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Bone marrow is associated with better patient-reported outcomes than peripheral blood in survivors 5 years after unrelated donor transplantation

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Authorship

SJL and BL designed the study. BL performed the statistical analysis. SJL drafted the manuscript. All authors interpreted the data and critically reviewed the manuscript for important intellectual content. MMH obtained funding.

Trial registration: NCT00075816

Conflict-of-interest disclosure

The authors declare no competing financial interests related to this study.

Abstract

Objective—Compare patient-reported outcomes between people randomized to receive one of two graft types for unrelated donor transplantation.

Design—Patient reported outcomes were collected from patients > 16 years old at enrollment and 0.5, 1, 2 and 5 years after transplantation.

Setting—Randomized, controlled, multicenter clinical trial.

Participants—English- or Spanish-speaking, age 16 years or older, participating in randomized trial of unrelated donor bone marrow vs. peripheral blood (N=551) in hematopoietic cell transplantation for hematologic malignancies.

Intervention—n/a

Main outcomes and Measures—Functional Assessment of Cancer Therapy – Bone Marrow Transplant, Mental Health Inventory, occupational functioning, Lee Chronic Graft-versus-Host Disease Symptom Scale.

Results—At 5 years after transplantation, 102 BM and 93 PB participants were alive and eligible for assessment. The mean Mental Health Inventory Psychological Well-Being scores (78.9 vs. 72.2, p=0.011, higher better) and the mean Lee chronic graft-versus-host disease (GVHD) symptom scores (13.1 vs. 19.3, p=0.004, lower better) are significantly better for bone marrow recipients, adjusting for baseline scores and missing data. Recipients of bone marrow were also more likely to be working full or part-time than recipients of peripheral blood (RR 1.5, 95% CI 1.2-2.0, p=0.002), adjusting for work status before transplantation. With a median follow up of 73 months for survivors, no differences in survival, relapse or treatment-related mortality between bone marrow and peripheral blood are observed.

Conclusions and Relevance—Recipients of unrelated donor bone marrow have better psychological well-being, less burdensome chronic GVHD symptoms, and are more likely to return to work than recipients of peripheral blood at 5 years after transplantation. Bone marrow should be the standard of care for these types of transplant procedures.

Introduction

More transplants are performed from unrelated donors than related donors according to statistics from the Center for International Blood and Marrow Transplantation (CIBMTR). More than 80% of transplants from unrelated donors currently use peripheral blood (PB) instead of bone marrow (BM). In 2012, the primary results of a large, multicenter, randomized study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) showed similar survival, non-relapse mortality and relapse using the two graft sources. There was a higher rate of graft failure with bone marrow (9% vs. 3%, p=0.002) and a higher rate of chronic graft-versus-host disease (GVHD) with peripheral blood (53% vs. 41%, p=0.01).[1] Since 2012, there has been no change in the proportion of PB grafts being used for unrelated donor transplantation, with greater than 80% PB, including for patients with early stage disease such as acute leukemia in first complete remission (M Horowitz, CIBMTR data, personal communication).

This study also included a patient-reported outcomes (PRO) component that has not been reported before. The PRO data collection was incorporated in recognition that knowledge about the quality of life (QOL), symptoms, and functional well-being associated with each graft source would be valuable information to help inform future patients and their physicians when choosing a graft source.

Methods

Participants

Patients enrolled in the parent BMT CTN 0201 study were eligible for participation in the patient-reported endpoints substudy if they were 16 years or older, could communicate in English or Spanish and had access to a telephone. Exclusion criteria included inability to participate in interviews due to cognitive, linguistic or emotional difficulties and current uncontrolled psychiatric illness. Five hundred and seventeen trial participants met these criteria and were included in the QOL study.

Study Design

The parent study was a randomized, open label, phase III, multicenter trial with a primary endpoint of two-year survival by intent-to-treat analysis. Enrollment began on March 31st, 2004 and ended on September 9th, 2009. Eligibility included age up to 66 years, acceptable organ function and a diagnosis of acute and chronic leukemia, myelodysplasia, or myelofibrosis. Unrelated donors were 5/6 or 6/6 matched at HLA-A, B and DRB1. Exclusion criteria included donor-specific antibodies, prior allogeneic or autologous transplants, HIV infection, pregnant or breastfeeding, with an active infection, or concomitant enrollment on phase I studies. Patients received one of four myeloablative or reduced intensity conditioning regimens and one of two GVHD prophylaxis regimens (methotrexate plus tacrolimus or cyclosporine), specified prior to randomization. Randomization was stratified based on transplant center and disease risk.

After written consent, contact information for participants was faxed to a central site for contact by the QOL data collection team. Participants were mailed a packet of materials from a central interview center then contacted by phone to collect responses. Interviews were conducted in English or Spanish. There was no allowance for paper or online completion of the instruments. Data were entered electronically by interviewers. Several attempts were made to contact participants prior to transplant. Post-HCT assessment times were 6 months, 1 year, 2 years and 5 years.

The research protocol was approved by a protocol review committee of the National Heart, Lung and Blood Institute (NHLBI), and by the relevant institutional review boards or ethics committees. A Data and Safety Monitoring committee of the NHLBI provided oversight. All prospective donors and recipients gave written informed consent. This study is registered with ClinicalTrials.gov, number NCT00075816.

Data Collection Instruments

Participants completed several validated patient-reported measures at all assessment points except as noted below. The Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) is a 37-item instrument composed of the FACT-G and transplant-specific subscale. The FACT-G is comprised of 4 domains, physical (7 items), social (7 items, including sexual satisfaction), emotional (6 items) and functional (7 items, including work, sleep and leisure activities). The transplant-specific module has10 scored items, addressing appetite, appearance, mobility, and fatigue.[2,3] Higher scores indicate better functioning. The published clinically important difference is 7-9 points based on the distribution method.[3,4] The Trial Outcome Index (TOI) is composed of the physical, functional, and transplant-specific modules.[5]

The Mental Health Inventory (MHI) is a 38 item scale divided into two summary scores (Psychological Well-Being [14 items, higher scores are better] and Psychological Distress [24 items, lower scores are better]) and five subscales that measure anxiety, depression, positive affect, emotional ties, and loss of behavioral and emotional control; it includes the entire mental subscale of the SF36). As transplantation is associated with both positive and negative psycho-emotional sequelae, it is important that the instrument detects both.[6]

The Lee Chronic GVHD symptom scale is a 30 item scale that measures degree of bothersome symptoms in skin, energy, lung, nutrition, psychological status, eye and mouth, and provides a summary score. Scores for each domain are converted to a 0-100 scale where higher scores indicate more bother. The published clinically important difference is 6-7 points based on the distribution method.[7,8] The chronic GVHD symptom scale was not collected at enrollment since no patient had chronic GVHD before HCT.

Additional questions collected self-assessed Karnofsky performance status, overall health and overall QOL, (excellent, very good, good, fair, poor) and a rating scale for overall QOL (where 0 equals death and 100 equals perfect quality of life). Occupational health was measured using 6 items that assess current job status, type of work (captured using Hollingshead categories), number of hours of paid and unpaid work, school attendance, importance of work and change in work goals.[9]

Additional information on late effects and outcomes after three years for participants were retrieved from the Center for International Blood and Marrow Transplant (CIBMTR) database.

Statistical Analyses

Four primary PRO measures were pre-specified for analysis, the FACT Trial Outcome Index, the MHI Psychological Well-Being, MHI Psychological Discomfort, and the Chronic GVHD Symptom Score.

An analysis of the mean QOL among survivors accounting for missingness was performed using the method of Kurland and Heagerty.[10] The missing data was modeled among survivors at each time point using stepwise logistic regression considering baseline

demographics, QOL at baseline or at the prior time point, concurrent clinical issues including development of chronic GVHD or relapse prior to the assessment time, as well as occurrence of death or relapse within 6 months post assessment time. The treatment group was forced into the model, and interactions with each variable were checked and included if significant. These logistic regression models were used to predict probabilities of missing data for each patient; these were used as inverse weights in a weighted least squares analysis of QOL at each time point. For time points after baseline, the baseline QOL measurement was included as a predictor in the outcome model, except for the chronic GVHD symptom tool which was not available at baseline. The resulting estimated means, standard errors, and p-values are reported. Robustness of the results to missing data was examined by also considering several multiple imputation approaches. First we considered a Missing at Random (MAR) assumption for imputation. Next we identified the mean shift in imputation distributions that would change the significance of the results under a Not Missing at Random (NMAR) assumption (a tipping point analysis).

For each scale, the “clinically meaningful difference” was calculated using a distribution-based approach, which is half the standard deviation of the population.[11-13] The clinically meaningful difference is the difference in QOL that would prompt adoption of an intervention or a change in practice because it has been established to be “noticeable” or “meaningful” to patients.

A weighted logistic regression model was used to compare the likelihood of working full-time or part-time between the graft types, adjusted for baseline work status and using inverse weights from the missing data model.

Results

Participant characteristics and enrollment assessments

Table 1 shows the characteristics of responders and non-responders at enrollment and five years. The response rate at enrollment was 71-73% (eTable 1). At enrollment, functional well-being, FACT-G total, and the Health Rating Scale were all significantly higher in the BM group ($p<0.05$), although none of these had $p<0.01$.

The QOL database is complete for 5 year follow up and was sealed as of 5/26/2015. The patient clinical database was updated using long-term follow up data as of June 30, 2015.

Six month through two year assessments

Response rates at 0.5, 1 and 2 years were 28-43% of survivors. There were no differences in any of the primary scores in the first two years after HCT using univariate comparisons, although missing data severely limit conclusions during this period. The chronic GVHD skin score was higher in the BM group ($p=0.009$) at 6 months, and the chronic GVHD mouth score was higher in the PB group at 2 years ($p=0.034$). There were no additional differences (data not shown).

Five year primary endpoints

The response rate was 74%-78% of survivors for each instrument (eTable 1). Missing PRO data at five years was associated with younger age and high risk disease, but not graft source (OR 1.05, p=0.89). At 5 years, the FACT-Trial Outcome Index (TOI), the MHI Psychological Well-Being, and the cGVHD symptom scale scores are all significantly better for BM compared to PB patients in univariate comparisons, although only the latter two are still significant after adjustment for multiple testing ($p<0.0125$ because of 4 primary QOL variables, Table 2). Results were similar when tested in multivariate models adjusting for baseline patient-reported scores and also imputing missing values based on patient characteristics (Table 3). Table 3 also provides the clinically significant difference for each measure. Although none of the observed differences in the scales clearly exceed the clinically significant difference when missing data were handled by inverse probability weighting, the limited overlap in the confidence intervals suggests that the observed differences are clinically meaningful. Multiple imputation of missing data under MAR generally led to slightly larger effects than inverse probability weighting, and the tipping points are fairly large for MHI Psychological Well-Being (5 points) and for the cGVHD symptom scale score (12 points), indicating that these findings are quite robust. (Table 3)

We explored whether inclusion of chronic GVHD variables in the multivariate models abrogated the statistical differences, which, if true, would suggest that the observed differences may be due to chronic GVHD. PRO differences remained significant in these models when chronic GVHD incidence and moderate-severe severity were included in the models (data not shown). However, when additional details about transplant-center reported organ involvement (specifically chronic GVHD of the skin, eye, and musculoskeletal system, and avascular necrosis) were included in the model, none of the PROs remain significantly different between BM and PB (eTable 3). These results suggest that chronic GVHD-associated complications accounted for the observed PRO differences between BM and PB, but that overall incidence and global severity information does not fully capture these deficits. A diagnosis of chronic GVHD was highly associated with patient-reported chronic GVHD symptoms but not with QOL or psychological status (eTable 4).

We explored predictors of PRO scores at five years. Results suggested that some baseline variables (age, gender, co-existing diseases, primary diagnosis, and baseline scores) were predictive of 5 year PROs, but no potentially modifiable factors other than graft type (eTable 5). In particular, interval from diagnosis to transplant, GVHD prophylaxis, conditioning regimen, HLA mismatching, and use of anti-thymocyte globulin were not significant predictors.

With a median follow up of 73 months for survivors, no differences between BM and PB were observed for all trial participants in survival (40% vs. 39%, p=0.84, Figure), relapse (32% vs. 29%, p=0.47) or treatment-related mortality (29% vs. 32%, p=0.44) were observed.

Five year secondary endpoints

At 5 years after transplant, the percentage of return to full or part time work for surviving and responding participants was 52% for BM and 40% for PB. Likelihood of working full or

part time outside the home at five years was higher for BM recipients (OR 1.5, 95% CI 1.2-2.0,p=0.002) adjusted for work status before HCT and missing data based on graft source, disease risk, and age, using inverse probability weighting. Of the 7 chronic GVHD subscales, symptoms in the eye, lung, and energy were significantly better with BM ($p<0.01$, eTable 2). There was a trend towards better functional well-being, FACT summary scores, higher health rating scale scores and perception of overall QOL in the BM group (all $0.01<p<0.05$).

Of the 5 year survivors, 72 (71%) receiving BM had no active chronic GVHD compared with 46 (49%) of PB recipients, with lower rates of mild (17% vs. 23%), moderate (9% vs. 17%) and severe (4% vs. 9%) favoring BM (p=0.03). A higher proportion of PB recipients experienced skin sclerosis (18% vs. 8%, p=0.03), eye GVHD (33% vs. 15%, p=0.002), and musculoskeletal involvement (15% vs. 3%, p=0.003). There were no statistically significant differences in the reported incidence of mouth, lung or gastrointestinal chronic GVHD ($p>0.05$). There was a higher incidence of avascular necrosis with PB (15% vs. 5%, p=0.02). No differences were detected in myocardial infarction, congestive heart failure, diabetes, hypothyroidism, dialysis, seizures, or cataracts. There were no secondary endpoints for which PB was better.

Discussion

This large, multicenter, randomized trial showed similar two- and five-year survival between people randomized to receive unrelated BM compared to those randomized to receive PB. While there was an increase in graft failure with BM (9% vs. 3%, p=0.002) there was a higher rate of chronic GVHD with PB at 2 years (53% vs. 41%, p=0.01).[1] Analyzing PROs collected from participants throughout the five years, we observed better psychological well-being, less burdensome chronic GVHD symptoms, and a 50% higher likelihood of returning to full or part time work in the BM recipients compared to PB recipients. There were no patient-reported endpoints for which PB was superior.

The reason for the improved self-reported health and well-being of BM recipients is unclear. We hypothesized that chronic GVHD might explain the difference. However, within the limits of the trial data collection and statistical models, we were not able to attribute the differences either to the occurrence or overall severity of chronic GVHD as measured in the study. However, patient-reported symptoms, center-reported chronic GVHD organ involvement, and avascular necrosis were greater for PB than BM, and a model that adjusted for chronic GVHD organ involvement and avascular necrosis abrogated the difference between BM and PB, suggesting that clinical chronic GVHD morbidity was worse with PB and may account for the observed PRO differences.

Patients randomized to bone marrow were more likely to return to full- or part-time work than patients receiving peripheral blood. The importance of work to family finances, insurance coverage, societal reintegration, and perceptions of health has been reported in transplantation survivors, and this metric adds an important dimension to how successful transplantation is defined. [13-21]

There are number of limitations to the study. Although the response rates were very high (greater than 75%) for the enrollment and five year assessments, a quarter of people did not provide patient-reported information at these timepoints. We addressed this limitation through modeling of missing data and a tipping point analysis which showed that the conclusions for MHI well-being and chronic GVHD symptoms were robust, in that the missing data would have to be completely opposite to the available data in order to change the conclusions. In contrast, for MHI Distress, the tipping analysis was less robust, only partially assuaging concern about potential non-responder bias since a smaller shift in non-responders' reports could result in lack of significant findings. Second, response rates at 6 months, 1 year and 2 years were much lower at 28-43% compromising our ability to confidently comment on these time points. In retrospect, the central data collection mechanism during this time was suboptimal and exacerbated by the demands on patients of the early recovery period, particularly at 6 months. Thus, we are only confident about our results at enrollment and 5 years, leaving a large section of time without accurate patient-reported experiences. Third, we administered validated instruments to participants. While these have the advantage of demonstrated reliability and validity, some information is inevitably lost by not collecting qualitative information about participants' QOL and functioning. The interviews already took 30-45 minutes and it was not felt that we could extend the time longer to collect more detailed information. Fourth, allowed GVHD prophylaxis only included calcineurin inhibitors, methotrexate and ATG. Novel approaches such as post-transplant cyclophosphamide and novel agents were not studied. Clinical trials of novel conditioning and GVHD prophylaxis regimens may require PB. Finally, this study focuses on PROs reported by patients. Studies of donors suggest that bone marrow harvests result in a longer recovery period than PB, although with time donors of both graft types achieve similar recovery.[22]

To date, the primary two-year results of the clinical trial have not resulted in any noticeable change in clinical practice with more than 80% of unrelated donor transplantations using PB. Explorations of potential reasons for continued frequent use of PB are the subject of ongoing studies. We hypothesize that several factors may contribute to the continued preference of PB despite a higher rate of chronic GVHD. First, ongoing clinical trials may require PB based on historical data for time to engraftment and GVHD since that has been the standard for the last few years. Second, clinicians may be worried about the higher rate of graft failure or delayed engraftment, both observed in our trial, or a higher rate of relapse, which was not observed in our trial but was seen with some prior studies. Third, donating PB is associated with a shorter duration of symptoms than donating BM so donors may prefer to give PB, although large donor studies suggest that almost all donors recover completely with time.[22]

In summary, patients randomized to receive BM instead of PB have better psychological well-being, fewer chronic GVHD symptoms, and are more likely to return to work although survival, relapse and treatment-related mortality are similar. The failure to see an increase in the proportion of HCTs using BM means that the clinical results published in 2013 were not compelling enough to change management of these patients. It remains to be seen whether the additional information provided by this study will be judged sufficient to recommend

BM instead of PB for unrelated donor transplantation when performed for the indications and using the approaches included in this study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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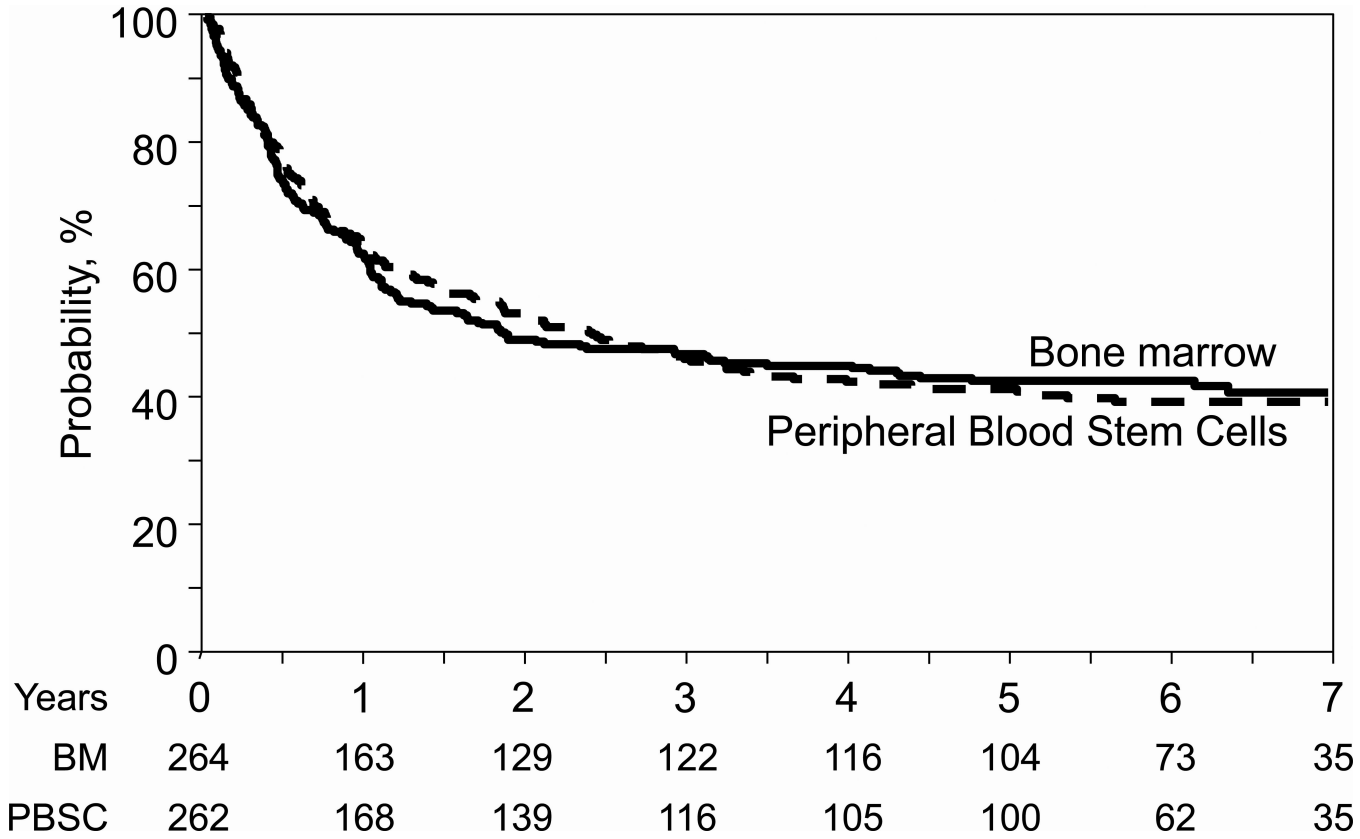

Figure 1.
Overall Survival

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Table 1

Characteristics of responders and non-responders at enrollment and 5 years

	Enrollment, pre-HCT			5 year assessment		
	Responders N=395	**Non-responders N=122**	**p-value**	**Responders N=152**	**Non-responders N=43**	**p-value**
Graft source, n (%)			0.82			0.87
Bone marrow	199 (50.4)	60 (49.2)		80 (52.6)	22 (51.2)	
Peripheral blood	196 (49.6)	62 (50.8)		72 (47.4)	21 (48.8)	
Diagnosis, n (%)			0.56			0.99
Acute myeloid leukemia	193 (48.9)	54 (44.3)		70 (46.1)	19 (44.2)	
Acute lymphoblastic leukemia	71 (18.0)	29 (23.8)		29 (19.1)	7 (16.3)	
Chronic myeloid leukemia	51 (12.9)	14 (11.5)		24 (15.8)	8 (18.6)	
Myelodysplastic syndrome	68 (17.2)	23 (18.9)		27 (17.8)	8 (18.6)	
Chronic myelomonocytic leukemia	12 (3.0)	2 (1.6)		2 (1.3)	1 (2.3)	
High risk disease, n (%)	102 (25.8)	47 (38.5)	0.007	24 (15.8)	14 (32.6)	0.014
Age ≥ 40, n (%)	245 (62.0)	72 (59.0)	0.55	89 (58.6)	15 (34.9)	0.006
Male, n (%)	221 (55.9)	70 (57.4)	0.78	79 (52.0)	22 (51.2)	0.93
White race, n (%)	339 (85.8)	101 (82.8)	0.41	136 (89.5)	36 (83.7)	0.30
Karnofsky performance score			<0.001			0.82
≥90%, n (%)	245 (62.0)	55 (45.1)		101 (66.4)	31 (72.1)	
<90%, n (%)	108 (27.3)	32 (26.2)		39 (25.7)	9 (20.9)	
Missing	42 (10.6)	35 (28.7)		12 (7.9)	3 (7.0)	
Conditioning regimen			0.73			0.76
Cyclophosphamide/Total body irradiation	173 (43.8)	64 (52.5)		66 (43.3)	15 (34.9)	
Cyclophosphamide/Busulfan	128 (32.4)	35 (28.7)		57 (37.5)	17 (39.5)	
Fludarabine/Melphalan	27 (6.8)	11 (9.0)		8 (5.3)	3 (7.0)	
Fludarabine/Busulfan/Anti-thymocyte globulin	67 (17.0)	12 (9.8)		21 (13.8)	8 (18.6)	

	Enrollment, pre-HCT			5 year assessment		
	Responders N=395	**Non-responders N=122**	**p-value**	**Responders N=152**	**Non-responders N=43**	**p-value**
GVHD prophylaxis			0.65			0.78
Cyclosporine/Methotrexate	83 (21.0)	23 (18.9)		36 (23.7)	8 (18.6)	
Tacrolimus/Methotrexate	275 (69.6)	90 (73.8)		104 (68.4)	31 (72.1)	
Other	37 (9.4)	9 (7.4)		12 (7.9)	4 (9.3)	
Donor mismatches at HLA-A, -B, -C, DRB1			0.51			0.08
None – 8/8 matched	313 (79.2)	100 (82.0)		130 (85.5)	41 (95.3)	
One or more – 6/8,7/8 matched	82 (20.8)	22 (18.0)		22 (14.5)	2 (4.7)	

GVHD, graft-versus-host disease; HLA, human leukocyte antigen

Table 2

Baseline and five year unadjusted results.

	Enrollment, pre-HCT			5 year assessment		
	Bone marrow	**Peripheral blood**	**p-value**	**Bone marrow**	**Peripheral blood**	**p-value**
FACT-BMT Trial Outcome Index (higher scores better)			0.12			0.01
Mean +/− SE	63.4 +/− 1.2 (n=190)	60.7 +/− 1.2 (n=184)		76.0+/− 1.7 (n=79)	69.1 +/− 2.2 (n=69)	
MHI – Psychological Well-Being (higher scores better)			0.09			0.005
Mean +/− SE	72.5 +/− 1.0 (n=186)	70.1 +/− 1.1 (n=182)		77.8 +/− 1.7 (n=80)	70.2 +/− 2.1 (n=72)	
MHI – Psychological Distress (lower scores better)			0.35			0.05
Mean +/− SE	19.0 +/− 0.7 (n=186)	20.0 +/− 0.8 (n=182)		17.3 +/− 1.5 (n=80)	21.4 +/− 1.5 (n=71)	
Chronic GVHD symptoms (lower scores better)						<0.001
Mean +/− SE	N/A	N/A		13.0 +/− 1.5 (n=80)	21.2 +/− 1.7 (n=72)	

HCT, hematopoietic cell transplantation; FACT-BMT TOI, Functional assessment of cancer therapy, bone marrow transplant subscae, Trial Outcome Index; MHA, Mental health inventory; GVHD, graft-versus-host disease; SE, standard error

Table 3

Comparison of primary patient-reported values at five years between bone marrow and peripheral blood recipients at five years, adjusted for enrollment values and missing data using inverse probability weighting using significant clinical characteristics.

	Adjusted for enrollment values and missing data using inverse probability weighting using significant clinical characteristics					Adjusted for missing data using multiple imputation		
Patient-reported measure	**Bone marrow (n=102)**	**Peripheral blood (n=93)**	**P value**	**Difference between bone marrow and peripheral blood (95% CI)**	**Clinically significant difference***	**Difference between bone marrow and peripheral blood (95% CI) under MAR assumption**	**P value**	**Tipping Point**
FACT-BMT TOI (higher scores better)			0.014	6.2 (1.3-11.1)	8.5	6.4 (1.4-11.3)	0.012	0.3
Mean +/− SE	76.7 +/− 1.6 (n=79)	70.5 +/− 1.9 (n=69)						
MHI – Psychological well-being (higher scores better)			**0.011**	6.7 (1.6-11.8)	8.4	7.4 (2.5-12.2)	**0.003**	−5.1
Mean +/− SE	78.9 +/− 1.7 (n=80)	72.2 +/− 1.9 (n=72)						
MHI - Psychological Distress (lower scores better)			0.128	−3.0 (−6.8,0.9)	6.5	−4.1 (−8.1,0.2)	0.039	−3.9
Mean +/− SE	16.0 +/− 1.3 (n=80)	19.0 +/− 1.5 (n=71)						
Chronic GVHD symptoms (lower scores better)			**0.004**	−6.3 (−10.5, −2.0)	7.1	−8.4 (−12.7, −4.1)	**<0.001**	12.6
Mean +/− SE	13.1 +/− 1.5 (n=80)	19.3 +/− 1.6 (n=72)						

FACT-BMT TOI, Functional assessment of cancer therapy, bone marrow transplant subscale, Trial Outcome Index; MHI, Mental health inventory; GVHD, graft-versus-host disease; SE, standard error; MAR=Missing at Random; Tipping Point=shifted difference in mean outcome between BM and PB for missing values which would lead to a different conclusion at alpha=0.0125

*clinically significant difference = 0.5 × standard deviation