inside blood

Blood or marrow stem cells?

In the beginning, there was bone marrow. A quarter of a century ago, the concept was simple: a patient had a bad bone marrow (eg, aplastic anemia) or a marrow destroyed by therapy (acute leukemia), and one substituted a healthy, allogeneic marrow. Gradually it became possible to distinguish and then manipulate marrow cellular subsets. For instance, T lymphocytes were found to be important in acute graft-versus-host disease (AGVHD), and strategies evolved to reduce their numbers in the marrow inoculum. The results were mixed, with graft failure and increased relapse replacing the problem of AGVHD. Once the hematopoietic progenitor cells were recognizable, it was seen that placental blood had large numbers of such and also that the T-lymphocyte population appeared naive: perhaps one could get engraftment with less AGVHD. Again, the results were mixed: less AGVHD, but slower engraftment. More recently, allogeneic cytokine-mobilized peripheral blood stem cells (PBSCs) have come under study. On the one hand, large numbers of $CD34^+$ cells can be collected, but there were concerns about an increased risk of chronic graft-versus-host disease (CGHVD). PBSC products contain large numbers of T lymphocytes, and previous experience using noncytokine mobilized peripheral blood cells clearly showed a higher risk of CGVHD (although with more reliable engraftment in aplastic anemia patients).

The study in this issue (page 1525) reports a multicenter, randomized trial comparing marrow to cytokine-moblized PBSCs. The results are similar to those previously published by the Seattle group: the PBSC group had faster engraftment (4 days for neutrophils, 6 days for platelets) and slightly better survival. The current study shows that most of the survival advantage is seen in the poor-risk patients, as opposed to the good-risk ones: this again is similar to what Seattle showed. The reason for the advantage in the poor-risk patients is not clear: 4 days faster engraftment would seem to be advantageous, but it might be useful to also study whether there are relevant differences in the cellular components in the respective products which could explain such an advantage, such as larger numbers of cells to suppress incipient infections or to speed healing of previous endothelial damage.

—Patrick G. Beatty
Montana Cancer Specialists

Adenovirus infections after BMT

Adenovirus infections are a common complication of allogeneic hematopoietic transplantation. In many patients, the infections are self-limited and resolve spontaneously, but in other transplant recipients, adenovirus disease occurs, which is relentlessly progressive and ultimately fatal. There is no established effective therapy for adenovirus infection. These infections are related to posttransplantation immunodeficiency and are most frequent in the most severely immunocompromised patients. Chakrabarti et al (page 1619) prospectively examine the incidence and outcome of adenovirus infections in 76 patients receiving allogeneic hematopoietic transplants, and they identify risk factors for the development of these infections and survival. Patients receiving in vivo alemtuzumab antibody treatment had the highest incidence of adenovirus infection and disease (45%). These patients also had the most severe lymphocytopenia. The authors attempted treatment of adenovirus infections by withdrawal of immunosuppression when possible. Although all 12 patients who were able to have immunosuppression withdrawal survived, and all 3 patients who continued immunosuppressive therapy succumbed to the infection, the later group likely had ongoing GVHD and were at greater risk for fatal disease. Since adenoviral disease is related to the severe posttransplantation immunodeficiency, withdrawal of immunosuppressive therapy or donor lymphocyte infusion are rational considerations for therapy. These measures to enhance immune reactivity also increase the risk of GVHD, particularly early after transplantation. Controlled studies are needed to demonstrate the safety and efficacy of this strategy.

—Richard Champlin
University of Texas
M.D. Anderson Cancer Center

In vivo gene transfer moves one step closer to success

Achieving *sustained* expression of clotting factors and achieving this expression at levels *high enough* to result in clinical improvement have been the two critical goals of efforts to treat hemophilia by gene transfer. In this issue Nathwani and colleagues (page 1662) demonstrate that they have achieved this goal, long-term expression of therapeutic levels of factor IX (4%-10% of normal levels in humans), by administration of a recombinant AAV vector into the hepatic circulation of Rhesus macaques. These data are in fairly close agreement with work published just weeks earlier by Mount et al (Blood. 2002;99:2670-2676), reporting similar findings in hemophilic dogs treated by portal-vein infusion of a recombinant AAV vector. Certainly, it is encouraging to see similar results and excellent safety profiles in 2 different large-animal models, and the current study lends further support to an ongoing clinical trial of hepatic artery infusion of rAAV in patients with hemophilia B (http://www4.od.nih.gov/oba/rac/trialquery.asp?C1=1&diseasename=25). But as is often the case in cutting-edge investigation, this study raises at least as many questions as it answers: the relationship between vector dose and factor IX levels; the effect of preexisting antibodies to the vector capsid on