



Risk Factors for Graft-versus-Host Disease in Haploidentical Hematopoietic Cell Transplantation Using Post-Transplant Cyclophosphamide

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A B S T R A C T

Post-transplant cyclophosphamide (PTCy) has significantly increased the successful use of haploidentical donors with a relatively low incidence of graft-versus-host disease (GVHD). Given its increasing use, we sought to determine risk factors for GVHD after haploidentical hematopoietic cell transplantation (haplo-HCT) using PTCy. Data from the Center for International Blood and Marrow Transplant Research on adult patients with acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, or chronic myeloid leukemia who underwent PTCy-based haplo-HCT (2013 to 2016) were analyzed and categorized into 4 groups based on myeloablative (MA) or reduced-intensity conditioning (RIC) and bone marrow (BM) or peripheral blood (PB) graft source. In total, 646 patients were identified (MA-BM = 79, MA-PB = 183, RIC-BM = 192, RIC-PB = 192). The incidence of grade 2 to 4 acute GVHD at 6 months was highest in MA-PB (44%), followed by RIC-PB (36%), MA-BM (36%), and RIC-BM (30%) ($P = .002$). The incidence of chronic GVHD at 1 year was 40%, 34%, 24%, and 20%, respectively ($P < .001$). In multivariable analysis, there was no impact of stem cell source or conditioning regimen on grade 2 to 4 acute GVHD; however, older donor age (30 to 49 versus <29 years) was significantly associated with higher rates of grade 2 to 4 acute GVHD (hazard ratio [HR], 1.53; 95% confidence interval [CI], 1.11 to 2.12; $P = .01$). In contrast, PB compared to BM as a stem cell source was a significant risk factor for the development of chronic GVHD (HR, 1.70; 95% CI, 1.11 to 2.62; $P = .01$) in the RIC setting. There were no differences in relapse or overall survival between groups. Donor age and graft source are risk factors for acute and chronic GVHD, respectively, after PTCy-based haplo-HCT. Our results indicate that in RIC haplo-HCT, the risk of chronic GVHD is higher with PB stem cells, without any difference in relapse or overall survival.

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For adults with advanced hematologic malignancies, haploidentical donors allow patients without a matched related or unrelated donor the opportunity to proceed with a potentially curative allogeneic hematopoietic cell transplant (HCT) [1-3]. The use of post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis has significantly improved outcomes for

haploidentical HCT, approaching those in the matched related and unrelated donor setting [4,5]. Studies evaluating T cell replete haploidentical HCT using PTCy have demonstrated rates of acute GVHD in the range of 14% to 41% and chronic GVHD rates of 0% to 31%, compared to historical rates of 20% to 80% and 30% to 70%, respectively, in matched related and matched unrelated donor transplants [6-8]. Most of these haplotransplants were done using

reduced-intensity conditioning (RIC) regimens with bone marrow (BM) as a graft source [3–5,9–21].

Peripheral blood (PB) grafts have also been increasingly used in the haploidentical setting, and there have been 2 retrospective analyses comparing BM and PB. A small study by O'Donnell et al. [14] demonstrated no differences in acute GVHD at 100 days, chronic GVHD at 2 years, or overall survival (OS) at 2 years between BM (33%, 23%, 58%, respectively) and PB (40%, 19%, 66%, respectively). However, the rate of relapse was higher with BM compared to PB (19% versus 49%). In contrast, a large Center for International Blood and Marrow Transplant Research (CIBMTR) analysis by Bashey et al. [9] demonstrated a significantly lower incidence of grade 2 to 4 acute GVHD (hazard ratio [HR], 0.45; $P < .001$) and chronic GVHD (HR, 0.35; $P < .001$) in BM compared to PB. Relapse was also higher with BM compared to PB (HR, 1.49; $P = .009$) specifically in patients with leukemia, but there were no differences in OS or nonrelapse mortality (NRM).

Although the incidences of GVHD after haploidentical HCT have been described, there are little data describing risk factors for GVHD in this setting. The aim of this study is to describe the incidence, characteristics, and risk factors for acute and chronic GVHD in adult patients with hematologic malignancies who underwent a PTCy-based haploidentical HCT from 2013 to 2016.

MATERIALS AND METHODS

Data Source

This was a retrospective analysis using data from the CIBMTR. The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. The CIBMTR comprises a voluntary network of more than 420 transplantation centers worldwide that contribute data on consecutive allogeneic and autologous HCTs to a centralized statistical center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in the capacity of the CIBMTR as a public health authority under Health Insurance Portability and Accountability Act regulations. The CIBMTR collects data at 2 levels: Transplant-Essential Data (TED) and Comprehensive Report Form (CRF). The TED-level data are an internationally accepted standard of data that contain key variables for all consecutive transplant recipients in the United States. When a transplant is registered with the CIBMTR, a subset of patients is selected for the CRF level of data collection. The CRF-level data capture additional data related to the patient, disease, and transplant. Thus, a greater number of patients contribute to TED-level data compared to CRF data. Additional details regarding the CIBMTR registry have been previously described [22].

Patients

Eligible patients were ≥ 18 years with acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and myelodysplastic syndrome. All patients underwent HCT from a haploidentical donor (defined in the CIBMTR registry as 1 or more antigen-level mismatch among HLA-A, -B, -C, and -DRB1) using BM or PB as a graft source and GVHD prophylaxis with PTCy, tacrolimus, and mycophenolate mofetil; other PTCy-based prophylaxis regimens were excluded to limit heterogeneity and due to low numbers of these regimens. Conditioning regimens included myeloablative conditioning (MAC) or RIC, with or without total body irradiation (TBI) [23,24]. An RIC regimen was defined as (a) TBI dose of ≤ 500 cGy as a single fraction or ≤ 800 cGy if fractionated, (b) < 9 mg/kg oral busulfan or intravenous equivalent, or (c) < 140 mg/m² melphalan. Transplants using ex vivo T cell depletion, anti-thymocyte globulin (ATG), or alemtuzumab were excluded.

Study Endpoints and Definitions

The primary endpoints of this study were incidence of grade 2 to 4 acute GVHD and chronic GVHD. Secondary endpoints included grade 3 to 4 acute GVHD, relapse, OS, NRM, and the composite endpoints of GVHD relapse-free survival (GRFS) (including survival without grade 3 to 4 acute GVHD, chronic GVHD requiring systemic treatment, relapse, or death) and chronic GVHD relapse-free survival (CRFS) (including survival without chronic GVHD requiring systemic treatment, relapse, or death) [25]. GVHD was graded according to consensus criteria [7,26,27]. Disease status was categorized into early, intermediate, and advanced [28], and the revised Disease Risk Index (DRI) was used to categorize patients into low, intermediate, and high/very high groups [29]. Relapse was defined by hematologic criteria by submitting

centers with NRM as a competing event. NRM was defined as death without evidence of disease recurrence, and relapse was considered a competing event. For relapse and NRM, patients alive in continuous complete remission were censored at last follow-up. For GVHD, death without the event was considered a competing event. HLA matching was defined as described previously [30].

Statistical Methods

Patient, disease, and transplant-related variables for donor types were compared using chi-square statistics for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate analysis with Gray's test and log-rank test was used for cumulative incidence and survival, respectively. Variables tested included patient and sex, Karnofsky performance score, hematopoietic cell transplantation comorbidity index (HCT-CI) [31], DRI, time from diagnosis to HCT, donor age and relation (parent, offspring, sibling), donor/recipient sex, donor/recipient cytomegalovirus status, use of TBI, and year of transplant. Patients were categorized into 4 groups based on conditioning intensity (myeloablative or reduced intensity) and graft source (BM or PB). Graft source and conditioning intensity were included in all models. The primary comparisons were RIC-BM versus RIC-PB and MAC-BM versus MAC-PB.

Multivariable models were built using the Cox proportional hazards model. All variables were tested to affirm the assumption of proportional hazards, and no variables violated the proportional hazards assumption. A stepwise model building procedure was used to select the adjusted factors for each outcome with a threshold of 0.05 for both entry and stay in the model. The "center" effect was adjusted for all endpoints. Two-way interactions between "donor type" and the adjusted clinical variables in the models were tested, and no significant interactions were detected. A threshold P value of .05 for the primary endpoint of chronic GVHD and of .01 otherwise was used for significance of the main testing variable. A threshold of P value of $.01/2 = .005$ (or $.05/2 = .025$ for the primary endpoint of chronic GVHD) was recommended for the significance of pairwise comparisons when the main variable was significant. The impact of chronic GVHD on relapse was analyzed by treating chronic GVHD as a time-dependent covariate in the model for relapse. Results were expressed as a hazard ratio with 95% confidence intervals. SAS software version 9.4 (SAS Institute, Cary, NC) was used in the analysis.

RESULTS

Patients, Disease, and Transplant Characteristics

Table 1 shows the characteristics of the study population ($n = 646$) grouped by graft source and conditioning intensity. As expected, the median age of patients undergoing MAC conditioning (45 and 42 years for MAC-BM and MAC-PB, respectively) was younger than those undergoing RIC (60 and 62 years for RIC-BM and RIC-PB, respectively). More patients receiving PB grafts had a higher HCT-CI (score ≥ 3) than those receiving BM: 52% MAC-PB compared to 43% MAC-BM and 62% RIC-PB compared to 42% RIC-BM. Likewise, more patients with a low HCT-CI (score 0) received BM (25% MAC-BM compared to 12% MAC-PB and 24% RIC-BM compared to 14% RIC-PB). As expected, patients receiving PB had overall higher CD34 and CD3 cell doses compared to BM. Forty-seven percent in the MAC groups received TBI as part of conditioning, with a median dose of 1200 (range, 550 to 1350) while 89% in the RIC groups received TBI, with a median dose of 200 (range, 200 to 400). Median follow-up was longer in the RIC groups compared to the MAC groups: 24 (range, 2 to 53) and 21 (range, 6 to 50) months in RIC-BM and RIC-PB, respectively, versus 13 (range, 4 to 49) and 14 (range, 6 to 50) months in MAC-BM and MAC-PB, respectively.

GVHD and Engraftment

In univariate analysis, the incidence of grade 2 to 4 acute GVHD at 100 days was highest in MAC-PB at 46% (95% CI, 39% to 54%), followed by RIC-PB at 36% (95% CI, 29% to 43%), MAC-BM at 33% (95% CI, 23% to 44%), and RIC-BM at 27% (95% CI, 21% to 33%) ($P = .002$). A similar pattern was observed for chronic GVHD, where the incidence at 1 year was highest in MAC-PB at 40% (95% CI, 32% to 47%), followed by RIC-PB at 34%

Table 1
Baseline Characteristics

Variable	MAC-BM (n = 79)	MAC-PB (n = 183)	RIC-BM (n = 192)	RIC-PB (n = 192)	P Value
Recipient age at transplant, yr					<.0001*
Median (range)	45 (18-72)	42 (18-71)	60 (18-77)	62 (18-76)	<.0001†
18-39	35 (44)	78 (43)	36 (19)	21 (11)	
40-59	24 (30)	77 (42)	56 (29)	55 (28)	
60+	20 (26)	28 (16)	100 (52)	116 (60)	
Recipient sex					.82 [‡]
Male	46 (58)	108 (59)	121 (63)	114 (59)	
Female	33 (42)	75 (41)	71 (37)	78 (41)	
Recipient race					.03 [‡]
Caucasian	57 (72)	116 (63)	138 (72)	139 (72)	
African American	13 (16)	56 (31)	34 (18)	38 (20)	
Asian/Pacific Islander	3 (4)	4 (2)	12 (6)	12 (6)	
Other/missing	6 (8)	7 (3)	8 (4)	3 (1)	
Karnofsky performance score prior to transplant					.002 [‡]
<90	30 (38)	96 (52)	77 (40)	101 (53)	
90-100	43 (54)	85 (46)	112 (58)	87 (45)	
Missing	6 (8)	2 (1)	3 (2)	4 (2)	
Sorrow HCT-Cl					<.0001 [‡]
0	20 (25)	22 (12)	46 (24)	26 (14)	
1-2	25 (32)	64 (35)	62 (32)	43 (22)	
3+	34 (43)	95 (52)	81 (42)	119 (62)	
Missing	0	2 (1)	3 (2)	4 (2)	
Disease					<.0001 [‡]
AML	39 (49)	115 (63)	94 (49)	111 (58)	
ALL	22 (28)	46 (25)	34 (18)	22 (11)	
CML	4 (5)	10 (5)	12 (6)	3 (2)	
MDS	14 (18)	12 (7)	52 (27)	56 (29)	
Disease Risk Index					
AML	39	115	94	111	.10 [‡]
Low	2 (3)	11 (6)	7 (4)	7 (4)	
Intermediate	20 (25)	57 (31)	66 (34)	69 (36)	
High/very high	15 (19)	44 (24)	18 (9)	29 (15)	
Missing	2 (3)	3 (2)	3 (2)	6 (3)	
ALL	22	46	34	22	.49 [‡]
Intermediate	15 (19)	23 (13)	20 (10)	14 (7)	
High/very high	7 (9)	23 (13)	14 (7)	8 (4)	
CML	4	10	12	3	.03 [‡]
Low	4 (5)	9 (5)	12 (6)	1 (1)	
Intermediate	0	1 (1)	0	1 (1)	
High/very high	0	0	0	1 (1)	
MDS	14	12	52	56	.15 [‡]
Intermediate	7 (9)	4 (2)	27 (14)	14 (7)	
High/very high	6 (8)	7 (4)	23 (12)	37 (19)	
Missing	1 (1)	1 (1)	2 (1)	5 (3)	
HLA matching					.19 [‡]
Haploidentical (1-antigen mismatch)	5 (6)	8 (4)	6 (3)	10 (5)	
Haploidentical (≥2-antigen mismatches)	74 (94)	173 (95)	181 (94)	182 (95)	
Haploidentical (mismatch number unknown)	0	2 (1)	5 (3)	0	
Donor type					<.001 [‡]
Parent donor	11 (14)	37 (20)	14 (7)	9 (5)	
Offspring donor	30 (38)	58 (32)	120 (63)	124 (65)	
Sibling donor	34 (43)	88 (48)	56 (29)	54 (28)	
Missing	4 (5)	0	2 (1)	5 (3)	

(continued)

Table 1 (Continued)

Variable	MAC-BM (n = 79)	MAC-PB (n = 183)	RIC-BM (n = 192)	RIC-PB (n = 192)	P Value
Donor age, yr					<.001 [†]
Median (range)	38 (12-65)	37 (9-68)	37 (8-73)	39 (8-71)	.44*
<29	25 (32)	52 (28)	55 (29)	43 (22)	
30-49	38 (48)	70 (38)	98 (51)	112 (58)	
≥50	12 (15)	60 (33)	35 (18)	34 (18)	
Missing	4 (5)	1 (1)	4 (2)	3 (2)	
Time from diagnosis to transplant, mo					.13 [†]
Median (range)	6 (3-180)	8 (2-144)	9 (<1-291)	8 (2-171)	.16*
<6	38 (48)	75 (41)	58 (30)	77 (40)	
6 to <12	18 (23)	47 (26)	64 (33)	52 (27)	
≥12	23 (29)	61 (33)	70 (36)	63 (33)	
CD34 cell dose, × 10 ⁶ /kg					<.001 [†]
Median (range)	3 (0-8)	5 (0-21)	3 (0-13)	6 (0-20)	<.001*
<2	28 (35)	4 (2)	49 (26)	8 (4)	
2 to <4	31 (39)	24 (13)	91 (47)	20 (10)	
4 to <8	17 (22)	96 (52)	37 (19)	107 (56)	
≥8	0	33 (18)	4 (2)	44 (23)	
Missing	3 (4)	26 (14)	11 (6)	13 (7)	
CD3 cell dose, × 10 ⁶ /kg					<.001 [†]
Median (range)	0 (0-1)	2 (0-11)	0 (0-12)	2 (0-14)	<.001*
<2	55 (70)	48 (26)	120 (63)	70 (36)	
2 to <4	0	54 (30)	0	73 (38)	
4 to <8	0	18 (10)	0	12 (6)	
≥8	0	2 (1)	1 (1)	1 (1)	
Missing	24 (30)	61 (33)	71 (37)	36 (19)	
Donor-recipient sex mismatch					.69 [†]
M/M	34 (43)	62 (34)	82 (43)	74 (39)	
M/F	21 (27)	47 (26)	46 (24)	45 (23)	
F/M	12 (15)	46 (25)	39 (20)	40 (21)	
F/F	12 (15)	28 (15)	25 (13)	33 (17)	
Donor-recipient CMV status					.03 [†]
-/-	16 (20)	31 (17)	48 (25)	37 (19)	
-/+	27 (34)	41 (22)	66 (34)	62 (32)	
+/-	7 (9)	16 (9)	16 (8)	14 (7)	
+/+	29 (37)	90 (49)	61 (32)	78 (41)	
Missing	0	5 (3)	1 (1)	1 (1)	
Conditioning regimen					NA
BU + FLU/CY (MAC)	35 (44)	80 (44)	0	0	
TBI ± FLU/CY (MAC)	24 (30)	100 (55)	0	0	
TBI ± FLU/CY (RIC)	0	0	159 (83)	167 (87)	
FLU + MEL (RIC)	0	0	29 (15)	19 (10)	
Others	20 (25)	3 (2)	4 (2)	6 (3)	
TBI dose, cGy					
Median (range)	1200 (200-1350)	1200 (200-1200)	200 (200-300)	200 (200-400)	<.001*
Year of transplant					<.001 [†]
2013	6 (8)	11 (6)	52 (27)	13 (7)	
2014	16 (20)	38 (21)	48 (25)	39 (20)	
2015	20 (25)	61 (33)	40 (21)	69 (36)	
2016	37 (47)	73 (40)	52 (27)	71 (37)	
Follow-up of survivors, median (range), mo	13 (4-49)	14 (6-50)	24 (2-53)	21 (6-50)	

Values are presented as number (%) unless otherwise indicated.

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; NA, not applicable; BU, busulfan; FLU, fludarabine; CY, cyclophosphamide; MEL, melphalan.

* Kruskal-Wallis test.

[†] Pearson chi-square test.

Table 2
Univariate Analysis of Transplant Outcomes by Stem Cell Source and Conditioning Regimen Intensity

	MAC-BM (n = 79)	MAC-PB (n = 183)	RIC-BM (n = 192)	RIC-PB (n = 192)	PValue
Outcomes	N (95% CI)	N (95% CI)	N (95% CI)	N (95% CI)	
Grade 2–4 acute GVHD at 6 months	36 (25–46)	46 (39–54)	30 (23–36)	36 (30–43)	.002
Chronic GVHD at 1 year	24 (15–35)	40 (32–47)	20 (14–26)	34 (27–41)	<.001
Grade 3–4 acute GVHD	13 (6–21)	14 (10–20)	5 (3–9)	9 (6–14)	.06
Relapse at 1 year	28 (18–39)	26 (20–33)	37 (30–44)	36 (29–43)	.16
Nonrelapse mortality at 1 year	14 (7–23)	18 (12–24)	9 (5–13)	18 (13–24)	.01
GVHD-free, relapse-free survival at 1 year	38 (28–49)	23 (17–30)	41 (34–49)	25 (19–32)	.002
Chronic GVHD-free, relapse-free survival at 1 year	42 (31–53)	26 (20–33)	43 (36–50)	26 (19–32)	.002
Overall survival at 1 year	67 (56–77)	64 (57–71)	70 (63–76)	58 (51–65)	.07
Neutrophil recovery at 100 days*	92 (85–97)	95 (91–98)	94 (90–97)	93 (89–96)	.004
Platelet recovery at 100 days	78 (67–86)	85 (79–90)	90 (85–94)	89 (84–93)	.10

* Number of graft failures: MAC-BM (n = 1), MAC-PB (n = 4), RIC-BM (n = 4), and RIC-PB (n = 6).

Table 3
Multivariate Analysis of Transplant Outcomes by Stem Cell Source and Conditioning Regimen Intensity

Outcome	Variable	HR (95% CI)	P Value
Primary endpoints			
Acute GVHD grades 2–4			
	MAC-PB vs MAC-BM	1.10 (0.66–1.82)	.73
	RIC-PB vs RIC-BM	1.24 (0.84–1.82)	.28
Chronic GVHD			
	MAC-PB vs MAC-BM	1.56 (0.86–2.82)	.14
	RIC-PB vs RIC-BM	1.70 (1.11–2.62)	.01
Secondary endpoints			
Acute GVHD grades 3–4			
	MAC-PB vs MAC-BM	0.78 (0.38–1.60)	.49
	RIC-PB vs RIC-BM	1.93 (0.94–3.96)	.07
Relapse			
	MAC-PB vs MAC-BM	0.95 (0.59–1.52)	.82
	RIC-PB vs RIC-BM	0.90 (0.65–1.26)	.55
Nonrelapse mortality			
	MAC-PB vs MAC-BM	1.31 (0.62–2.78)	.48
	RIC-PB vs RIC-BM	2.06 (1.15–3.68)	.01
GVHD-free, relapse-free survival			
	MAC-PB vs MAC-BM	1.32 (0.94–1.85)	.11
	RIC-PB vs RIC-BM	1.31 (1.02–1.69)	.03
Chronic GVHD-free, relapse-free survival			
	MAC-PB vs MAC-BM	1.36 (0.94–1.98)	.10

(continued)

Table 3 (Continued)

Outcome	Variable	HR (95% CI)	P Value
Primary endpoints			
	RIC-PB vs RIC-BM	1.23 (0.94–1.61)	.12
Overall survival			
	MAC-PB vs MAC-BM	1.02 (0.64–1.62)	.93
	RIC-PB vs RIC-BM	1.17 (0.86–1.61)	.32

Bold values represent statistically significant values

(95% CI, 27% to 41%), MAC-BM at 24% (95% CI, 15% to 35%) and RIC-BM at 20% (95% CI, 14% to 26%) ($P < .001$) (Table 2).

In multivariable analysis, there was no significant difference in grade 2 to 4 acute GVHD or grade 3 to 4 acute GVHD between conditioning and graft source groups (Table 3). Adjusted cumulative incidence of grade 2 to 4 acute GVHD between all 4 conditioning and graft source groups is shown in Figure 1. The only significant factor for grade 2 to 4 acute GVHD in multivariable analysis was donor age 30 to 49 versus <29 years (HR, 1.53; 95% CI, 1.11 to 2.12, $P = .01$). For grade 3 to 4 acute GVHD, older donor age was also the only significant factor (≥ 50 versus <29 years; HR, 3.89; 95% CI, 1.81 to 8.35; $P = .0005$). Despite the impact of donor age, donor relation was not a significant factor for acute GVHD. There was a significantly higher risk for chronic GVHD in the RIC-PB group compared to RIC-BM (HR, 1.70; 95% CI, 1.11 to 2.62; $P = .01$). There

Acute GVHD, Grades II–IV

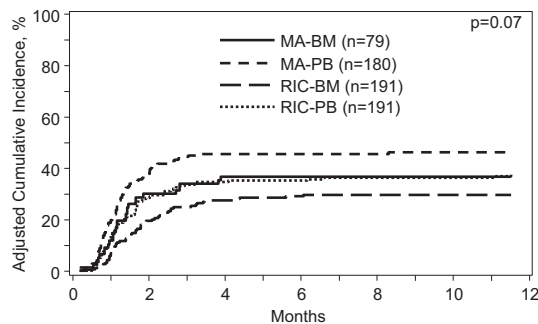


Figure 1. Incidence of acute GVHD grades 2 to 4 by conditioning intensity and graft source.

Chronic GVHD

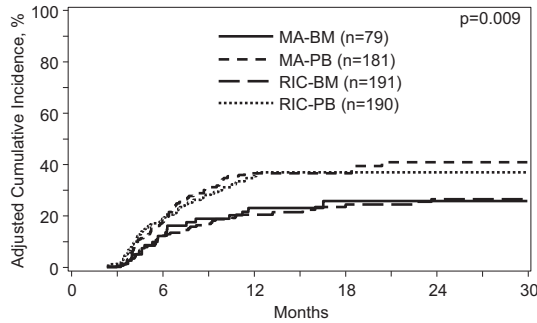


Figure 2. Incidence of chronic GVHD by conditioning intensity and graft source.

was no difference in chronic GVHD between MAC-PB and MAC-BM (Table 3). Adjusted cumulative incidence curves for chronic GVHD are shown in Figure 2. There were also no differences in chronic GVHD severity among any of the groups; overall, 59% were categorized as mild, 28% were moderate, and 13% were severe (Table 4).

To further determine the significance of graft source on chronic GVHD, subset analyses of MAC (n = 262) and RIC (n = 384) cohorts were performed. This confirmed an increased incidence of chronic GVHD with PB compared to BM in both MAC (HR, 1.81; 95% CI, 1.00 to 3.28; P = .05) and RIC (HR, 1.72; 95% CI, 1.10 to 2.70; P = .02) groups, but this met the predetermined significance level only in the RIC group. Due to the known differences in age between MAC and RIC groups, an age-adjusted analysis for chronic GVHD was also performed and demonstrated similar results (data not shown). We further analyzed chronic GVHD in a larger cohort of CIBMTR patients receiving a haploidentical transplant (n = 1401) using TED level data and confirmed that in the RIC setting, PB was associated with higher rates of chronic GVHD (P = .0015) (Table 5).

Regarding hematopoietic recovery, neutrophil recovery at 28 days was highest in MAC-PB (95%), followed by RIC-BM (94%), RIC-PB (93%), and MAC-BM (92%) (P = .004). Time to neutrophil recovery was comparable across the groups: 19 days in MAC-BM (range, 5 to 125), 16 days in MAC-PB (range, 1 to 90), 18 days in RIC-BM (range, 2 to 48), and 17 days in RIC-PB (range,

Relapse

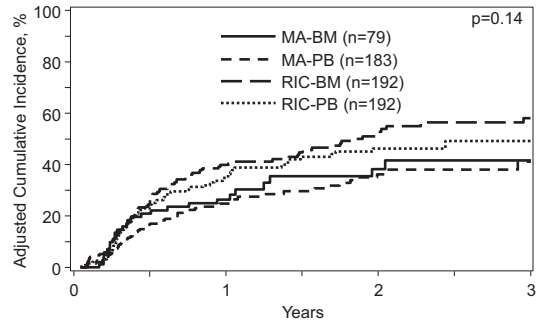


Figure 3. Incidence of relapse by conditioning intensity and graft source.

1 to 105). There was no difference in platelet recovery at 100 days between groups (Table 2). Given the small numbers, there was no notable trend regarding graft failure: 6 in RIC-PB, 4 in RIC-BM, 4 in MAC-PB, and 1 in MAC-BM.

Relapse and Survival Outcomes

Relapse at 1 year was similar among the groups (Table 2; adjusted cumulative incidence shown in Figure 3). In multivariable analysis, revised DRI high/very high versus low (HR, 2.11; 95% CI, 1.21 to 3.68; P = .008) was the only significant factor

Non-Relapse Mortality

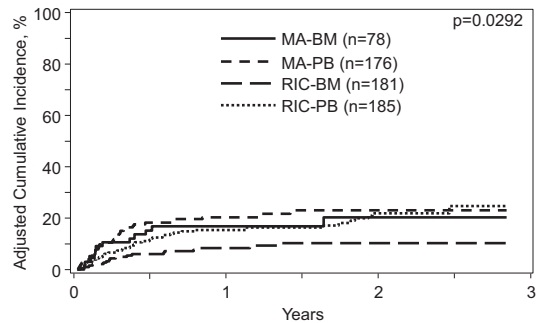


Figure 4. Incidence of nonrelapse mortality by conditioning intensity and graft source.

Table 4
Chronic GVHD Severity by Stem Cell Source and Conditioning Regimen

Characteristic	MAC-BM (n = 19), No. (%)	MAC-PB (n = 70), No. (%)	RIC-BM (n = 43), No. (%)	RIC-PB (n = 65), No. (%)	P Value
Chronic GVHD severity					.44
Mild	13 (68)	33 (47)	26 (60)	44 (68)	
Moderate	5 (26)	25 (36)	12 (28)	13 (20)	
Severe	1 (5)	11 (16)	5 (12)	8 (12)	
Missing		1 (1)			

Table 5
Multivariate Analysis of Chronic GVHD by Stem Cell Source and Conditioning Regimen Intensity Based on TED-Level Data (n = 1401)

Outcome	Variable	HR (95% CI)	P Value
Chronic GVHD	MAC-PB vs MAC-BM	1.44 (0.96-2.16)	.08
	RIC-PB vs RIC-BM	1.75 (1.24-2.47)	.0015

Bold values represent statistically significant values

GVHD-Free, Relapse-Free Survival

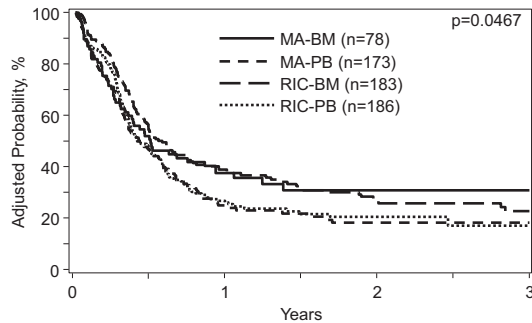


Figure 5. GVHD-free, relapse-free survival by conditioning intensity and graft source.

for relapse. We further analyzed the impact of chronic GVHD on relapse and found no significant associations between chronic GVHD and relapse in the entire cohort (HR, 1.00; 95% CI, 0.70 to 1.44; $P = .99$) or in a subset analysis of MAC ($P = .80$) and RIC ($P = .75$) cohorts.

NRM at 1 year was highest in RIC-PB at 18% (95% CI, 13% to 24%) and MAC-PB at 18% (95% CI, 12% to 24%), followed by 14% (95% CI, 7% to 23%) in MAC-BM and 9% (95% CI, 5% to 13%) in RIC-BM ($P = .01$) (Table 2). In multivariable analysis, there was a higher risk of NRM in RIC-PB compared to RIC-BM (HR, 2.06; 95% CI, 1.15 to 3.68; $P = .01$). There was no difference in NRM between MAC-PB and MAC-BM. Adjusted cumulative incidence of NRM between groups ($P = .0292$) is shown in Figure 4. The other significant factors for NRM were older patient age ≥ 60 versus 18 to 29 years (HR, 2.31; 95% CI, 1.18 to 4.54; $P = .015$) and higher HCT-CI ≥ 3 versus 0 (HR, 3.32; 95% CI, 1.50 to 7.35; $P = .003$).

GRFS and CRFS at 1 year were lowest in the PB groups for both RIC (25% and 26% respectively, compared to 41% and 43% in BM groups) and MAC (23% and 26%, compared to 38% and 42%) (Table 2), but in multivariable analysis, these outcomes were not significantly impacted by graft source or conditioning regimen (adjusted probability, Figure 5). Donor age ≥ 50 versus < 29 years (HR, 1.43; 95% CI, 1.08 to 1.88; $P = .012$) and Karnofsky performance score 90 to 100 versus < 90 (HR, 0.74; 95% CI, 0.61 to 0.90; $P = .003$) were significant factors for GRFS, whereas patient age 50 to 59 versus 18 to 29 years (HR, 1.53; 95% CI, 1.09 to 1.96; $P = .013$) and patient race non-Caucasian versus Caucasian (HR, 1.33; 95% CI, 1.07 to 1.65; $P = .010$) were significant factors for CRFS.

OS at 1 year in univariate analysis was similar among all groups (Table 2). In multivariable analysis, patient age 50 to 59 (HR, 1.73; 95% CI, 1.12 to 2.68; $P = .013$) or ≥ 60 years (HR, 1.84; 95% CI, 1.20 to 2.82; $P = .005$) versus 18 to 29 years, donor age ≥ 50 versus < 29 years (HR, 1.77; 95% CI, 1.24 to 2.52; $P = .002$), and revised DRI high/very high versus low (HR, 2.68; 95% CI, 1.46 to 4.90; $P = .001$) were significant factors contributing to OS. Relapse was the leading cause of death in all groups (Table 6).

DISCUSSION

This study demonstrates that donor age and graft source are important risk factors for acute and chronic GVHD, respectively, after PTCy-based haploidentical HCT. Similar to previous findings in both matched [32–34] and alternative [35] donor settings, PB grafts in RIC haplotransplant were found to be significantly associated with chronic GVHD of any severity. Although the impact of specific components of transplant is historically studied as distinct entities [36], we report a significant association of graft source and conditioning (RIC-PB) on chronic GVHD.

Previous studies have reported incidences of acute and chronic GVHD after PTCy-based haploidentical HCT with varying combinations of stem cell sources and conditioning regimens, but only 2 prior studies have compared BM and PB grafts. O'Donnell et al. [14] reported no difference in GVHD or OS but lower relapse with PB, whereas Bashey et al. [9] demonstrated higher incidences of acute and chronic GVHD, as well as lower relapse with PB, without a difference in OS. Our study confirms the finding of increased chronic GVHD with PB grafts but only in the RIC setting. Despite the incidence of chronic GVHD at 1 year being highest in the MAC-PB cohort, there was no difference confirmed in multivariable analysis in the myeloablative setting. While GRFS and CRFS were inferior in the PB groups in both RIC and MAC groups, there was no difference in risk of relapse or OS between any of the groups. These results suggest that PTCy does not fully negate the risk of chronic GVHD using PB in the RIC setting. Moreover, no other factors emerged as significant risk factors for development of chronic GVHD after haploidentical HCT with PTCy. Notably, the higher risk of chronic GVHD with the use of PB was not offset by a lower relapse rate or difference in overall survival. The ability to detect these differences in relapse and survival is likely to be limited by power. There was also no increase in graft failure with BM compared to PB grafts, with a similar time to neutrophil engraftment in all groups.

The effect of both graft source and conditioning was also confirmed in our analyses of a larger cohort of CIBMTR patients

Table 6

Causes of Death

	MAC-BM(n = 79)	MAC-PB(n = 183)	RIC-BM(n = 192)	RIC-PB(n = 192)
No. of dead patients	32	75	84	99
Cause of death, No. (%)				
Primary disease	16 (50)	35 (47)	60 (71)	45 (45)
Graft failure	1 (3)	1 (1)	2 (2)	0
GVHD	1 (3)	7 (9)	4 (5)	3 (3)
Infection	3 (9)	6 (8)	3 (4)	2 (2)
IPn/ARD	6 (19)	12 (16)	8 (10)	16 (16)
Organ failure	2 (6)	6 (8)	3 (4)	17 (17)
Secondary malignancy	1 (3)	8 (11)	3 (4)	14 (14)
Others	2 (6)	0	1 (1)	2 (2)

IPn/ARDS is interstitial pneumonitis and acute respiratory distress syndrome

using TED-level data receiving haplotransplant. Thus, although conditioning intensity is usually determined by a patient's age, comorbidities, and other nonmodifiable factors, graft source is a potentially modifiable variable.

It is also notable that overall incidence of grade 3 to 4 acute GVHD was low, especially in the RIC setting, a similar finding to what has been recently reported by McCurdy et al. [37], suggesting that PTCy immunomodulation decreases the risk of severe acute GVHD without reduction of grade 2 GVHD, which was significantly associated with higher progression-free survival. In contrast to this recent analysis, we demonstrate older donor age as a significant risk factor for both grade 2 to 4 and grade 3 to 4 acute GVHD, as opposed to donor relation, which did not have an impact. We were unable to evaluate cell doses for this analysis. Of note, the distribution of donor age between RIC and MAC was similar. This may have implications on donor selection when there is more than 1 haploidentical donor available (eg, older sibling versus younger offspring). Other studies have also shown donor age to be a factor in outcomes after haploidentical transplant, and our findings support this as a recommended consideration in donor selection [38–40].

There are several limitations that should be considered in interpreting these results. First, this was a retrospective analysis based on data submitted to a registry, and thus factors that led to decisions regarding stem cell source and conditioning regimen cannot be determined. We did restrict the analysis to select conditioning and prophylaxis regimens to limit heterogeneity. In addition, although the use of the registry data allowed for a large study population, it is possible that we did not have the power to elicit other risk factors contributing to GVHD or significant relationships in the observed trends. The power to detect significant differences in chronic GVHD in our subset analysis of MAC and RIC groups was just 48% and 66%, respectively, and this may be why we were unable to detect significant differences in graft source in the MAC setting for GVHD. Nevertheless, our findings of increased chronic GVHD in the RIC groups were further confirmed by a larger cohort using TED-level data. This was one of the largest analyses of this type, allowing the ability to evaluate conditioning regimen and graft source as specific risk factors for GVHD after haploidentical HCT. Another limitation includes the duration of follow-up for the MAC groups, which was only 13 and 14 months, compared to the RIC groups, which had 24 and 21 months of follow-up. Notably, the follow-up was similar between the BM and the PB groups, and thus the subset analyses within the MAC and the RIC groups were not impacted by different follow-up periods. Although most relapse and chronic GVHD occur within 1 year of transplant, longer follow-up, particularly in the MAC groups, is necessary, especially given that there was not a difference in chronic GVHD between the MAC groups. In addition, we excluded patients (n = 24) who received in vivo T cell depletion with ATG or alemtuzumab, as it is known that these agents decrease the incidence of chronic GVHD [41,42]. Patients who received both PTCy and in vivo T cell depletion may potentially have had lower risks of chronic GVHD, although this was overall a small number of patients. Finally, we included only patients with acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and myelodysplastic syndrome, and thus our findings are applicable to only this patient population.

In sum, our results show that PB stem cells contribute to an increased risk of chronic GVHD and NRM in RIC PTCy-based haploidentical HCT and that other outcomes such as relapse and OS are similar. These results aid in decision making regarding graft source in RIC PTCy-based haploidentical HCT.

Prospective evaluation of PB versus BM using PTCy platforms is needed to confirm these findings.

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Authorship statement:

A.I., A.R., and B.K.H. designed the study, analyzed results, and wrote the manuscript; T.W. and M.H. provided statistical analysis and support; S.S. and M.A. critically reviewed design of study, provided data analysis, and reviewed the manuscript; M.M., J.P., and M.J. provided input into interpretation of data analysis and critically reviewed the manuscript; S.P., N.M., and

D.W. reviewed design of study, provided data analysis, and critically reviewed the manuscript; GVHD Working Committee members provided review of study design, analysis, and review of manuscript.

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