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EDITORIAL

Ex Vivo T Cell Depletion of Allogeneic PBSC as Acute and Chronic GVHD Prophylaxis after Myeloablative HCT: Time to Reconsider?

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Although established as an effective method for mitigating graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (HCT), ex vivo donor T cell depletion (TCD) has yet to gain wide application. Randomized clinical trials to date have shown TCD reduces acute GVHD (aGVHD), but offers no survival advantage over conventional pharmacologic GVHD prophylaxis [1,2]. The benefits of TCD in GVHD reduction were often counterbalanced by an increased risk of relapse, graft failure, posttransplant lymphoproliferative disease, and infections. Further, these studies primarily involved TCD of bone marrow grafts using inefficient and time-consuming antibody-based and/or mechanical separation techniques. The landscape of HCT has changed significantly over the past decade. More patients are now receiving mobilized peripheral blood stem cell (PBSC) instead of marrow grafts. With higher $CD34^+$ and $CD3^+$ content in PBSC, the risk of graft failure is diminished, and there is a greater risk of acute and particularly chronic GVHD (cGVHD). Posttransplant supportive care measures, especially pertaining to infection monitoring and treatments, are vastly improved. Acute myelogenous leukemia (AML) has replaced chronic myeloid leukemia (CML) as the leading indication for HCT. A recent multicenter trial has already demonstrated that addition of rabbit antithymocyte globulin (ATG) (Fresenius Biotech GmbH, Germany) as in vivo TCD to cyclosporine/methotrexate after matched unrelated donor transplantation (82% PBSC, 18% marrow) is associated with significant reduction in aGVHD and cGVHD [3]. As such, could PBSC then be a better venue to test again the merits of ex vivo TCD after myeloablative HCT? The advent of standardized and efficient $CD34^+$ selection columns renders 4-5 log T cell depletion possible, even with large-volume PBSC products, and it is now possible to engineer grafts containing 10^3-10^4 $CD3^+$/kg, a full 1-2 logs below the threshold where posttransplant exogenous immune suppression is necessary in matched sibling transplantation [4]. The question is: With this extent of T cell depletion, how would immune reconstitution and the graft-versus-leukemia (GVL) effect be affected?

In this issue, 2 separate phase II prospective trials involving a total of 79 patients show very promising results for myeloablative transplantation using ex vivo $CD34^+$ selected PBSC grafts [5,6]. The striking findings are that aGVHD and cGVHD control are excellent despite no posttransplant immune suppression, and importantly, disease relapse is very respectable even with extended follow-up. In the study by Jakubowski et al. [5], which included 35 patients receiving matched or mismatched unrelated donor grafts after a fludarabine/thiotepa/fractionated total-body irridiation (TBI)/ATG conditioning, the aGVHD and cGVHD incidence were 9% and 29%, respectively, and cumulative incidence of relapse was only 6%. Immune reconstitution studies demonstrated that numbers of circulating $CD8^+$ cells normalized and $CD4^+$ cells surpassed 200/μL at a median of 4-6 months and 6-9 months, respectively. In the report by Devine et al. [6], which is a multicenter trial conducted through the BMT CTN, 44 patients with AML in CR1 or CR2 received $CD34^+$-selected PBSC grafts from matched sibling donors after cytoxan/thiotepa/fractionated total body irradiation/anti-thymocyte globulin (TBI/ATG). The grade 2-4 aGVHD incidence was 22.7%, and the incidence of cGVHD was only 19% (7% extensive) at 24 months posttransplant. Cumulative incidence of relapse was 23% at 3 years. Among patients transplanted in CR1, disease-free survival at 3 years was 58%, which appears to be in keeping with survival data in HCT using conventional GVHD prophylaxis. Importantly, the incidence of bacterial, fungal, and cytomegalovirus (CMV) infections appear to be comparable to conventional PBSC transplantation, with the exception of Epstein-Barr virus (EBV) reactivation and PTLD manageable with rituximab. Together, these 2 studies suggest that TCD of PBSC could be a viable means for reducing both aGVHD and cGVHD without compromising

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relapse in related and unrelated donor myeloabaltive PBSC transplantation. Although quality-of-life metrics were not used in these trials, it is tempting to speculate that the drastic reduction in cGVHD could translate to increased patient satisfaction and, ultimately, healthcare cost savings. Phase III studies testing ex vivo TCD with $CD34^+$ selection after myeloablative PBSC transplantation appear to be warranted.

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