Peripheral Blood Stem Cells for T Cell–Replete Nonmyeloablative Hematopoietic Transplants Using Post-Transplant Cyclophosphamide

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Unmanipulated (T cell–replete) hematopoietic transplants from HLA-haploidentical donors performed using conventional pharmacologic graft-versus-host disease (GVHD) prophylaxis (eg, calcineurin antagonist and methotrexate) were largely unsuccessful because of severe post-transplant alloreactivity [1,2]. More successful strategies for transplants from haploidentical donors have included extensive ex vivo and/or in vivo T cell depletion [3-5], or more recently, T cell–replete grafts using post-transplant cyclophosphamide (ptCy) to control alloreactivity [6-9]. Whereas mobilized donor peripheral blood stem cells (PBSC) have been the preferred graft source for strategies that involve T cell depletion, unmobilized donor marrow has been the graft source with T cell–replete transplants utilizing ptCy. The reasons behind a preference for bone marrow grafts in studies of T cell–replete haploidentical transplants using ptCy are complex. They include the pioneering work in this field at Johns Hopkins University, where unmobilized bone marrow (BM) is the institutionally preferred graft source for almost all transplants, and concerns that the larger number of T cells typically present in BM may be realized if mobilized PBSC are shown to be safe in this setting. Specifically, the scheduling challenges of bone marrow harvests in an era of limited access to operating room and physician resources

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may be ameliorated. The higher T cell dose associated with PBSC may possibly result in stronger graft-versus-malignancy effects for patients with advanced malignancies (as has been seen in the setting of matched related donor transplants), and donor preferences for avoiding general anesthesia and autologous blood donation may be accommodated. Our group has previously demonstrated that G-CSF mobilized PBSC can be safely and effectively utilized for T cell–replete haploidentical donor transplantations when used with myeloablative preparative regimens [9]. However, the use of PBSC as the graft source with the most frequently used preparative regimen for T cell–replete HLA-haploidentical donor transplantation using ptCy, namely the combination of fludarabine, single (2Gy) fraction total body irradiation, and pre- and post-transplant cyclophosphamide developed at Johns Hopkins University, has not been widely reported. In this issue of Biology of Blood and Marrow Transplantation, Castagna et al. [10] report on a nonrandomized comparison of 23 T cell–replete haploidentical donor transplants performed using ptCy and using G-CSF mobilized PBSC, with 46 such transplants contemporaneously performed using conventional BM grafts. A preparative regimen very similar to the nonmyeloablative regimen developed at Johns Hopkins University was used for all patients. Median times to neutrophil and platelet engraftment were 24 to 48 hours slower in the BM patients, but the differences were not statistically significant. Similarly, no statistically significant differences in rates of acute and chronic GVHD, infection, nonrelapse mortality, overall survival, and progression-free survival were seen between the BM and PBSC patients. This study suggests that G-CSF mobilized PBSC can safely be used as the graft source for patients receiving a T cell–replete BM-haploidentical donor transplant using the nonmyeloablative preparative regimen developed at Johns Hopkins University. However, the equivalence of PBSC and BM cannot be established without an adequately powered prospective randomized comparison and several imbalances between the PBSC and BM groups necessitate appropriate caution when interpreting the results of this study by Castagna et al [10]. The PBSC transplants were exclusively performed in one of the two centers authoring this study, while the calcineurin antagonist and antifungal prophylaxis used were different between the two centers. There were also differences between the BM and PBSC patients with respect to age, frequency and types of prior transplant, median hematopoietic cell transplantation–comorbidity index score, and, importantly, in median follow-up (332 days for PBSC versus 726 days for BM patients). For example, one of the more important questions is whether chronic GVHD incidence and severity would be higher in patients transplanted with HLA-haploidentical PBSC than with haploidentical marrow, as has been shown for HLA-matched donors. Whereas no significant difference in chronic GVHD incidence was found in this study, the shorter median follow-up for PBSC patients limits the effectiveness of this comparison. Furthermore, the relatively small number of PBSC patients impairs the statistical power of the comparison in outcome measures. For example, nonrelapse mortality was 12% in PBSC patients versus 22% in BM patients, and BK virus hemorrhagic cystitis occurred in 0% versus 11%, respectively, but these differences were not statistically significant.

Despite these limitations, this study provides the first published evidence that PBSC can safely be used with the nonmyeloablative regimen developed by Johns Hopkins University investigators for T cell–replete HLA-haploidentical transplantation and will help widen the options available to centers and donors where such transplantation is performed.

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