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# Peripheral Blood versus Bone Marrow from Unrelated Donors: Bone Marrow Allografts Have Improved Long-Term Overall and Graft-versus-Host Disease-Free, Relapse-Free Survival

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A B S T R A C T

Peripheral blood (PB) and bone marrow (BM) from unrelated donors can serve as a graft source for hematopoietic cell transplantation (HCT). Currently, PB is most commonly used in roughly 80% of adult recipients. Determining the long-term impact of graft source on outcomes would inform this decision. Data collected by the Center for International Blood and Marrow Transplant Research from 5200 adult recipients of a first HCT from an 8/8 or 7/8 HLA antigen-matched unrelated donor for treatment of acute leukemia, chronic myelogenous leukemia, or myelodysplastic syndrome between 2001 and 2011 were analyzed to determine the impact of graft source on graft-versus-host disease (GVHD) relapse-free survival (GRFS), defined as freedom from grade III/IV acute GVHD, chronic GVHD requiring immunosuppressive therapy, relapse, and death, and overall survival. GRFS at 2 years was

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superior in BM recipients compared with PB recipients (16%; 95% confidence interval [CI], 14% to 18% versus 10%; 95% CI, 8% to 11%; $P < .0001$) in the 8/8 HLA-matched cohort and 7/8 HLA-matched cohort (11%; 95% CI, 8% to 14% versus 5%; 95% CI, 4% to 7%; $P = .001$). With 8/8 HLA-matched unrelated donors, overall survival at 5 years was superior in recipients of BM (43%; 95% CI, 40% to 46% versus 38%; 95% CI, 36% to 40%; $P = .014$). The inferior 5-year survival in the PB cohort was attributable to a higher frequency of deaths while in remission compared with the BM cohort. For recipients of 7/8 HLA-matched grafts, survival at 5 years was similar in BM recipients and PB recipients (32% versus 29%; $P = .329$). BM grafts are associated with improved long-term GRFS and overall survival in recipients of matched unrelated donor HCT and should be considered the unrelated allograft of choice, when available, for adults with acute leukemia, chronic myelogenous leukemia, and myelodysplastic syndrome.


## INTRODUCTION

The majority of allogeneic hematopoietic cell transplantations (HCTs) performed use unrelated donor (URD) grafts, with peripheral blood (PB) selected over bone marrow (BM) as the graft source in >80% of adult recipients [1]. In 2012, the results of a randomized trial of BM versus PB in URD graft recipients conducted by the Blood and Marrow Clinical Trials Network (BMT CTN 0201 trial) were reported [2]. Overall survival (OS) at 2 years was similar in the 2 groups, as were the rates of acute graft-versus-host disease (aGVHD), relapse, and nonrelapse mortality (NRM). However, PB recipients had higher rates of chronic GVHD (cGVHD) and were more likely to require immunosuppressive therapy (IST) at 2 years. In contrast, BM recipients had worse engraftment kinetics, including higher rates of primary graft failure. Long-term patient-reported outcomes from this trial identified receipt of BM as associated with higher psychological well-being scores, a lower cGVHD symptom burden, and a 50% greater likelihood of returning to work at 5 years compared with PB [3].

Recently the BMT CTN has incorporated a novel endpoint, GVHD and relapse-free survival (GRFS), defined as freedom from grade III-IV aGVHD, cGVHD requiring IST, relapse, or death, into the network's prospective trials [4]. This endpoint accounts for competing risks (relapse and NRM) while capturing the clinically most significant GVHD events [5]. The Center for International Blood and Marrow Transplant Research (CIBMTR) has reported an estimated GRFS of 23% at 1 year [4]. A recent analysis found the highest GRFS in adult recipients of BM grafts from matched siblings, with PB stem cells from matched sibling donors resulting in a 50% greater risk of events contributing to GRFS at 1 and 2 years compared with BM [6]. Accordingly, the aim of this study was to determine long-term GRFS and OS in adult recipients of either PB or BM allografts from HLA-A, -B, -C, and -DR-matched or 1 locus-mismatched URDs. We hypothesized that the higher rates of cGVHD associated with PB allografts will result in worse long-term survival, which may be detected through analysis of a larger dataset with sufficient data on long-term outcomes. If confirmed, these findings would support a change from the current practice favoring PB over BM.

## METHODS

### *Patients*

The CIBMTR is a voluntary working group of more than 450 centers that contribute detailed data on consecutive allogeneic and autologous HCTs to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis, Minnesota. Participating centers are required to report all transplantations consecutively, and compliance is monitored by onsite audits. All patients provided written informed consent in accordance with the Declaration of Helsinki for data submission and research participation. The NMDP's Institutional Review Board approved this study.

### *Inclusion Criteria*

Included patients were age ≥18 years and underwent a first HCT from an URD for acute leukemia, chronic myelogenous leukemia (CML), or myelodysplastic syndrome (MDS) between 2001 and 2011. All donor-recipient pairs were fully matched or had a single mismatch at HLA-A, -B, -C, or -DRB1 at the allele level (8/8 or 7/8 HLA match), and 89% were also matched at HLA-DQ. Of the total 5200 donor-recipient pairs, 81% had HLA typing at HLA-A, -B, -C, and -DRB1 performed through the NMDP retrospective high-resolution typing project as described previously [7], and the remaining pairs were reported to the CIBMTR by the transplantation centers and validated by the NMDP. Ex vivo T cell-depleted graft recipients were excluded.

### *Patient and Treatment Characteristics*

Graft source was the primary variable for this study. Additional factors examined included patient and donor age, Karnofsky Performance Score, the use of T cell antibodies (antithymocyte globulin [ATG] or alemtuzumab), GVHD prophylaxis regimen, diagnosis, disease status (early, intermediate, or advanced), time from diagnosis to HCT (<6, 6 to 12, and >12 months), year of HCT (2001 to 2004, 2005 to 2007, and 2008 to 2011), conditioning regimen intensity, and cytomegalovirus serostatus, ABO blood group, and sex match in the donor-recipient pairs.

### *Endpoints*

The primary endpoint was GRFS at 2 years post-HCT. Patients who were event-free for GRFS were those who did not experience grade III-IV aGVHD, cGVHD necessitating IST, disease relapse, or death from any cause. Kaplan-Meier estimates were used to determine the unadjusted probability of GRFS, with differences between the curves determined using log-rank tests. Cox regression was used to determine the independent factors impacting GRFS. Outcomes for the 8/8 HLA- and 7/8 HLA-matched cohorts were performed separately, because patient characteristics were strongly correlated with HLA matching. Incidence data for primary graft failure, aGVHD, and cGVHD requiring IST were based on reports from each center using standard criteria. aGVHD was graded according to standard criteria, and cGVHD was diagnosed according to CIBMTR criteria, which includes all patients with clinical criteria of cGVHD regardless of the time of onset of symptoms [8-10]. NRM was defined as death not related to disease recurrence, and relapse was defined as disease recurrence based on morphologic evaluation.

### *Statistical Analysis*

Multivariate analysis was performed using the Cox proportional hazards model [11]. With respect to the primary analysis, all endpoints were examined within 2 years of HCT, and patients who survived after 2 years were censored at 2 years. All variables were tested for affirmation of the proportional hazards assumption. In the 8/8 HLA-matched cohort, the proportional hazards assumption (which assumes that the relative risk remains constant over time) was violated when examining the impact of graft source for several endpoints (except relapse and aGVHD grade III-IV), indicating that the impact of graft source varied over time. To account for this, we determined optimal cutpoints of ≤5 and >5 months for the GRFS endpoint and cGVHD and ≤2 and >2 months for OS, disease-free survival (DFS), and NRM based on the maximum likelihood approach. For these endpoints, separate hazard ratios (HRs) for graft source within these 2 time intervals were estimated via a time-dependent manner in fitting the Cox models.

Additional factors (apart from graft course) that did not conform to the proportional hazards assumption were adjusted through stratification. A stepwise procedure was used to develop models for each outcome with a threshold of .05 for both entry and to stay in the model. Interactions between the graft source and adjusted covariates were tested at a significance level of .01. No significant interactions were detected. Similarly, as a secondary analysis, we also examined the late effect of outcomes at specific time points. The center effect was adjusted in all the multivariable models. All $P$ values are 2-sided. Data analyses were performed using SAS version 9.4 (SAS institute, Cary, NC).

## RESULTS

### *Patient Characteristics*

A total of 3901 patients underwent an 8/8 HLA-matched URD HCT between 2001 and 2011, of whom 72% received PB grafts and 28% received BM grafts. PB was increasingly used over time (56%

**Table 1**
Characteristics of Adult Patients Undergoing First Allogeneic MAC/RIC HCT for AML, ALL, CML, or MDS from an 8/8 HLA-HLA-matched URD HCT between 2001 and 2011, as Reported to the CIBMTR

| Variables | BM Group | PB Group | *P* Value |
|---|---|---|---|
| Number of patients | 1087 | 2814 | |
| Number of centers | 113 | 138 | |
| Patient-related factors | | | |
| Age at HCT, yr, median (range) | 44 (18-71) | 48 (18-76) | <.001 |
| Age at HCT, yr, n (%) | | | <.001 |
| 18-29 | 272 (25) | 455 (16) | |
| 30-39 | 189 (17) | 459 (16) | |
| 40-49 | 255 (23) | 608 (22) | |
| 50+ | 371 (34) | 1292 (46) | |
| Disease, n (%) | | | <.001 |
| AML | 552 (51) | 1631 (58) | |
| ALL | 201 (18) | 474 (17) | |
| CML | 192 (18) | 288 (10) | |
| MDS | 142 (13) | 421 (15) | |
| Disease status, n (%)* | | | .07 |
| Early | 542 (50) | 1417 (50) | |
| Intermediate | 276 (25) | 627 (22) | |
| Advanced | 266 (24) | 767 (27) | |
| Missing | 3 (<1) | 3 (<1) | |
| Time from diagnosis to HCT, mo, median (range) | 8 (<1-238) | 7 (<1-607) | <.001 |
| Time from diagnosis to HCT, mo, n (%) | | | .005 |
| <6 | 379 (35) | 1139 (40) | |
| 6 to ≤12 | 293 (27) | 744 (26) | |
| >12 | 413 (38) | 924 (33) | |
| Missing | 2 (<1) | 7 (<1) | |
| Karnofsky Performance Score at HCT, n (%) | | | <.001 |
| < 90 | 278 (26) | 953 (34) | |
| ≥ 90 | 691 (64) | 1695 (60) | |
| Missing | 118 (11) | 166 (6) | |
| Donor-related factors | | | |
| Age at HCT, yr, median (range) | 33 (19-60) | 32 (18-61) | .03 |
| Age at HCT, yr, n (%) | | | .43 |
| 18-32 | 538 (49) | 1458 (52) | |
| 33-49 | 486 (45) | 1200 (43) | |
| 50+ | 63 (6) | 156 (6) | |
| Donor-recipient sex match, n (%) | | | .08 |
| Male/male | 403 (37) | 1153 (41) | |
| Male/female | 314 (29) | 811 (29) | |
| Female/male | 175 (16) | 393 (14) | |
| Female/female | 195 (18) | 457 (16) | |
| Donor-recipient CMV status, n (%) | | | .14 |
| Negative/negative | 303 (28) | 843 (30) | |
| Negative/positive | 384 (35) | 1049 (37) | |
| Positive/negative | 129 (12) | 286 (10) | |
| Positive/positive | 259 (24) | 576 (20) | |
| Missing | 12 (1) | 60 (2) | |
| Donor-recipient ABO mismatch, n (%) | | | .87 |
| Matched | 485 (45) | 1235 (44) | |
| Minor mismatch | 276 (25) | 699 (25) | |
| Major mismatch | 248 (23) | 662 (24) | |
| Bidirectional mismatch | 78 (7) | 218 (8) | |
| Transplantation-related factors | | | |
| Year of HCT, n (%) | | | <.001 |
| 2001-2004 | 424 (39) | 547 (19) | |
| 2005-2007 | 424 (39) | 1242 (44) | |
| 2008-2011 | 239 (22) | 1025 (36) | |
| Conditioning regimen intensity and TBI use, n (%) | | | <.001 |
| MAC, TBI | 477 (44) | 905 (32) | |
| MAC, no TBI | 452 (42) | 1143 (41) | |
| RIC, TBI | 17 (2) | 88 (3) | |
| RIC, no TBI | 141 (13) | 678 (24) | |
| ATG/Campath used in conditioning regimen or GVHD prophylaxis?, n (%) | | | .90 |
| Yes | 338 (31) | 881 (31) | |
| No | 749 (69) | 1933 (69) | |
| GVHD prophylaxis, n (%) | | | <.001 |
| Tac-based | 721 (66) | 2177 (77) | |
| CsA-based | 327 (30) | 537 (19) | |
| Others | 39 (4) | 100 (4) | |
| Follow-up of survivors, mo, median (range) | 60 (1-124) | 48 (1-122) | <.001 |

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CMV, cytomegalovirus; Tac, tacrolimus, CsA, cyclosporine.
*Disease status is defined as follows:
• Early: AML/ALL (first complete response [CR]), CML (first chronic phase [CP]), MDS (refractory anemia [RA]/RA with ring sideroblasts/pre-HCT marrow blasts <5%)
• Intermediate: AML/ALL (≥CR2), CML (acute phase or ≥CP2)
• Advanced: AML/ALL (relapse/primary induction failure), CML (blast phase), MDS (RA with excess blasts/RAEB in transformation/chronic myelomonocytic leukemia or marrow blasts ≥5%).

from 2001 to 2004 versus 81% from 2008 to 2011). Patient characteristics are detailed in Table 1. The median duration of follow-up for survivors was 60 months (range, 1 to 124 months) in the BM recipients and 48 months (range, 1 to 122 months) in the PB recipients ($P < .001$).

Another 1299 patients underwent a 7/8-HLA matched URD between 2001 and 2011, again with 72% receiving PB and 28% receiving BM. In this group, PB use increased over time (55% in 2001 to 2004 versus 81% in 2008 to 2011). Patient characteristics for the 7/8- HLA cohort are presented in Table 2. The median duration of follow-up for survivors was 97 months (range, 4 to 156 months) in the BM recipients and 73 months (6-168) in the PB recipients ($P < .001$).

### *Multivariate Analysis for GRFS and OS*

GRFS after 8/8 HLA-matched URD HCT was superior in BM recipients compared with PB recipients when evaluated at >5 months post-transplantation (HR, 1.62; 95% confidence interval (CI), 1.38 to 1.89; $P < .0001$) (Figure 1A and Table 3). However, before 5 months (when chronic GVHD is less common), GRFS was similar in PB and BM recipients (HR, .92; 95% CI, .83 to 1.02; $P = .10$). In addition to graft source (beyond 5 months), patient age >50 years, donor age >32 years, lack of T cell antibody, a diagnosis of CML, <1 year from diagnosis to HCT, and HCT during 2001 to 2004 were associated with worse GRFS (Table 3).

In the 7/8 HLA-matched cohort, receipt of PB grafts was associated with worse GRFS (HR, 1.15; 95% CI, 1.00 to 1.33; $P = .0476$) (Figure 1B and Table 4). Additional factors associated with worse GRFS in the 7/8 HLA-mated cohort included lack of T cell antibody, a diagnosis of CML or MDS, advanced disease, and use of a mycophenolate mofetil-containing GVHD prophylaxis regimen (Table 4).

For patients receiving an 8/8 HLA-matched URD, within the first 2 months, OS was significantly better in PB recipients compared with BM recipients (HR, .63; 95% CI, .50 to .79; $P < .0001$). Over time, the survival advantage of PB disappeared, such that at 2 years, OS became statistically comparable in the 2 graft sources ($P = .27$) (Table 5 and Figure 1C). Proportionality assumptions were maintained for the 7/8 HLA-matched cohort with no significant difference in OS at 2 years between the PB and BM (HR, 1.01; 95% CI, .86 to 1.19; $P = .91$) (Table 6 and Figure 1D).

**Table 2**
Characteristics of Adult Patients Undergoing First Allogeneic MAC/RIC HCT for AML, ALL, CML, or MDS from a 7/8 HLA-matched URD HCT between 2001 and 2011, as Reported to the CIBMTR

| Variable | BM Group | PB Group | *P* Value |
|---|---|---|---|
| Number of patients | 370 | 929 | |
| Number of centers | 103 | 113 | |
| Patient-related factors | | | |
| Age at HCT, yr, median (range) | 41 (18-72) | 46 (18-71) | <.001 |
| Age at HCT, yr, n (%) | | | <.001 |
| 18-29 | 103 (28) | 168 (18) | |
| 30-39 | 74 (20) | 169 (18) | |
| 40-49 | 109 (29) | 220 (24) | |
| 50+ | 84 (23) | 372 (40) | |
| Disease, n (%) | | | <.001 |
| AML | 183 (49) | 546 (59) | |
| ALL | 95 (26) | 170 (18) | |
| CML | 67 (18) | 102 (11) | |
| MDS | 25 (7) | 111 (12) | |
| Disease status, n (%)* | | | .006 |
| Early | 152 (41) | 413 (44) | |
| Intermediate | 126 (34) | 229 (25) | |
| Advanced | 91 (25) | 283 (30) | |
| Missing | 1 (<1) | 4 (<1) | |
| Time from diagnosis to HCT, mo, median (range) | 10 (<1-269) | 8 (<1-229) | .005 |
| Time from diagnosis to HCT, mo, n (%) | | | .04 |
| <6 | 98 (26) | 304 (33) | |
| 6 to ≤12 | 106 (29) | 284 (31) | |
| >12 | 165 (45) | 339 (36) | |
| Missing | 1 (<1) | 2 (<1) | |
| Karnofsky Performance Score at HCT, n (%) | | | .01 |
| <90 | 231 (62) | 542 (58) | |
| ≥90 | 105 (28) | 331 (36) | |
| Missing | 34 (9) | 56 (6) | |
| Donor-related factors | | | |
| Age at HCT, yr, median (range) | 36 (19-60) | 36 (18-59) | .57 |
| Age at HCT, yr, n (%) | | | .70 |
| 18-32 | 138 (37) | 370 (40) | |
| 33-49 | 196 (53) | 472 (51) | |
| 50+ | 36 (10) | 87 (9) | |
| Number of patients | 370 | 929 | |
| Donor-recipient sex match, n (%) | | | .29 |
| Male/male | 136 (37) | 313 (34) | |
| Male/female | 98 (26) | 251 (27) | |
| Female/male | 60 (16) | 191 (21) | |
| Female/female | 76 (21) | 174 (19) | |
| Donor-recipient CMV status, n (%) | | | .50 |
| Negative/negative | 83 (22) | 228 (25) | |
| Negative/positive | 38 (10) | 97 (10) | |
| Positive/negative | 131 (35) | 317 (34) | |
| Positive/positive | 116 (31) | 272 (29) | |
| Missing | 2 (<1) | 15 (2) | |
| Donor-recipient ABO mismatch, n (%) | | | .94 |
| Matched | 155 (42) | 381 (41) | |
| Minor mismatch | 90 (24) | 226 (24) | |
| Major mismatch | 91 (25) | 242 (26) | |
| Bidirectional mismatch | 34 (9) | 79 (9) | |
| Missing | 0 | 1 (<1) | |
| Transplantation-related factors | | | |
| Year of HCT, n (%) | | | <.001 |
| 2001-2004 | 184 (50) | 228 (25) | |
| 2005-2007 | 116 (31) | 407 (44) | |
| 2008-2011 | 70 (19) | 294 (32) | |
| Conditioning intensity, TBI use, n (%) | | | <.001 |
| MAC, TBI | 203 (55) | 346 (37) | |
| MAC, no TBI | 129 (35) | 349 (38) | |
| RIC, TBI | 2 (<1) | 34 (4) | |
| RIC, no TBI | 36 (10) | 200 (22) | |
| ATG/Campath used in conditioning regimen or GVHD prophylaxis?, n (%) | | | .83 |
| Yes | 139 (38) | 343 (37) | |
| No | 231 (62) | 586 (63) | |
| Number of patients | 370 | 929 | |
| GVHD prophylaxis, n (%) | | | <.001 |
| Tac + MMF ± others | 18 (5) | 139 (15) | |
| Tac + MTX ± others | 184 (50) | 428 (46) | |
| Tac ± others | 35 (9) | 115 (12) | |
| CsA + MMF ± others | 4 (1) | 35 (4) | |
| CsA + MTX ± others | 99 (27) | 138 (15) | |
| CsA ± others | 6 (2) | 32 (3) | |
| Others | 24 (6) | 42 (5) | |
| Follow-up of survivors, mo, median (range) | 97 (4-156) | 73 (6-168) | <.001 |

MMF indicates mycophenolate mofetil; MTX, methotrexate.
*Disease status is defined as follows:
• Early: AML/ALL (first complete response [CR]), CML (first chronic phase [CP]), MDS (refractory anemia [RA]/RA with ring sideroblasts/pre-HCT marrow blasts <5%).
• Intermediate: AML/ALL (≥CR2), CML (acute phase or ≥CP2).
• Advanced: AML/ALL (relapse/primary induction failure), CML (blast phase), MDS (RA with excess blasts/RAEB in transformation/chronic myelomonocytic leukemia or marrow blasts ≥5%).

### *Composite Factors: Multivariate Analysis for Cumulative Incidences for Acute GVHD Grade III-IV, Chronic GVHD Requiring IST, Relapse, and NRM Within 2 Years Post-Transplantation in Recipients of BM or PB Grafts*

The incidence of aGVHD grade III-IV was not statistically significantly different in PB and BM recipients (HR, 1.08; 95% CI, .89 to 1.30; $P = .44$). In contrast, the cumulative incidence of cGVHD requiring IST was worse with receipt of PB (>5 months; HR, 1.80; 95% CI, 1.50 to 2.15; $P < .0001$). Additional factors associated with increased cGVHD requiring IST included a lack of T cell antibody, diagnosis of CML, mycophenolate mofetil-containing GVHD prophylaxis, and female donor with male recipient. Within the first 2 months of HCT, PB was protective for NRM (HR, 0·49; 95% CI, .39 to .63; $P < .0001$); however, at 2 years post-HCT, NRM was similar in BM and PB recipients (27% versus 24%; $P = .14$) (Table 7), whereas at 5 years post-HCT, NRM was worse in the PB recipients (30% versus 34%; $P = .0087$). The presence of cGVHD was associated with an elevated risk for NRM in the PB recipients (HR, 1.58; 95% CI, 1.20 to 2.08; $P = .0012$). The impact of cGVHD on NRM in BM recipients was not significant (HR, 1.29; 95% CI, .84 to 1.99; $P = .25$). The rate of relapse did not differ significantly between the 2 groups (HR, .93; 95% CI, .81 to 1.07; $P = .29$).

In the 7/8 HLA-matched cohort, aGVHD III-IV did not differ between PB and BM recipients (HR, 1.14; 95% CI, .87 to 1.49; $P = .32$); whereas cGVHD requiring IST was more common in PB recipients (HR, 1.39; 95% CI, 1.12 to 1.73; $P = .0031$). There were no significant between-group differences in relapse rate (HR, .92; 95% CI, .73 to 1.17; $P = .49$) or NRM (HR, 1.11; 95% CI, .89 to 1.39; $P = .3404$).

### *Contributors to Treatment Failure*

Figure 2 shows a stacked plot analysis of causes of treatment failure (with respect to GRFS) in 8/8 HLA-matched BM (A) and PB (B) recipients and 7/8 HLA-matched BM (C) and PB (D) recipients. cGVHD requiring IST was the main cause of treatment failure for all cohorts; however, it was a more

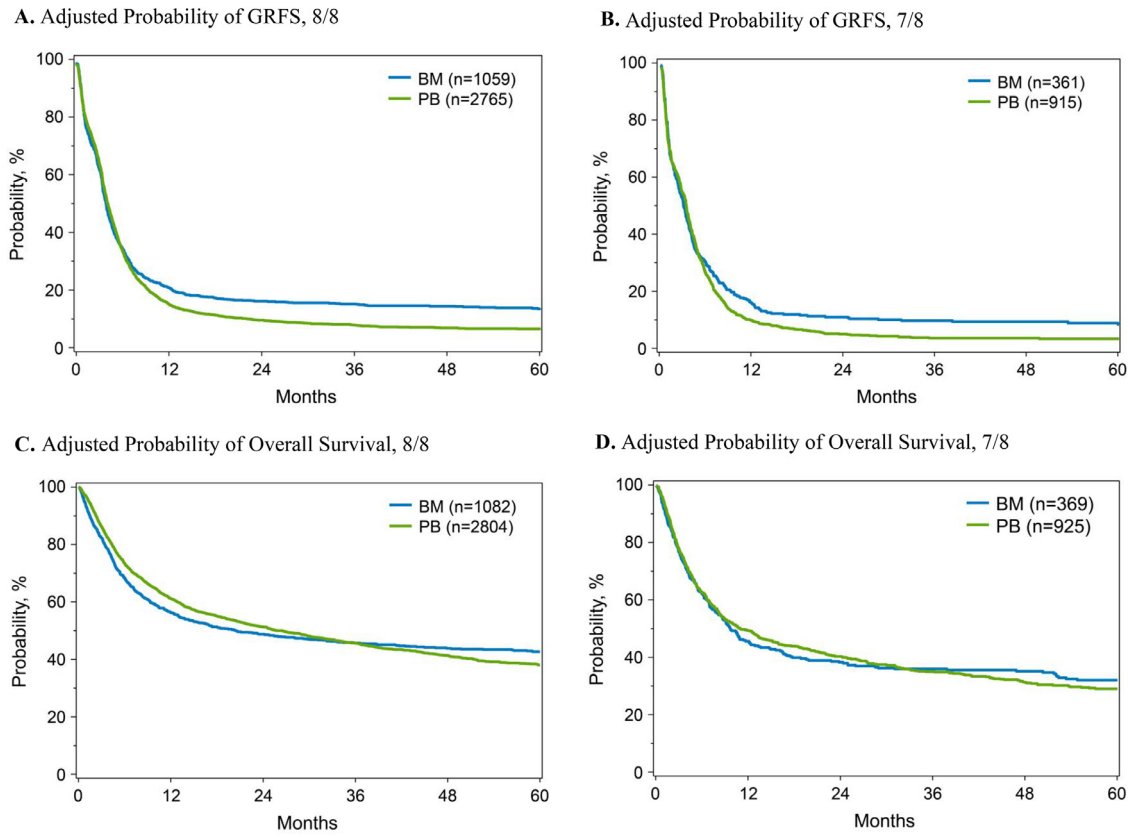


**Figure 1.** (A and B) GRFS in 8/8 HLA-matched (A) and 7/8 HLA-matched (B) URD graft recipients. (C and D) OS in 8/8 HLA-matched (C) and 7/8 HLA-matched (D) URD graft recipients.

common cause of failure in PB recipients than in BM recipients among the 8/8 HLA-matched recipient (42% versus 31%; $P < .001$) and 7/8-HLA cohort (35% versus 29% at 5 years post-HCT; $P = .02$). In addition, death in remission more often contributed to failure in PB recipients compared with BM recipients in the 8/8 HLA-matched cohort (16% versus 11% at 5 years post-HCT; $P < .001$). The contributions of relapse and aGVHD III/IV to treatment failure did not differ based on graft source in either the 8/8 HLA-matched or 7/8 HLA-matched cohort.

### *Long-Term Outcomes: OS and GRFS at 5 Years*

To determine the impact of late complications (namely cGVHD) with respect to long-term OS, the adjusted survival rates were estimated at 5 years and were found to be significantly higher in BM recipients compared with PB recipients (43%; 95% CI, 40% to 46% versus 38%; 95% CI, 36% to 40%; $P = .014$ (Table 7). Additional factors impacting OS included donor-recipient ABO match, cytomegalovirus serostatus, conditioning regimen, time from diagnosis to transplant and Karnofsky Performance Score (Table 5, with predictors of DFS shown in Supplementary Table 1). Note that the multivariable Cox models in Table 6 also show different hazards for OS between PB grafts and BM grafts within the first 2 months after HCT (PB superior to BM), but no significant differences beyond 2 months post-HCT. The probabilities of OS at 5 years depend on the hazard functions of PB and BM over the entire period from HCT up to 5 years. Similar trends in OS at 5 years were seen in the 7/8 HLA-matched cohort, but they did not reach statistical significance ($P = .33$) (Table 6; DFS shown in Supplementary Table 2). The cumulative incidence for GRFS at 5 years was almost twice as high for BM recipients as for PB recipients in both the 8/8 HLA-matched cohort (14% versus 7%; $P < .0001$) and the 7/8 HLA-matched cohort (9% versus 4%; $P < .0001$) (Table 7 and Figure 1A-D).

## DISCUSSION

The first attempt to definitively address the question of graft source was the BMT CTN 0201 trial, which enrolled its first patient in 2004, at which time PB had already surpassed BM as the predominant graft source in patients undergoing URD HCT. In 2013, the primary results from BMT CTN0201 were published demonstrating comparable survival at 2 years for those randomized to PB and BM [2]. The failure to show a survival benefit in this trial as well as previous retrospective analyses [12-19] may have contributed to PB remaining the predominant graft source in roughly 80% of all URD recipients despite significantly higher rates of cGVHD and the need for prolonged immunosuppressants [1]. More recently published long-term patient-reported quality of life (QoL) data from the BMT CTN 0201 trial showed that at 5-years post-HCT, BM recipients reported significantly better QoL and were more likely to have returned to work compared with PB recipients; however, survival remained equivalent at 5 years [3]. In contrast, our results show superior OS at 5 years post-transplantation in recipients of BM following 8/8 HLA-matched URD HCT. It should be noted that the 0201 trial was powered to detect a 12.5% absolute survival difference at 2 years. In contrast, our sample size was roughly 10 times larger and allowed for detection of a smaller absolute difference, which only became apparent with sufficient follow-up to allow for the impact of late mortality in patients with cGVHD to be appreciated. The demonstration of improved survival and GRFS at 5-years

**Table 3**
Predictors of GRFS in Recipients of 8/8 HLA-matched URD HCT

| Risk Factor | Number (%) | HR (95% CI) | *P* Value |
|---|---|---|---|
| Graft source, ≤5 mo | | | .0977 |
| BM | 1059 (28) | 1.00 | |
| PB | 2765 (72) | .92 (.83-1.02) | .0977 |
| Graft source, >5 mo | | | <.0001 |
| BM | 418 (27) | 1.00 | |
| PB | 1122 (73) | 1.62 (1.38-1.89) | <.0001 |
| Patient age, yr | | | .0074 |
| 18-29 | 712 (19) | 1.00 | |
| 30-39 | 634 (16) | .97 (.86-1.09) | .6257 |
| 40-49 | 847 (22) | 1.06 (.95-1.18) | .3299 |
| 50+ | 1631 (43) | 1.15 (1.03-1.27) | .0104 |
| ATG/Campath | | | <.0001 |
| Yes | 1191 (31) | 1.00 | |
| No | 2633 (69) | 1.35 (1.23-1.48) | <.0001 |
| Disease | | | .0760 |
| AML | 2155 (56) | 1.00 | |
| ALL | 658 (17) | 1.02 (.92-1.13) | .7076 |
| CML | 467 (12) | 1.17 (1.04-1.32) | .0096 |
| MDS | 544 (15) | 1.02 (.91-1.13) | .7572 |
| Donor age, yr | | | .0375 |
| 18-32 | 1966 (51) | 1.00 | |
| 33-49 | 1644 (43) | 1.08 (1.01-1.16) | .0360 |
| 50+ | 214 (6) | 1.16 (.99-1.35) | .0596 |
| Time from diagnosis to HCT, mo | | | .0449 |
| <6 | 1495 (39) | 1.00 | |
| 6-12 | 1018 (27) | 1.01 (.93-1.11) | .7502 |
| >12 | 1312 (34) | .90 (.81-.99) | .0384 |
| Year of HCT | | | .0001 |
| 2001-2004 | 959 (25) | 1.00 | |
| 2005-2007 | 1628 (43) | .90 (.82-.98) | .0221 |
| 2008-2011 | 1237 (32) | .80 (.72-.88) | <.0001 |

Stratified variables include disease stage, GVHD prophylaxis, Karnofsky Performance Score, and transplantation centers. Sixty-two patients had GRFS endpoint missing, 6 had disease stage missing, and 9 had time from diagnosis to HCT missing.

post-transplantation with the use of BM grafts calls into question the current practice favoring PB grafts in recipients of 8/8 HLA-matched URD transplants.

Our analysis did not demonstrate a clear survival advantage for BM grafts in the 7/8 HLA-matched cohort. It is important to note that graft failure rates were comparable in the 7/8 HLA-

**Table 4**
Predictors of GRFS in Recipients of 7/8 HLA-matched URD HCT

| Risk Factor | Number (%) | HR (95% CI) | *P* Value |
|---|---|---|---|
| Graft source | | | .0476 |
| BM | 361 (28) | 1.00 | |
| PB | 915 (72) | 1.15 (1.00-1.33) | .0476 |
| ATG/Campath | | | <.0001 |
| Yes | 469 (37) | 1.00 | |
| No | 807 (63) | 1.36 (1.19-1.56) | <.0001 |
| Disease | | | .0378 |
| AML | 718 (56) | 1.00 | |
| ALL | 263 (21) | 1.09 (.93-1.27) | .2915 |
| CML | 168 (13) | 1.21 (1.00-1.46) | .0496 |
| MDS | 127 (10) | 1.27 (1.04-1.56) | .0203 |
| Disease status | | | <.0001 |
| Early | 556 (44) | 1.00 | |
| Intermediate | 350 (27) | 1.21 (1.04-1.40) | .0120 |
| Advanced | 370 (29) | 1.54 (1.34-1.78) | <.0001 |
| GVHD prophylaxis | | | .0015 |
| CNI + MMF ± others | 190 (15) | 1.00 | |
| CNI + MTX ± others | 834 (65) | .72 (.60-.87) | .0005 |
| Others | 252 (20) | .80 (.65-.99) | .0413 |

CNI indicates calcineurin inhibitor.
Nineteen patients had GRFS endpoint missing, and 5 patients had disease status data missing.

**Table 5**
Adjusted Cumulative Incidence and Survival Rates in Recipients of 8/8 HLA-matched URD HCT

| Outcome | BM, % (95% CI) | PB, % (95% CI) | Pointwise *P* Value |
|---|---|---|---|
| Relapse at 1 yr | 29 (26-31) | 28 (27-30) | .91 |
| Relapse at 2 yr | 33 (30-36) | 33 (31-35) | .97 |
| Relapse at 5 yr | 37 (34-40) | 37 (35-39) | .96 |
| NRM at 1 yr | 24 (21-27) | 20 (18-21) | .0047 |
| NRM at 2 yr | 27 (24-30) | 24 (23-26) | .14 |
| NRM at 5 yr | 30 (27-33) | 35 (33-37) | .016 |
| GRFS at 1 yr | 21 (19-23) | 15 (14-16) | <.0001 |
| GRFS at 2 yr | 16 (14-19) | 10 (8-11) | <.0001 |
| GRFS at 5 yr | 14 (11-16) | 7 (5-8) | <.0001 |
| OS at 1 yr | 56 (53-59) | 61 (59-63) | .0030 |
| OS at 2 yr | 48 (45-51) | 51 (50-53) | .11 |
| OS at 5 yr | 42 (39-46) | 38 (36-40) | .022 |

Adjusted covariates for (1) relapse: donor-recipient ABO type match, conditioning regimen intensity and TBI use, GVHD prophylaxis, time from diagnosis to HCT, Karnofsky Performance Score (KPS), disease type, and year of HCT; (2) NRM: patient age, donor age, donor-recipient ABO type match, donor-recipient CMV match, ATG/Campath use, conditioning regimen intensity and TBI use, GVHD prophylaxis, KPS, disease type, disease stage, and year of HCT; (3) GRFS: patient age, donor age, ATG/Campath use, time from diagnosis to HCT, GVHD prophylaxis, KPS, disease type, disease stage, and year of HCT; (4) OS: patient age, donor-recipient ABO type match, donor-recipient CMV match, conditioning regimen intensity and TBI use, time from diagnosis to HCT, KPS, disease stage, GVHD prophylaxis, year of HCT, and donor-recipient sex match.

**Table 6**
Predictors of OS in Recipients of 8/8 HLA-matched URD HCT

| Risk Factor | Number (%) | HR (95% CI) | *P* Value |
|---|---|---|---|
| Graft source, ≤2 mo | | | <.0001 |
| BM | 1082 (28) | 1.00 | |
| PB | 2804 (72) | .63 (.50-.79) | <.0001 |
| Graft source, >2 mo | | | |
| BM | 939 (27) | 1.00 | |
| PB | 2546 (73) | 1.10 (.97-1.24) | .1427 |
| Donor-recipient ABO type match | | | .0018 |
| Matched | 1713 (44) | 1.00 | |
| Minor mismatch | 971 (25) | 1.11 (.99-1.24) | .0763 |
| Major mismatch | 907 (23) | 1.24 (1.11-1.39) | .0001 |
| Bidirectional mismatch | 295 (8) | 1.05 (.88-1.24) | .5999 |
| Patient age, yr | | | <.0001 |
| 18-29 | 724 (19) | 1.00 | |
| 30-39 | 646 (17) | 1.02 (.87-1.20) | .7766 |
| 40-49 | 860 (22) | 1.27 (1.09-1.47) | .0015 |
| 50+ | 1656 (43) | 1.64 (1.43-1.89) | <.0001 |
| Donor-recipient CMV match | | | .0233 |
| +/+ | 1141 (29) | 1.00 | |
| +/- | 1428 (37) | 1.20 (1.08-1.34) | .0012 |
| -/+ | 413 (11) | 1.18 (1.01-1.38) | .0410 |
| -/- | 832 (21) | 1.14 (1.00-1.30) | .0442 |
| Missing | 72 (2) | 1.15 (0.83-1.59) | .4149 |
| Conditioning regimen intensity, TBI use | | | <.0001 |
| MAC, TBI | 1379 (35) | 1.00 | |
| MAC, no TBI | 1591 (41) | .78 (.70-.87) | <.0001 |
| RIC, TBI | 105 (3) | .92 (.68-1.23) | .5595 |
| RIC, no TBI | 811 (21) | .76 (.66-.88) | .0002 |
| Time from diagnosis to HCT, mo | | | .0193 |
| <6 | 1515 (39) | 1.00 | |
| 6-12 | 1035 (27) | 1.11 (.99-1.24) | .0746 |
| >12 | 1336 (34) | .93 (.82-1.05) | .2482 |
| Karnofsky Performance Score | | | <.0001 |
| <90 | 1226 (32) | 1.00 | |
| ≥90 | 2377 (61) | .74 (.67-.82) | <.0001 |
| Missing | 283 (7) | .80 (.66-.97) | .0218 |

Stratified variables include disease stage, GVHD prophylaxis, year of HCT, donor-recipient sex match, and transplantation center. Nine patients had time from diagnosis to HCT data missing.

**Table 7**
Predictors for OS in Recipients of 7/8 HLA-matched URD HCT

| Risk Factor | Number (%) | HR (95% CI) | *P* Value |
|---|---|---|---|
| Graft source | | | .9070 |
| BM | 369 (29) | 1.00 | |
| PB | 925 (71) | 1.01 (.86-1.19) | .9070 |
| Patient age | | | <.0001 |
| 18-29 | 269 (21) | 1.00 | |
| 30-39 | 242 (19) | 1.41 (1.12-1.78) | .0038 |
| 40-49 | 328 (25) | 1.58 (1.27-1.97) | <.0001 |
| 50+ | 455 (35) | 1.68 (1.35-2.08) | <.0001 |
| Disease | | | .0003 |
| AML | 730 (56) | 1.00 | |
| ALL | 265 (20) | 1.44 (1.19-1.73) | .0002 |
| CML | 169 (13) | .99 (.78-1.25) | .9117 |
| MDS | 130 (10) | 1.34 (1.06-1.69) | .0158 |
| Disease stage | | | <.0001 |
| Early | 565 (44) | 1.00 | |
| Intermediate | 355 (27) | 1.42 (1.19-1.70) | .0001 |
| Advanced | 374 (29) | 1.94 (1.64-2.30) | <.0001 |
| Donor age, yr | | | .0199 |
| 18-32 | 506 (39) | 1.00 | |
| 33-49 | 665 (51) | 1.10 (.95-1.28) | .2009 |
| 50+ | 123 (10) | 1.41 (1.10-1.79) | .0057 |
| Karnofsky Performance Score | | | .0035 |
| <90 | 435 (34) | 1.00 | |
| ≥90 | 770 (60) | .77 (.66-.90) | .0009 |
| Missing | 89 (7) | .82 (.61-1.11) | .1996 |

Stratified variables include disease stage, GVHD prophylaxis, year of HCT, donor-recipient sex match, and transplantation center. Five patients had disease stage data missing.

and 8/8 HLA-matched cohorts. As such, theoretical concerns about a greater risk of rejection when using a 7/8 HLA-matched donor, justifying the selection of PB over BM, is not supported by our findings (data not shown). Despite the lack of survival advantage for BM in the 7/8 HLA-matched cohort, GRFS was superior, owing to a lower risk for cGVHD requiring IST. With comparable survival but worse GRFS, the routine use of PB grafts in recipients of 7/8 HLA-matched URD HCT should be reconsidered as well.

Our study highlights the challenges of using composite endpoints. GRFS has been recently suggested as an important endpoint for trials evaluating GVHD prophylaxis strategies [4]. An advantage of GRFS is its ability to assess the impact of clinically important GVHD events while capturing competing risks of relapse and NRM. The challenges with this endpoint are that when comparing treatment strategies, events can occur at different time points, resulting in major differences over time. This was seen here; patients who received BM had higher rates of early NRM (primarily in the first 2 months post-HCT), whereas patients who received PB grafts had higher rates of cGVHD (a late event), which ultimately contributed to higher long-term rates of NRM. Therefore, it is essential that GRFS be assessed at a sufficiently long interval to account for all these competing events. In addition, GRFS fails to account for patients who develop grade III-IV aGVHD or cGVHD requiring IST but subsequently recover. Adoption of a "current" GRFS, defined as survival without evidence of relapse, grade III-IV aGVHD, or cGVHD requiring IST at the point of last follow-up would be one method to reflect the long-term impact of these events [20].

Our analysis has several limitations. Importantly, 75% of the patients received myeloablative conditioning. Although conditioning intensity was accounted for in the modeling of all outcomes, whether graft source has the same impact in less-intense conditioning regimens is not clear. The question of graft source in non-TBI-based reduced-intensity conditioning (RIC) unrelated allografts has been examined by the CIBMTR, which found similar outcomes with respect to OS, aGVHD, and cGVHD in recipients of BM and PB grafts; however, GRFS was

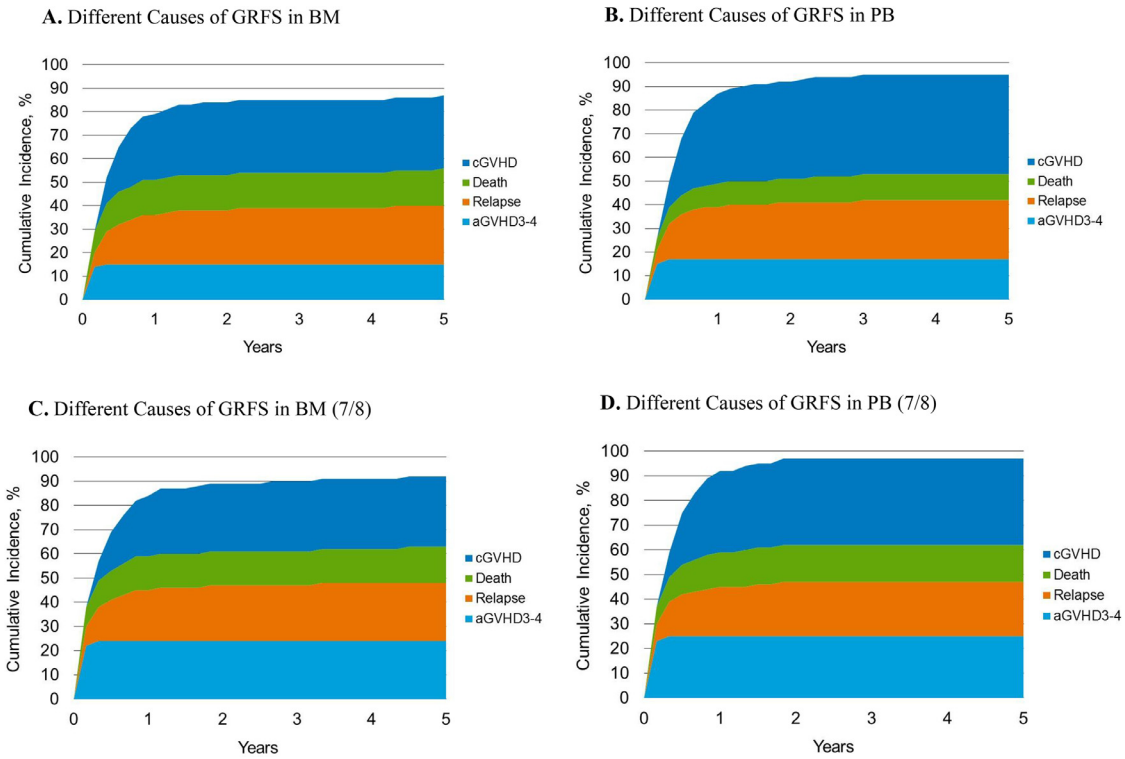


**Figure 2.** Causes of treatment failure with respect to GRFS in recipients of 8/8 HLA-matched BM (A) and PB (B) and 7/8 HLA-matched BM (C) and PB (D) allograft from unrelated donors.

not examined in that report [13]. As in our analysis, this earlier CIBMTR study also found a strong interaction with GVHD prophylaxis regimens, with worse outcomes when mycophenolate mofetil-based prophylaxis was used. In contrast, a separate analysis from the European Registry found associations between the use of PB and higher rates of aGVHD, cGVHD, and NRM but lower relapse rates in recipients of URD HCT following RIC compared with BM, with no difference in survival [14]. However, follow-up was considerably shorter in the European analysis, and roughly one-half of the subjects had missing data on GVHD prophylaxis, which may account for differences in these 2 reports.

An additional limitation of this study is the absence of newer prophylaxis regimens using post-transplantation cyclophosphamide-based approaches, which have demonstrated low rates of cGVHD [21,22]. Recently, a 3-armed randomized trial of prophylaxis regimens in the setting of RIC followed by PB HCT was presented in abstract form demonstrating improved GRFS and lower rates of chronic GVHD requiring IST in recipients of post-transplantation cyclophosphamide, tacrolimus, and mycophenolate compared with a contemporary CIBMTR matched cohort [23]. In that trial, participants could receive only PB grafts, and whether further reductions in the rate of cGVHD would have been seen had the use of BM grafts been allowed remains untested.

Finally, our analysis is limited to recipients of URD HCT. The question of graft source in recipients of other donor sources has been an area of interest. An advantage of BM over PB in the setting of HLA-matched sibling HCT with respect to GRFS has recently been reported in a 2-center retrospective analysis [6], whereas a 3-center prospective, randomized trial showed comparable OS but significantly lower relapse in those randomized to PB HLA-matched sibling donor HCTs [24]. The graft source following haploidentical HCT using GVHD prophylaxis with post-transplantation cyclophosphamide remains an area of debate, with limited data suggesting comparable outcomes in PB and BM recipients in the setting of nonmyeloablative conditioning [25].

In conclusion, 8/8 HLA-matched URD HCT using BM allografts results in improved long-term OS and GRFS in adults with acute leukemia, CML, or MDS compared with the use of PB allografts. Thus, BM should be considered the graft source of choice if available. When PB is used, strategies to minimize the impact of cGVHD should be implemented.

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## SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.bbmt.2018.09.004.

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