Brief report

Long-term outcomes after transplantation of HLA-identical related G-CSF–mobilized peripheral blood mononuclear cells versus bone marrow

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Between 1996 and 1999, 172 patients (median age, 42 years) with hematologic malignancies were randomly assigned to receive either HLA-identical related bone marrow or G-CSF–mobilized peripheral blood mononuclear cells (G-PBMCs) after myeloablative conditioning. Early results showed that transplantation of G-PBMCs, compared with marrow, was associated with significantly superior 2-year disease-free survival (DFS) and overall survival. Ten-year follow-up showed a sustained DFS benefit associated with G-PBMCs (mortality or relapse hazard ratio, 0.64; 95% confidence interval, 0.4-1.0; *P* = .03), although the likelihood of overall survival was not significantly different between the 2 groups (mortality hazard ratio, 0.75; 95% confidence interval, 0.5-1.2; *P* = .20). The 10-year cumulative incidence of chronic GVHD and the duration of systemic immunosuppression were similar in the 2 groups. In summary, transplantation of HLA-identical related G-PBMCs, compared with marrow, was associated with superior short-term and long-term DFS, and there was no evidence that this benefit was outweighed by GVHD-related late mortality. (*Blood*. 2012;119(11): 2675-2678)

Introduction

Because of ease of collection, faster hematopoietic recovery, and improved short-term survival, G-CSF–mobilized peripheral blood mononuclear cells (G-PBMCs) have become the preferred source of hematopoietic stem cells for matched related allogeneic hematopoietic cell transplantation (HCT).[1] In most comparative studies with bone marrow, however, long-term transplantation outcomes associated with these 2 stem cell products have yet to be reported. Although evidence has suggested that the use of G-PBMCs is associated with an increased risk of chronic graft-versus-host disease (GVHD), the net impact of this complication on long-term outcomes has not been fully delineated.[2-9] Early results of our randomized 3-institution study between HLA-identical related G-PBMCs and marrow for HCT after myeloablative conditioning for patients with hematologic malignancies showed that transplantation of G-PBMCs was associated with significantly superior rates of 2-year overall survival (OS) and disease-free survival (DFS).[8] To assess the longer-term impact of chronic GVHD on outcomes, we analyzed follow-up data from all participating patients and found that transplantation of G-PBMCs conferred sustained protection against relapse, and there was no evidence that this benefit was outweighed by GVHD-related late mortality.

Methods

Patients

Full details of the study design have been reported previously.[8] In brief, between 1996 and 1999, 172 patients (median age, 42 years; range, 12-55 years) with hematologic malignancies were randomly assigned to receive either marrow or G-PBMCs from HLA-identical relatives after myeloablative conditioning. The trial was conducted by the Fred Hutchinson Cancer Research Center (n = 137), City of Hope National Medical Center (n = 20), and Stanford University Medical Center (n = 15), and eligible patients and donors gave written informed consent in accordance with the Declaration of Helsinki with approval from all participating centers. Patients were eligible for the study if they had a hematologic malignancy for which allogeneic HCT with marrow or G-PBMCs from an HLA-identical, related donor who was at least 12 years of age was indicated, provided that no comorbidities were present that precluded the use of a myeloablative preparative regimen.

Patients were stratified according to treatment center, age ($\leq$ 30 or $>$ 30 years), and stage of malignancy (standard-risk or high-risk). Standard-risk hematologic malignancies were defined as acute leukemia in first remission; chronic myeloid leukemia (CML) in chronic phase; lymphoma in first remission, untreated first relapse, or second remission; and refractory anemia without excess blasts. All other stages of these malignancies and all other types of hematologic malignancies were considered high risk.

Disease-specific conditioning regimens were administered before HCT, according to the usual protocols at each institution and included high-dose chemotherapy with or without total body irradiation (total dose, 12-13.5 Gy). Methotrexate and cyclosporine were given for the prevention of GVHD after transplantation.[10] The primary endpoint of the original study was grade 2 to 4 acute GVHD.

Statistical methods

All comparisons were performed according to the intention-to-treat principle. OS was estimated according to the Kaplan-Meier method.[11] The cumulative rates of acute and chronic GVHD, nonrelapse mortality (NRM), and discontinuation of all systemic immunosuppression were computed according to the method described by Kalbfleisch and Prentice.[12] The statistical significance of differences

Submitted December 1, 2011; accepted January 24, 2012. Prepublished online as *Blood* First Edition paper, February 3, 2012; DOI 10.1182/blood-2011-12-396275.

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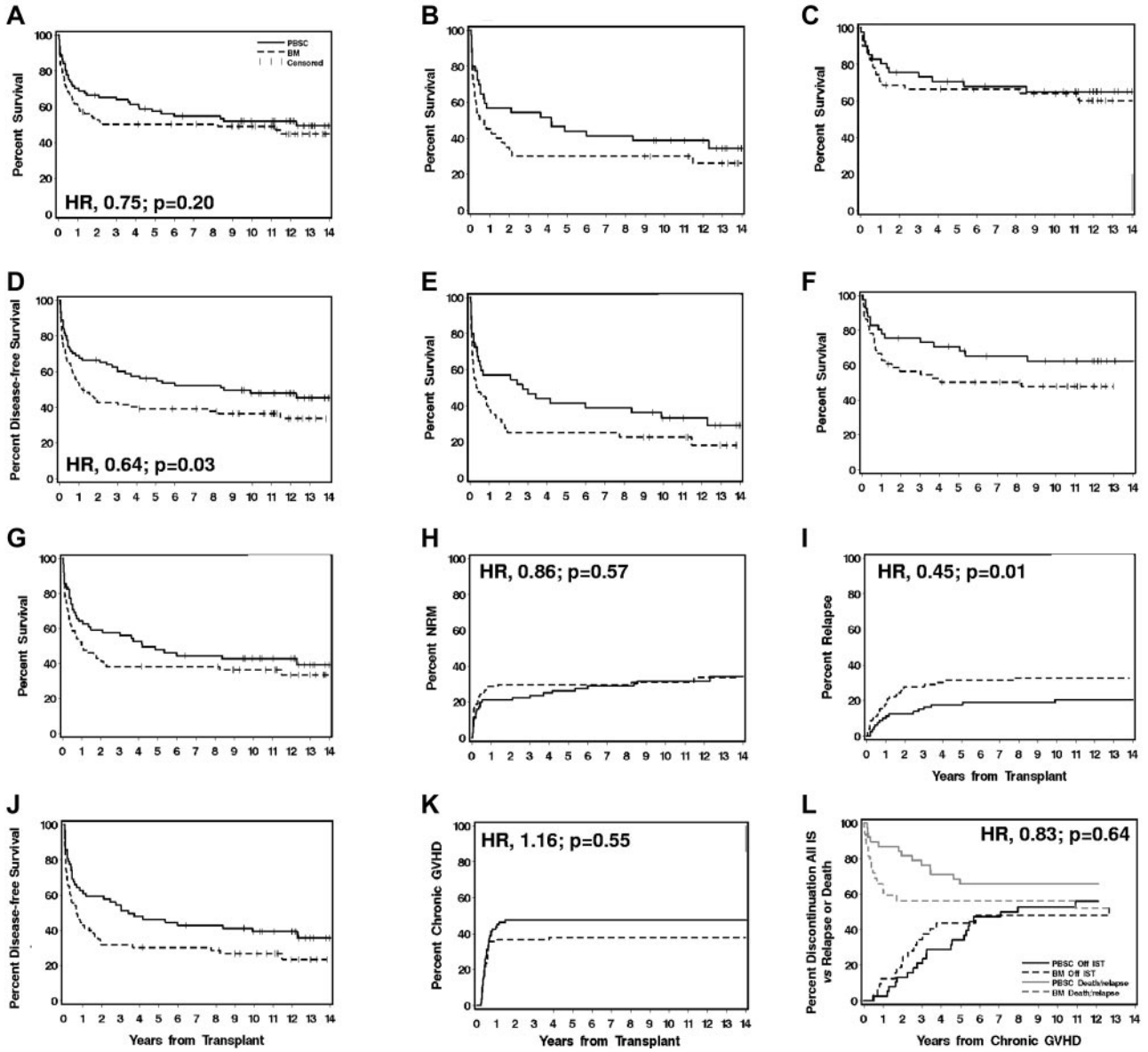

Figure 1. Long-term outcomes after transplantation of G-PBMCs (n = 81) or bone marrow (n = 91) from HLA-identical siblings after myeloablative conditioning.[8] Kaplan-Meier estimates of OS among all patients (A), and among those with high-risk malignancies (B) and standard-risk malignancies (C); DFS among all patients (D), and among those with high-risk malignancies (E) and standard-risk malignancies (F). (G) OS and (J) DFS after exclusion of 47 patients transplanted for CML in chronic phase. Also shown are cumulative incidence curves of NRM (H), relapse (I), extensive chronic GVHD (K), and discontinuation of all immunosuppressive treatment (L; lower 2 curves). The competing risks of relapse and death are shown in the upper 2 curves. Also shown are the adjusted HRs for respective outcomes using marrow recipients as the reference group. Solid line indicates G-PBMC group; and hyphenated line, bone marrow group.

in the endpoints between the 2 groups was calculated with use of the likelihood-ratio statistics for proportional-hazards regression models, with stratification on disease risk, age, and institution, and hazard ratios (HRs) were estimated from these models. All *P* values are 2-sided.

Results and discussion

Our initial analysis was performed after a median follow-up time of 2.2 years.[8] The results showed that transplantation of G-PBMCs, compared with that of marrow, resulted in higher rates of OS and DFS. The superior survival in the G-PBMC group was largely explained by better protection against relapse, an effect that was more pronounced among patients with high-risk malignancies than among those with standard-risk malignancies. Subsequent detailed analyses of outcomes pertaining to chronic GVHD (median follow-up, 3.4 years) showed that, although the 2-year cumulative incidence of chronic GVHD was similar in the 2 groups, the number of successive glucocorticoid treatments was higher and the overall duration of treatments was longer after transplantation of G-PBMCs compared with marrow.[5]

The present analysis was performed after a median follow-up time of 12.2 years. The results showed sustained protection against relapse and superior DFS associated with the use of G-PBMCs compared with marrow (Figure 1). The estimated 10-year probability of relapse was 20% with G-PBMCs and 32% with marrow (HR for G-PBMCs vs marrow, 0.45; 95% confidence interval [CI], 0.2-0.8; $P = .01$). In contrast to the earlier analysis, the likelihood of OS for all patients was not significantly different between the 2 groups (mortality HR, 0.75; 95% CI, 0.5-1.2; $P = .20$). The smaller difference in OS may be explained by successful treatment

Table 1. Causes of deaths according to time of event (≤ 3 years after transplantation vs > 3 years after HCT)

	≤ 3 y after HCT		> 3 y after HCT	
Cause of death	**G-PBMC (N = 81)**	**BM (N = 91)**	**G-PBMC (N = 51)**	**BM (N = 48)**
Nonrelapse				
Noninfectious pneumonia	7	13	0	0
Sinusoidal obstruction syndrome	1	1	0	0
Multiorgan failure	2	2	0	0
Hemorrhage	1	1	0	0
Cardiac failure	1	1	0	0
GVHD with or without infection	3	3	5	1
Infection (without concurrent GVHD)	4	6	0	2
Secondary cancer	0	0	0	1
Other	0	0	0	1
Relapse	11	16	3	1
Total	30	43	8	6

Overall, 5 of 172 patients were not treated per intent. The results for these patients were included in the intention-to-treat analysis according to their randomly assigned treatment. Two patients randomized to BM received G-PBMC, and 3 patients randomized to G-PBMC received BM; the latter 3 patients experienced late NRM (infection without GVHD, n = 2; pancreatitis, n = 1). Because of the small number of late (> 3 years after HCT) deaths, Table 1 shows causes of deaths according to types of stem cell product given (not based on intention to treat). Causes of late deaths were determined by retrospective review of medical records. In the G-PBMC group, causes of late NRM were bacterial pneumonia (n = 3), sepsis (n = 1), and bronchiolitis obliterans without apparent infection (n = 1). In the BM group, causes of late NRM were sepsis (n = 2), ovarian cancer (n = 1), pancreatitis (n = 1), and systemic sclerosis without apparent infection (n = 1).

of relapse and durable second remission in some patients who received marrow, and by a few excess late (> 3 years after HCT) deaths among patients randomized to G-PBMCs. The conclusion that, compared with marrow, transplantation of G-PBMCs was associated with sustained protection against relapse and superior DFS was not changed after exclusion of all patients with CML in chronic phase (n = 47) from the analysis (Figure 1J). In keeping with the earlier analyses, the 10-year cumulative incidence of chronic GVHD requiring systemic immunosuppressive treatment was not significantly different between the 2 groups (48% with G-PBMCs and 37% with marrow; HR, 1.16; 95% CI, 0.7-1.9; $P = .55$). We also found no evidence that the use of G-PBMCs prolonged the duration of systemic immunosuppressive treatment in patients with chronic GVHD (HR for discontinuation of systemic immunosuppression, 0.83; 95% CI, 0.4-1.8; $P = .64$).

Although the incidence of late NRM based on intention to treat was higher among patients randomized to G-PMBCs (late deaths, 8 vs 2), the interpretation of this result is complicated by the fact that 3 of the patients randomized to G-PBMCs and experiencing late NRM actually received marrow. Analysis of late NRM according to the actual types of stem cell products given showed that the incidence of late NRM was the same in the 2 groups (Table 1). The results suggested, however, that late NRM attributable to chronic GVHD might have occurred more frequently after HCT with G-PBMCs than with marrow (late nonrelapse deaths with/of GVHD: 5 among G-PBMC recipients vs 1 among marrow recipients).

Very few studies have compared long-term HCT outcomes with G-PBMCs versus marrow. Schmitz et al reported long-term (median follow-up, > 6 years) outcomes in retrospective evaluation of HLA-identical related HCT for treatment of leukemia.[7] The use G-PBMCs was associated with an increased risk of chronic GVHD among all patients and with superior DFS among patients with advanced CML (33% vs 25%), but not among those with early-stage CML (41% vs 61%). Among patients with acute leukemia, DFS in the 2 groups was similar. More recently, Friedrichs et al analyzed long-term (median follow-up, 10.8 years) outcomes from a randomized study comparing HCT with HLA-identical related G-PBMCs versus marrow and showed that OS and DFS in the 2 groups were similar.[9] The incidence of chronic GVHD and the proportion of patients continuing immunosuppressive treatment at 5 years, however, were higher with G-PBMCs than with marrow. No statistically significant difference was found in performance status, return to work, incidence of bronchiolitis obliterans, OS, or DFS between the 2 groups.

The power to detect possible long-term survival differences of smaller magnitude was limited by the low number of late deaths (total, n = 14; NRM, n = 10) in our trial. Within these limitations, we conclude that HCT with HLA-identical related G-PBMCs, compared with marrow, was associated with superior short-term and long-term DFS, a benefit that was not observed in a similar study with unrelated donors and a median follow-up of 3 years.[13] We found no statistically significant evidence that this benefit was outweighed by GVHD-related late mortality.

Acknowledgments

The authors thank Helen Crawford for assistance with manuscript preparation; the physicians, nurses, physician assistants, nurse practitioners, pharmacists, and support staff who cared for their patients; and the patients who participated in this clinical trial.

This work was supported by the National Institutes of Health (grant R01 HL108307, M.M.; grants P01 HL036444 and P01 CA018029, R.S.; and grant P30 CA015704) and the Cuyamaca Foundation (M.M.). Y.I. is a recipient of the Japan Society for the Promotion of Science Postdoctoral Fellowships for Research Abroad.

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Authorship

Contribution: M.M. analyzed and interpreted data and wrote the manuscript; B.S. performed statistical analysis; W.I.B., S.J.F., R.S.N., and F.R.A. designed the original trial; and P.J.M., S.J.F., R.S.N., M.E.F., Y.I., T.R.C., R.S., and F.R.A. assisted with data interpretation and edited the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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