Early Trilineage Recovery by Granulocyte Colony-Stimulating Factor in a Patient with Aplastic Anemia

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Among the cytokines active in hematopoiesis, granulocyte colony-stimulating factor (G-CSF) has functions mainly on cells of neutrophilic granulocyte lineage [1]. A large number of clinical trials have suggested that G-CSF can accelerate the recovery of neutrophils when used after high-dose cytotoxic chemotherapy or bone marrow transplantation [2, 3]. In addition, G-CSF have been shown to have beneficial effects in patients with aplastic anemia (AA) who suffer from severe neutropenia [4]. With the exception of rare instances, however, G-CSF is known to have little or no effect on erythrocyte or platelet counts [2, 4-7]. We report here a unique case with acquired AA who showed trilineage recovery shortly after administration of rhG-CSF.

Case Report

A 57-year-old man was referred to Osaka University Hospital because of pancytopenia in April 1993. He had a 3-month history of pancytopenia and had received a total of 800 ml of red blood cell (RBC) in a previous hospital. Laboratory data were as follows: hemoglobin (Hb), 11.2 g/dl (immediately after RBC transfusion); reticulo-cytes $88 \times 10^9/l$, white blood cells (WBC), $3.2 \times 10^9/l$ with differentials of 35% neutrophils and 56% lymphocytes; and platelets (PLT) $73 \times 10^9/l$. Bone marrow aspirate and biopsy revealed uniform hypocellularity (nucleated cell count, $14 \times 10^9/l$) with normomegakaryo-cytes and no morphological abnormalities. Based on these findings, he was diagnosed as having mild AA [8]. Daily anabolic steroids were thus administered orally at a dose of 30 mg/kg body weight in April 1993. This treatment did not improve the hematologic parameters and hemoglobin decreased (fig. 1).

Because RBC transfusions were required every 2 or 4 weeks, the patient was admitted to our hospital on September 21, 1993. Hemoglobin was 8.6 g/dl, reticulocytes $80 \times 10^9/l$, WBC $2.71 \times 10^9/l$ (47.8% neutrophils, 3.8% eosinophils, 39.9% lymphocytes, 8.1% monocytes), and PLT

$56 \times 10^9/l$. Bone marrow aspirate revealed severe hypocellularity, and cytogenetic examination showed normal karyotype. After admission, his neutrophil count gradually decreased to less than $1.0 \times 10^9/l$. Because of little response to anabolic steroid therapy, daily rhG-CSF was administered at the initial dose of 250 μ g (5.0 μ g/kg) subcutaneously. A rise of the WBC and neutrophil counts was seen 1 day after the initiation of this treatment. After a 1-week course, G-CSF was discontinued, and WBC and neutrophil counts rapidly decreased. The daily subcutaneous injection of rhG-CSF was returned after a 1-week interruption, but its dose was reduced to 125 μ g/day. Shortly (< 2 weeks) after the treatment, RBC and PLT counts started to increase in addition to the expected rise of neutrophil count. Also, the number of reticulocytes increased and reached a maximum ($246 \times 10^9/l$) at the 8th week of rhG-CSF treatment. The anabolic steroid was then stopped. Since the WBC and neutrophil counts exceeded $30 \times 10^9/l$ 8 weeks after the initiation of therapy, the schedule of rhG-CSF administration was changed (250 μ g two or three times a week). This rhG-CSF treatment maintained the WBC count between $4 \times 10^9/l$ and $10 \times 10^9/l$. Unexpectedly, both hemoglobin and PLT gradually increased the normal range. In addition to the improvement in peripheral blood, bone marrow aspirate exhibited normocellularity with almost normal differentials 6 weeks after the initiation of treatment. However, despite a slight increase in the number of multilineage progenitor cells (CFU-Mix), the numbers of granulocyte-macrophage progen-

250/day 12S/day

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250x2~3/week 100x3/we

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tor cells (CFU-GM), erythroid progenitor cells (BFU-E) and megakaryocytic progenitor cells (CFU-Meg) were not increased by the rhG-CSF treatment: they remained considerably low even after tri-lineage recovery (table 1), suggesting further requirement of rhG-CSF administration for maintenance of peripheral blood cell counts. He was then well controlled by subcutaneous injection of rhG-CSF (100 μ g) three times a week in our outpatient clinic and a clinic of his company.

rhG-CSF treatment has recently been reported to stimulate bi- or trilineage response, albeit in a limited number of patients with AA [10]. In these reports, the bi- or trilineage response was achieved only by long-term (> 2-4 months) administration of rhG-CSF but not by short-term administration. In contrast, the patient presented here showed an early trilineage response to rhG-CSF. This early response appeared to exclude the possibility that the trilineage recovery was spontaneous, but rather suggested that rhG-CSF might have some functions to stimulate proliferation and differentiation of hematopoietic stem cells at least in some AA patients, even if its action was indirect or cooperative. However, the precise mechanisms responsible for such a response are not known at this time. Further clinical trials of rhG-CSF on a large number of AA should provide useful information not only to clarify the clinical significance of rhG-CSF in the treatment of AA, but also to understand the mechanism underlying the heterogeneous pathogenesis of AA.

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G-CSRμ³/₈ Anabolic Steroid (mg/day) 30

RBC Transfusion

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150

100

50

0J

Mar. Apr. May Jun. Jul.

1993

Aug. Sep. Oct. Nov. Dec. Jan. Feb.

1994

Fig. 1. Clinical course. WBC = White blood cells; ANC ■■ neutrophil count; Hb = hemoglobin; PLT = platelets.

Table 1. Numbers of hematopoietic progenitor cells in bone marrow before and after rhG-CSF treatment

a Numbers of progenitor cells (per 5×10^4 cells) were measured using methylcellulose clon-al cultures [9]. All cultures were performed with a combination of interleukin-3 (10 ng/ml), granulocyte-macrophage colony-stimulating factor (10 ng/ml), granulocyte colony-stimulating factor (10 ng/ml), and erythropoietin (2 U/ml). The results are shown as the mean $\pm$ SEM of triplicate cultures. CFU-E = late erythroid progenitor cells; CFU-GM = granulocyte-macrophage progenitor cells; BFU-E = erythroid progenitor cells; CFU-Meg = megakaryocytic progenitor cells; CFU-Mix = multilineage progenitor cells.

b Control value was obtained from 2 male volunteers (ages 57 and 68) showing normal hematopoiesis. The results are shown as the mean $\pm$ SEM of the 2 controls.

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