Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor (rhGM-CSF) and rhG-CSF in the Treatment of a Child With Severe Chronic Neutropenia

To the Editor:

Recombinant human granulocyte colony-stimulating factor (rhG-CSF) has been widely and successfully used in treating childhood congenital or idiopathic neutropenia. Recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) has been less commonly used and, in some patients in whom it failed, rhG-CSF was able to restore normal granulocyte count. We report a case with a negative response to rhG-CSF and a positive one to rhGM-CSF. G.A. is a 6-year-old boy in whom chronic severe congenital neutropenia was diagnosed since the first days of life. He suffered from several recurrent bacterial infections requiring hospitalization and intravenous antibiotic administration. Bone marrow (BM) biopsy samples showed reduced myeloid lineage, normal erythroid, megakaryocytic and lymphoid series. BM aspirate smears confirmed the decrease of myeloid cells (myeloid/erythroid [M/E] ratio = 0.5; normal values at matched age = 2.6) with no maturative arrest. The median absolute neutrophil count (ANC) until 2 + 6/12 years of life was 0.37 × 10⁹/L. Chromosomal abnormalities, myelodysplasia, hematologic malignancy, aplastic anemia and presence of antineutrophil antibodies were excluded. At the age of 2 + 6/12 years the child was enrolled in the GCSF-8902 G-I2930 (Amgen, Thousand Oaks, CA) protocol, starting with a 5 μg/kg/die dose subcutaneously. In absence of positive response, the dose was progressively increased until the maximum level scheduled from protocol (10 μg/kg/die, 20 μg/kg/die, 30 μg/kg/die, 30 × 2 μg/kg/die). Median of ANCs during 38 months of rhG-CSF treatment was 0.6 × 10⁹/L (Fig 1). BM cellularity remained unchanged, M/E ratio was 0.6, and no maturation arrest was present. Over this period the number but not the severity of infections was reduced. In March 1994 rhG-CSF was interrupted and rhGM-CSF (Sandoz/Shering-Plough, Basel, Switzerland) introduced at 3 μg/kg/die subcutaneously. An increase of ANC greater than 1.0 × 10⁹/L was recorded within 24 hours and a maximum level of 5.0 × 10⁹/L was reached on the following days. After interruption of treatment, the granulocyte count decreased to 0.2 × 10⁹/L; normal level was reached again restarting the treatment, confirming that ANC increase was sustained by rhGM-CSF (Fig 1). Throughout a 2-month period (March and April 1994) the most appropriate dose and injection schedule of rhGM-CSF was found to be 1.5 μg/kg every 4 days. During this period eosinophil level was considerably high, with a 1.3 × 10⁹/L median value. On the definitive rhGM-CSF administration regimen the granulocyte median count oscillated between 3.8 × 10⁹/L and 1.1 × 10⁹/L, respectively, 24 and 96 hours after rhGM-CSF administration. While the median record during the last 3 months (May through July 1994) was 1.4 × 10⁹/L, the eosinophil median count decreased to 0.67 × 10⁹/L, showing a dose-related behavior. BM cellularity, assessed 2 months after rhGM-CSF treatment, was normal.
mal and M/E ratio was 2.5. The only observed side effect was a local erythema, minimized by joining 3 mg hydrocortisone to rhGM-CSF.

In vitro clonogenic capability (assay of CFU-GM) in presence of G-CSF and GM-CSF at optimal concentrations expressed as number of colonies/3 × 10^6 BM mononuclear cells, were, respectively, 43 and 51 on pretreatment period, 69 and 370 on rhG-CSF treatment, 10 and 250 on rhGM-CSF treatment (normal range 49 ± 13 for G-CSF- and 59 ± 10 for GM-CSF-induced colonies). Granulocyte function (superoxide production and chemotaxis) assessed during treatment with rhGM-CSF was within normal range.

In the attempt to explain the success of rhGM-CSF in our patient, some mechanisms could be postulated. The complete normalization of myeloid line following rhGM-CSF and the knowledge that GM-CSF and G-CSF observe a hierarchy of action on myelopoiesis could corroborate the hypothesis of a quantitative or qualitative defect of GM-CSF production. This could also be confirmed by the increase of clonogenic capability of GM-CSF-conditioned culture during rhG-CSF and rhGM-CSF treatment, which, on the other hand, testifies that synergism between these two cytokines is needed for a normal lineage differentiation and proliferation. A second hypothesis could involve a mechanism of disregulation of the GM-CSF receptor, which justifies exogenous rhGM-CSF supply. Furthermore, the extremely rapid increase of ANC.s after rhGM-CSF injection suggests that the cytokine has an action on granulocyte dismission from the BM.

REFERENCES


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