CORRESPONDENCE

Response to Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) But Not to G-CSF in a Case of Agranulocytosis Associated With Large Granular Lymphocyte (LGL) Leukemia

To the Editor:

Large granular lymphocyte (LGL) leukemia is an uncommon lymphoproliferative disorder characterized by an expansion of CD3+ and less frequently CD3- lymphocytes.1 In more than 80% of cases, severe neutropenia (neutrophils <0.5 x 10^9/L) is observed.2 The mechanism responsible for inhibition of granulopoiesis remains controversial. LGL proliferation may suppress granulopoiesis either directly or indirectly by means of immune factors such as circulating antibodies. Granulocyte colony-stimulating factor (G-CSF) has been tested in chronic idiopathic neutropenia and in Felty’s syndrome.3,4 Responses to G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) in agranulocytosis associated with LGL leukemia have been reported in a few cases.5-6 It has been recently suggested that T beta clonal diseases respond better to G-CSF than GM-CSF.7 We report a patient suffering from agranulocytosis associated with monoclonal LGL leukemia who failed to respond to G-CSF and had a transient remission after GM-CSF.

CASE REPORT

A 60-year-old man was known to have been suffering from LGL leukemia with agranulocytosis for 4 years. He had no history of rheumatoid arthritis. His spleen was moderately enlarged, but he had no lymph node involvement. During the 4 years, he had experienced benign recurrent infections such as sinusitis and one episode of severe pneumonia. His peripheral blood values were as follows: WBC, 10.2 x 10^9/L with 1% neutrophils, 8% monocytes, 90% lymphocytes, hemoglobin (Hb), 16.1 g/dL, platelets, 171 x 10^9/L. Ninety percent of the lymphocytes exhibited LGL morphology with CD3+ (98%), CD8+ (82%), alpha beta (85%), CD4+ (10%), CD16+ (69%), CD56+ (6%), CD57+ (39%) phenotype. T-cell antigen receptor gamma gene showed a monoclonal rearrangement by using polymerase chain reaction. A T-cell receptor beta antigen screening panel showed positivity with V beta 22 (92%) monoclonal antibody (IMMU 546; Immuno- tech, Marseille, France). Natural killer and lymphokine-activated killer activity against K562 and DAUDI target cell lines, respectively, were lower than control. Detection of antineutrophil antibodies was negative. Marrow examination showed LGL infiltration (60%) and maturation arrest of the myeloid series. Bone marrow (BM) culture showed a normal concentration of granulocyte precursors (CFU-GM) and colony growth. The number of CFU-GM at day 14 was identical either to interleukin-3 (IL-3) plus stem cell factor (SCF) + G-CSF, IL-3 + SCF + GM-CSF, conditioned placenta medium (CMP) or CPM + cyclosporine A (CsA). Culturing the marrow after CD8 depletion did not modify the growth of CFU-GM.

A 2-month course of corticosteroids (1 mg/kg/d for 28 consecutive days with progressive dose reduction) and a 4-month course of CsA (5 mg/kg/d) were unsuccessful. Subcutaneous (SC) G-CSF injection was started at a 5 μg/kg daily dose for 10 days and 10 μg/kg for the following 2 weeks, but did not modify the neutrophil count. Two
months later, GM-CSF at a daily SC dose of 5 μg/kg was delivered. Neutrophil count had increased to 1.2 × 10⁹/L on the third day, 1.8 × 10⁹/L on day 8 (Fig 1). We did not observe an increase in eosinophil count. On day 8, the patient experienced fever, myalgia, and edema with no renal dysfunction leading up to the end of the GM-CSF treatment. One week later, neutrophil count returned to the previous level.

There is a considerable heterogeneity among LGL leukemia phenotypes. However, response to hematopoietic growth factors does not seem to be influenced by the phenotype. There are few data on the response to G or GM-CSF in LGL-associated neutropenia to appraise the best schedule. Vickers et al recently published the case reports of G- or GM-CSF use in LGL neutropenia. The number is too small to suggest that G-CSF is superior to GM-CSF in correcting neutropenia. In our case, G-CSF dose escalation failed to increase neutrophil count contrary to existing reports. Interestingly, there was a rapid response to GM-CSF after G-CSF failure. However, we did not observe any in vitro explanation. Neither GM-CSF nor G-CSF enhanced the growth of CFU-GM.

The most frequently adverse effects of hematopoietic growth factors consist of bone and muscle ache, skin rashes and fever. Some authors suggest that G-CSF is better tolerated than GM-CSF, but this remains controversial. Side effects could be the limiting factor for the use of GM-CSF in LGL leukemia. Our patient rapidly developed symptoms close to capillary leak syndrome as was previously described. In all patients, efficacy of G- or GM-CSF was immediate but short-term and did not provide long-term benefit. However, they may be useful when severe infections or chronic ulcers occur. Prolonged administration is not easy to propose because of the high cost but injection two or three times a week could be suggested to maintain an acceptable neutrophil count. Recently, a good and durable response to low-dose methotrexate has been reported, but the time to partial response can be up to 1 month. The mechanism whereby G- or GM-CSF is effective in neutropenia-associated LGL remains unclear. It requires greater understanding of the etiology of neutropenia and the exact target cells of the cytokines in BM. Experience with hematopoietic growth factors in LGL leukemia is limited and merits further evaluation.

Laurence Amiot
Bernard Drenou
Renee Fauchet
Laboratoire D’Hematologie-Immunologie
Noelle Genetet
Gilbert Semana
Laboratoire D’Immunologie
Centre De Transfusion Sanguine
CHRU De Rennes, France

REFERENCES

2. Loughran TP: Clonal diseases of large granular lymphocytes. Blood 82:1, 1993
Response to granulocyte-macrophage colony-stimulating factor (GM-CSF) but not to G-CSF in a case of agranulocytosis associated with large granular lymphocyte (LGL) leukemia [letter]

T Lamy, PY LePrise, L Amiot, B Drenou, R Fauchet, N Genetet and G Semana