Randomized Trial of Autologous Filgrastim-Primed Bone Marrow Transplantation Versus Filgrastim-Mobilized Peripheral Blood Stem Cell Transplantation in Lymphoma Patients

To the Editor:

We have read with interest the work by Damiani et al,1 showing that bone marrow (BM) can be efficiently “primed” with granulocyte colony-stimulating factor (G-CSF) before harvest, and its reinfusion will lead to results similar to the G-CSF mobilized peripheral blood (PB) in lymphoma patients submitted to autologous transplantation. Does G-CSF really “prime” marrow stem cells? Experimental evidence from several studies in the murine model suggest that this might not be the case and that, on the contrary, G-CSF alone or in combination with other cytokines most probably leads to significant early depletion of stem cells from their marrow niches. First, when G-CSF is combined with cyclophosphamide for mobilization, there is a 19-fold reduction in the BM colony-forming unit-spleen (CFU-S) at the expense of a 13-fold increase in the PB and a 140-fold increase in the spleen at day 6 posttreatment.2 Second, when G-CSF is used in combination with flt-3 to mobilize hematopoietic progenitors, there is a dramatic decrease in BM CFU below control levels and an elevated PB CFU at day 6 posttreatment.3 Finally, the concomitant administration of G-CSF with stem cell factor in mice leads to a dramatic increase in the repopulating ability of the PB stem cells after cytokine treatment. However, after 5 days of treatment, the repopulating ability of BM decreased to 0.27 relative to untreated marrow. The repopulating activity of the BM increased only after day 14 of cytokine treatment.4 These observations provide evidence for an early marrow stem/progenitor cell “depletion” or redistribution effect induced by G-CSF rather than a “priming” effect. It is probable that at day 4 postcytokine therapy, which was the time of harvest in this randomized study, the marrow was in a negative stem/progenitor cell balance, that is with BM CD34+ cells × 10^6/kg being 5.5 times less than in the PB. However, recent data from Morrison et al5 suggest that the combination of cyclophosphamide and G-CSF can result in a 12-fold increase in hematopoietic stem cells by day 2 of cytokine therapy (derived from self-renewing divisions in the BM). This dramatic expansion was subsequently followed by a decrease in marrow stem/progenitor cell frequency and number by day 3, which corresponded to an abrupt appearance and increase in the PB and spleen.

It still remains to be seen if G-CSF alone, as used in the Damiani study, can trigger proliferation and expansion of marrow stem/progenitor cells before their appearance in the periphery. Recruitment or priming of hematopoietic progenitor/stem cells generally can occur only through combined activation of at least two cytokine receptors, a task that G-CSF alone probably cannot accomplish.6 Papayannopoulou et al7 recently suggested that growth factors like G-CSF could initiate the mobilization event in mature neutrophils rather than in the stem cells themselves; this was based on recent findings showing that G-CSF−/− mice and patients with chronic granulomatous disease mobilize poorly.

The results of the trial by Damiani et al1 can be reasonably interpreted in the light of a significant PB contamination at the time of marrow harvest, which was not objectively assessed in their study. This could have been done by comparing the lymphocyte subsets and the CD4/CD8 ratios of BM and PB at the time of harvest. The investigators state that the amount of marrow aspirated on day 1 and on day 4 to perform the biological studies was only 5 mL, which would decrease to a minimum the possibility of massive PB contamination. However, Batinic et al8 have shown by comparing the lymphocyte subsets in 4- to 5-mL BM samples taken at the start and at the end of harvesting that these samples were heavily contaminated with PB. Batinic and other colleagues9 later showed that the number of CFU-granulocyte-macrophage per liter of cell suspension of the first 1.0-mL puncture sample of a BM harvest was 10 times higher than that in the harvest aliquots, again demonstrating the significant hemodilution of standard BM harvests. In the randomized study of Damiani et al,1 at the time of BM harvest which was day 4 post G-CSF administration, the mean number of CD34+ cells per microliter in the PB had increased from 1.6 before G-CSF to 15.7 at the time of harvest, thus providing a significant source of PB progenitor cell contamination.

Therefore, we suggest that the results of this trial be interpreted with caution; in planning for future trials, we would also like to stress that at the present time there is no sound scientific evidence suggesting that G-CSF can by itself “prime” or expand marrow stem/progenitor cell numbers.

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REFERENCES


Dr Gyger and colleagues, in reply to our work on granulocyte colony-stimulating factor (G-CSF) bone marrow (BM) purging, have pointed out three aspects of the problem: the possible negative balance of marrow cells after short-term G-CSF administration, the need for at least two cytokines for priming BM stem cells (BMSC), and the probable contamination of BM harvest.

Overall, we agree on each of these three points and we would like to stress that the misinterpretation of the term “priming” could be the origin of the observations made by Gyger et al. In fact this term was already used in previous reports1-3 on the same subject showing early expansion of CD34+ BMSC and their mobilization. We agree that the term should be used only to mean “activation” of SC and not mobilization.

To this purpose we have used the term priming to differentiate it from peripheral blood (PB) mobilization. On the other hand, our data overlap those of Dicke et al.,4 where the term “activation” was used with the same meaning of our “priming.” As far as PB contamination, we have stressed this point in the discussion and confirm that the purpose of our study was essentially clinical: in other words, we wanted to show that short-term G-CSF can increase the BMSC, allowing for a positive engraftment compared with steady-state BM. The availability of an alternative source of SC with rapid engraftment may find clinical application in the pediatric and the allogeneic settings.

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Rituxan in the Treatment of Cold Agglutinin Disease

To the Editor:

The use of the monoclonal antibody C2B8 (Rituxan; IDEC Pharmaceuticals Corp, San Diego, CA) directed at CD20 has been shown to be of benefit to patients with relapsed/refractory low-grade lymphomas of B-cell origin.1 We report a case of a patient with evidence of a non-Hodgkin’s lymphoma of B-cell origin associated with a monoclonal IgM and cold agglutinin disease.

A 75-year-old woman presented to the hospital on September 30, 1997 for weakness of 2 to 4 weeks duration. The only medical history was of hypertension treated with Aldomet (Merck & Co, West Point, PA), which the patient still took at a dose of 250 mg orally daily. Other medications were Premarin (Wyeth-Ayerst, Philadelphia, PA) and Provera (Pharmacia & Upjohn, Kalamazoo, MI). There was no history of recent infection, malignancy of any kind, or adenopathy. Physical examination was notable for jaundice and pallor, but there was no adenopathy or enlargement of liver or spleen. Laboratory studies showed a hemoglobin level of 5.1 g/dL, a hematocrit of 14.4%, and a reticulocyte count of 14.8%. The white blood cell (WBC) count was 4,700/µL with 51% neutrophils, 2% eosinophils, 33% lymphocytes, and 14% monocytes. Two nucleated red blood cells (RBCs) were noted per 4,700/µL with 51% neutrophils, 2% eosinophils, 33% lymphocytes, and 14% monocytes. Two nucleated red blood cells (RBCs) were noted per 4,700/µL with 51% neutrophils, 2% eosinophils, 33% lymphocytes, and 14% monocytes. Two nucleated red blood cells (RBCs) were noted per 4,700/µL with 51% neutrophils, 2% eosinophils, 33% lymphocytes, and 14% monocytes.

A bone marrow aspirate and biopsy showed erythroid hyperplasia and an interstitial and vaguely nodular lymphocytosis. Immunophenotyping of peripheral blood was performed because of the possible negative balance of marrow cells after short-term G-CSF administration, the need for at least two cytokines for priming BM stem cells (BMSC), and the probable contamination of BM harvest. In short-term liquid cultures. Exp Hematol 22:80, 1994

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