Comment on Hölig et al, page 3757

Donors, donors, and more donors

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In this issue of Blood, Hölig and colleagues report on their 12-year experience with healthy unrelated donors. Their data outline the challenges involved in safeguarding donor safety and the need for ongoing surveillance.

The safety of healthy peripheral blood stem cell (PBSC) donors receiving recombinant human granulocyte colony-stimulating factor (rhG-CSF) is a topic that has received considerable attention in recent literature.1-3 The short-term adverse events related to both mobilization and collection as well as the problem of long-term safety monitoring have been discussed extensively, although the latter issue is far more complex and logistically more challenging for investigators.

Hölög and colleagues4 provide a major contribution to this debate. They managed an impressive number of donors (3928) over a 12-year period, a noteworthy (and quite possibly unique) accomplishment for a single center. As it has been said, quantity has a quality of its own. Their data on short-term donor outcome are, indeed, remarkable. One leukapheresis was adequate to collect the target CD34+ cell dose in 78% of the donors. Only 1.1% of them experienced serious complaints requiring hospitalization, and there were no cases of splenic rupture. Their “mobilization failure” rate was as low as 0.45%, and a central venous access was needed in only 0.6% of cases. That being said, it should be acknowledged that these are selected, healthy, presumably very committed young volunteer donors (median age, 34 years) being followed at a highly skilled referral center. Therefore, these results may not necessarily be reproducible in other settings, particularly those involving older related donors.

As impressive as these figures may be, the contribution from Hölög and colleagues is even more valuable when it comes to long-term follow-up and their ability to monitor their cohort of 3928 unrelated volunteers for a period of up to 5 years (see figure). Most donors reported good or very good general health. With a follow-up including 8234 donor-years, the fact that the incidence of myeloid malignancies was not significantly different from the one expected from an age-adjusted population is undoubtedly reassuring. The finding of a higher incidence of Hodgkin lymphoma defies an immediate explanation. It is provocative and deserves to be explored further. Similar data have recently been reported by the National Marrow Donor Program (NMDP).5 Among 4015 donors who have passed the first anniversary of their PBSC donation, the NMDP has accumulated 9785 years of follow-up (range, 1-9 years, with 897 donors ≥ 4 years). The incidence of cancer in this group was consistent with the age-adjusted US incidence of cancer in the normal adult population, with no reports of leukemia or lymphoma. To put all of this in perspective, it is appropriate to draw from the original analysis from Hasenclever and Sextro.6 The annual incidence of acute leukemia in the United States is estimated to be 5/100,000 per year, yielding a cumulative incidence of 0.05% cases at 10 years. Assuming a 10-fold increase in leukemia risk in these donors, which is clearly a pessimistic scenario, more than 2000 donors would need to be followed for longer than 10 years. It could be argued that the use of a normal adult control population does not take into account the fact that these donors are HLA-identical to patients with hematologic
malignancies, and therefore ignores any possible genetic or familial predisposition to leukemia development. It is difficult to see, however, how this potential confounding factor can be bypassed in the real world.

Although this study is indeed reassuring, there is an ongoing need for surveillance and caution. A flurry of reports on possible effects of rhG-CSF on chromosomal integrity and gene expression have been published in recent years and have been recently reviewed.7 The effects described on gene expression were self-limiting and transient. In addition, these studies are small, have been subject to criticism, have not been widely replicated so far, and should be viewed as inconclusive. Still, safeguarding donor safety is such a high priority that one can only welcome efforts to evaluate these leads. The United Kingdom Donor Registries will have a study to screen normal donors treated with recombinant human granulocyte colony-stimulating factor for long-term genetic damage using interphase fluorescence in situ hybridization and array comparative genomic hybridization analysis.1 Marrow donors will be used as negative controls and patients with hematologic malignancies as positive controls. The NMCP and University of Minnesota are working on a similar study.1 Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

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Comment on Kuter et al, page 3748

TPO-mimetics and myelofibrosis? A reticulin question!

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In this issue of Blood, Kuter and colleagues present further information about the incidence and temporal course of bone marrow reticulin fiber formation after treatment with a TPO-mimetic.

Reticulin fiber formation is present to some degree in normal bone marrows of healthy adults,1 whereas collagen fibrosis (trichrome staining) is considered to be abnormal and associated with more severe disease.2 Both reticulin fibrosis and trichrome staining have been associated with myelofibrosis and other hematopoietic disorders. A study by Mufti et al showed that patients with immune thrombocytopenia (ITP) have normal reticulin fiber formation in the bone marrow1 so that excitement over potential benefits of thrombopoietin (TPO)–mimetic drugs in the treatment of ITP has been tempered by emerging reports of bone marrow fibrosis.3,5 These reports were especially concerning because previous animal data suggested that long-term stimulation of bone marrow with TPO (by virally induced overexpression) resulted in a phenotype that resembled primary myelofibrosis.6 In this issue of Blood, Kuter and colleagues present further information about the incidence and temporal course of bone marrow reticulin fiber formation after treatment with the TPO-mimetic romiplostim both in an animal model and in ITP patients.7 Romiplostim is a hybrid protein that contains a TPO receptor–binding region conjugated to the Fc portion of an antibody (peptibody).8

In the first part of this study, the authors describe findings in rats treated with romiplostim at up to 10 times the recommended dose for treatment of patients with chronic ITP. All of the animals showed dose–dependent increases in platelet count with a relatively short treatment course (4 weeks); a subgroup of animals was evaluated 4 weeks after discontinuation of therapy. Within 4 weeks, many of the rats showed dose–dependent changes in bone marrow; both an increase in bone marrow fiber content and hyperostosis, suggestive of collagen fibrosis (although trichrome staining was not done). All of these changes resolved after a 4-week washout period with none of the animals showing residual changes. These findings suggest that, in animals at least, romiplostim actually does alter marrow fiber content, but if treatment is short, the changes induced are reversible. Certainly a longer course of therapy in this animal model is needed to determine whether eventually, these changes become progressive or irreversible.

Next, the authors present data from 2 clinical trials: a retrospective analysis of 271 patients with chronic ITP (treated June 2002 to January 2008) who received different doses of romiplostim and a smaller, prospective study in which bone marrow biopsies were obtained before initiation of treatment as well as at 3, 6, and 9 months after initiation of therapy. Photomicrographs were reviewed by an expert panel to determine level of bone marrow reticulin. In the retrospective study, bone marrow examination was left to the discretion of the investigators and only 11 patients had at least one sample. Of these, 10 patients showed reticulin fiber formation. Given the study design, one can say only that reticulin fiber formation in patients treated with this TPO-mimetic is somewhere between 4% (10 of 271 total patients enrolled) and 91% (10 of 11 who had bone marrow studies). The available data suggest that the real incidence may be closer to 5% to 10%. Of the 10 patients who were positive for reticulin staining, 6 received higher than the currently recommended 1 to 10 μg/kg dosing. Five of these patients had both a pretreatment and on-treatment marrow evaluation. Four of these showed an increase in reticulin formation on treatment, and 3 patients had subsequent bone marrow studies that
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