days (IQR, 16 to 21 days) in the PB group ($P = .07$). Among recipients of an RIC regimen, the median time to neutrophil engraftment was 20 days (IQR, 17 to 22 days) in the BM group and 18 days (IQR, 16 to 20 days) in the PB group ($P = .02$), and among MAC recipients, it was 19 days (IQR, 17 to 21 days) in the BM group and 18 days (IQR, 16 to 22 days) in the PB group ($P = .8$) (Table 2). The median duration of hospitalization for HCT was 33 days (IQR, 28 to 39 days) in the BM group versus 31 days (IQR, 26 to 36 days) in the PB group ($P = .05$).

The median time to platelet engraftment (20K) was 28 days (IQR, 23 to 36 days) in the BM group and 26 days (IQR, 20 to 35 days) in the PB group ($P = .3$). The median time to platelet engraftment (50K) was 35 days (IQR, 28 to 45 days) in the BM group and 30 days (IQR, 26 to 41 days) in the PB group ($P = .06$). There was no difference in the median time to platelet engraftment between the groups when analyzed by conditioning intensity (Table 2).

Chimerism analysis revealed a median of 100% donor cells in both myeloid and T cell compartments in the BM and PB groups at all time points tested: day +30, day +100, 6 months, and 12 months (Supplementary Table S1).

Table 3
Other Outcomes

Outcome	BM Group (N = 180), %, median (range)	PB Group (N = 84), %, median (range)	PB vs BM, Univariate Analysis, Entire Cohort (N = 264)			PB vs BM, Univariate Analysis, MAC (N = 64)			PB vs BM, Univariate Analysis, RIC (N = 199)		
			HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
aGVHD, grade II-IV	49 (42-57)	44 (34-57)	0.8	0.6-1.2	.3	1.03	0.4-2.3	.9	0.8	0.5-1.2	.2
aGVHD, grade III-IV	7 (4-13)	12 (6-23)	1.5	0.7-3.6	.3	10.9	1.3-89	**.03**	0.9	0.3-2.5	.8
SR aGVHD*	9 (5-18)	32 (19-54)	**3.7**	1.5-9.3	**.006**	14	1.8-110	**.01**	2.4	0.8-7	.1
cGVHD	8 (4-13)	22 (14-36)	**3.0**	1.4-6.6	**.005**	NE	-	**.002**	1.9	0.8-4.7	.1
Therapy-requiring cGVHD	2.5 (1-7)	14 (7-27)	**5.6**	1.7-18	**.004**	NE	-	-	4.7	1.4-16	**.01**
Extensive cGVHD	3 (1-7)	18 (10-31)	6.4	2.2-17	**.001**	NE	-	**.002**	3.6	1.2-11	**.02**
Limited cGVHD	4 (1-17)	4 (1-17)	0.8	0.2-3.8	.8	-	-	-	-	-	-
NRM	27 (22-35)	28 (19-41)	1.1	0.6-1.8	.8	0.7	0.2-2.3	.5	1.2	0.7-2.1	.5
Relapse/progression	21 (16-28)	20 (12-32)	0.8	0.4-1.6	.6	0.3	0.04-2.1	.2	1	0.5-1.9	.9
PFS	50 (43-58)	52 (40-65)	0.98	0.7-1.5	.9	0.6	0.2-1.7	.3	1.1	0.7-1.7	.8
OS	58 (51-66)	61 (49-73)	0.9	0.6-1.5	.8	0.5	0.2-1.3	.2	1.2	0.7-1.8	.5
GRFS	48 (41-56)	36 (25-48)	1.3	0.9-1.9	.1	-	-	-	-	-	-

Significant values are in bold type.
* Among patients with grade II-IV acute GVHD
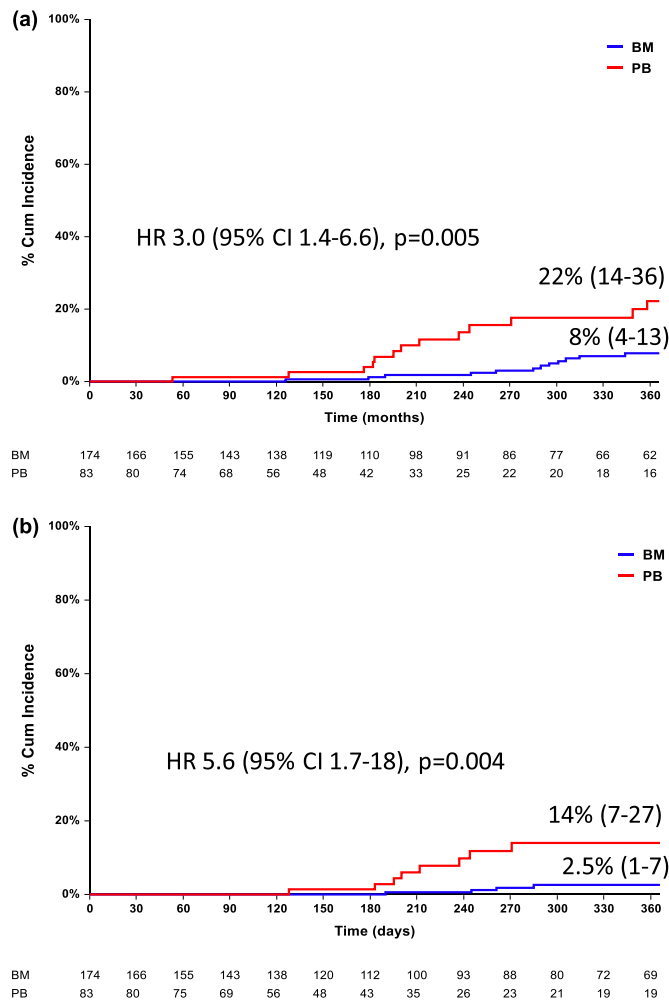
Figure 2. Cumulative incidence of overall chronic GVHD (A) and systemic therapy-requiring grade chronic GVHD (B) in recipients of BM grafts (blue) and PB grafts (red).

GVHD

The cumulative incidence of grade II-IV aGVHD was 49% (95% CI confidence interval [], 42% to 57%) in the BM group versus 44% (95% CI, 34% to 57%) in the PB group (hazard ratio [HR], 0.8; 95% CI, 0.6 to 1.2; P = .3). The cumulative incidence of grade III-IV aGVHD was 7% (95% CI, 4% to 13%) in the BM group versus 12% (95% CI, 6% to 23%) in the PB group (HR, 1.5; 95% CI, 0.7 to 3.6; P = .3). In the patients who developed grade II-IV aGVHD, the incidence of SR-aGVHD in the 2 groups was 9% (95% CI, 5% to 18%) versus 32% (95% CI, 19% to 54%), respectively (HR, 3.7; 95% CI, 1.5 to 9.3; P = .006) (Figure 1A-C; Table 3). When analyzed by conditioning intensity, PB was associated with significantly higher risks of grade III-IV aGVHD (HR, 10.9; 95% CI, 1.3 to 89; P = .03) and SR-aGVHD (HR, 14; 95% CI, 1.8 to 110; P = .01) compared with the BM group in the MAC setting but not in the RIC setting (Table 3). Patients with SR-aGVHD required second-line treatment with therapies including extracorporeal photopheresis, ruxolitinib, tacrolimus, sirolimus, vedolizumab, and infliximab. Four patients required reinitiation of high-dose corticosteroids on multiple occasions due to recurrence of GVHD after tapering off steroids.

The cumulative incidence of cGVHD at 1 year was 8% (95% CI, 4% to 13%) in the BM group versus 22% (95% CI, 14% to 36%) in the PB group (HR, 3.0; 95% CI, 1.4 to 6.6; P = .005). The cumulative incidence of extensive cGVHD at 1 year in the 2 groups was 3% (95% CI, 1% to 7%) and 18% (95% CI, 10% to 31%), respectively (HR, 6.4; 95% CI, 2.2 to 17; P = .001) and the cumulative

incidence of systemic therapy-requiring cGVHD was 2.5% (95% CI, 1% to 7%) and 14% (95% CI, 7% to 27%), respectively (HR, 5.6; 95% CI, 1.7 to 18; P = .004) (Figure 2 and B; Table 3). Similar findings were seen when analyzed by conditioning intensity, especially in the RIC setting (Table 3). Among patients with therapy-requiring cGVHD, 66.7% (n = 14) had moderate cGVHD, 23.8% (n = 5) had severe cGVHD, and 9.5% (n = 2) had mild cGVHD as defined by the 2015 National Institutes of Health consensus criteria [11]. A majority of these patients (57.1%; n = 12) had skin involvement; 38.1% (n = 8) had ocular involvement, 28.5% (n = 6) had oral involvement, 33.3% (n = 7) had gastrointestinal tract involvement, and 2 patients had bronchiolitis obliterans with or without other organ involvement (Supplementary Table S2).

The median time to the development of grade II-IV aGVHD was 44 days (IQR, 32 to 73 days) in the BM group versus 55 days (IQR, 35 to 75 days) in the PB group, and that for grade III-IV aGVHD was 44 days (IQR, 32 to 97 days) versus 55 days (IQR, 40 to 119 days), respectively. The median time to the development of cGVHD in the 2 groups was 295 days (IQR, 245 to 344 days) and 240 days (IQR, 183 to 389 days), respectively, and that for systemic therapy-requiring cGVHD was 374 days (IQR, 253 to 524 days) and 244 days (IQR, 200 to 392 days), respectively.

In univariate analysis, receipt of a PB graft was associated with a significantly higher risk of SR-aGVHD (HR, 2.9; 95% CI, 1.1 to 7.3; P = .03) and systemic therapy-requiring cGVHD (HR, 5.6; 95% CI,

1.7 to 18; $P = .004$). CMV-seropositive patients and those with lymphoid (versus myeloid) malignancies had a higher risk of systemic therapy-requiring cGVHD. No other factor, including conditioning intensity, donor/recipient age, donor relationship, donor/recipient sex, ABO matching, or performance status, was a predictor of either SR-aGVHD or systemic therapy-requiring cGVHD. There were no significant predictors of grade III-IV aGVHD and overall cGVHD (Supplementary Table S3). In multivariate analysis, PB graft was the sole factor associated with a significantly higher risk of SR-aGVHD (HR, 2.9; 95% CI, 1.1 to 7.3; $P = .03$). Predictors of systemic therapy-requiring cGVHD included receipt of a PB graft (HR, 5.4; 95% CI, 1.7 to 17; $P = .005$) and lymphoid malignancies (HR, 5.4; 95% CI, 1.4 to 20; $P = .01$) (Table 4). No other variable, including female donor to male recipient, was a predictor of either aGVHD or cGVHD. Further subgroup analysis of patients with AML/MDS (n = 151) showed that receipt of a PB graft was associated with substantially greater risks of grade III-IV aGVHD (HR, 3.4; $P = .02$), SR-aGVHD (HR, 4.6; $P = .02$), cGVHD (HR, 9.6; $P = .006$), and systemic therapy-requiring cGVHD (HR N.E. = non-evaluable; $P = .001$).

Relapse and NRM

The rate of NRM at 1 year was 27% (95% CI, 22% to 35%) in the BM group and 28% (95% CI, 19% to 41%) in the PB group (HR, 1.1; 95% CI, 0.6 to 1.8; $P = .8$) (Figure 3A; Table 3). On multivariate analysis, age ≥50 years (HR, 2.8; 95% CI, 1.7 to 4.7; $P < .001$) and HCT-CI ≥3 (HR, 2.1; 95% CI, 1.2 to 3.5; $P = .005$) were predictors of NRM, where there was no effect of graft source (PB: HR, 1.1; 95% CI, 0.7 to 1.9; $P = .6$) (Table 4). The rate of relapse at 1 year was 21% (95% CI, 16% to 28%) in the BM group and 20% (95% CI, 12% to 32%) in the PB group (HR, 0.8; 95% CI, 0.4 to 1.6; $P = .6$) (Figure 3B; Table 3). On multivariate analysis, there was no effect of graft source (PB: HR, 0.97; 95% CI, 0.5 to 1.9; $P = .9$). High/very high Disease Risk Index (DRI) (HR, 2.2; 95% CI, 1.2 to 3.8; $P = .007$) was the sole factor associated with a significantly higher risk of relapse (Table 4). No differences in relapse or NRM between the BM and PB groups were noted when analyzed by conditioning intensity (Table 3).

Survival

PFS at 1 year was 50% (95% CI, 43% to 58%) in the BM group and 52% (95% CI, 40% to 65%) in the PB group (HR, 0.98; 95% CI, 0.7 to 1.5; $P = .9$). The rate of OS at 1 year in the 2 groups was 58% (95% CI, 51% to 66%) and 61% (95% CI, 49% to 73%), respectively (HR, 0.9; 95% CI, 0.6 to 1.5; $P = .8$) (Figure 3C and D; Table 3). On multivariate analysis, there was no effect of graft source on OS (PB: HR, 1.1; 95% CI, 0.7 to 1.7; $P = .7$). Age ≥50 years (HR, 2.4; 95% CI, 1.5 to 3.6; $P < .001$), HCT-CI ≥3 (HR, 2.3; 95% CI, 1.5 to 3.6; $P < .001$), and high/very high DRI (HR, 1.7; 95% CI, 1.1 to 2.5; $P = .01$) were associated with worse OS (Table 4). There were no differences in survival between the BM and PB groups when analyzed by conditioning intensity (Table 3). Seventy-two patients in the BM group and 27 in the PB group died by 1 year. Infection was the most common cause of death in the BM group (n = 25; 35%), followed by relapse (n = 24; 33%), and GVHD (n = 10; 14%). Despite the higher risk of infections and GVHD in the PB group, organ toxicity (cardiac, pulmonary, liver, or multiorgan failure) was the most common cause of death (n = 10; 37%), followed by relapse (n = 6; 22%), infection (n = 5; 18.5%), and GVHD (n = 3; ~11%) (Supplementary Table S4).

At 1 year, GRFS was 48% (95% CI, 41% to 56%) in the BM group and 36% (95% CI, 25% to 48%) in the PB group (Figure 3E; Table 3). On multivariate analysis, there was a significant interaction between graft source and DRI. Receipt of a PB graft was associated with significantly worse GFRS (HR, 2.2; 95% CI, 1.4 to 3.5; $P = .001$)

Table 4
Multivariate Analysis for Predictors of Outcomes

Outcome	Graft source (PB vs BM)			Age>50 yr			HCT-CI ≥3			High/Very High DRI			Lymphoid (vs Myeloid) Malignancy		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
SR aGVHD	2.9	1.1-7.3	.03	-			-			-			-		
Therapy requiring chronic GVHD	5.4	1.7-17	.005	-			-			-			5.4	1.4-20	.01
NRM	1.1	0.7-1.9	.6	2.8	1.7-4.7	<.001	2.1	1.2-3.5	.005	-			-		
PFS	0.97	0.5-1.9	.9	-			-			2.2	1.2-3.8	.007	-		
OS	1.1	0.7-1.7	.7	2.4	1.5-3.6	<.001	2.3	1.5-3.6	<.001	1.7	1.1-2.5	.01	-		
GRFS	2.2*	1.4-3.5	.001	1.9	1.3-2.7	<.001	1.7	1.2-2.4	.003	2.1†	1.4-3.2	.001			

* HR reflects the impact of PB in low/intermediate DRI; HR in high/very high, 0.7 (95% CI, 0.4 to 1.5); $P = .4$
† HR reflects the impact of high/very high DRI in BM; HR in PB, 0.7 (95% CI, 0.3 to 1.4); $P = .3$.
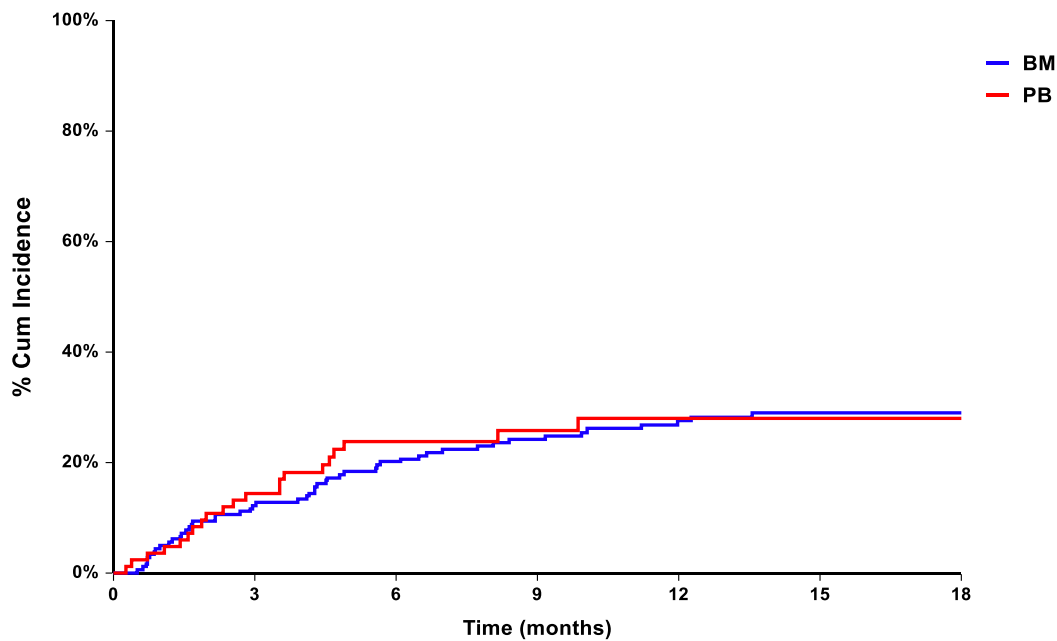
BM	180	147	115	94	73	66	58
PB	84	68	44	24	21	14	11

BM: 27% (95% CI 22-35)
PB: 28% (95% CI 19-41)
HR 1.1, 95% CI 0.6-1.8, p=0.8

Figure 3. Other outcomes, including NRM (A), relapse/progression (B), PFS (C), OS (D), and GRFS (E) in recipients of BM grafts (blue) and PB grafts (red).

among patients with low/intermediate DRI. Age $\geq$50 years (HR, 1.9; 95% CI, 1.3 to 2.7; $P < .001$) and HCT-CI $\geq$3 (HR, 1.7; 95% CI, 1.2 to 2.4; $P = .003$) were significant predictors of worse GRFS (Table 4).

Immune Reconstitution

Day 100 (range, 70 to 147 days) comprehensive immune reconstitution data were available for 56 patients. Except for a greater number of class-switched memory B cells in the PB group compared with the BM group, there were no significant differences in any cell subset analyzed (Table 5). The median absolute lymphocyte count (ALC) was 410 cells/μL (range, 0 to 1900 cells/μL) in the BM group and 530 cells/μL (range, 160 to 2100 cells/μL) in the PB group ($P = .4$). The absolute CD4 cell count (99 cells/μL versus 100 cells/μL), CD8 cell count (40 cells/μL versus 59 cells/μL), CD4/CD8 ratio (2.2 versus 1.6), absolute Treg count (9 cells/μL versus 10 cells/μL), absolute CD19 B cell count (38 cells/μL versus 51 cells/μL), and absolute NK cell count (165 cells/μL versus 226 cells/μL) were similar in in the 2 groups. Among B cell subsets, the numbers of naïve B cells and IgM memory B cells were similar in the 2 groups, but there were more class-switched memory B cells in the PB group compared with the BM group (median, 2 cells/μL [range,

0 to 25 cells/μL] versus 1 cell/μL [range, 0 to 1193 cells/μL]; $P = .02$). Among CD4 and CD8 cell subsets, the numbers of naïve, central memory, effector memory, and terminally differentiated effector cells were similar in the 2 groups. Similarly, no between-group differences were noted in Treg subsets, including central memory and naïve Tregs, or in NK cell subsets, including CD56(bright) and CD56(dim) NK cells. Similar results were noted at the day +180 evaluation in a subset of patients (n = 24) in whom comprehensive data were available, which showed no statistically significant between-group differences in any of the cell subsets analyzed (Supplementary Table S5).

Infections

The cumulative incidence of any viral infection by day +180 was 7% (95% CI, 4% to 12%) in the BM group and 17% (95% CI, 10% to 27%) in the PB group (HR, 2.4; 95% CI, 1.1 to 5; $P = .02$). The cumulative incidence of bacterial infections by day +180 in the 2 groups was 4% (95% CI, 2% to 9%) versus 13% (95% CI, 8% to 23%), respectively (HR, 3.1; 95% CI, 1.3 to 7.7; $P = .01$).

Viral infections constituted the majority of infection events: 32 in the BM group and 26 in the PB group within 6 months of transplantation. These included BK virus (7 in the
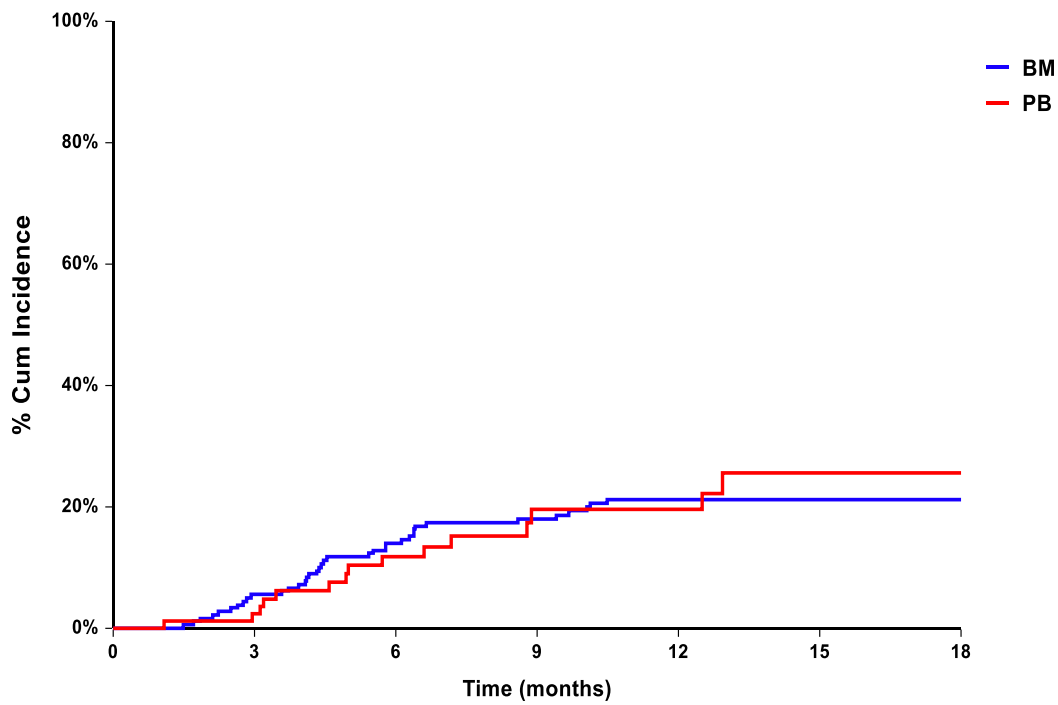
BM: 21% (95% CI 16-28)
PB: 20% (95% CI 12-32)
HR 0.8, 95% CI 0.4-1.6, p=0.6.

Figure 3. Continued.

BM group versus 6 in the PB group), CMV (7 versus 6), adenovirus (0 versus 1), EBV (2 versus 1), human herpesvirus 6 (7 versus 5), herpes simplex virus (1 versus 1), respiratory syncytial virus (0 versus 2), parainfluenza (3 versus 1), rhinovirus (3 versus 1) and others (2 versus 2). Eight bacterial infection events occurred in the BM group, compared with 10 in the PB group. There was only 1 case of fungal infection. Despite the higher rate of infections in the PB group, infection was a less common cause of death in this group.

*Qo*L

Ninety-seven patients (75 in the BM group and 22 in the PB group) who were alive and in remission and had at least 1 year of follow-up post-HCT were selected. Of these, 28 patients could not be reached after 2 attempts, 9 patients answered but did not return the survey, 11 patients were either international or did not speak English, and 1 patient refused to participate. The remaining 48 patients (33 in the BM group and 15 in the PB group) comprised the study cohort. The median patient age was 44 years (range, 19 to 72 years) in the BM group versus 45 years (range, 21 to 68 years) in the PB group ($P = .71$), and the median follow-up in the 2 groups was 1079 days (range, 449 to 2205 days) versus 960 days (range, 394 to 1605 days) ($P = .32$). No between-group differences were noted in the global FACT-BMT score or any subdomains (Supplementary Table S6). The most troubling symptoms reported were satisfaction with sex life, sleep, and perception of body image. When patients were asked whether they regretted undergoing HCT, the median response was "not at all."

DISCUSSION

We show that in the setting of haploidentical HCT with PTCy/Tac/MMF GVHD prophylaxis, the use of PB grafts was associated with a significantly higher risk of SR-aGVHD, overall cGVHD, systemic therapy-requiring cGVHD, and bacterial and viral infections compared with the use of BM grafts. Moreover, the PB group had no advantage in terms of engraftment, duration of hospitalization, immune reconstitution, relapse, NRM, or OS. Furthermore, PB was associated with significantly worse GFRS among patients with low/intermediate DRI.
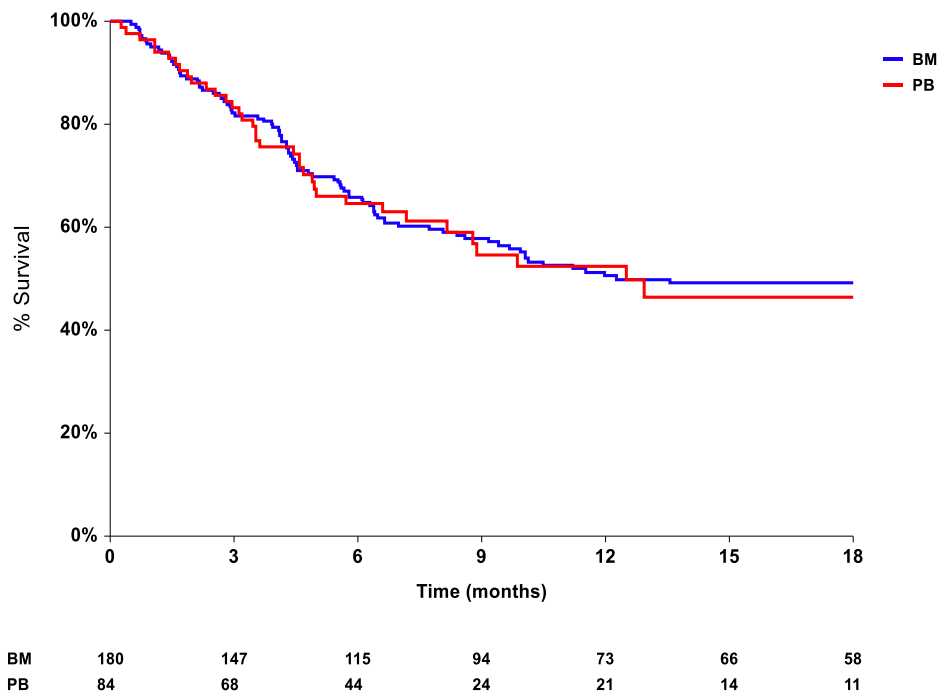
BM: 50% (95% CI 43-58)
PB: 52% (95% CI 40-65)
HR: 0.98, 95% CI 0.7-1.5, p=0.9

Figure 3. Continued.

An appreciably greater number of patients in the PB group developed SR-aGVHD or therapy-requiring cGVHD, which likely contributed to their increased risk of both bacterial and viral infections. Although these patients were effectively "salvaged" with treatment, and thus neither NRM nor survival differed between the groups, the clinical burden and morbidity associated with GVHD and its treatment cannot be captured by these statistics. Because the use of PTCy has reduced the risk of GVHD, a much larger study population will be needed to demonstrate any statistical differences in survival. The rate of grade III-IV aGVHD was also higher in the PB group than in the BM group (12% versus 7%), which, although clinically meaningful, did not reach statistical significance owing to the small number of events. The higher graft cell dose in the PB group might have contributed to the greater risk of GVHD [12].

The rate of graft failure was generally low, and there were no noticeable clinically significant differences in either neutrophil or platelet engraftment between the BM and PB groups in the entire cohort. Among the patients who received RIC, the time to neutrophil engraftment, but not that of platelet engraftment, was 2 days faster in the PB group. This is likely a reflection of the lower BM harvest cell dose achieved than those reported in previous studies [6,13,14]. Although there is no specific optimal cell dose for transplantation, generally superior outcomes are seen with higher total nucleated cell and CD34 cell doses in both related and URD HCT [15−18], as well as improved survival in haploidentical HCT [19].

Encouragingly, the pace of immune reconstitution was similar in the BM and PB groups. This is in contrast to the URD setting with conventional GVHD prophylaxis, in which receipt of a PB graft is associated with faster T cell immune reconstitution [20], although this is expected to be different with PTCy prophylaxis [21]. Previous studies have assessed immune reconstitution after haploidentical HCT with PTCy and compared it with HCT with other donor types or with antithymocyte globulin [22−28]. However, a direct comparison of immune reconstitution by graft source in haploidentical setting has been lacking, which is provided by our present study. Given that GVHD can negatively affect thymic function and immune reconstitution [29], the lower incidence of GVHD in the BM group might have facilitated immune recovery.

Several retrospective studies have assessed the differences in outcomes of haploidentical HCT with BM or PB grafts using PTCy prophylaxis and have yielded controversial results. Almost all the studies showed higher risks of aGVHD and/or cGVHD with PB grafts; one study showed an increased risk of both aGVHD and cGVHD [3], one showed an increased risk of aGVHD but not of cGVHD [4], and one showed an increased risk of cGVHD but not of aGVHD [5], Only one study [3] found a greater risk of relapse with BM in patients with acute leukemia. On the other hand, a study in patients with acute lymphoblastic leukemia [6] showed significantly inferior PFS, OS, and GRFS and trends toward higher rates of grade II-IV aGVHD (HR, 1.52; *P* = .07), cGVHD (HR, 1.58; *P* = .05), and NRM
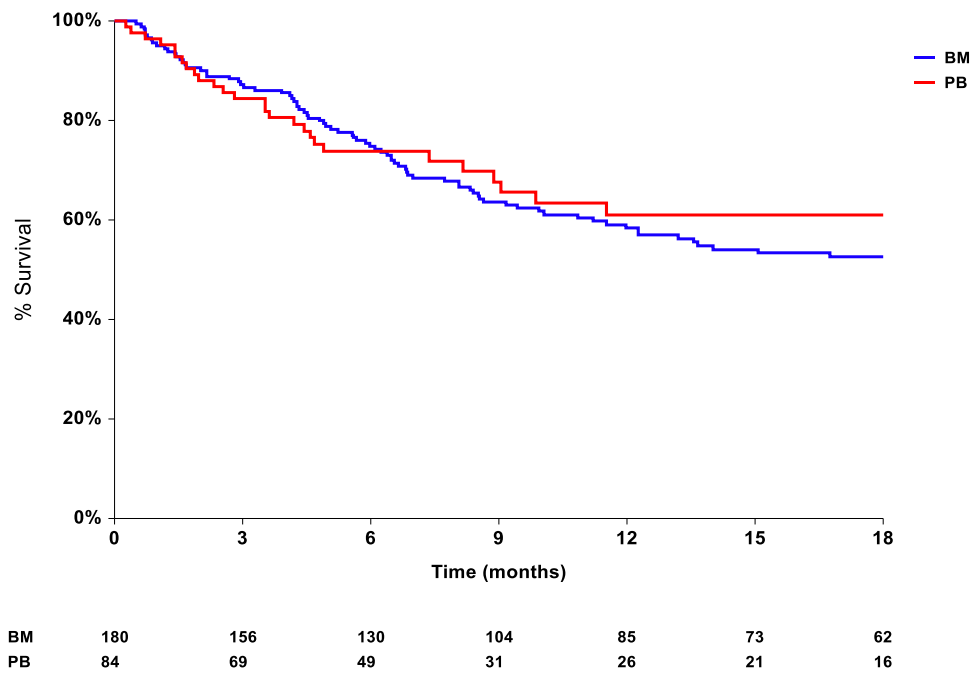
BM: 58% (95% CI 51-66)
PB: 61% (95% CI 49-73)
HR: 0.9, 95% CI 0.6-1.5, p=0.8

Figure 3. Continued.

(HR, 1.66; *P* = .06) with PB grafts. One reason for these variable outcomes seen in different studies may be related to the inclusion of patients across centers who are treated differently. Our study minimizes these biases and adds to the literature by providing crucial data on SR-aGVHD, therapy-requiring cGVHD, differences in immune reconstitution, and patient-reported QoL by graft source, which were lacking previously. Nevertheless, our outcomes should be validated in future studies involving larger numbers of PB recipients.

We acknowledge the limitations of our study, including a lack of data on the morbidity of GVHD as assessed by long-term complications, including the risk of avascular necrosis, and endocrine and cardiovascular complications, to name a few. Moreover, the QoL assessment was restricted to only those who had at least 1 year of follow-up and was done at the time of this study rather than at a fixed time point post-HCT, and thus it might not be representative of the entire cohort. Moreover, although the survey response rates can vary from 30% to 85% [30,31], the completion rate of approximately 50% noted in our study is consistent with previous studies [32]. Thus, the possibility of participation bias should be considered when assessing the QoL data. Future studies should consider the prospective collection of QoL data and a cost-effectiveness analysis and also consider assessing the T cell receptor excision circle and T cell receptor repertoire, data that were lacking in our study. Finally, although data on all post-HCT complications, including infections, are captured prospectively by a dedicated team at our institution, certain infection events might have been missed, especially in the early COVID-19 era for patients who were discharged to home after day +100 to follow-up with their local physicians. Most of those patients are still followed closely at our institution for the first 1 to 2 years post HCT. Because in-person follow-up visits for many patients were limited during the COVID-19 pandemic, most of the patients were still followed-up via virtual televisits.

Our data show a compelling benefit of using BM over PB grafts for haploidentical HCT with PTCy, tacrolimus, and MMF prophylaxis, which was associated with a significantly lower risk of severe aGVHD and cGVHD, fewer bacterial and viral infections, and comparable pace of recovery of neutrophils, platelets, and immune reconstitution, relapse, NRM, and survival.
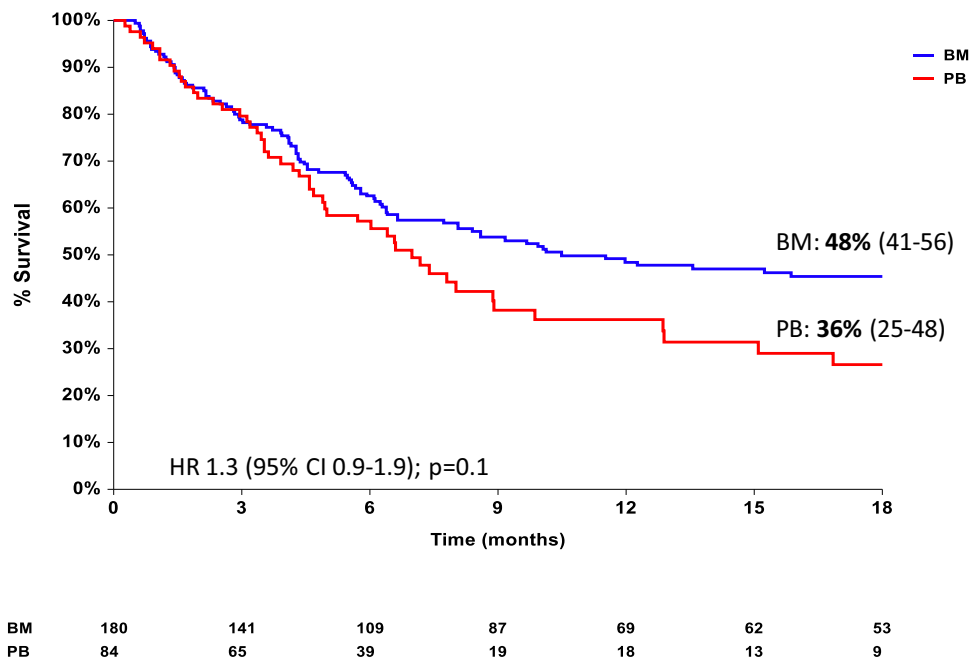
Figure 3. Continued.

Table 5
Immune Reconstitution, Day +100 Post-HCT

Cells	Immunophenotype	Absolute Cell Count/μL, median (range)		
		BM (N = 38)	PB (N = 18)	P Value
Absolute lymphocyte count		410 (0-1900)	530 (160-2100)	.4
CD4/CD8 ratio		2.2 (0.1-18)	1.6 (0.2-22)	.4
CD3$^+$ T cells		176 (16-2769)	168 (24-1433)	
CD4$^+$ T cells		99 (8-682)	100 (17-400)	.7
CD4 naïve	CD3$^+$CD4$^+$CD45R0$^-$CD62L$^+$	5 (0-118)	4 (0-80)	.8
CD4 effector memory	CD3$^+$CD4$^+$CD45R0$^+$CD62L$^-$	28 (2-175)	24 (7-196)	.9
CD4 central memory	CD3$^+$CD4$^+$CD45R0$^+$CD62L$^+$	58 (5-437)	53 (9-209)	.8
CD4 terminally differentiated effector	CD3$^+$CD4$^+$CD45R0$^-$CD62L$^-$	1 (0-13)	1 (0-11)	.7
CD8$^+$ T cells		40 (3-2302)	59 (2-1017)	.7
CD8 naïve	CD3$^+$CD8$^+$CD45R0$^-$CD62L$^+$	5 (0-323)	5 (0-287)	.8
CD8 effector memory	CD3$^+$CD8$^+$CD45R0$^+$CD62L$^-$	10 (1-958)	14 (0-328)	.8
CD8 central memory	CD3$^+$CD8$^+$CD45R0$^+$CD62L$^+$	9 (0-393)	15 (1-317)	.9
CD8 terminally differentiated effector	CD3$^+$CD8$^+$CD45R0$^-$CD62L$^-$	4 (0-605)	5 (0-213)	.9
CD19$^+$ B cells		38 (0-1472)	51 (0-554)	.4
Naïve B cells	CD19$^+$CD27$^-$	29 (0-441)	42 (0-529)	.8
Class-switched memory B cells	CD19$^+$CD27$^+$IgM$^-$	1 (0-1193)	2 (0-25)	.02
IgM memory B cells	CD19$^+$CD27$^+$IgM$^+$	2 (0-227)	1.5 (0-25)	.8
CD56 NK cells		165 (44-549)	226 (40-758)	
CD56(bright) NK cells	CD56$^{bright+}$CD3$^-$	62 (7-398)	84 (9-356)	.4
CD56(dim) NK cells	CD56^{dim+}CD3$^-$	93 (25-305)	116 (18-664)	.8
Tregs	CD3$^+$CD4$^+$CD25$^+$CD127$^-$	9 (1-259)	10 (1-54)	.9
Naïve Tregs	CD3$^+$CD4$^+$CD25$^+$CD127$^-$CD45R0$^-$CD62L$^+$	1 (0-49)	0.5 (0-4)	.9
Central memory Tregs	CD3$^+$CD4$^+$CD25$^+$CD127$^-$CD45R0$^+$CD62L$^+$	8 (1-197)	8 (1-51)	.9

grading and management, enrolled patients in the study, monitored responses, and supervised the study. R.S.M. and R.M.S. had full access to the raw data. All authors approved the manuscript. The corresponding author had the final responsibility to submit for publication.

Data availability statement: Deidentified data may be available upon request to the study's principal investigator and will require Institutional Review Board approval.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.09.003.

REFERENCES

1. D'Souza A, Fretham C, Lee SJ, et al. Current use of and trends in hematopoietic cell transplantation in the United States. *Biol Blood Marrow Transplant*. 2020;26:e177−e182.
2. Hamadani M, Zhang MJ, Tang XY, et al. Graft cryopreservation does not impact overall survival after allogeneic hematopoietic cell transplantation using post-transplantation cyclophosphamide for graft-versus-host disease prophylaxis. *Biol Blood Marrow Transplant*. 2020;26:1312−1317.
3. Bashey A, Zhang MJ, McCurdy SR, et al. Mobilized peripheral blood stem cells versus unstimulated bone marrow as a graft source for T-cell-replete haploidentical donor transplantation using post-transplant cyclophosphamide. *J Clin Oncol*. 2017;35:3002−3009.
4. Ruggeri A, Labopin M, Bacigalupo A, et al. Bone marrow versus mobilized peripheral blood stem cells in haploidentical transplants using posttransplantation cyclophosphamide. *Cancer*. 2018;124:1428-1437.
5. Im A, Rashidi A, Wang T, et al. Risk factors for graft-versus-host disease in haploidentical hematopoietic cell transplantation using post-transplant cyclophosphamide. *Biol Blood Marrow Transplant*. 2020;26:1459−1468.
6. Nagler A, Dholaria B, Labopin M, et al. Bone marrow versus mobilized peripheral blood stem cell graft in T-cell-replete haploidentical transplantation in acute lymphoblastic leukemia. *Leukemia*. 2020;34:2766−2775.
7. McQuellon RP, Russell GB, Cella DF, et al. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant*. 1997;19:357−368.
8. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825−828.
9. Lee SJ, Klein JP, Barrett AJ, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood*. 2002;100:406−414.
10. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med*. 1980;69:204−217.
11. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21. 389-401.e1.
12. Bacigalupo A, Raiola AM, Dominietto A, et al. Graft-versus-host disease in unmanipulated haploidentical marrow transplantation with a modified post-transplant cyclophosphamide (PT-CY) regimen: an update on 425 patients. *Bone Marrow Transplant*. 2019;54(suppl 2)):708−712.
13. Prokopishyn NL, Logan BR, Kiefer DM, et al. The concentration of total nucleated cells in harvested bone marrow for transplantation has decreased over time. *Biol Blood Marrow Transplant*. 2019;25:1325−1330.
14. Pruszczyk K, Skwierawska K, Król M, et al. Bone marrow harvest from unrelated donors: up-to-date methodology. *Eur J Haematol*. 2017;99:357−365.
15. Fagioli F, Quarello P, Pollichieni S, et al. Quality of harvest and role of cell dose in unrelated bone marrow transplantation: an Italian Bone Marrow Donor Registry-Gruppo Italiano Trapianto di Midollo Osseo Study. *Hematology*. 2014;19:1−9.
16. Rocha V, Labopin M, Gluckman E, et al. Relevance of bone marrow cell dose on allogeneic transplantation outcomes for patients with acute myeloid leukemia in first complete remission: results of a European survey. *J Clin Oncol*. 2002;20:4324−4330.
17. Bittencourt H, Rocha V, Chevret S, et al. Association of CD34 cell dose with hematopoietic recovery, infections, and other outcomes after HLA-identical sibling bone marrow transplantation. *Blood*. 2002;99:2726−2733.
18. Mavroudis D, Read E, Cottler-Fox M, et al. CD34+ cell dose predicts survival, posttransplant morbidity, and rate of hematologic recovery after allogeneic marrow transplants for hematologic malignancies. *Blood*. 1996;88:3223−3229.
19. McCurdy SR, Kanakry CG, Tsai HL, et al. Grade II acute graft-versus-host disease and higher nucleated cell graft dose improve progression-free survival after HLA-haploidentical transplant with post-transplant cyclophosphamide. *Biol Blood Marrow Transplant*. 2018;24:343−352.
20. Waller EK, Logan BR, Fei M, et al. Kinetics of immune cell reconstitution predict survival in allogeneic bone marrow and G-CSF-mobilized stem cell transplantation. *Blood Adv*. 2019;3:2250-2263.
21. Ranspach P, Zhou JM, Nishihori JAPT, et al. Delayed CD4+ T-cell but faster B-cell immune reconstitution after PTCY-based compared to conventional GVHD prophylaxis after allogeneic transplantation. *Biol Blood Marrow Transplant*. 2020;26:S308−S309.
22. Rambaldi B, Kim HT, Reynolds C, et al. Impaired T- and NK-cell reconstitution after haploidentical HCT with posttransplant cyclophosphamide. *Blood Adv*. 2021;5:352-364.
23. Nakamae H, Fujii K, Nanno S, et al. A prospective observational study of immune reconstitution following transplantation with post-transplant reduced-dose cyclophosphamide from HLA-haploidentical donors. *Transpl Int*. 2019;32:1322−1332.
24. McCurdy SR, Luznik L. Immune reconstitution after T-cell replete HLA-haploidentical transplantation. *Semin Hematol*. 2019;56:221−226.
25. Willem C, Makanga DR, Guillaume T, et al. Impact of KIR/HLA incompatibilities on NK cell reconstitution and clinical outcome after T cell-replete haploidentical hematopoietic stem cell transplantation with posttransplant cyclophosphamide. *J Immunol*. 2019;202:2141−2152.
26. Retière C, Willem C, Guillaume T, et al. Impact on early outcomes and immune reconstitution of high-dose post-transplant cyclophosphamide vs anti-thymocyte globulin after reduced-intensity conditioning peripheral blood stem cell allogeneic transplantation. *Oncotarget*. 2018;9:11451−11464.
27. Russo A, Oliveira G, Berglund S, et al. NK cell recovery after haploidentical HSCT with posttransplant cyclophosphamide: dynamics and clinical implications. *Blood*. 2018;131:247−262.
28. Raiola AM, Dominietto A, di Grazia C, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. *Biol Blood Marrow Transplant*. 2014;20:1573−1579.
29. Clave E, Busson M, Douay C, et al. Acute graft-versus-host disease transiently impairs thymic output in young patients after allogeneic hematopoietic stem cell transplantation. *Blood*. 2009;113:6477−6484.
30. Perneger TV, Chamot E, Bovier PA. Nonresponse bias in a survey of patient perceptions of hospital care. *Med Care*. 2005;43:374−380.
31. Lee SJ, Fairclough D, Parsons SK, et al. Recovery after stem-cell transplantation for hematologic diseases. *J Clin Oncol*. 2001;19:242−252.
32. Perneger TV, Peytremann-Bridevaux I, Combescure C. Patient satisfaction and survey response in 717 hospital surveys in Switzerland: a cross-sectional study. *BMC Health Serv Res*. 2020;20:158.