A randomized, prospective comparison of allogeneic bone marrow and peripheral blood progenitor cell transplantation in the treatment of hematologic malignancies: an update

There is an apparent conflict regarding the use of bone marrow (BM) or peripheral blood progenitor cells (PBPC) as the source of allogeneic bone marrow transplant (BMT) mainly because of the severity and frequency of graft-versus-host disease (GVHD) as reported using PBPC as the graft. We present our updated results of a randomized trial comparing both sources in the therapy of hematologic malignancies.

Allogeneic peripheral blood progenitor cells have shown advantages over bone marrow in terms of favorable kinetics of hematopoietic reconstitution leading to accelerated platelet and neutrophil recovery, without an increase in the incidence or severity of acute graft-versus-host-disease (a-GvHD). The most important problems related to the PBPC transplant seem to be those associated with chronic GvHD (c-GvHD).

Some groups suggest that the incidence of c-GVHD may be higher after the use of PBPC than after marrow grafting. However, few formal comparisons have been made between the outcomes of patients receiving HLA-identical allogeneic PBPC transplants and those receiving BM transplants. A recent meta-analysis showed that both acute and chronic GVHD are more common after allogeneic PBPC than BM. Our previous published randomized study showed that the incidences of acute and chronic GVHD were similar between the two types of graft, but that the severity of c-GvHD was higher with PBPC: no differences in survival and disease-free survival (DFS) were observed.

This is a prospective, randomized, phase III trial, without randomization blocks, performed in a single Institution. It began in February 1995 and closed in May 1999. Eligibility criteria were age between 10-60 years, hematologic malignancies as primary disease and HLA identical siblings as donors. According to intention-to-treat, 60 patients were randomized; 30 to receive BM and 30 PBPC. Four patients were excluded from the analysis: three in the PBPC group (one refusal, one due to HLA non-identical sibling, and the other did not have a hematologic malignancy), and one in the BM group whose malignancy was non-hematologic. At the end, 29 patients in the BM and 27 in the PBPC group were analyzed. Patients, donors, and treatment characteristics are shown in Table 1.

All PBPC donors received recombinant human granulocyte colony-stimulating factor (rhG-CSF) (Granulokine; Roche) by subcutaneous injection (10 µg/kg daily for 5 consecutive days). Apheresis was performed on day five of G-CSF administration. A schema of pre-treatment preparative regimens and GVHD prophylaxis is shown in Table 1. No growth factor was used after Apheresis was performed on day five of G-CSF administration.

Analysis was based on data recorded September 30th, 2000. Proportions within each group of characteristics and outcome for patients receiving PBPC or BM were compared by Fisher’s test or χ² test, when appropriate. Comparisons of continuous variables were performed with the Mann–Whitney test. Univariate probabilities of neutrophil and platelet recovery, a-GvHD, c-GvHD, OS and DFS were estimated using Kaplan–Meier method and compared using the log-rank test or Breslow’s test. Each outcome was evaluated using Cox proportional hazard regression models, with stepwise selection. The level of statistical significance was 0.05. All analyses were performed by SPSS Software version 8.0 for Microsoft Windows 95.

The median of CD34⁺ cells for recipients of BM and PBPC was 3.96×10⁹/kg (1.19-17.35) and 5.12×10⁹/kg (1.25-71.61), respectively (p=0.32). The median day post-transplant to achieve an absolute neutrophil count (ANC)>0.5×10⁹/L was 18 (13-30) for BM recipients and 15 (11-25) for PBPC recipients (p=0.02). The median time to a platelet count of 20×10⁹/L was 18 (10-40) for BM and 12 (7-36) for PBPC recipients (p=0.001). Moreover, the median day for discharge was 27 (18-69) and 21 (16-42) for the BM and PBPC groups, respectively (p=0.01). The probabilities of developing grades 2 to 4 a-GvHD were 23% for evaluable patients transplanted with BM and 26% for those receiving PBPC (p=0.53). Among 20 patients in the BM group and 21 patients in the PBPC group, the probabilities of extensive c-GvHD were 61% and 77% in BM and PBPC (p=0.05), respectively (Figure 1).

Furthermore, all patients in the PBPC group developed extensive disease, while 6 out of 11 (54.5%) in the BM group did so (p=0.01). The estimates of overall survival (OS) for BM and PBPC recipients at 2000 days are 48% and 56%, respectively (p=0.67), the estimates of disease-free survival (DFS) at 2000 days are 50% and 60% respectively (p=0.47). In multivariate analysis, the neutrophil engraftment was affected by peripheral blood (PB) graft, mononuclear cells independent of the graft and the interaction of bone marrow graft and nucleated cells. Moreover, platelet engraftment was also influenced by PB graft, CD3⁺ and nucleated cells, both independently of graft type. Only the PB graft influenced the c-GvHD. Regarding OS and DFS, early disease showed best outcomes and transplant-related mortality was influenced only by patients’ age.
In conclusion, our randomized trial confirmed faster engraftment of neutrophils and platelets in the PBPC group, earlier discharge for PBPC recipients and no difference in acute GVHD. However, the greater severity of c-GVHD in the PBPC group, with more extensive disease, seems to be the more important problem. We have not found differences in OS and DFS between both groups so far, although Cox analysis has shown best outcomes for early diseases. As a consequence of these results, our Institution has decided to use PBPC only for advanced disease, being concerned about the severity of c-GVHD and worse quality of life in the PBPC group of recipients in our study.

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Figure 1. Probability of extensive c-GVHD.

References


