Case Report

Received: May 22, 1990

Accepted: September 27, 1991

Acta Haematol 1992;87:148-150

Treatment of Methimazole-Induced Severe Aplastic Anemia with Recombinant Human Granulocyte-Monocyte Colony-Stimulating Factor and Glucocorticosteroids

X.	Xavier	López-Karpovitch ^a
A.	Alfredo	Ulloa-Aguirre ^b
C.	Carlos	von Eiff ^b
R.	Rafael	Hurtado-Monroy ^a
A.	Alfonso	Alanis ^b

^aHaematology Department, Instituto Nacional de la Nutrición Salvador Zubirán, México;

^bDepartment of Internal Medicine, American British Cowdray Hospital, Mexico, México

Key Words

Drug-induced severe aplastic anemia

Glucocorticosteroids

rHu GM-CSF

Abstract

The in vivo response to recombinant human granulocyte-monocyte colony-stimulating factor (rHu GM-CSF) in facilitating the reconstitution of granulopoiesis was evaluated in a patient with Graves' disease who developed severe aplastic anemia during methimazole therapy. After 10 days of treatment with rHu GM-CSF, the neutrophil and monocyte counts rose to $1.65 \times 10^9/l$ and $0.41 \times 10^9/l$, respectively. However, the patient was still dependent on erythrocyte and platelet transfusions. Two days after rHu GM-CSF withdrawal, the neutrophil count dropped off to $0.41 \times 10^9/l$. rHu GM-CSF was reinitiated for 2 days along with glucocorticosteroids. With this combined therapeutic approach, the neutrophil count returned to normal and remained stable, and both Hb and platelet values began to improve. It is concluded that the combination of rHu GM-CSF and glucocorticosteroids can be used as a therapeutic option that may lead to beneficial results in drug-induced aplastic anemia.

Dr. Xavier López-Karpovitch, Hospital Angeles del Pedregal, Office 243, Camino Real Santa Teresa 1055, Col. Héroes de Padierna, Magdalena Contreras 10700 Mexico, DF (México)

The approximate occurrence of agranulocytosis from methimazole, an antithyroid drug, is 1 in 500 as a maximal figure [1]. Apparently, methimazole-induced aplastic anemia (AA) is a rare condition, since information concerning this association has been provided mainly through isolated case reports [2, 3]. In vitro colony-forming assays have provided evidence favoring a humoral, and most probably autoimmune mechanism, rather than a direct toxic effect of methimazole on abnormally sensitive cells as the cause of bone marrow (BM) aplasia [2, 4]. Hence, glucocorticosteroid administration has been the therapeutic approach in antithyroid drug-induced AA. How-

ever, their use in severely neutropenic patients is often hampered due to bacterial or fungal infections.

rHu GM-CSF has been shown to increase neutrophil counts in neutropenic patients with idiopathic AA [5] or AA secondary to accidental heavy irradiation (⁶⁰Co) [6], and in drug-induced agranulocytosis [7, 8].

This report presents data showing complete, although transient, recovery of granulomonopoiesis with rHu GM-CSF and sustained restoration of BM function soon after glucocorticosteroid treatment in a patient with Graves' disease who developed severe AA secondary to methimazole ingestion.

Case Report

Ⓢ rHu GM-CSF

□ Glucocorticosteroids

6 4 H

2-

A 17-year-old female who had been treated with methimazole (45 mg/day for 5 weeks) due to Graves' disease was admitted with a sore throat, dysphagia, myalgia, arthralgia, and dysuria. Physical examination revealed: fever (39.2°C), tachycardia and functional holosystolic grade II murmur, enlarged and painful thyroid, generalized rash, and oral thrush. Her peripheral blood values were: Hb 12.4 g/dl, 0.16% re-ticulocytes (corrected for PCV), neutrophils $0 \times 10^9/l$, monocytes $0.10 \times 10^9/l$, lymphocytes $1.1 \times 10^9/l$, and platelets $233 \times 10^9/l$. The BM was hypocellular (cellularity < 25%) with scanty megakaryocytes, 13% late erythroblasts, 79% lymphocytes, 3% lymphoblasts, 2% plasma cells, and 3% granulocytes. The diagnosis of severe AA was based on peripheral blood and BM data (neutrophils < $0.5 \times 10^9/l$, re-ticulocytes < 1% and BM cellularity < 30%) [9]. Because of septicemia and urinary sepsis no glucocorticosteroids were given and the patient was treated with antibiotics. The patient's clinical status remained stable but the platelet count started to decline (fig. 1).

With the patient's informed consent and after approval of the local Ethic Committee, rHu GM-CSF (Scheramex, SA. de C.V., Mexico) was given intravenously in a 2-hour infusion at a daily dose of 10 µg/kg. Moderate anorexia, chills, and fatigue, as well as severe bone pain were noticed and interpreted as side effects of the rHu GM-CSF treatment. At day 4, a second bone biopsy was performed, since both the Hb and platelet values continued to decrease, the neutrophil count remained low and mucocutaneous bleedings appeared, requiring platelet transfusion. Although the BM examination still showed decreased cellularity (< 30%), incipient signs of haematopoietic recovery were observed, such as the presence of proerythroblasts, increase in erythroblasts, megakaryocytes, and granulocyte precursors. Based on these findings the dose of rHu GM-CSF was increased to 12.5 µg/kg and at day 10 the neutrophil and monocyte counts rose to $1.65 \times 10^9/l$ and $0.41 \times 10^9/l$, respectively. However, the patient was still dependent on erythrocyte and platelet transfusions. rHu GM-CSF was stopped, according to the protocol, and 2 days later, the neutrophil count dropped to $0.41 \times 10^9/l$. rHu GM-CSF was resumed for 2 days (12.5 µg/kg) along with glucocorticosteroids (methylprednisolone 2 g daily on days 12-14 and 1.5 g on day 15; prednisone, 75 mg daily, was tapered off during a 3-week period). With this combined therapeutic approach the neutrophil count returned to normal and remained stable. Both the Hb and platelet values gradually improved. Two years after the patient's discharge her clinical condition and peripheral blood picture remain normal.

r14

1 -

-12

0.5-

0.1
0.05-
- 9

0.01 J
L 10 20

Fig. 1. Hb (O), neutrophil (•) and platelet (Δ) values during treatment with rHu GM-CSF and glucocorticosteroids. Data were plotted in a semi-logarithmic 3-cycle scale. Left-hand arrows indicate platelet transfusions and right-hand arrow erythrocyte transfusion.

Discussion

Drug-induced agranulocytosis has been reported to be associated with a mortality in excess of 20%. In about 68% of the patients, the BM shows hypoplasia. The recovery of the peripheral neutrophil count starts in 4-7 days if the BM is normocellular, but takes 7-56 days (mean 14 days) if the BM is hypoplastic [8]. Thus every therapeutic approach to restore BM function to reduce the period of pancytopenia, particularly neutropenia, must be attempted. BM transplantation, a first-line strategy in severe idio-pathic AA, is not the procedure of choice in drug-induced

AA due to the frequent spontaneous recovery observed in these patients following drug withdrawal. Glucocortico-steroid therapy in immune-mediated haematopoietic suppression is rational, however, its use in severely neutropenic and infected patients is hazardous.

Because initial data in phase I and II studies with rHu GM-CSF in neutropenic patients were found to be encouraging [5-8], we decided to treat our patient aiming at either to overcome possible immune-mediated haematopoietic suppression or to enhance neutrophil functions [10]. Recovery of neutrophil and monocyte counts occurred 10 days after starting rHu GM-CSF. In our patient,

149

CD4 (OKT4) 48%; CD8 (OKT8) 2%; CD2 (OKT11) 2%; CD7 (Leu9) 4%; CD5 (TI) 9%; CD1 (OKT6) 0%; OKT9 0%; CD38 (OKT10) 18%; Kappa 4%; Lambda 3%; SmIg 33%; CD20 (B1) 1%; CD19 (B4) 5%; CD10 (J5) 0%; Cμ 0%; CD13 (My7) 0%; CD14 (My4) 5%; CD33 (My9) 3%, and OKIa-1 (HLA-DR) 75%. The significant findings were CD4 48%; SmIg 33% and Ia 75%, and negative myeloid and monocytic markers.

Discussion

Ia and SmIg are known to occur on monoblasts [10,11]. Polyclonal SmIg positivity without a light chain preponderance in acute monoblastic leukaemia is mostly ascribed to exogenous binding of immunoglobulin to the Fc receptor and does not necessarily denote B-lymphocyte differentiation [12]. The polyclonal SmIg positivity in this case, supported by the erythrophagocytosis observed, implies the presence of the Fc receptor.

The CD4 antigen is expressed on both mature peripheral blood monocytes as well as on immature monoblasts [1]. Since little is known about the appearance and disappearance of surface markers during the ontology of early progenitors, it is of note that CD4 is expressed without the expression of myeloid and monocytic lineage-specific markers on the blasts in our patient. Studies of the expression of CD4 in acute monoblastic leukaemia and in leukaemic cell lines [3, 4] do not clarify the chronological relationship of CD4 and monocytic lineage-specific markers

during monocyte differentiation. Whether CD4 precedes the myeloid and monocytic markers in this case could not be determined but should be considered.

The expression of T-cell antigens in the absence of early myeloid and monocytic markers may lead to confusion in the classification of morphological or cytochemically indefinite cases, and it is therefore worthwhile to be aware of this occurrence.

Our patient had no particularly distinguishing features in his history or clinical findings. Since it is well known that M5 has a worse prognosis than other subtypes of acute myeloid leukaemia [13], investigation into the role of the CD4 receptor in prognosis could be of importance. A recent study [2] showed that the CD4-positive monocyte subset has increased antigen presentation, but also increased tumor necrosis factor production. Both factors could influence prognosis.

The extent of the clinical and biological implications of CD4+, CD33-, CD13-, CD14- acute monoblastic leukaemia can only be elucidated by studying a series of patients with this marker profile although this may be difficult due to the small number of cases reported.

Acknowledgements

We would like to thank the staff of our Bone Marrow Laboratory for their invaluable technical assistance as well as Dr. E. Wilken for the use of her clinical data.

References

- Wood GS, Warner NL, Warnke RA: Anti-Leu-3/T4 antibodies react with cells of monocyte/macrophage/Langerhans lineage. *J Immunol* 1983;131:212-216.
- Szabo G, Miller CL, Kodys K: Antigen presentation by the CD4 positive monocyte subset. *J Leukoc Biol* 1990;47:111-120.
- Kaplan SS, Pechansky L, Stole V, Contis L, Krause JR: Immunophenotyping in the classification of acute leukaemia in adults. Interpretation of multiple lineage reactivity. *Cancer* 1989; 63:1520-1527.
- Neudorf S, DeLaat C, Jones M: Expression of the CD4 molecule of acute nonlymphocytic leukaemia (ANLL) cell lines. *J Clin Lab Anal* 1989;3:312-315.
- Tauchi T, Ohyashiki K, Ohyashiki J, Kawanishi OY, Kimura Y, Saito M, Nakazawa S, Kawai Y, Toyama K: CD4+ and CD56+ acute monoblastic leukaemia. *Am J Hematol* 1990;34:228-229.
- 10
- Bennet JM, Catovsky D, Daniel MT, Flandren G, Galton DAG, Gralnick HR, Sultan C: Proposed revised criteria for the classification of acute myeloid leukaemia. A report of the French-American-British cooperative group. *Ann Intern Med* 1985;103:626-629.
- Sandberg AA: The chromosomes in human leukaemia. *Semin Hematol* 1986;23:201-217.
- Ortho Diagnostic Systems: Product Information Insert. Raritan, Ortho Diagnostic Systems, 1984.
- Kung PC, Talle MA, DeMaria ME, Butler MS, Lifter J, Goldstein G: Strategies for generating monoclonal antibodies defining human T-lymphocyte differentiation antigens. *Transplant Proc* 1980;12(suppl 1):141.
- Mirchandani I, Tabaczka P, Palutke M: Acute monocytic leukaemia: A surface marker study. *Am J Hematol* 1982;12:139-147.
- Parker AC, Dewar AE, Wilson CD, Young S, Stuart AE: Surface membrane characteristics of cells from human acute monocytic leukaemia. *Scand J Haematol* 1978;20:467-478.
- Tubbs RR, Valenzuela R, Savage RA, Deodhar SD: The nature of surface immunoglobulin in pure monocytic (M5) leukaemia. *Am J Clin Pathol* 1979;72:614-617.

Tobelem G, Jacquillat C, Chastang C, Auclerc M, Lechevallier T, Weil M, Daniel M, Flandrin G, Harrousseau J, Schaison G, Boiron M, Bernard J: Acute monoblastic leukaemia: A clinical and biologic study of 74 cases. *Blood* 1980; 55:71-76.

152

Lombard/Mansvelt

CD4+ Acute Monoblastic Leukaemia