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ORIGINAL REPORT

Bone Marrow or Peripheral Blood for Reduced-Intensity Conditioning Unrelated Donor Transplantation

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ABSTRACT

Purpose
There have been no randomized trials that have compared peripheral blood (PB) with bone marrow (BM) grafts in the setting of reduced-intensity conditioning (RIC) transplantations for hematologic malignancy. Because immune modulation plays a significant role in sustaining clinical remission after RIC, we hypothesize that higher graft-versus-host disease (GVHD) associated with PB transplantation may offer a survival advantage.

Patients and Methods
The primary outcome evaluated was overall survival. Cox regression models were built to study outcomes after transplantation of PB (n = 887) relative to BM (n = 219) for patients with acute myeloid leukemia, myelodysplastic syndrome, or non-Hodgkin lymphoma, the three most common indications for unrelated RIC transplantation. Transplantations were performed in the United States between 2000 and 2008. Conditioning regimens consisted of an alkylating agent and fludarabine, and GVHD prophylaxis involved a calcineurin inhibitor (CNI) with either methotrexate (MTX) or mycophenolate mofetil (MMF).

Results
After adjusting for age, performance score, donor-recipient HLA-match, disease, and disease status at transplantation (factors associated with overall survival), there were no significant differences in 5-year rates of survival after transplantation of PB compared with BM: 34% versus 38% with CNI-MTX and 27% versus 20% with CNI-MMF GVHD prophylaxis.

Conclusion
Survival after transplantation of PB and BM are comparable in the setting of nonirradiation RIC regimens for hematologic malignancy. The effect of GVHD prophylaxis on survival merits further evaluation.

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INTRODUCTION

A phase III randomized trial comparing peripheral blood (PB) versus bone marrow (BM) as cell sources for unrelated-donor hematopoietic transplantation reported no significant differences in survival and an increase in risk and severity of chronic graft-versus-host disease (cGVHD) with PB.[1] One limitation of that trial was that most patients received myeloablative transplantation conditioning regimens. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) indicate that 40% of transplantations for adults with hematologic cancers now use reduced-intensity conditioning (RIC) regimens. PB has been advocated as the hematopoietic cell source for RIC transplantations as a result of rapid hematopoietic recovery and engraftment. All reports to date confirm that cGVHD rates are higher after PB transplantation relative to BM transplantation.[1-7] In the setting of RIC, immune modulation through graft-versus-tumor effects plays a role in sustaining clinical remission. Therefore, it is plausible that the higher rates of cGVHD associated with PB transplantation may offer a survival advantage, particularly for patients with advanced hematologic cancer. There have been no prospective clinical trials to directly compare GVHD rates or survival after PB versus BM transplantation in the setting of RIC regimens and, to the best of our knowledge, none are planned in the United States. Therefore, we explored whether there were differences in acute GVHD (aGVHD) and cGVHD relapse and mortality risks after PB or BM transplantation in the setting of RIC regimens for treatment of adults with hematologic cancer by using data reported to the CIBMTR.

PATIENTS AND METHODS

Data Source

The CIBMTR is a voluntary working group of transplantation centers worldwide that contribute data on consecutive allogeneic and autologous transplantations. Participating centers report transplantations consecutively, and compliance is monitored. Patients are followed longitudinally. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Eligibility Criteria

Included are patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and non-Hodgkin lymphoma (NHL). All transplantations occurred in the United States between 2000 and 2008, and patients provided written informed consent for research. Eighty-eight transplantation centers contributed patients. Patients with acute lymphoblastic leukemia were excluded because only a few received RIC regimens. Donors were matched to patients at the allele level at HLA-A, -B, -C, and -DRB1 loci or mismatched at a single HLA locus. All patients received RIC regimens defined as busulfan ≤ 8 mg/kg (orally) or ≤ 6.4 mg/kg (intravenously) or melphalan less than 150 mg/m^2.[8] Recipients of low-dose total-body irradiation (TBI; 2 Gy) were excluded because PB was the sole graft used with this conditioning regimen. All patients received calcineurin inhibitor (CNI) GVHD prophylaxis (cyclosporine or tacrolimus) with methotrexate (MTX) or mycophenolate mofetil (MMF). The MTX dosing schedule included 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11 or 5 mg/m^2 on days +1, +3, +6, and +11. The MMF dosing schedule included 2 g per day or 3 g per day. Transplantations that were either ex vivo T-cell depleted or CD34 selected were excluded.

Outcomes

The primary outcome evaluated was overall survival (OS); death as a result of any cause was considered an event. Survival time is the interval from date of transplantation to last contact or death. Other outcomes evaluated included aGVHD and cGVHD, nonrelapse mortality, disease recurrence, or disease progression. aGVHD and cGVHD were defined by using standard criteria.[9,10] Nonrelapse mortality was defined as death occurring in complete continuous remission. Disease recurrence or progression was defined as morphologic evidence of progressive disease or molecular, cytogenetic, or morphologic evidence of disease recurrence.

Statistical Methods

The study population of 887 recipients of PB and 219 recipients of BM transplantations was expected to maintain type I error of 5% and provide 80% power to detect a 10% difference in 5-year OS between BM and PB transplant recipients. The characteristics of patients, their disease, and transplantation were compared by using the χ^2 statistic for categorical variables (Table 1). The probabilities of hematopoietic recovery, aGVHD and cGVHD, nonrelapse mortality, and relapse or progression were calculated by using the cumulative incidence estimator.[11] Log transformation was used to generate 95% CIs.

Marginal Cox regression models were built for all outcomes of interest in comparing transplantation of PB with transplantation of BM and were adjusted for an effect of transplantation center on OS, the primary end point.[12-14] Survival probabilities adjusted for other factors held in the final multivariable model were generated from Cox models. Preliminary analysis suggested an interaction ($P < .01$) between graft type and GVHD prophylaxis. Therefore, four treatment groups were created that considered graft type and GVHD prophylaxis regimens: PB CNI-MTX, PB CNI-MMF, BM CNI-MTX, and BM CNI-MMF. The variable for treatment group was held in all steps of model building and the final model, regardless of the level of significance. Other variables tested are provided in Table 1 and include patient age groups (18 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and 70 to 74 years), sex (male *v* female), performance score (90 to 100 *v* < 90), cytomegalovirus serostatus (positive *v* negative), disease and disease status (AML first complete remission/MDS refractory anemia *v* AML second complete remission *v* AML in relapse/MDS refractory anemia with excess blasts *v* NHL chemotherapy-sensitive *v* NHL chemotherapy-resistant), donor age (18 to 32, 33 to 50, > 50 years), donor-recipient HLA-match (8/8 *v* 7/8), sex match (female donors/male recipients *v* other), blood group ABO match (matched *v* minor/major ABO match), conditioning regimen (busulfan *v* melphalan *v* cyclophosphamide containing), cell dose (low *v* high), and transplant period (2000 to 2004 *v* 2005 to 2008). Variables that attained a significance level of 0.05 or less were retained in the final model, and for treatment effect, a value less than 0.01 was considered significant. Interactions between the treatment group and other variables held in the final model were tested to ensure that the effects of variables on transplantation outcomes were independent of the treatment groups. All variables met the assumptions for proportionality. All *P* values are two-sided. Analyses were performed by using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patients, Disease, and Transplantation Characteristics

The characteristics of patients, their disease, and transplantations by graft type are summarized in Table 1. The median ages of PB and BM recipients were similar at 57 years but recipients of PB transplantations were more likely to report performance scores of 80 or lower. AML was the predominant indication for PB transplantations. Among patients with AML or MDS, disease risk at transplantation did not differ by graft type. Conversely, for patients with NHL, BM recipients were more likely to have chemotherapy-sensitive disease. There were also differences in transplantation characteristics; BM transplantations were more likely to use melphalan-containing regimens, CNI-MTX, and in vivo T-cell depletion for GVHD prophylaxis. In keeping with clinical practice, PB transplants were more common after 2004, resulting in a median follow-up of 5 years compared with 6 years after BM transplants.

Hematopoietic Recovery, aGVHD, and cGVHD

The likelihood of neutrophil recovery did not differ by graft type. The median time to neutrophil recovery after transplanting PB and BM was 12 days and 15 days, respectively, with CNI-MMF GVHD prophylaxis. The corresponding day-28 probabilities of neutrophil recovery were 95% (95% CI, 93% to 97%) and 94% (95% CI, 84% to 98%). The median times to neutrophil recovery after PB and BM transplants with CNI-MTX GVHD prophylaxis were 13 days and 14 days, respectively. The corresponding day-28 probabilities of neutrophil recovery were 94% (95% CI, 91% to 96%) and 93% (95% CI, 87% to 96%).

The likelihood of platelet recovery did not differ by graft type. Platelet recovery at 3 months after BM transplant was 83% (95% CI, 76% to 88%) compared with 90% (95% CI, 87% to 93%) for PB transplant with CNI-MTX GVHD prophylaxis ($P = .03$). The corresponding probabilities of platelet recovery after PB and BM transplants with CNI-MMF GVHD prophylaxis were 87% (95% CI, 84% to 90%) and 78% (95% CI, 66% to 86%; $P = .09$), respectively.

Risks of grade 2 to 4 and grade 3 to 4 aGVHD and cGVHD were not significantly different after PB transplant compared with BM transplant (Table 2). Grade 2 to 4 aGVHD (hazard ratio [HR], 1.43; 95% CI, 1.19 to 1.72; $P < .001$) and grade 3 to 4 aGVHD (HR, 2.13; 95% CI, 1.52 to 3.03; $P < .001$) were higher after 7/8 HLA-matched transplantations with either graft. In vivo T-cell depletion was associated with lower grade 2 to 4 aGVHD (HR, 0.69; 95% CI, 0.54 to 0.88; $P = .002$) and cGVHD (HR, 0.52; 95% CI, 0.40 to 0.68; $P < .001$) with either graft.

Table 1. Patient, Disease, and Transplantation Characteristics

Characteristic	BM (n = 219) No.	%	PB (n = 887) No.	%	P
Age groups (years)					
18-59	145	66	561	63	.53
60-74	74	34	326	37	
Sex					
Male	128	58	531	60	.70
Female	91	42	356	40	
Performance score					.008
90-100	140	64	474	53	
≤ 80	57	26	329	37	
Not reported	22	10	84	10	
Recipient CMV serostatus					.22
Positive	141	64	521	59	
Negative	77	35	355	40	
Not reported	1	< 1	11	1	
Disease					< .001
AML	108	49	519	59	
MDS	17	8	110	12	
NHL	94	43	258	29	
Disease status					
AML/MDS					.79
First CR/RA	49	39	262	42	
Second CR	30	24	124	20	
Relapse, RAEB	46	37	243	38	
NHL					.01
Chemotherapy-sensitive lymphoma	77	82	175	68	
Chemotherapy-resistant lymphoma	17	18	83	32	
Donor-recipient HLA-match*					.49
8/8 allele-level HLA-match	182	83	717	81	
1-locus HLA-mismatch	37	17	170	19	
Donor-recipient sex match					.17
Female-male	29	13	145	16	
Other	186	85	709	80	
Not reported	4	2	33	4	
Donor-recipient ABO match					< .001
Matched	103	47	314	35	
Minor mismatch	36	16	194	22	
Major match	66	30	254	29	
Not reported	14	7	125	14	
Donor age group (years)					.03
18-32	93	42	333	38	
33-50	96	44	375	42	
> 50	13	6	44	5	
Not reported	17	8	135	15	
Cell dose					NA
Nucleated cells < 3×10^8/kg	134	61	—		
Nucleated cells ≥ 3×10^8/kg	79	36	—		
CD34 < 4.5×10^6/kg	—		170	19	
CD34 ≥ 4.5×10^6/kg	—		716	81	
Not reported	6	3	1	< 1	
Conditioning regimen†					< .001
Busulfan + fludarabine	55	25	401	45	
Cyclophosphamide + fludarabine	55	25	141	16	
Melphalan + fludarabine	109	50	345	39	
GVHD prophylaxis					< .001
CNI-MMF	69	32	493	56	
CNI-MTX	150	68	394	44	
In vivo T-cell depletion‡					< .001
Yes	150	68	406	46	
None	69	32	481	54	
Year of transplantation					< .001
2000-2004	113	52	262	30	
2005-2008	106	48	625	70	
Follow-up, months					
Median	73		61		
Range	10-124		6-123		

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CR, complete remission; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; NHL, non-Hodgkin lymphoma; PB, peripheral blood; RA, refractory anemia; RAEB, RA with excess blasts.

*In all, 836 of 899 donor-recipient pairs that were 8/8 HLA-matched were also 10/10 HLA-matched (HLA-A, -B, -C, -DRB1, and –DQ).

†BM recipients: busulfan 4 to 8 mg/kg orally or 3.2 to 6.2 mg/kg intravenously (n = 51); busulfan < 4 mg/kg orally or < 3.2 mg/kg intravenously (n = 4); melphalan 140 mg/m^2 (n = 84) or 120 mg/m^2 (n = 24); cyclophosphamide 40 mg/kg (n = 10), 60 mg/kg (n = 32), 100 mg/kg (n = 10), 120 mg/kg (n = 3). PB recipients: busulfan 4 to 8 mg/kg orally or 3.2 to 6.2 mg/kg intravenously (n = 310); busulfan < 4 mg/kg orally or < 3.2 mg/kg intravenously (n = 77); melphalan 140 mg/m^2 (n = 261) or 120 mg/m^2 (n = 73); cyclophosphamide 40 mg/kg (n = 51), 60 mg/kg (n = 61), 100 mg/kg (n = 23), 120 mg/kg (n = 7). There may be differences in toxicity between busulfan 4 to 8 mg/kg oral dosing/intravenous equivalent and < 4 mg/kg oral dosing/intravenous equivalent. Because only four patients received the lower dose (ie, < 4 mg/kg), we present the data so readers are aware that the majority of patients who received busulfan received 4 to 8 mg/kg orally/intravenous equivalent.

‡BM grafts: antithymocyte globulin, rabbit (n = 76), horse (n = 25), not reported (n = 5) or alemtuzumab (n = 44). PB grafts: antithymocyte globulin, rabbit (n = 223), horse (n = 98), not reported (n = 5) or alemtuzumab (n = 88).

Nonrelapse Mortality and Relapse

Nonrelapse mortality risks were not significantly different after PB transplant compared with BM transplant (Table 2). Other factors associated with higher nonrelapse mortality and independent of graft type included 7/8 HLA-matched transplantations (HR, 2.17; 95% CI, 1.72 to 2.70; $P < .001$) and melphalan with fludarabine conditioning regimen (HR, 1.66; 95% CI, 1.20 to 2.28; $P = .002$).

Relapse risks were not significantly different after PB and BM transplant with CNI-MTX GVHD prophylaxis (Table 2). However, risks were higher after BM transplant compared with PB transplant when CNI-MMF GVHD prophylaxis was used. Performance score, disease status, and conditioning regimen were associated with higher relapse independent of graft type. Relapse risks were higher for patients with poor performance scores (HR, 1.23; 95% CI, 1.06 to 1.42; $P = .005$), AML transplantation in relapse (HR, 2.21; 95% CI, 1.77 to 2.76; $P < .001$), and chemotherapy-resistant NHL (HR, 2.44; 95% CI, 1.75 to 3.40; $P < .001$). Relapse risks were lower after melphalan plus fludarabine compared with busulfan plus fludarabine (HR, 0.72; 95% CI, 0.59 to 0.89; $P = .002$).

OS

There were no significant differences in survival after PB and BM transplant adjusting for age, performance score, donor-recipient HLA-match, and disease and disease status (Table 2 and Fig 1). Independent of graft type, survival was lower after 7/8 HLA-matched transplantations (HR, 0.63; 95% CI, 0.55 to 0.72; $P < .001$) and AML

Table 2. Multivariable Analysis: Outcomes After Transplantation by Graft Type

Outcome	CNI + MTX			CNI + MMF		
	HR	95% CI	*P*	HR	95% CI	*P*
Grade 2 to 4 aGVHD*						
PB	1.00			1.00		
BM	0.88	0.66 to 1.18	.39	1.43	0.95 to 2.14	.09
Grade 3 to 4 aGVHD*						
PB	1.00			1.00		
BM	0.62	0.40 to 0.97	.04	1.31	0.72 to 2.39	.37
cGVHD†						
PB	1.00			1.00		
BM	0.78	0.58 to 1.04	.09	1.06	0.64 to 1.74	.83
Nonrelapse mortality‡						
PB	1.00			1.00		
BM	0.73	0.53 to 1.01	.06	1.34	0.85 to 2.09	.20
Relapse§						
PB	1.00			1.00		
BM	1.13	0.88 to 1.44	.34	1.55	1.13 to 2.12	.006
Overall mortality‖						
PB	1.00			1.00		
BM	0.90	0.74 to 1.09	.29	1.47	1.06 to 2.04	.02

Abbreviations: aGVHD, acute graft-versus-host disease; BM, bone marrow; cGVHD, chronic GVHD; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MTX, methotrexate; PB, peripheral blood.
*Adjusted for donor-recipient HLA-match and in vivo T-cell depletion.
†Adjusted for donor-recipient HLA-match, in vivo T-cell depletion, and conditioning. regimen.
‡Adjusted for age, conditioning regimen, and donor-recipient HLA-match.
§Adjusted for performance score, disease and disease status, and conditioning regimen.
‖Adjusted for age, performance score, disease and disease status, and donor-recipient HLA-match.

transplantations in relapse (HR, 0.66; 95% CI, 0.52 to 0.85; $P = .001$). We also tested for the effect of graft type, including all covariates tested in the final model regardless of level of significance, and confirmed that there were no significant differences in survival after PB and BM transplant with CNI-MTX (HR, 0.87; 95% CI, 0.72 to 1.07; $P = .18$) and CNI-MMF (HR, 1.44; 95% CI, 1.02 to 2.03; $P = .04$) GVHD prophylaxis. There were no significant differences in risks of cGVHD-free survival by graft type; survival after PB transplant compared with BM transplant with CNI-MTX had an HR of 0.85 (95% CI, 0.69 to 1.04; $P = .11$) and HR of 1.20 (95% CI, 0.90 to 1.59; $P = .21$) with CNI-MMF GVHD prophylaxis.

Subset Analyses

Although the effect of graft type (PB *v* BM) on survival was independent of disease (interaction test $P = .08$), we built separate Cox models for AML and NHL. For AML, survival rates were not significantly different after BM compared with PB transplant with CNI-MTX (HR, 0.84; 95% CI, 0.66 to 1.07; $P = .15$), but survival was higher after PB transplant with CNI-MMF GVHD prophylaxis (HR, 1.71; 95% CI, 1.28 to 2.28; $P < .001$). For NHL, survival rates were not significantly different after BM compared with PB transplant with CNI-MTX (HR, 1.13; 95% CI, 0.71 to 1.79; $P = .60$) and CNI-MMF (HR, 1.07; 95% CI, 0.57 to 1.99; $P = .83$) GVHD prophylaxis.

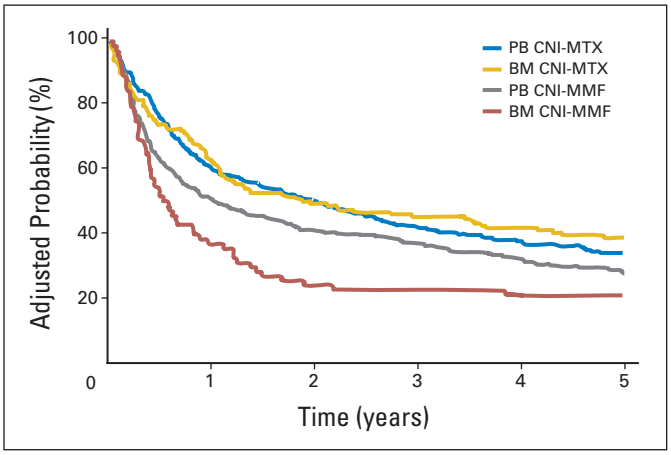

Fig 1. Overall survival by graft type and graft-versus-host disease (GVHD) prophylaxis adjusted for age, performance score, disease and disease status, and donor-recipient HLA-match. The 5-year adjusted probabilities of overall survival after transplantation of bone marrow (BM; 38% [95% CI, 31% to 46%]) and peripheral blood (PB; 34% [95% CI, 29% to 38%]) with calcineurin inhibitor-methotrexate (CNI-MTX) GVHD prophylaxis. The corresponding probabilities with CNI-mycophenolate mofetil (MMF) GVHD prophylaxis were 20% (95% CI, 11% to 29%) and 27% (95% CI, 23% to 31%), respectively.

Effect of GVHD Prophylaxis Regimen on aGVHD, cGVHD, Nonrelapse Mortality, and OS

Although the primary purpose of our analyses was to explore whether there are differences in survival after PB compared with BM transplant, we identified a statistically significant interaction between graft type and GVHD prophylaxis ($P < .01$). Post hoc analysis of the effects of GVHD prophylaxis on transplantation outcomes revealed significant differences in risks of grade 2 to 4 and grade 3 to 4 aGVHD, nonrelapse mortality, and overall mortality. As depicted in Table 3, independent of whether the transplanted graft was PB or BM, risks of grade 2 to 4 and grade 3 to 4 aGVHD nonrelapse mortality were higher and survival rates were lower with CNI-MMF compared with CNI-MTX GVHD prophylaxis.

DISCUSSION

The ideal study design to compare treatment outcomes is a randomized clinical trial. However, it is not always feasible to conduct randomized trials, and treatments are offered without sufficient data to support a change in clinical practice. In the setting of unrelated-donor RIC allogeneic transplantation, PB is the preferred graft accounting for 80% of transplantations. Although it can be argued that the choice of PB relative to BM in a nonrandomized manner can introduce biases that may affect transplantation outcomes, it is noteworthy that to date, the results of randomized trials and reports from transplantation registries are consistent in their observations.[1,5-7] Therefore, by using data reported to a transplantation registry, we compared the effectiveness of transplanting PB and BM from unrelated donors with RIC regimens for AML, MDS, and NHL, the three most common indications for RIC transplantation. Transplantation conditioning regimens included an alkylating agent with fludarabine and CNI-MTX or CNI-MMF GVHD prophylaxis.

Several of our findings are consistent with that observed after myeloablative transplantation conditioning regimens, but there were also differences. First, rates of OS are not different after transplants

Table 3. Multivariable Analysis: Outcomes After Transplantation by GVHD Prophylaxis

	PB Progenitor Cells			BM		
Outcome	HR	95% CI	*P*	HR	95% CI	*P*
Grade 2 to 4 aGVHD*						
CNI + MTX	1.00			1.00		
CNI + MMF	2.04	1.57 to 2.67	< .001	3.30	1.92 to 5.69	< .001
Grade 3 to 4 aGVHD*						
CNI + MTX	1.00			1.00		
CNI + MMF	2.15	1.55 to 3.00	< .001	4.55	2.21 to 9.37	< .001
cGVHD†						
CNI + MTX	1.00			1.00		
CNI + MMF	1.29	1.03 to 1.60	.03	1.75	1.05 to 2.90	.03
Nonrelapse mortality‡						
CNI + MTX	1.00			1.00		
CNI + MMF	1.56	1.30 to 1.87	< .001	2.85	1.63 to 5.01	< .001
Relapse§						
CNI + MTX	1.00			1.00		
CNI + MMF	0.85	0.68 to 1.06	.15	1.17	0.84 to 1.63	.36
Overall mortality‖						
CNI + MTX	1.00			1.00		
CNI + MMF	1.27	1.08 to 1.48	.003	2.06	1.50 to 2.83	< .001

Abbreviations: aGVHD, acute graft-versus-host disease; BM, bone marrow; cGVHD, chronic GVHD; CNI, calcineurin inhibitor; HR, hazard ratio; MMF, mycophenolate mofetil; MTX, methotrexate; PB, peripheral blood.
*Adjusted for donor-recipient HLA-match and in vivo T-cell depletion.
†Adjusted for donor-recipient HLA-match, in vivo T-cell depletion, and conditioning regimen.
‡Adjusted for age, conditioning regimen, and donor-recipient HLA-match.
§Adjusted for performance score, disease and disease status, and conditioning regimen.
‖Adjusted for age, performance score, disease and disease status, and donor-recipient HLA-match.

with PB compared with BM grafts, and this is consistent with reports after myeloablative transplantation conditioning regimens.[1,6,15] Second, there were no significant differences in rates of grade 2 to 4 and cGVHD after PB and BM transplants. The lack of a significant difference in grade 2 to 4 aGVHD after PB and BM transplants is consistent with the findings of the randomized trial that compared PB and BM transplants from unrelated donors and myeloablative transplantation conditioning regimens.[1] However, the lack of a significant difference in the risk of cGVHD after PB and BM transplants is in contrast to other reports after unrelated-donor transplantation with myeloablative transplantation conditioning regimens.[1,2,6,15] In the setting of RIC transplantations (the focus of this analysis), cGVHD rates are high with either graft type because the regimen relies on an immune-mediated effect to eradicate the malignancy rather than cytoreductive effects of the conditioning regimen, which may explain the observed comparable cGVHD rates between the treatment groups.

Our findings differ from those in a report from the European Group for Blood and Marrow Transplantation.[2] In that report, although there were no differences in leukemia-free survival after PB compared with BM transplants, grade 2 to 4 and grade 3 to 4 aGVHD, cGVHD, and nonrelapse mortality were higher and relapse rates were lower after PB transplants. The observed difference between our analysis and the European report is likely a result of different transplantation strategies and the duration of follow-up for surviving patients. The European report was limited to AML. Our subset analysis limited to AML also differed from the European report. Although there were no differences in survival after BM and PB transplants with CNI-MTX GVHD prophylaxis, survival was better after a PB transplant compared with a BM transplant with CNI-MMF GVHD prophylaxis, an observation that merits further exploration in a larger independent data set. We hypothesize that transplantation strategy, including conditioning regimen and GVHD prophylaxis, may have mitigated outcomes. The European report included low-dose TBI as well as alkylating agents with or without fludarabine. Low-dose TBI regimens were excluded from our analysis because PB was the sole graft used with this regimen in the United States. Information on GVHD prophylaxis regimens was not available for half the European cohort and therefore was not considered, and the median follow-up of their surviving patients was only 17 months compared with the more than 5 years of follow-up in our analysis.

The role of CNI with MTX or MMF as effective GVHD prophylaxis has been established.[16-19] All reports to date, including a meta-analysis that compared MMF to MTX with CNI, suggest that the incidence of grade 2 to 4 aGVHD was comparable but the incidence of grade 3 to 4 aGVHD was higher; however, none of those reports have demonstrated a survival difference.[20,21] In our analyses, an observation that merits attention is the high rate of nonrelapse mortality and consequently lower survival with CNI-MMF GVHD prophylaxis regardless of whether the transplanted graft was PB or BM. Higher mortality is attributed to higher grade 2 to 4 and 3 to 4 aGVHD and cGVHD. Although these are the results of post hoc analyses and consequently are subject to overinterpretation, the observed magnitude of risk of dying merits further exploration. It is plausible that we observed significant differences in survival between CNI-MTX and CNI-MMF groups because our study population was substantially larger than those previously reported and therefore adequately powered to detect absolute differences of 7% to 15% in survival rates. We hypothesize that the observed adverse effects of MMF on aGVHD and cGVHD and survival may be attributed to potential drug interactions

and/or mycophenolic acid levels. Others have reported that cyclosporine, omeprazole, and pantoprazole are the most common drugs affecting mycophenolic acid pharmacokinetics.[22] In this analysis, we cannot determine which medications were given during the immediate post-transplantation period, but it is highly likely patients received omeprazole or pantoprazole during the early post-transplantation period, which may have affected mycophenolic acid pharmacokinetics. In our analyses, tacrolimus was the predominant CNI used, with only a third of patients receiving cyclosporine. Although it is not the standard for measuring mycophenolic acid levels, pharmacokinetic studies have shown that in the setting of nonmyeloablative unrelated-donor transplantation, low levels of mycophenolic acid are associated with higher graft failure, grade 2 to 4 aGVHD, and nonrelapse mortality.[23,24] We do not have mycophenolic acid levels, which prohibits us from studying this further in this analysis.

We acknowledge that there are differences in patient, disease, and transplantation characteristics between those who received PB and BM transplants. We addressed this by performing a carefully controlled analysis that considered patient, disease, and transplantation characteristics as well as any transplantation center effects. In addition, there may be unmeasured and unknown factors that have not been considered, a limitation when conducting retrospective studies. With the available data, we show that survival after PB and BM transplants with RIC transplantation regimens with an alkylating agent and fludarabine are comparable. Unlike after myeloablative transplantation, cGVHD, a major contributor to late post-transplantation morbidity and mortality, is similar after PB and BM transplants.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Bone Marrow or Peripheral Blood for Reduced-Intensity Conditioning Unrelated Donor Transplantation

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