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Influence of Stem Cell Source on Outcomes of Allogeneic Reduced-Intensity Conditioning Therapy Transplants Using Haploidentical Related Donors

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We compared outcomes for 2 retrospective cohorts of patients undergoing reduced-intensity conditioning (RIC) therapy transplants using haploidentical related donors and post-transplant prophylaxis against graft-versus-host disease (GVHD) with high-dose cyclophosphamide, tacrolimus, and mycophenolate. The first cohort of 13 was transplanted with bone marrow (BM) as the stem cell source, whereas the second cohort of 23 used peripheral blood stem cells (PBSCs) mobilized with granulocyte colony-stimulating factor. The BM cohort received a single 60-mg/kg dose of cyclophosphamide on day +3, whereas the PBSC cohort received 2 doses on days +3 and +4. Patients in the first cohort were slightly older and had a higher proportion of acute myeloid leukemia, but there were no differences in the distribution of Disease Risk Index scores between the 2 groups. Patients in the PBSC group received double the number of $CD34^+$ cells in the stem cell graft. Times to neutrophil and platelet recovery were not different between the 2 groups. Three patients, all in the PBSC group, failed to engraft but recovered with autologous hemopoiesis and survived. The 6-month cumulative incidences of acute GVHD were 55.1% for BM and 48.5% for PBSCs ($P = .651$), whereas 24-month cumulative rates for chronic GHVD were 28.6% for BM and 32.3% for PBSCs ($P = .685$). Only 2 patients, both in the BM group, died of nonrelapse causes, both of second cancers. The 2-year cumulative incidences of relapse were 43.9% for BM and 23.5% for PBSCs ($P = .286$). Overall survival at 2 years was significantly better for PBSC patients ($P = .028$), at 83.4% versus 52.7% for BM. Relapse-free and event-free survival did not differ significantly between BM and PBSC groups. In this retrospective analysis, we conclude that the use of PBSCs for haploidentical RIC transplants is a feasible strategy, with equivalent rates of acute and chronic GVHD and risk of relapse and low nonrelapse mortality compared with BM.

INTRODUCTION

Allogeneic hemopoietic cell transplantation (alloHCT) is widely used to treat a variety of serious hematological malignancies, bone marrow (BM) failure syndromes, immune deficiency states, and inherited disorders. The ideal stem cell donor is a sibling fully matched for HLA coded by the MHC located on chromosome 6. However, only around 30% of patients in need of an alloHCT have an HLA-matched sibling. A matched volunteer unrelated donor is frequently identified for patients lacking a matched relative, but the likelihood of finding a suitable unrelated donor is highly influenced by the ethnic background of the patient [1]. Alternative options for patients lacking HLA-matched related or unrelated donors consist of unrelated umbilical cord blood or relatives who share 1 HLA haplotype with the patient (haploidentical relatives) [2,3].

Historically, the use of haploidentical donors was associated with high risks of graft rejection and graft-versus-host disease (GVHD) [4]. However, the field of haploidentical alloHCT has been revolutionized in the last decade by the use of high-dose cyclophosphamide soon after stem cell infusion to delete alloreactive donor T lymphocytes infused with the stem cell graft, resulting in relatively low rates of graft rejection and GVHD [5,6]. Initially, BM harvested under

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general anesthesia from haploidentical relatives was used as the stem cell source [7-9]. However, more recently it has been reported that hemopoietic cells mobilized into the peripheral blood by administration of granulocyte colony-stimulating factor (G-CSF) to donors could be used safely in the context of haploidentical transplants [10,11].

We previously reported our experience of the use of haploidentical BM transplants in a small cohort of patients with hematological malignancies [9] and contributed to a multicenter series of cases given G-CSF–mobilized peripheral blood stem cells (PBSCs) from haploidentical relatives [10]. However, the relative toxicity and efficacy of the use of these 2 sources of haploidentical stem cells remains unclear. In this study we compare outcomes of haploidentical transplants using BM with an expanded cohort given G-CSF–mobilized PBSCs.

METHODS

Patient demographic and disease details are summarized in Table 1. The 12 patients in the BM cohort were previously reported [9]. An additional transplant was subsequently performed using BM, chosen instead of PBSCs because the donor had splenomegaly due to β-thalassemia trait. In the PBSC cohort, 10 patients were previously reported in a multicenter survey [10]; an additional 12 patients have subsequently been transplanted and are included in this report. All patients lacked HLA-matched siblings, and searches of international unrelated donor registries failed to identify a fully matched donor or did not locate a donor who was able to undergo stem cell collection within a clinically appropriate time frame. Searches of other family members identified at least 1 haploidentical match. Patients gave informed consent to undergo the procedure and for release of deidentified data.

Details of transplant procedures were previously published [9,10]. In brief, conditioning therapy consisted of the Baltimore nonmyeloablative protocol, with cyclophosphamide 14.5 mg/kg daily i.v. on days −6 and −5, fludarabine 30 mg/m^2 daily i.v. on days −6 to −2, and a single 2-Gy dose of total body irradiation on day −17. In virtually all cases, conditioning therapy and stem cell infusion were administered in the outpatient clinic. Hemopoietic cells, either harvested BM or PBSCs, were infused on day 0. All stem cell grafts were unmanipulated, with no processing to remove T lymphocytes and no peritransplant in vivo administration of anti–T cell antibodies.

Prophylaxis against GVHD consisted of cyclophosphamide 50 mg/kg i.v. daily, given on day +3 in the case of BM grafts or as 2 daily doses on days +3 and +4 in PBSC transplants, with an equivalent dose of mesna as urothelial prophylaxis. In all cases, this was followed on day +4 or +5, respectively, by oral tacrolimus, adjusted to produce a trough blood level of 5 to 15 ng/mL, and in the absence of GVHD tapered between days 90 and 180, and mycophenolate mofetil 15 mg/kg 3 times daily orally until day 35 and then weaned. Prophylaxis against infection consisted of ganciclovir 5 mg/kg i.v. on days −8 to −1 for cytomegalovirus (CMV)-seropositive patients, acyclovir 800 mg twice daily for herpes simplex–seropositive patients, fluconazole 400 mg daily as yeast prophylaxis, and penicillin and cotrimoxazole for pneumococcal and *Pneumocystis jiroveci* prophylaxis, respectively. Transfusions of RBC and platelet concentrates were given as clinically indicated. G-CSF 5 μg/kg was given daily subcutaneously from day +4 until neutrophil recovery to .5 × 10^9/L. Documentation of donor cell engraftment was carried out by DNA chimerism analysis of flow-sorted blood T lymphocytes and granulocytes, according to previously published methods [9].

The closeout date for survival analyses was March 31, 2015. The main outcome parameters examined were times to neutrophil and platelet count recovery, graft rejection, incidence and severity of acute and chronic GVHD, disease relapse, death without relapse, and overall, relapse-free, and event-free survival. Acute and chronic GVHD were graded as previously published [12,13]. Overall survival was calculated for all 36 patients. One patient in the BM group with acute myeloid leukemia (AML), who had a myelodysplastic relapse 49 months later, subsequently had a second haploidentical transplant; he was censored from the survival analyses at the time of second transplant. Three patients transplanted for nonmalignant conditions were excluded from analysis of relapse and event-free survival. Relapse-free survival was defined as survival without relapse or death without relapse, whereas event-free survival was defined as survival without graft rejection, relapse, or death without relapse. Competing factors for calculating cumulative incidences of GVHD were relapse and death without relapse, whereas for calculating cumulative incidence of relapse the competing factor was death without relapse. Survival was calculated according to the method of Kaplan and Meier [14].

Table 1
Patient Demographic and Disease Details

	BM Group (n = 13)	PBSC Group (n = 23)	Total (N = 36)
Median age, yr (range)	53 (27-63)	44 (23-69)	48 (23-69)
Sex, male/female	7/6	14/9	21/15
Diagnosis			
AML	10	9	19
NHL	2	4	6
ALL	0	4	4
MDS	0	2	2
HL	0	1	1
SAA	0	2	2
CML	1	0	1
Other	0	1	1
DRI*			
Low	3	1	4
Intermediate	6	15	21
High	4	4	8
Median CD34$^+$ cells × 10^6/kg recipient body weight (range)	2.5 (1.3-4.8)	5.8 (2.0-10.0)	
Median days to reach absolute neutrophil count, .5 × 10^9/L on 3 successive days (range)	15 (4-55)	16 (11-33)	
Median days to reach sustained platelet count of 20 × 10^9/L on 3 successive days without platelet transfusion for 7 days (range)	18 (1-66) (1 not achieved)	24 (1-45)	

NHL indicates non-Hodgkin lymphoma; MDS, myelodysplastic syndrome; HL, Hodgkin lymphoma; SAA, severe aplastic anemia; CML, chronic myeloid leukemia.

* Fisher's exact test for comparison of distribution of DRI categories in BM and PBSC groups, $P = .161$.

RESULTS

Thirty-six consecutive reduced-intensity conditioning (RIC) haploidentical transplants between April 2008 and October 2014 are included in this report. Details are provided in Table 1. Thirteen patients received BM grafts and 23 received PBSCs. Patients were aged between 23 and 69 years (median, 48 years); PBSC patients were slightly younger (median, 44 years; range, 23 to 69) than BM patients (median, 53 years; range, 27 to 63). Donors were siblings in 24 cases, sons in 6, daughters in 4, mothers in 2, and father in 1.

Nineteen patients had AML, 10 in the BM group and 9 in PBSC ($P = .029$). Six patients had non-Hodgkin lymphoma, 4 acute lymphoblastic leukemia (ALL) (3 were Philadelphia chromosome positive), 2 myelodysplastic syndrome, 2 severe aplastic anemia, and 1 each with Hodgkin lymphoma, chronic myeloid leukemia, and metachromatic leukodystrophy. Three patients had the haploidentical transplant as a rescue procedure after a failed first transplant; 2 were for graft rejection (rejection of a matched unrelated donor graft for severe aplastic anemia and rejection of a mismatched unrelated cord blood graft for metachromatic leukodystrophy), whereas one patient with Hodgkin lymphoma relapsed after a matched unrelated donor transplant and had a haploidentical transplant as salvage treatment. Of the 33 transplants for hematological malignancies, 4 were classified as low risk, 21 as intermediate, and 8 as high by the modified Disease Risk Index (DRI) criteria [15]. There were no significant differences in the distribution of DRI categories between BM and PBSC groups (Table 1). Patients receiving BM grafts were given a median CD34$^+$ cell dose of 2.5 × 10^6/kg (range, 1.3 to 4.8), whereas those receiving