Brief report

Effect of stem cell source on outcomes after unrelated donor transplantation in severe aplastic anemia

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Outcome after unrelated donor bone marrow (BM) transplantation for severe aplastic anemia (SAA) has improved, with survival rates now approximately 75%. Increasing use of peripheral blood stem and progenitor cells (PBPCs) instead of BM as a graft source prompted us to compare outcomes of PBPC and BM transplantation for SAA. We studied 296 patients receiving either BM (n = 225) or PBPC (n = 71) from unrelated donors matched at human leukocyte antigen-A, -B, -C, -DRB1. Hematopoietic recovery was similar after PBPC and BM transplantation. Grade 2 to 4 acute graft-versus-host disease risks were higher after transplantation of PBPC compared with BM (hazard ratio = 1.68, P = .02; 48% vs 31%). Chronic graft-versus-host disease risks were not significantly different after adjusting for age at transplantation (hazard ratio = 1.39, P = .14). Mortality risks, independent of age, were higher after PBPC compared with BM transplantation (hazard ratio = 1.62, P = .04; 76% vs 61%). These data indicate that BM is the preferred graft source for unrelated donor transplantation in SAA. (*Blood*. 2011; 118(9):2618-2621)

Introduction

In most cases, severe aplastic anemia (SAA) is an immune-mediated disorder; T lymphocytes inhibit or destroy hematopoietic progenitor cells resulting in marrow failure.[1,2] Treatment options include immune suppressive therapy (IST) with antithymocyte globulin (ATG), which lyses lymphocytes, and cyclosporine, which blocks T lymphocyte function, and hematopoietic stem cell transplantation (HSCT), which replaces lymphohematopoietic progenitor cells.[1,2] When a human leukocyte antigen (HLA)-matched sibling is lacking, IST is first-line treatment and HSCT is reserved for those who fail IST.[3] Although historically, unrelated HSCT was performed using cells collected directly from the bone marrow (BM), in recent years, most transplantations are done with peripheral blood progenitor cells (PBPCs) collected by leukapheresis. In 2008, worldwide PBPC collections from unrelated donors numbered 7260 compared with 3221 BM collections.[4] Whereas PBPC transplantations are associated with faster hematopoietic recovery, graft-versus-host disease (GVHD), particularly in its chronic form, is more frequent than with BM transplantation. The higher incidence of chronic GVHD is associated with inferior overall survival after transplantation of PBPCs from HLA-matched siblings for SAA.[5,6] In this analysis, we examined whether a similar pattern is observed with unrelated donor transplantation.

Methods

Patients

Data on HSCT were obtained from the Center for International Blood and Marrow Transplant Research a voluntary group of > 450 transplant centers that contribute data prospectively on consecutive transplantations performed at each center. All patients are followed longitudinally annually. Eighty-nine centers contributed patients, and HSCTs were performed in 2000 to 2008. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Inclusion criteria

Patients were 1 to 71 years old with an established diagnosis of SAA and received BM or PBPCs from adult unrelated donors matched at the allele-level for HLA-A, -B, -C, and -DRB1 (8 of 8 HLA-matched).

Endpoints

The primary endpoint was overall survival. Neutrophil recovery was defined as achieving an absolute neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days; and platelet recovery as platelets $\geq 20 \times 10^9$/L, unsupported by transfusion for 7 days. Incidences of grades 2 to 4 acute GVHD and chronic GVHD were based on reports from each transplant center using standard criteria.[7,8]

Statistical analysis

Patients were considered in 2 groups: BM and PBPC recipients. Variables related to patients, disease, and transplantation (Table 1) were compared between the groups using the χ^2 statistic. Probabilities of overall survival were calculated with the Kaplan-Meier estimator.[9] Probabilities of neutrophil and platelet recovery and acute and chronic GVHD were calculated with the cumulative incidence estimator to accommodate competing risks.[9] In all analyses, data on patients without an event were censored at last follow-up.

Table 1. Patient, disease, and transplant characteristics

Variable	BM	PB	P
No. of patients	225	71	
Median age, y (range)	19 (2-66)	36 (1-71)	< .001
Age at transplantation, y			< .001
≤ 20	133 (59)	16 (23)	
21-40	66 (29)	29 (41)	
> 40	26 (12)	26 (37)	
Sex			.005
Male	109 (48)	48 (68)	
Female	116 (52)	23 (32)	
Karnofsky score			.04
< 90	45 (20)	23 (32)	
≥ 90	163 (72)	44 (62)	
Not reported	17 (8)	4 (6)	
Median time from diagnosis to transplantation, mo (range)	13 (2-318)	11 (1-121)	.37
Time from diagnosis to transplantation, mo			.42
< 12	108 (48)	38 (54)	
≥ 12	117 (52)	33 (46)	
Conditioning regimen			< .001
TBI 200-800 cGy + Cy ± ATG ± fludarabine	136 (61)	32 (45)	
TBI ≥ 1200 + Cy ± ATG	16 (7)	3 (4)	
Busulphan or melphalan + fludarabine ± ATG	9 (4)	15 (21)	
Cy + ATG ± fludarabine	64 (28)	21 (30)	
Donor-recipient sex match			.010
Male-male	84 (37)	32 (45)	
Male-female	81 (36)	13 (18)	
Female-male	25 (11)	16 (23)	
Female-female	35 (16)	10 (14)	
Year of transplantation			.120
2000-2002	38 (17)	5 (7)	
2003-2005	80 (36)	29 (41)	
2006-2008	107 (48)	37 (52)	
GVHD prophylaxis			< .001
Cyclosporine + methotrexate ± other	135 (59)	15 (21)	
Cyclosporine ± other	19 (8)	13 (18)	
Tacrolimus	62 (28)	28 (38)	
Mycophenylate mofetil + other	0	1 (1)	
Tacrolimus + other	9 (4)	14 (20)	
Median follow-up of survivors, months	35 (3-111)	35 (3-61)	

Cy indicates cyclophosphamide.

Multivariate Cox proportional hazards regression models[10] were built with forward stepwise selection procedures and confirmed with backward stepwise selection procedures. All variables significant at levels ≤ .05 were included in the final models. Results are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The variable for graft type was held in all steps of model building. Individual covariates were entered as categorical variables: age (≤ 20 vs > 20 years), Karnofsky performance score (90-100 vs < 90), time from diagnosis to transplantation (< 12 vs ≥ 12 months), conditioning regimen (total body irradiation [TBI] vs non-TBI), GVHD prophylaxis (cyclosporine vs tacrolimus), and donor-recipient sex match (female donor/male recipient vs other). All P values are 2-sided. Analyses were done with SAS software, Version 9.2.

Results and discussion

Characteristics of the study population are shown in Table 1. There were differences between BM and PBPC recipients. PBPC recipients were older, more likely to be male, and more likely to have Karnofsky performance scores < 90. PBPC recipients were more likely to be transplanted after 2005 and to have received non-TBI conditioning regimens, ATG and tacrolimus. The median times

from diagnosis to HSCT and follow-up were similar for both groups.

Hematopoietic recovery

Although the median time to neutrophil recovery was faster after transplantation of PBPCs compared with BM (13 vs 19 days), probabilities of neutrophil recovery at day 28 (96% vs 90%) were similar (P = .13). The median time to platelet recovery was also faster after transplantation of PBPCs (18 vs 27 days) and the day 100 probability of platelet recovery higher than with BM (91% vs 81%, P = .02). The proportions of patients with secondary graft failure were 8% and 3% after transplantation of BM and PBPCs, respectively (P = .12).

Acute and chronic GVHD

Grades 2 to 4 acute GVHD risks were higher after transplantation of PBPCs compared with BM (HR = 1.68; 95% CI, 1.10-2.55, P = .02; Figure 1A). However, chronic GVHD risks were not significantly different in the 2 groups after adjusting for patient age (HR = 1.39; 95% CI, 0.90-2.16, P = .14; Figure 1B). Although the
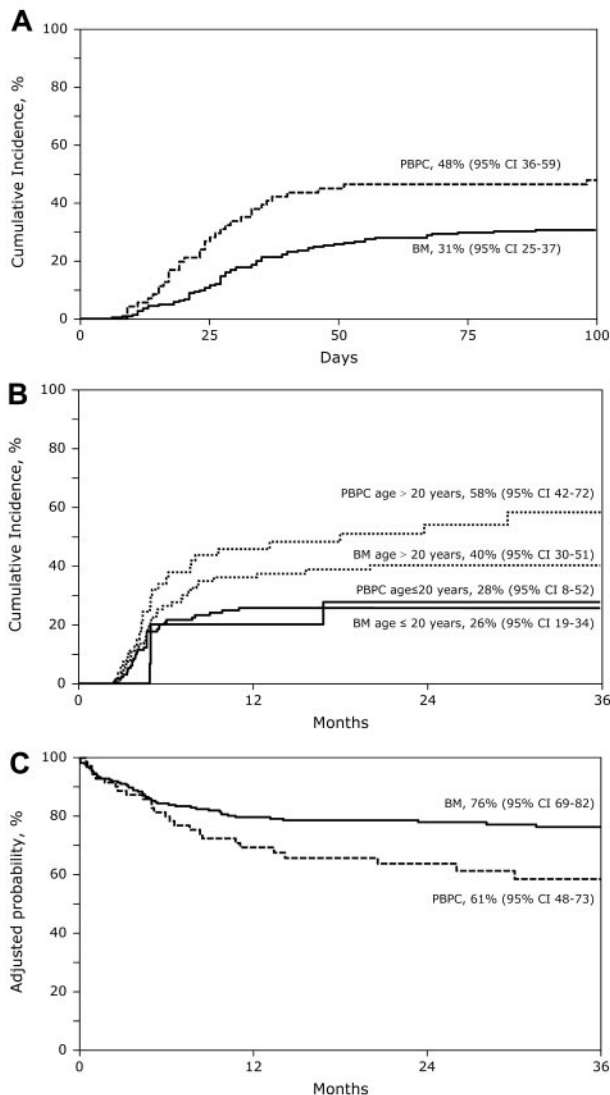
Figure 1. Acute and chronic GVHD and overall survival after transplantation of BM and PBPCs. (A) The day 100 cumulative incidence of grades 2 to 4 acute GVHD after PBPC and BM transplantation. Grades 2 to 4 acute GVHD risks were higher after transplantation of PBPCs compared with BM (HR = 1.68; 95% CI, 1.10-2.55, $P = .02$) and transplantation of either graft in male recipients from female donors (HR = 2.33; 95% CI, 1.45-3.57, $P = .0004$). (B) The 3-year cumulative incidence of chronic GVHD after PBPC and BM transplantation in patients younger than 20 years and 20 years or older at transplantation. After adjusting for age at transplantation, chronic GVHD risks were not different after transplantation of PBPC and BM (HR = 1.39; 95% CI, 0.90-2.16, $P = .14$). Risks were higher in patients older than 20 years (HR = 1.97; 95% CI, 1.29-3.01, $P = .002$). (C) The 3-year probabilities of overall survival after PBPC and BM transplantation, adjusted for performance score and transplant conditioning regimen. Overall mortality risks were higher after transplantation of PBPCs compared with BM (HR = 1.62; 95% CI, 1.01-2.58, $P = .04$), in patients with performance score less than or equal to 80 (HR = 1.93; 95% CI, 1.20-3.10, $P = .01$), and those who received non-TBI conditioning regimens (HR = 1.68; 95% CI, 1.08-2.62, $P = .02$). Mortality risks were higher in patients older than 20 years, although this did not reach statistical significance (HR = 1.61; 95% CI, 0.98-2.63, $P = .06$).

3-year probability of chronic GVHD for patients older than 20 was higher after PBPCs compared with BM transplantation, this difference was not statistically significant.

Overall mortality

Overall mortality risks were higher after transplantation of PBPCs compared with BM (HR = 1.62; 95% CI, 1.01-2.58, $P = .04$).

Other factors associated with higher mortality were poor performance score (HR = 1.93; 95% CI, 1.20-3.10, $P = .01$) and non-TBI conditioning regimens (HR = 1.68; 95% CI, 1.08-2.62, $P = .02$). The 3-year probabilities of overall survival, adjusted for these factors, were 61% after transplantation of PBPCs and 76% after BM ($P = .02$; Figure 1C). Despite faster neutrophil recovery, higher acute GVHD after PBPC transplantation contributed to excess mortality and lower overall survival compared with BM. However, mortality risks were higher in patients without platelet recovery (HR = 7.30, 95% CI, 3.76-14.29, $P < .0001$) regardless of graft type. The adverse effect on mortality of PBPC versus BM grafts in the HLA-matched sibling setting has been reported previously and is presumed secondary to higher rates of GVHD.[5,6]

Efforts to lower the acute toxicities and late malignancies associated with high-dose TBI-containing conditioning regimens[11-13] prompted the use of regimens with low-dose (200 cGy) TBI, cyclophosphamide, and ATG for transplantation in SAA.[14] Lowering the dose of TBI did not affect graft failure, and it improved survival rates, especially in patients 20 years of age or younger for whom survival rates now approach those after matched sibling transplantation. In the current analysis, mortality risks after non-TBI regimens were higher than with low-dose TBI regimens. The length of the interval between diagnosis and transplantation was not associated with survival in this study; however, all patients had received at least one course of IST. Data on courses of IST were not available. The most common causes of death were infection, pulmonary toxicity, and GVHD (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article); we did not observe differences in their distribution by graft type or conditioning regimen.

These data were not derived from a randomized trial; therefore, results may be influenced by the effect of unknown or unmeasured factors that influenced the choice of graft. However, the analyses are adjusted for factors known to have an adverse effect on mortality. Although we acknowledge a randomized trial will better define the role of PBPC grafts for SAA, these results cannot be ignored. Our analysis revealed 2 findings important for clinical practice. The first, the lower overall survival after PBPC transplantation, confirms BM is the preferred source of stem cells. The second, survival after matched unrelated donor BM transplantation, has improved substantially from 32% (before 1998) and 61% (before 2005) to 75% now, which is approaching that reported after HLA-matched sibling transplantation and after IST alone.

Authorship

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