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The Bottom Line

# As Time Goes by …

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It is time to look back to the last 15 to 20 years of stem cell transplantation. One of the most obvious changes has been the replacement of bone marrow by peripheral blood leukocytes enriched for stem cells. It is more convenient to collect stem cells from the peripheral blood after a 4-day treatment with hematopoietic growth factor, mostly granulocyte colony–stimulating factor. It spares anesthesia and multiple wounds of the pelvic crest necessary for bone marrow aspiration. In the short term, serious adverse events are rare and long-term effects of blood stem cells donation have not been defined yet [1].

Is there an advantage for the patient? Most randomized studies show faster recovery of neutrophils and some show even faster recovery of platelets [2-8]. Therefore, it is not surprising that peripheral blood stem cells are the preferred graft for frail patients, sick patients with advanced disease, and patients conditioned with a regimen of reduced intensity [8]. There were no differences in survival in patients given bone marrow compared with those who received peripheral blood stem cells, except for patients who underwent transplantation in first remission of chronic myelogenous leukemia (CML) [9]. In other forms of leukemia and in advanced stages of CML, there was no significant survival advantage of bone marrow over blood stem cells [10]. There are many differences between the group given blood stem cells and that given marrow (Table 1 from reference [10]). In the group given blood stem cells, there were more elderly patients, more patients with a poorer performance, and more patients with conditioning of reduced intensity, including busulfan and fludarabine or busulfan and cyclophosphamide. Patients with blood stem cell transplantation were more frequent in recent years of 2005 to 2009, compared with marrow transplant recipients in 2000 to 2004; they received more cells and more often received tacrolimus instead of cyclosporine A for graft-versus-host disease (GVHD) prophylaxis. Therefore, the blood stem cell group may have had several favorable factors that cannot be controlled in a multicenter retrospective analysis. In spite of these favorable factors, nonrelapse mortality is not lower than in the bone marrow group (Table 2 of reference [10]). It is even higher in patients with CML in first chronic phase and preleukemic myelodysplasia (refractory anemia with excess blasts (RAEB)-1 and refractory anemia with excess blasts-2). In the latter, nonrelapse mortality is counterbalanced by a lower relapse rate, so that survival is the same as in the marrow group. In patients with CML in first chronic phase, the relapse rate is low in both groups, so the lower nonrelapse mortality of the marrow group results in a better survival.

Better survival of patients who underwent transplantation with blood stem cells was reported by Bensinger et al. [8], but this effect was most pronounced in patients with advanced disease. The survival curves of Eapen et al. [10] in the second and third year after transplantation for acute leukemia also show better survival of patients given blood stem cells, but the curves come together after 5 years, confirming the early advantage of blood stem cells in this disease (Figure 1 of reference [10]). The same can be seen in RAEB patients (Figure 2 in reference [10]). In patients with CML, those given bone marrow fare better than those given blood stem cells (Figure 3 of reference [10]), but this difference is only significant in patients who underwent transplantation in first chronic phase.

Certainly, it is highly speculative to draw any conclusions from a retrospective multicenter study with so many uncontrollable factors. Nevertheless, a pattern can be recognized: bone marrow may be the preferred stem cell source for patients with less progressive forms of leukemia and myelodysplasia and certainly for patients with nonmalignant diseases [11]. Obviously, blood stem cell transplantatoins produce more GVHD that is harmful in nonmalignant diseases and not helpful in chronic phase CML. Chronic GVHD is helpful in the control of acute leukemia and it may improve survival, as long as it is limited.

The role of T cells has been most convincingly shown in CML; patients given T cell–depleted grafts had a significantly increased risk of relapse [12], and transfusion of lymphocytes from the marrow donor could induce lasting remissions [13].

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Better survival and leukemia control may have been expected from blood stem cell transplantation, but more severe GVHD was a matter of concern because the content of T cells is about 10-fold higher than in aspirated marrow [14]. The higher content of T cells and the higher content of $CD34^+$ $CD38^-$ stem cells may be responsible for the faster recovery of leukocytes and platelets [3,5,8,15-17], less frequent graft failures [9], and better immune recovery [18]. A higher incidence of chronic GVHD was found in large retrospective studies [19,20], but the rate and severity of acute GVHD, incidence of relapse, and survival were not different. However, as time goes by, chronic GVHD charges toll in reducing survival of good-risk patients. Unlike these patients with nonmalignant or slowly progressive malignant disease, those with acute leukemia and progressive disease, elderly and frail patients, and patients conditioned with reduced intensity may benefit from blood stem cell transplantations and better control of leukemia with some chronic GVHD.

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# Is Any Donor Too Old?

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The paper by Rezvani et al. [1], "The Impact of Donor Age on Outcome after Allogeneic Hematopoietic Cell Transplantation" appearing in this issue and on which this commentary is based, demonstrates that an older donor age does not negatively affect engraftment, graft-versus-host disease (GVHD), relapse, or mortality after blood and marrow transplantation. The authors evaluated the peripheral blood progenitor cell (PBPC) product in donors over the age of 60 years compared with that of younger donors. Their conclusion is surprising, as it is well established that use of younger donors, under 20 years of age, is associated with lower rates of acute and chronic GVHD than use of donors older than 20 years [2]. Moreover, use of umbilical cord blood, the youngest donor source, is associated with the lowest rate of GVHD of any donor source. Umbilical cord blood as a donor product is limited by its high graft failure rate, probably because of its low numbers of memory T cells, even when high cell numbers are infused [3]. On the other

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