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INTERMITTENT – LOW DOSE G – CSF TREATMENT IN A PATIENT WITH CHRONIC NEUTROPENIA*

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Chronic neutropenia in childhood has many definable causes and thus a clear cause cannot be identified in a large group of patients. Since the committed stem cell is involved in this disorder, growth factors such as granulocyte colony-stimulating factor (G-CSF) may play an important role in the treatment of severely affected children. Because of the side effects and cost, the use of G-CSF should be restricted to a minimum dose. Here we report a child with chronic neutropenia in whom intermittent-low doses of G-CSF were successfully used over a long period. *Key words: chronic neutropenia, intermittent-low dose G-CSF.*

Chronic neutropenias (CN) of childhood are a group of uncommon disorders which involve committed myeloid stem cells with normal numbers of red cells and platelet precursors. Decreased or ineffective production of neutrophils has been suggested as a mechanism for this disorder. Spontaneous remissions in some children with CN, usually around the age of two to four, may occur. In the majority of patients, there is no genetic pattern. However, a rare, autosomal dominant form has been described[1]. Chronic neutropenia may present with recurrent infections in severely affected children. The use of recombinant human granulocyte colony-stimulating factor (rhG-CSF) may be an effective therapy in these patients. However, there is a risk of malignant transformation and of some other side effects with G-CSF therapy in patients with different forms of neutropenia[2]. Therefore, the use of G-CSF in these patients should be restricted to a minimum.

Here we report a child with CN with recurrent infectilons who responded to intermittent-low doses of G-CSF therapy.

Case Report

A two-year-old boy was admitted to our hospital with complaints of recurrent bronchopneumonia and cough. On physical examination, breath sounds were decreased on the left side and there was minimal hepatosplenomegaly. A chest radiograph revealed cardiac enlargement and pleural effusion on the left side.

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The blood picture was compatible with absolute neutropenia (< 500/mm^3). Bone marrow examination disclosed 24 percent erythroid cells, 46 percent myeloid cells, 6 percent monocytoid cells and 24 percent lymphoid cells. However, no myeloid element was noted beyond the myelocytic stage. Echocardiogram showed pericardial effusion, and a chylous-like fluid was obtained by pericardiocentesis. Surgical pericardiectomy was performed successfully. Pathologic examination showed that chylous pericarditis was due to intrathymic ectatic lymphangiomatous malformation. The patient was neutropenic during recovery and for three months follow-up thereafter with recurrent infections. No cyclic pattern was observed during the follow-up period.

Because of his recurrent infections, persistence of a neutropenic state and past history, the patient was given G-CSF therapy. All the doses of G-CSF were administered subcutaneously. Initially, he was started on 5 µg/kg/day, subcutaneously. The dose was tapered down to 2.5 µg/kg/day after a week, 1 µg/kg/day after 20 days and then to 1 µg/kg/day every other day for 27 days with normal neutrophil counts. He did not maintain this neutrophil count with a G-CSF dose of 0.5 µg/kg/day every other day. However, reintroduction of 1 µg/kg/day G-CSF was successful in maintaining normal neutrophil counts for 20 days. Intermittent therapy was started with 1 µg/kg/day G-CSF being given every other day. The patient was then started on a three-month course with 1 µg/kg/day G-CSF every three days (Table I). At the writing of this report, he has maintained a neutrophil count > 500/mm^3 and no severe infections have occurred over the last year.

Table I: Neutrophil and White Blood Cell (WBC) Counts During Follow-up

Day	WBC Count (per mm^3)	PNL Count (per mm^3)	Treatment*
0	7800	468	–
7	4800	480	–
15	5200	884	–
25	5800	406	–
40	3200	128	–
55	4000	480	–
70	5000	250	–
80	5600	280	–
90	5000	250	–
90-97**	21000	15170	5 µg/kg/day
97-104**	20300	14120	25 µg/kg/day
104-124***	7700 (6000-8400)	5467 (4734-6200)	1 µg/kg/day
124-151***	8100 (7700-8500)	3350 (3000-3700)	1 µg/kg/day, every other day
151-171***	4000 (2800-5700)	360 (235-435)	0.5 µg/kg/day, every other day
171-191***	6000 (5800-6600)	3240 (2800-3900)	1µg/kg/day
191-231***	4600 (4400-4800)	1656 (995-2098)	1 µg/kg/day, every other day
231***	4800 (3000-5700)	1228 (522-1680)	1 µg/kg/day, every three days

* All the doses of G-CSF were given subcutaneously.

** White blood cell and PNL counts were obtained at the end of the week.

*** White blood cell and PNL counts were obtained every week. All the numbers represent the mean of these values. Numbers in the parentheses represent minimum and maximum values for each treatment period.

Discussion

Granulocyte colony-stimulating factor is a hematopoietic growth factor which increases the number of hematopoietic progenitor cells in the bone marrow and peripheral blood of normal subjects and of patients with various types of neutropenia. It also controls activation and late maturation stages of neutrophil development and synergises with GM-CSF and IL-3 in inducing proliferation of primitive hematopoietic progenitor cells in vitro[3]. In a recent article, a defect in the endogenous G-CSF production at the post-transcriptional level was suggested to be an etiologic factor in CN[4]. Therefore, G-CSF treatment is a good aproach for maintaining a normal neutrophil count in CN patients with infections. However, the use of G-CSF has been associated with a number of side effects, such as severe bone pain, splenomegaly, Sweet's syndrome, leukocytoclastic vasculitis and disseminated intravascular coagulation[5-7]. Leukocytoclastic vasculitis was shown to be dose dependent, with the lesions disappearing at doses of < 1 mg/kg-day and recurring at 2 mg/kg/day. Malignant disorders such as aplastic anemia and Kostmann syndrome[8] have been reported in some patients with neutropenia receiving G-CSF therapy. In some cases with severe congenital neutropenia, mutations in the gene for the G-CSF receptor were found. It is suggested that these mutations interrupted signals required for the maturation of myeloid cells. However, the mechanism of malignant evolution is not clear. Possible propensity toward malignant disease in these disorders or G-CSF therapy itself may be the cause of malignant transformation.

In our patient, neutrophil counts over 500/mm^3 were achieved with low and intermittent-low doses of G-CSF. However, the minimum dose to which the patient responded was 1 µg/kg/day. With lower doses of G-CSF the neutrophil count decreased below 500/mm^3. Interestingly, further treatment with 1 µg/kg/day G-CSF dose and intermittent treatment with this same dose was successful. No severe infections or adverse reactions due to G-CSF treatment occurred for a year. In a recent article, Jayabose et al.[9] reported successful results with a three-day-a-week G-CSF regimen in a patient with cyclic neutropenia.

In conclusion, intermittent doses of G-CSF may be used in patients with various types of neutropenia. However, it is suggested that the dose be tapered to a minimum that maintains normal neutrophil counts and that dosages be determined on an individual basis. This approach may be useful in diminishing side effects as well as the cost of treatment.

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