ABSTRACT: TREATMENT OF PATIENTS WITH MYELODYSPLASTIC SYNDROMES WITH G-CSF AND ERYTHROPOIETIN

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Key Words: Myelodysplastic syndromes, Granulocyte colony-stimulating factor, Erythropoietin.

Background: Treatment with granulocyte colony-stimulating factor (G-CSF) increases the granulocyte counts in a majority of patients with myelodysplastic syndromes (MDS), but has only limited effects on hemoglobin levels and platelet counts. Erythropoietin (epo) improves the anaemia in approximately 20% of anaemic MDS-patients. In vitro, G-CSF and epo have shown synergistic effects both on normal and myelodysplastic erythropoiesis. In an attempt to obtain a synergistic effect on the hemoglobin levels in anaemic patients with myelodysplastic syndromes (MDS), granulocyte colony-stimulating factor (granulocyte-CSF) and erythropoietin were combined in a clinical phase II trial.

Methods: Twenty-two patients with MDS (six with stable anaemia and sixteen with transfusion-need) were included in the study. Granulocyte-CSF was given alone for six weeks and then in combination with erythropoietin for the following twelve weeks. The G-CSF-dose (0.3, 1.0 or 3.0 μg/kg/day, s.c.) was adjusted to obtain a granulocyte count between 6–10×10⁹/1. Treatment with epo started at a dose of 60 U/kg/day, s.c. and was increased to 120 U if no effect was obtained after 6 weeks.

Results: Eight (38%) of 21 evaluable patients showed a significant increase in hemoglobin. A complete response with a hemoglobin level above 115 g/l was obtained in four patients (3 with stable anaemia and 1 with transfusion-need). Another four transfusion-dependent patients became transfusion-free at a hemoglobin level above 100 g/l. One patient with a previous response and subsequent failure to erythropoietin alone improved in hemoglobin after the addition of granulocyte-CSF. Sixteen patients showed an increase in granulocyte count of ≥ 2 × 10⁹/1. No significant effects on the platelet counts were observed. The percentage of bone marrow blasts increased in four patients of whom one progressed to acute myelogenous leukemia. Responses in hemoglobin were more frequent in patients with less advanced pancytopenia and in patients with lower endogenous levels of serum-erythropoietin. 6/10 patients with ring sideroblasts in the bone marrow responded to treatment, compared to 2/11 of those without (p = 0.063)

Conclusions: Treatment with granulocyte-CSF and epo resulted in a response frequency of 38%, which is higher than in any study of erythropoietin as monotherapy. Patients with ring sideroblasts, who respond poorly to erythropoietin alone, showed a response rate of 60%. These findings, in combination with the case with a granulocyte-CSF-induced second response to erythropoietin, are highly suggestive for a synergistic effect in vivo of granulocyte-CSF and erythropoietin in patients with myelodysplastic syndromes.

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ABSTRACT: CHRONIC NEUTROPENIA: THERAPY WITH RECOMBINANT HUMAN GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF)

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Background: Neutropenia is defined as an absolute neutrophil count (ANC) < 1x10^9/L. Chronic neutropenia is a poorly defined group of disorders. Included are Kostmann’s disease, other forms of congenital neutropenia, cyclic neutropenia, Schwachmann’s syndrome and neutropenia associated with primary immunodeficiency syndromes. Kostmann’s syndrome was described by Rolf Kostmann in 1949 in an isolate of families in Northern Sweden. The marrow shows a characteristic maturation arrest at promyelocyte/myelocyte level and in both marrow and peripheral blood an increase of monocytes and eosinophils is found. As in other cases of chronic neutropenia the patients have skin infections, parodontitis, bacterial respiratory infections, and deep infections such as septicemia, meningitis and osteomyelitis.

Patients and Methods: Twelve children, 5–19 years old, with chronic neutropenia were treated with recombinant human G-CSF (rhG-CSF) (Neupogen®, Amgen-Roche). Starting dose was 5 µg/kg subcutaneously once daily. The dose was adjusted to keep ANC > 1.5x10^9/L and < 5x10^9/L.

The diagnoses were: Kostmann’s disease, 5 girls and 2 boys; Hyper-IgM syndrome with neutropenia, 2 boys; combined immunodeficiency with neutropenia, 1 boy; and undefined congenital severe neutropenia, 2 boys.

Results: All patients responded to G-CSF treatment with normalization of ANC, infectious rate and healing of their mouth lesions. The Kostmann patients were treated for a mean of 593 days (range 332–704 days). They needed 10 days (mean; range 2–24 days) to achieve ANC > 1.5x10^9/L and a G-CSF dose of 4.2 µg/kg (mean; 1.5–10 µg/kg). The other 5 patients were treated for 536 days (mean; range 135–777 days). The mean time to ANC > 1.5x10^9/L was 3 days (range 1–6 days) and the dose 0.9 µg/kg (mean; range 0.2–1.4 µg/kg). Few side effects were noted: 2 children suffered back pain during the first week of treatment.

Conclusion: G-CSF promptly restores ANC in chronic neutropenia and effectively stops further infections.