EFFECT OF RECOMBINANT HUMAN GRANULOCYTE COLONY-STIMULATING FACTOR IN RETICULAR DYSGENESIS

To the Editor:

A.P. Gillio and J.L. Gabriolove have recently reviewed in detail the use of cytokines in inherited bone marrow (BM) failure syndromes. Reticular dysgenesis (RD) is an inherited syndrome characterized by agranulocytosis associated with severe combined immunodeficiency. We have treated two infants suffering from RD with hematopoietic growth factor to correct the profound granulocytopenia presented by these patients. Treatment of the first patient with recombinant human granulocyte colony-stimulating factor (rhG-CSF) has already been reported. In brief, RD was diagnosed in a newborn female born from consanguinous parents when she presented with septicemia 24 hours after delivery. She was treated by rhG-CSF (Amgen Inc, Thousand Oaks, CA) at the dose of 4 μg/kg once a day subcutaneously for a total of 14 days. There were no effects on peripheral blood cell counts and BM examinations. She was grafted 6 weeks after delivery, with a genoidentical BM donor. At time of BM transplantation (BMT), she was still profoundly granulocytopenic. In vitro BM cultures with a cocktail of different growth factors including G-CSF, GM-CSF, IL-6, and IL-3 failed to promote any growth of myeloid precursors.

The second patient, a male newborn, was diagnosed at birth because of a similarly RD affected sister. Starting at 3 weeks of age, the patient was treated subcutaneously with rhG-CSF (Amgen Inc) at escalating doses starting at 5 μg/kg/d up to 30 μg/kg/d for a total treatment time of 40 days. There was no change in peripheral blood cell counts except mild thrombocytopenia. BM examination disclosed persistent myeloid arrest. The patient subsequently underwent hemiologeneic BMT from his mother, which led to rapid and complete lympho-hematopoietic reconstitution by donor cells.

Children with inherited BM failure syndrome associated with agranulocytosis have responded to variable degrees to GM-CSF or G-CSF. No response was seen in our two patients suffering from RD and exposed to rhG-CSF. The lack of in vivo and in vitro responses of myeloid precursor cells to G-CSF suggest that these cells are resistant to the growth-promoting effect of this CSF. Of interest, in vitro combination of stem cell factor (SCF) with G-CSF produces a 10-fold enhancement of granulocyte production. In addition, G-CSF injected in mice with the Steel mutation which have a defective production of SCF is relatively inactive. Thus, we cannot exclude that the failure of rhG-CSF in our two patients might also be related to additional defects such as an intrinsic defect of SCF production. This hypothesis should be evaluated in the future in this group of patients.

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Effect of recombinant human granulocyte colony-stimulating factor in reticular dysgenesis [letter; comment]

W Bujan, A Ferster, E Sariban and W Friedrich

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