

Successful Treatment of Refractory Anemia With High-Dose Methylprednisolone

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Five patients with refractory anemia were treated with high-dose methylprednisolone. An immediate and long-lasting hematological improvement without serious side effects was achieved in two of the patients, although chromosomal abnormalities persisted in both. The clinical course and laboratory data of these two patients are described. Restoration of normal hematopoiesis was achieved regardless of the enhancement of colony formation of granulocyte progenitor cells by the simultaneous addition of hydrocortisone in vitro. The same treatment was given to six patients who had refractory anemia with an excess of myeloblasts (RAEB), but no improvement was observed in any of these patients. It appears that high-dose methylprednisolone can be valuable in the treatment of refractory anemia, but is not useful for RAEB.

Key words: myelodysplastic syndrome, steroid therapy, chromosome abnormalities

INTRODUCTION

Refractory anemia shows a relatively low incidence of the subsequent development of acute leukemia and a relatively long survival among the myelodysplastic syndromes (MDS) [1,2]. However, no effective treatment of this disease has yet been established [3,4]. Improvement has been reported in 9% of a group of MDS patients treated with daily high-dose prednisone [5], although this therapy can be hazardous due to the serious side effects that frequently occur with prolonged administration. Bolus high-dose methylprednisolone therapy has been reported as effective in the treatment of aplastic anemia [6]. It has no serious side effects since the treatment regimen involves administration of the drug for only a short period of time. Recently, we gave this treatment to five patients with refractory anemia and to six patients with refractory anemia with an excess of myeloblasts (RAEB). A complete remission was achieved in two of the patients with refractory anemia.

this, no hematological improvement was observed in any of the six patients with RAEB. Here, we report in detail on the two cases of refractory anemia that were successfully treated.

Case 1

A 36 year old man was admitted on February 1, 1983. His previous treatment include prednisolone, gamma globulin, and androgen, but there had been no hematological improvement. Splenomegaly was not present at admission. Hematological data are shown in Table I. The LDH level was within normal limits. Bone marrow aspiration and biopsy revealed hypocellular fatty marrow (Fig. 1) with dyserythropoiesis, a predominance of the erythroid lineage, and a decrease in megakaryocyte numbers. Ringed sideroblasts were not observed. A bone marrow scan with ^{111}In showed uneven uptake with less uptake in the pelvis and enhanced uptake in the femurs. Chromosomal analysis showed no abnormality at this

CASE REPORTS

Five patients with refractory anemia were given high-dose methylprednisolone therapy (Table I), and complete remission was achieved in cases 1 and 3. In contrast to

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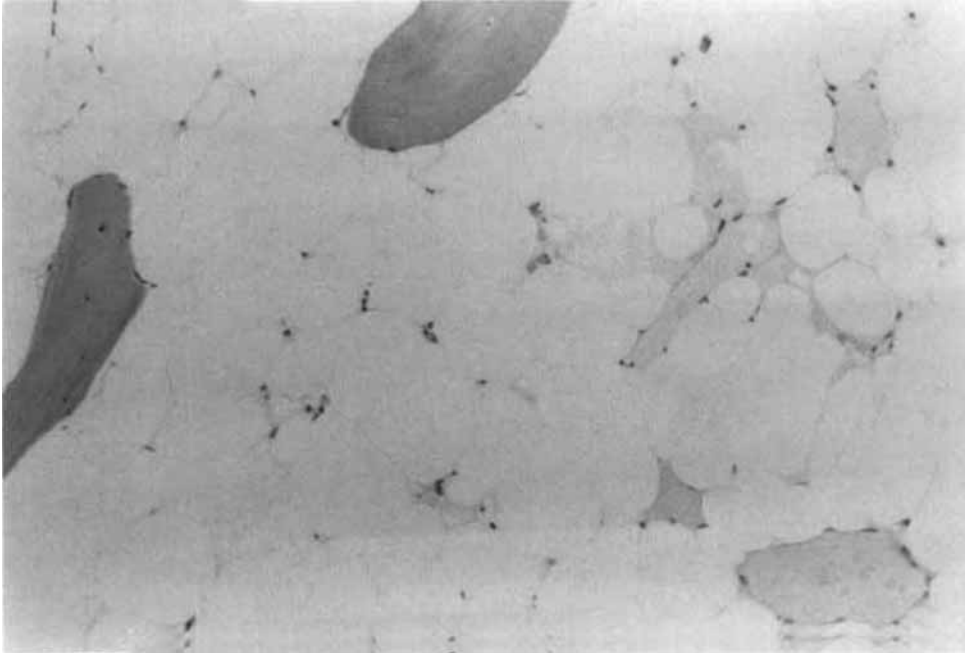


Fig. 1. Bone marrow biopsy of case 1 (first admission).

time (Table I). The number of colonies formed by granulocyte progenitor cells from the bone marrow (colony-forming units in culture, CFU-C) was only $6/2 \times 10^5$ cells (control: 93 ± 21), and the number formed by erythroid precursor cells (colony-forming units-erythroid, CFU-E) was $0/2 \times 10^5$ cells (control: 293 ± 16).

He was given anabolic steroid for 18 months with no improvement. He required transfusion of 5 U of packed red blood cells and 50 U of packed platelets per month to maintain acceptable hemoglobin and platelet levels plus 20 mg of prednisolone daily to prevent bleeding (Fig. 2). He was readmitted on October 29, 1984, because of hyperglycemia due to the prolonged prednisolone treatment. Physical examination showed mild hepatomegaly and petechiae in the lower extremities, but no splenomegaly. Laboratory data from the second admission are shown in Table I. There were no significant changes in the laboratory data and bone marrow findings. ^{111}In uptake by the bone marrow was almost completely absent. In the CFU-C assay, bone marrow cells formed only a few colonies, and simultaneous addition of hydrocortisone did not augment the colony numbers (data not shown). Chromosomal analysis showed cells with a normal karyotype plus three clones with an abnormal karyotype (Table I). Because of the presence of these chromosomal abnormalities and the results of ferrokinetic studies, a diagnosis of refractory anemia was made, even though the bone marrow was still hypocellular.

The patient was given 1,000 mg of methylpred-

nisolone daily for 3 consecutive days. Within 2 months of this treatment, his hemoglobin level increased significantly and his requirement for packed platelets was reduced to one-third of the previous amount (Fig. 2). Normalization of the red cell, white cell, and platelet counts was achieved after 1 year. One year after treatment, he had normocellular marrow and *in vitro* colony formation by CFU-C had increased to a level roughly equivalent to normal marrow progenitor cells. Chromosomal analysis, however, still revealed the mixture of normal and abnormal clones that had been observed previously (46, XY, 11/30 cells; 45, XY, -7, 3/30; 47, XY, +8, 15/30; 49, XY, +X, +8, +8, 1/30). The patient has been in complete hematological remission ever since, and no maintenance therapy has been required in the 4 years following treatment.

Case 3

A 27 year old woman was admitted on October 7, 1985. She had a 5 year history of leukocytopenia (WBC $3.1 \times 10^9/\text{l}$) and a 1 year history of anemia (Hb 7.3 g/dl) requiring packed red blood cell transfusion. Hepatosplenomegaly was not present. The laboratory data at admission are shown in Table I. The number of CFU-C colonies was markedly decreased and did not improve with hydrocortisone. Chromosomal analysis revealed a mixture of karyotypically normal and abnormal clones (Table I). A diagnosis of refractory anemia was made, and she was treated with 1,000 mg of methylprednisolone daily for 3 consecutive days. In the following 2

TABLE I. Laboratory Data of the Five Patients at Admission

Case	1		2	3	4	5
Age	36		51	27	49	44
Sex	M		M	F	M	M
	1st	2nd				
Peripheral blood						
WBC ($\times 10^9/l$)	2.0	2.3	1.0	2.1	2.3	2.7
Granulocytes (%)	33	25	13	30	74	45
Hb (g/dl)	8.2	6.0	10.8	8.8	8.2	10.0
Platelets ($\times 10^9/l$)	10	17	14	80	57	134
Reticulocytes (%)	2.4	0.4	0.3	0.4	2.2	1.5
Bone marrow						
Cellularity	Hypo	Hypo	Hypo	Hyper/normo ^a	Normo	Hypo
Blasts (%)	0.6	1.5	1.5	3.9	0.9	1.2
Dyspoiesis	(+)	(+)	(+)	(+)	(++)	(+)
Ferrokinetics ^b						
PID T 1/2 (min)	129	97	109	118	106	117
PIT (mg/dl blood/day)	0.70	1.67	0.71	0.93	1.69	0.98
ET (mg/dl blood/day)	0.30	1.10	0.44	0.54	1.06	0.58
% RCU (%)	85	12	41	37	52	65
RBC T 1/2 (days) ^c	24	32	15	28	20	21
Karyotype ^d	Normal	46,XY, 7/31 45,XY, -7 5/31 47,XY, +8 10/31 49,XY, +X, +8, +8, 9/31	46,XY,t(1;7) 30/30	46,XX 3/30 46,XX,20q- 24/30 47,XX, +8,20q- 2/30 92,XXXX,20q-,20q- 1/30	46,XY 5/30 46,XY,20q- 25/30	Normal
Follow-up duration (months)		52	15	40	10	9
Improvement		(++)	(-)	(++)	(-)	(\pm) (transient)

^aThis is the only case in which bone marrow biopsy could not be performed. Aspirate from the posterior superior iliac spine was hypercellular, but that from the sternum was normocellular.

^bMean values \pm SD of ferrokinetic studies were obtained from six patients without erythropoietic disturbance. Plasma iron disappearance rate T 1/2 (PID T 1/2) 92 ± 25 min; plasma iron turnover (PIT) 0.60 ± 0.17 mg/dl blood/day; erythron turnover [7] 0.40 ± 0.12 mg/dl blood/day; percent red cell iron utilization (% RCU) $98 \pm 5\%$ /10–14 days. Red cell survival (RBC T 1/2) 25 ± 7 days.

^c⁵¹Cr was used to measure RBC T 1/2.

^dCytogenetic studies were performed using the Q-banding technique.

weeks, the reticulocyte count temporarily rose to 4.5%, and hemoglobin and platelet levels normalized within 2 months (Fig. 3.) After hematological remission, she had normocellular marrow with slightly hypogranular neutrophils. Chromosomal analysis, however, revealed persistence of the same karyotypically abnormal cells (46, XX, 4/20 cells; 46, XX, 20q-, 16/20). She remained in remission for 2 years and then again developed mild pancytopenia. High-dose methylprednisolone was given again, and a complete remission was again achieved, which has lasted until the present.

DISCUSSION

High-dose methylprednisolone has been shown to be effective in the treatment of aplastic anemia [6]. Patients 1, 2, and 5 required distinguishing from aplastic anemia since the bone marrow was hypocellular. Patients 1 and 2, however, showed chromosomal abnormalities of a

type associated with hematological malignancies like acute myeloblastic leukemia and myeloproliferative disorders. In addition, the presence of dyspoiesis and the results of ferrokinetic studies (1, 2, and 5) indicated the diagnosis of refractory anemia. The presence of hypoplastic marrow in MDS has been reported by Nand et al. [8].

Bagby et al. [5] have reported that it is possible to predict the responsiveness to prednisone by an in vitro bone marrow culture technique. Although enhanced CFU-C colony formation as suggested by Bagby et al. was not observed in the present two patients, immediate and long-lasting hematological remission was achieved. The results of in vitro bone marrow culture, therefore, do not necessarily coincide with the efficacy of high-dose methylprednisolone therapy in refractory anemia. The laboratory data from all patients were analyzed in an attempt to determine the factors related to responsiveness to high-dose methylprednisolone. However, there were

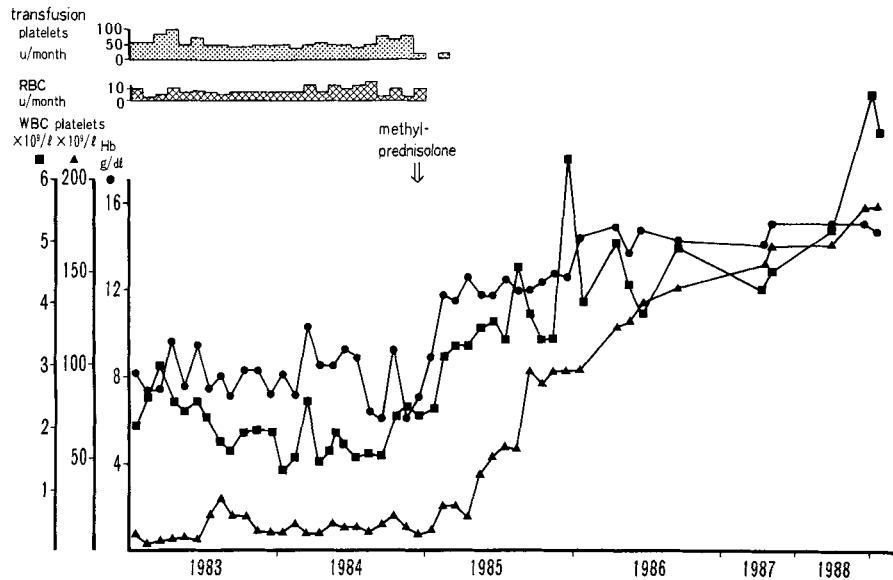


Fig. 2. Clinical course of case 1.

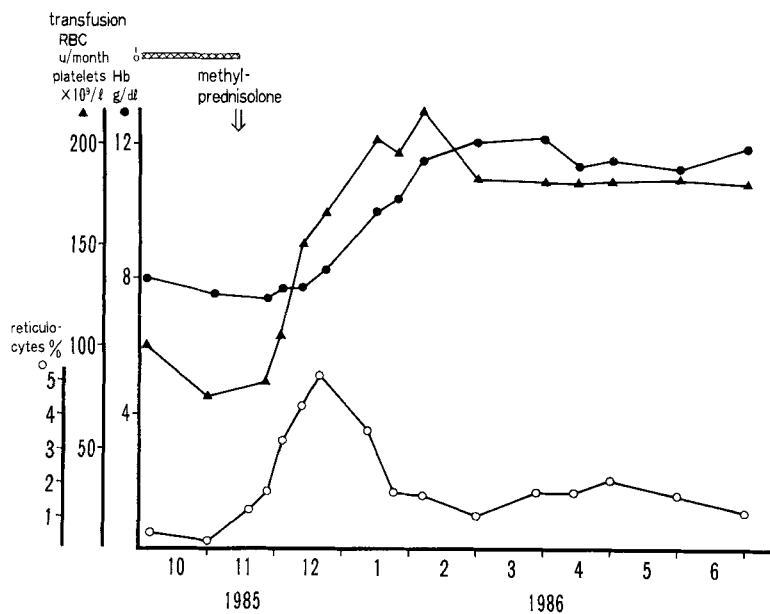


Fig. 3. Clinical course of case 3.

no significant differences between the responding patients (cases 1 and 3) and the nonresponding ones (cases 2, 4, and 5) in bone marrow cellularity, the degree of dyspoiesis, ferrokinetics, colony formation, and the presence or absence of chromosomal abnormalities.

Serious side effects related to steroid therapy were not observed in these patients, and an advantage of this treatment is that it requires only a short period of administration, thereby limiting the total dose. This is an obvious

contrast with ordinary steroid treatment that requires an indefinite period of administration.

The ultimate goal in the treatment of MDS is to restore normal hematopoiesis and to prevent the development of acute leukemia. The data from the two successfully treated patients indicate that high-dose methylprednisolone restores normal hematopoiesis, but it does not eliminate karyotypically abnormal clones. This may still allow the possibility of future leukemic evolution. Meth-

ylprednisolone is thought to exert a therapeutic effect in aplastic anemia by immunosuppression. It has been reported that in aplastic anemia autologous lymphocytes (T- γ) or their culture medium supernatant was able to inhibit colony formation in CFU-C assay [9]. Accordingly, our success in treating refractory anemia may also indicate that such an immunological mechanism is involved in its clinical progression. Indeed, immunological abnormalities such as a reduction in the number of T cells and functional abnormalities of T and B cells have been reported in MDS [10,11]. Bagby [12] documented enhanced CFU-C colony formation following elimination of T cells in four MDS patients. This also supports immunological involvement of T lymphocytes in the pathogenesis or clinical progression of refractory anemia. The possibility that methylprednisolone induced the differentiation of karyotypically abnormal cells also cannot be denied.

It has been proposed that MDS, including refractory anemia, is the result of neoplastic transformation at the level of the pluripotent stem cells and has a multistep pathogenesis [13,14]. Tricot et al. [15] reported that MDS is divided into three categories of disease progression. Our present two patients are likely to belong to his group A, which is characterized by stable clones with low proliferative capacities. We also applied the same treatment to six patients with RAEB but did not observe any improvement. RAEB is considered to be a more aggressive and progressive stage of the disease compared with refractory anemia. It may be that a therapeutic effect from high-dose methylprednisolone treatment can be expected in Tricot et al.'s group A patients, but not for those in the progressive stages of the disease. Furthermore, Colombat et al. have reported that a decrease in T3, T4, and T8 lymphocytes was more pronounced among patients with RAEB than among those with refractory anemia [10]. Such an immunological deficiency in RAEB may partly explain the lack of responsiveness to methylprednisolone. Although we did not attempt it, it may be that repeated administration of methylprednisolone could still have a beneficial effect in RAEB. It has been shown that the presence of leukemic blast cells inhibits the proliferation of normal CFU-C [16]. Thus, the high proliferative activity of myeloblasts in RAEB may prevent the growth of normal hematopoietic precursor cells.

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