Response

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 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 reports 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., 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.

REFERENCES


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. The platelet count was 290,000/µL. RBC agglutination was noted. The direct coombs test was positive attributable to complement (3+) and IgG (weak). Westergren sedimentation rate was 138 mm/h. Haptoglobin level was <5.8 mg/dL.

Corticosteroid therapy (prednisone 1 mg/kg) was initiated with folic acid, and Aldomet was discontinued with an improvement in hematocrit to 21% to 23% over the next 4 to 5 days. The patient was discharged from the hospital. Several weeks of outpatient monitoring showed no further improvement in hematocrit, and a repeat DAT was positive (complement 4+; IgG ). A cold agglutinin with anti-I specificity was identified. A computed tomographic (CT) scan of the abdomen showed no adenopathy and normal liver and spleen size. Serum protein electrophoresis showed a monoclonal protein defined by immunofixation as IgMα. Quantitative Ig levels were: IgG, 943 mg/dL; IgA, 110 mg/dL; and IgM, 547 mg/dL. A bone marrow aspirate and biopsy showed erythroid hyperplasia and an interstitial and vaguely nodular lymphocytosis (36%) comprised of small mature lymphocytes. Immunophenotyping of peripheral blood was performed because of lymphocytosis (4,900/µL) and demonstrated an abnormal B-cell phenotype: CD19, CD20 bright, CD22, CD23 dim, CD24 dim, CD25 dim, CD71 dim, FMC7, and HLADR. Surface Ig was negative as were the following markers: CD5, CD10, CD11c, CD21, CD103. The lymphocytes were small to intermediate in size with mature nuclear chromatin, occasional nuclear notching or clefts and agranular cytoplasm. Cytoplasmic...
projections were absent. Gene rearrangement studies demonstrated clonal rearrangement of the immunoglobulin heavy chain.

Cyclophosphamide was added on November 5, 1997 at a dose of 3 mg/kg by mouth daily. Although the treatment and the anemia had been well tolerated, on November 6, 1997 she was admitted to the hospital with palpitations and weakness. No cause other than severe anemia (hematocrit 19.8%) was identified, and she was discharged on November 10, 1997 only to be readmitted on November 11, 1997 with similar complaints. Steroids and cyclophosphamide were continued. She was becoming progressively less able to care for herself and her husband, and became very anxious. She received her first transfusion of RBCs on November 15 with a transient increase in hematocrit; an apheresis catheter was inserted on November 17 and a plasma exchange performed on November 18. The IgM level was 437 mg/dL before the exchange and 85 mg/dL 1 week after the procedure. She was again discharged on December 6, 1997 but was readmitted on December 8, 1997 with catheter-associated bacteremia. She received intravenous antibiotics and was supported with RBC transfusions receiving 12 U between November 15 and December 15, 1997, and expressed a desire to be transferred to hospice care and to be allowed to die.

Shortly after rituxan became available, treatment was initiated at the doses used in the trials in low-grade non-Hodgkin’s lymphoma (375 mg/m² by vein weekly for 4 weeks). She tolerated the infusions well. Both steroids and cyclophosphamide were continued although the dose of steroids had been tapered down to 20 mg/d. The IgM level before the first dose of rituxan was lower at 116 mg/dL, although laboratory evidence of hemolysis continued unabated (elevated LDH, bilirubin, and reticulocyte counts). After the first dose of rituxan, 2 U of RBCs were given on December 23, 1997 (2 days before the second dose), but no further transfusions were necessary. The IgM level decreased to 57 mg/dL on December 25, 1997 and to 26 mg/dL on January 6, 1998. The hematocrit stabilized and began to increase, and the LDH level decreased to 245 IU/dL on January 6, 1998 (normal levels 100 to 190 IU/dL) and the bilirubin normalized at 0.5 mg/dL, at which time she was discharged home.

Since discharge, cyclophosphamide was stopped because of a WBC count of 1,800/µL (with subsequent recovery to normal), and her corticosteroid therapy was tapered and discontinued. Her hematocrit level increased steadily to its current level of 37% with a normal reticulocyte count, LDH, and bilirubin. Her most recent IgM level was 10 mg/dL and no paraprotein is detectable by SPEP or immunofixation. Attempts to restart cyclophosphamide after WBC recovery resulted in skin rash requiring discontinuation of the drug. Neither the bone marrow aspirate/biopsy nor the CT of the abdomen has been repeated, and she continues to be fully functional at home having resumed her oral estrogen therapy. Her blood pressure has remained normal.

This patient has a lymphoproliferative disease with only a marrow lymphocytosis and an IgM paraprotein with cold agglutinin activity. She had a severe hemolytic anemia unresponsive to steroids. She did not improve clinically during the 6 weeks of cyclophosphamide therapy, although her IgM level decreased but had rapid clinical improvement after the initiation of rituxan therapy, and has had a sustained response.

Cold agglutinin–mediated hemolytic anemia is a difficult disease to treat. Those patients with hemolysis associated with infections often have only a short episode requiring no specific therapy, whereas patients who have lymphomas and cold agglutinins may have a more chronic course and treatment is often necessary. Therapeutic maneuvers that are often successful in patients with warm antibody associated autoimmune hemolytic anemia such as corticosteroids, intravenous IgG, and splenectomy are usually ineffective with cold autoimmune hemolytic anemia.2 Treatment of the underlying lymphoma may be associated with improvement in the hemolysis. Although it is not possible to be certain about which components of treatment contributed to the very good outcome in this case, it seems very likely that rituxan played a significant role. Further studies of rituxan in patients with cold agglutinins and refractory autoimmune hemolytic anemia are warranted.

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REFERENCES
Rituxan in the Treatment of Cold Agglutinin Disease

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