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ORIGINAL ARTICLE

Survival and graft-versus-host disease in patients receiving peripheral stem cell compared to bone marrow transplantation from HLA-matched related donor: retrospective analysis of 334 consecutive patients

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Abstract

Objectives: The objective of this study was to compare the major transplant outcomes between patients receiving hematopoietic stem cell transplantation (HSCT) from bone marrow (BM) or peripheral blood stem cells (PBSC). *Methods:* All consecutive HSCT patients using BM or PBSC from an HLA-matched related donors for haematological malignancies after high intensity conditioning at seven Brazilian transplant centres between January 2008 and December 2009 were retrospectively evaluated. *Results:* In the study period, 334 patients were treated in the centres and included in the evaluation. The cumulative incidence of grades II–IV and III–IV acute graft-versus-host disease (GVHD) at one year was 36.7% and 9.7% for BM recipients and 34.4% and 15.1% for PBSC recipients, respectively (not statistically different). The cumulative incidence of chronic GVHD at three years was 53.7% and 79.8% (HR 1.93; 95% CI 1.38–2.69, $P < 0.001$) for BM and PBSC, respectively. Median overall survival was 2.85 and 2.39 years for BM and PBSC recipients, respectively (HR 1.19; 95% CI, 0.84–1.68, $P = 0.34$). *Conclusions:* Our results confirm previous findings of increased chronic GVHD incidence in patients receiving PBSC when compared to patients receiving BM as the graft source in HSCT. Acute GVHD incidence, progression-free survival and overall survival were not different between the groups.

Key words hematopoietic stem cell transplantation; peripheral blood stem cell transplantation; haematological neoplasms; multicenter study

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Introduction

Utilisation of peripheral blood stem cells (PBSC) over bone marrow (BM) for hematopoietic stem cell transplantation (HCT) has significantly increased over time. Several randomised trials after high intensity conditioning HCT from HLA-matched related donors demonstrated that the use of PBSC resulted in better engraftment but an increased risk of

graft-versus-host disease (GVHD) when compared to bone BM grafts (1–3). While in some studies, the use of PBSC conferred a decreased risk of relapse and better survival when compared to BM grafts, especially among patients with high-risk blood cell cancers (1, 2, 4, 5), other reports failed in producing the same results (6–8). BM and PBSC represent the two main graft sources for patients transplanted from HLA-matched donor for haematological malignancies; nevertheless, the graft of choice for distinct subset of patients remains to be determined.

Numerous transplant centres around the world have adopted PBSC as the preferable source for HCT, especially for high-risk haematological malignant diseases, based on prior advantages reported by some but not all studies. Thus, determining major outcomes between these two graft sources is important to support this practice in Brazil and as a benchmark for future clinical trials aimed to improve HCT major outcomes.

The aim of this retrospective study was to determine major transplant outcomes among 334 consecutive HCT using BM or PBSC from an HLA-matched related donor for haematological malignancies after high intensity conditioning at seven Brazilian transplant centres between 2008 and 2009. Outcomes analysed included the following: GVHD incidence, progression-free survival (PFS), overall survival (OS), cumulative incidence of relapse, non-relapse mortality (NRM) and the rate of patients who were both GVHD-free and relapse-free at 1 year after transplant. This work was conducted by GEDECO, a study group established by the Brazil-Seattle Consortium in 2008 to conduct studies in chronic GVHD and other late complications of hematopoietic stem cell transplantation (9).

Methods

From January 2008 to December 2009, 334 patients with acute leukaemia or chronic myeloid malignancies were treated with myeloablative HCT using BM (n = 239) and PBSC (n = 95) at seven transplantation centres in Brazil. Ethical committee evaluation was waived, because this is an observational, retrospective study, based on medical charts, and conforming to the provisions of the Helsinki Declaration.

Patients received distinct myeloablative conditioning regimens, based on the protocols of each institution, and included busulfan (Bu) and cyclophosphamide (Cy), Bu and fludarabine, Cy and total body irradiation (TBI) and others. All patients received unmanipulated grafts from HLA-matched related donors. GVHD prophylaxis consisted of a combination of a calcineurin inhibitor with methotrexate. Patients were stratified according to age and risk of relapse based on diagnosis and disease stage at transplant as previously described. Standard risk patients were defined as acute myeloid leukaemia in any complete remission (CR), acute lymphoblastic leukaemia in first CR, chronic myeloid leukaemia in first CR, myelodysplastic syndromes with less than 5% bone marrow blasts and myeloproliferative disease in chronic phase. All other cases were considered as having high-risk disease (10).

Overall survival and progression-free survival were estimated using the Kaplan–Meier method. NRM, acute and chronic GVHD were calculated based on cumulative incidence. Patients' characteristics were compared with the use of chi-squared or Student's t-test. The statistical significance of differences between endpoint comparisons was calculated with log-rank test. All tests were performed with a two-sided significance level of 5%.

Results

Patient's characteristics are depicted in the Table 1. PBSC recipients were older (median age 37 years vs. 31 years,

Table 1 Cohort characteristics

Variables	Hematopoietic stem cell source		*P#*
	Bone marrow	Peripheral blood	
Number of patients	239	95	
Age (years)			
Median (range)	31 (1–60)	37 (7–75)	<0.001
Patient gender, *n* (%)			
Female	100 (42)	40 (43)	
Male	139 (58)	55 (57)	
Disease risk at transplant			
Standard	174 (73)	50 (55)	<0.001
High	64 (27)	43 (45)	
Donor/patient gender, *n* (%)			
Female/male	62 (27)	18 (19)	
Other	170 (73)	77 (81)	
Diagnosis at transplant, *n* (%)			
Acute lymphocytic leukemia	56 (23)	26 (26)	
Acute myeloid leukemia	110 (46)	35 (36)	
Chronic myeloid leukemia	43 (18)	21 (22)	
Mylodysplastic syndrome and other myeloid neoplasmas	30 (13)	13 (13)	
Number of patients per center, *n* (%)			
Hospital Amaral Carvalho	151 (63)	48 (51)	
Centro de Transplante de Medula Óssea (CEMO)	24 (10)	12 (13)	
Universidade Federal do Rio Grande do Sul (UFRGS)	35 (15)	2 (2)	
Universidade Estadual de Campinas (UNICAMP)	11 (5)	11 (12)	
Universidade Federal do Paraná (UFPR)	13 (5)	6 (6)	
Hospital Albert Einstein	5 (2)	7 (7)	
Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP)	0	9 (9)	

Only shown statistically significant results by Chi-square test are shown; t-Student test; Fisher's exact test.

$P < 0.001$) and had high-risk disease more frequently (46.2% vs. 26.9%, $P < 0.001$). Median follow-up of surviving patients was 2.70 and 2.74 years for BM and PBSC recipients, respectively (range, 0.29–4.60 years).

The cumulative incidence of grades II–IV and III–IV acute GVHD at one year was 36.7% and 9.7% for BM recipients and 34.4% and 15.1% for PBSC recipients, respectively (not statistically different). The cumulative incidence of chronic GVHD at three years was 53.7% and 79.8% (HR 1.93; 95% CI 1.38–2.69, $P < 0.001$) for BM and PBSC, respectively (Fig. 1). Median PFS was 2.48 years and 2.18 years for BM and PBSC recipients, respectively (HR 1.07; 95% CI, 0.77–1.48, $P = 0.70$). Median OS was 2.85 and 2.39 years for BM and PBSC recipients, respectively (HR 1.19; 95% CI, 0.84–1.68, $P = 0.34$). The cumulative incidence of relapse at three years was 34.7% and 34.0% for BM and PB, respectively (HR 0.98; 95% CI, 0.63–1.52, $P = 0.91$). NRM at three years was 21.9% for BM and 26.6% for PBSC recipients (HR 1.15; 95% CI, 0.70–1.89, $P = 0.58$).

When only high-risk patients were analysed, median OS was 2.1 for BM recipients and 1.72 years for PBSC group (HR 1.18; 95% CI, 0.73–1.91, $P = 0.50$), and PFS was 0.46 and 0.58 years (HR 1.04; 95% CI, 0.66–1.64, $P = 0.86$) for BM and PBSC recipients, respectively.

Although the difference was not statistically significant, the proportion of patients in continued remission and without receiving systemic immunosuppression at one year was lower for the BM recipients compared to the PBSC recipients (20% vs. 30%, $P = 0.08$).

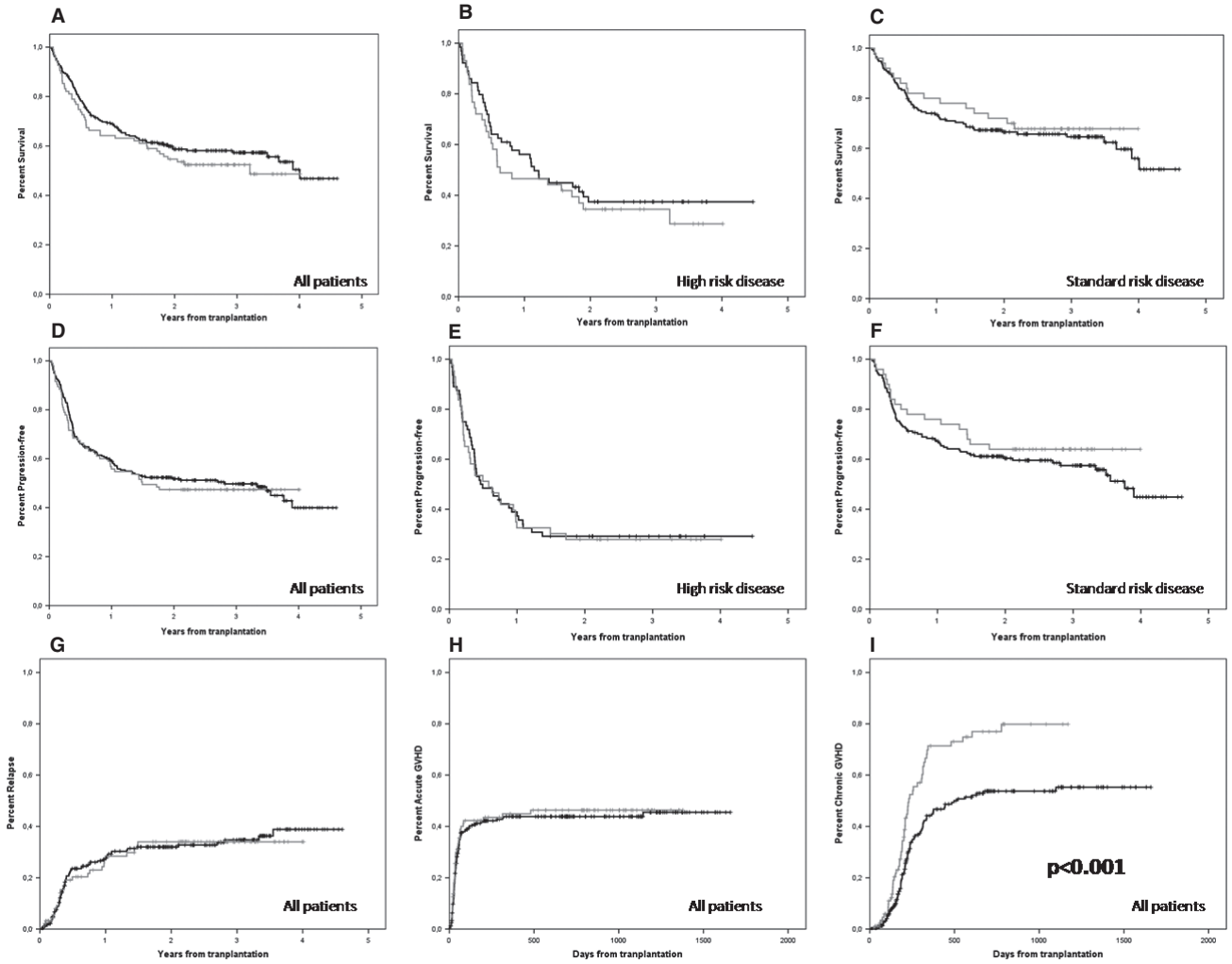

Figure 1 Major outcomes after transplant according to bone marrow (dark line) and peripheral blood (grey line) as the graft sources. Overall survival for the whole cohort (panel A), for the high risk (panel B) and for the standard risk (panel C) patients; progression-free survival for the whole cohort (panel D), for the high risk (panel E) and for standard risk (panel F) patients; the overall cumulative incidence of relapse (panel G), grades II-IV acute GVHD (panel H) and chronic GVHD (panel I) for the whole cohort. The only outcome that was statistically different between the graft courses was chronic GVHD, higher in the PBSC group (panel I).

Discussion

Our results support the notion that PBSC and BM are equivalent graft sources in terms of OS, PFS, NRM and acute GVHD incidence and severity for patients with haematological malignancies receiving a myeloablative HCT from an HLA-matched related donor. Several studies have reached similar conclusions (2, 6, 7). However, in agreement with previous reports (2, 5–7), we found significant higher rates of chronic GVHD in PBSC recipients than in the BM group. Our results should be interpreted with caution, considering the limitations of retrospective case series studies, the lack of graft content information, such as CD3 and TNC count, and the fact that patients in the PBSC group were older than patients in the BM group, since it is known that the risk of chronic GVHD increases with age (11, 12). Yet, results of the analysis conducted only in patients with high-risk disease revealed no differences in the OS and DFS outcomes between BM and PBSC recipients.

While overall PFS and OS were not statistically different between BM and PBSC recipients, in clinical practice, the choice between BM and PBSC remains crucial, because patients receiving PBSC have an increased incidence and severity of chronic GVHD (13), and worse quality of life (8). On the other hand, while some studies have found an increased PFS (4, 5) and OS (5) for patients receiving PBSC transplants, others failed to demonstrate such benefit (6, 8). Therefore, the ideal graft source for patients receiving an HLA-matched donor HCT after a myeloablative regimen remains to be determined.

In conclusion, our case series corroborate previous findings of equivalent major outcomes for patients receiving BM or PBSC as the graft source in HLA-matched myeloablative HSCT. The well-known increased incidence of chronic GVHD was again demonstrated in our case series. In our opinion, the graft source should be defined based on a case-by-case analysis, taking into consideration, primarily, the risk for chronic GVHD development.

Conflict of interest

The authors declare no conflict of interest.

Authorship

All authors performed the research and contributed with data collection. PVC and NH designed the research study, analysed the data and wrote the paper. All authors revised the final version to be published.

Ethical standards

This study was performed conforming to the provisions of the Helsinki Declaration Ethical. Because this is an observational, retrospective study, based on medical charts, the Institutional Review Board evaluation was waived.

Financial disclosure statement

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