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PURE RED CELL APLASIA FOLLOWING PERIPHERAL STEM CELL TRANSPLANTATION: COMPLETE RESPONSE TO A SHORT COURSE OF HIGH-DOSE RECOMBINANT HUMAN ERYTHROPOIETIN

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ABSTRACT

We studied a patient who developed pure red cell aplasia (PRCA) following peripheral stem cell transplantation for non-Hodgkin lymphoma. Serum erythropoietin was appropriate for the degree of anemia. Corticosteroid treatment was ineffective. Four months after transplantation rHuEpo was administered subcutaneously at a dose of 150 U/Kg per day, five days a week for 8 weeks. Treatment induced an erythropoietic response and corrected anemia. Response was maintained following discontinuation of rHuEpo. This study and previous reports indicate that high doses of rHuEpo given over a short time can resolve PRCA following autologous or allogeneic stem cell transplantation.

Key words: erythropoietin, pure red cell aplasia, bone marrow transplantation

Endogenous erythropoietin production becomes inadequate in most recipients of allogeneic bone marrow transplantation (BMT) 2-3 weeks after transplant.[1]

Administration of rHuEpo to these patients can accelerate erythroid recovery and reduce red cell transfusion requirements, not only with no stem-cell competition but with a beneficial effect on platelet recovery.[2]

Long-lasting anemia is frequently observed following autologous BMT (using either bone marrow or peripheral stem cells). In this setting, however, endogenous erythropoietin production in generally adequate and the development of erythropoiesis is mainly determined by marrow proliferative capacity.[3] Due to this and to the scarcity of committed progenitors infused, administration of rHuEpo is usually not effective in stimulating erythroid repopulation after autologous BMT.[4]

In this report, we describe a patient who developed pure red cell aplasia (PRCA) following peripheral stem cell transplantation. In spite of appropriate endogenous erythropoietin production, he responded to pharmacological doses of recombinant human erythropoietin with complete correction of anemia.

Case report

A 48-year-old man was first seen at the Department of Hematology, Rome, in 1988 for a non-Hodgkin lymphoma (follicular, predominantly large cell; D according to the Working Formulation). There was bone marrow infiltration, indicating a clinical stage IV. Treatment with F-MACHOP produced a partial remission but mild bone marrow involvement persisted; since the patient was asymptomatic, it was decided to follow him without further therapy.

In September, 1990, lymph node enlargement reappeared. The patient was treated with an alternative drug combination (PROVECIP: procarbazine, vinblastine, cyclophosphamide,

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prednisone) and achieved complete remission after four cycles. Remission was maintained with 12 additional cycles.

In 1992, at the end of this maintenance therapy, the patient agreed to undergo high-dose chemotherapy with peripheral stem cell transplantation. Peripheral stem cells were mobilized with high-dose cyclophosphamide followed by G-CSF, and the BEAC protocol was adopted as conditioning regimen. Transplantation was performed in July 1992.

Hemopoietic recovery was delayed; in particular, the patient showed a high transfusion requirement in order to maintain a hemoglobin level around 8 g/dL (Figure 1). Two months after transplantation, bone marrow biopsy showed a hypoplastic marrow with an almost total absence of erythroid precursors, a picture indicating PRCA. Corticosteroid treatment was ineffective and reticulocyte count remained fixed at zero.

Serum erythropoietin was 420 mU/mL and the observed/predicted log(erythropoietin) ratio (O/P ratio) was 1.11 (the O/P ratio averages 1.00±0.11 in reference subjects, 95% confidence interval: 0.80-1.22). The value found in our patient indicated normal endogenous erythropoietin production.[5]

Despite this, we decided to administer rHuEpo on a compassionate basis. rHuEpo was kindly provided by Boehringer Mannheim Italia, Monza, Italy, and was administered subcutaneously daily at a dose of 150 units per kilogram of body weight, five days a week.

Response to treatment was initially suggested by steady increases in serum transferrin receptor (TfR) and reticulocyte count. Available evidence indicates that serum transferrin receptor is a truncated form of surface receptors, that its major source is the erythroid precursors in the bone marrow and that its serum level is a measure of erythroid marrow activity.[6] Normal TfR levels average 5.0±1.1 mg/L and 95% confidence limits range from 2.9 to 7.1 mg/L. Serum TfR concentration ranged from 0.4 to 0.8 mg/L in our patient before beginning rHuEpo, values typically found in aplastic anemia. TfR level normalized after four weeks of treatment (Figure 1). Corrected reticulocyte count increased from 0 to 4.3 % by week 5; rHuEpo treatment was discontinued after 8 weeks and Hb remained stable in a range of 13.5 to 15 g/dL. The serum erythropoietin level was 29 mU/mL post-therapy, with a Hb of 14.9 g/dL. Erythropoietic response to rHuEpo was also typical in terms of body iron status parameters. In fact, serum ferritin fell from 2106 to 169 μ/L, and serum iron from 237 to 37 μg/dL (Figure 1).

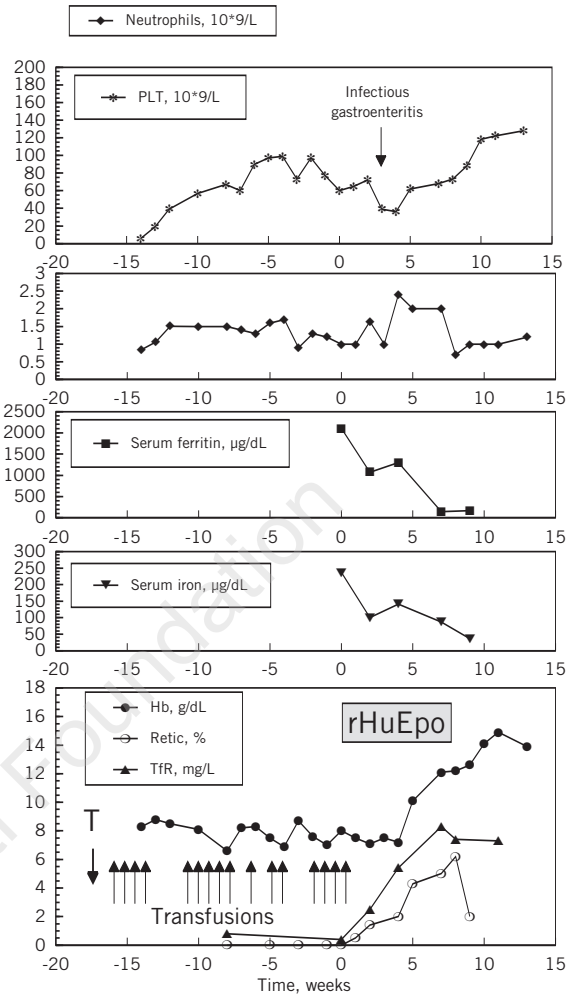

Figure 1. Clinical course of our patient. rHuEpo was started at time 0. T indicates peripheral stem cell transplantation.

Discussion

Following autologous BMT our patient developed PRCA while maintaining normal endogenous erythropoietin production. In spite of

this, he responded to high doses of rHuEpo with complete correction of anemia. Other reports have also described the positive effects of rHuEpo in PRCA (Table 1).

Heyll et al.[7] treated a patient with PRCA after major ABO-incompatible bone marrow transplantation. Serum erythropoietin was markedly increased (560 mU/mL): treatment with rHuEpo induced reticulocytosis and corrected the anemia. Similar cases were later reported by Paltiel et al.[8] and Taniguchi et al.[9] It is noteworthy that two of these three cases did not respond to standard doses of rHuEpo (about 75 U/kg 3 times a week). Escalation from alternate-day to daily administration resolved PRCA.

Responses to rHuEpo in PRCA patients have also been observed outside the transplantation setting. Finelli et al.[10] reported a patient with idiopathic PRCA who did not respond to corticosteroids. Subsequent treatment with rHuEpo was effective in ameliorating anemia. Zeigler et al.[11] studied a patient with PRCA associated with myeloid metaplasia who failed to respond to immunological agents. Her serum erythropoietin level was 907 mU/mL with a Hb of 7.9 g/dL. rHuEpo was administered at 500 U/Kg intravenously three times a week. Hemoglobin increased from 7.9 to 12 g/dL after 2 months. When the patient declined further therapy, she suffered a relapse of her red cell aplasia. Overall, all these responsive patients with idiopathic PRCA relapsed after discontinuation of rHuEpo.

Although PRCA is frequently observed following ABO-incompatible allogeneic BMT, the mechanism behind this is still not clear.[8] All but one case reported involved blood group O recipients of bone marrow from blood group A

Table 1. Case reports on the use of rHuEpo in the treatment of pure red cell aplasia after stem cell transplantation.

Authors	*Condition and endogenous erythropoietin production*	*Treatment and outcome*
Heyll et al (7)	PRCA after major ABO-incompatible allogeneic BMT lasting > 230 days. Serum epo was markedly increased (560 mU/mL)	rHuEpo at a dose of 4,000 U sc three times weekly was ineffective. The dose was increased to 4,000 U daily and an erythropoietic response was soon observed: reticulocytes appeared within one week. Complete correction of anemia was achieved in 3-4 weeks and was maintained after discontinuation of rHuEPO.
Paltiel et al (8)	PRCA after major ABO-incompatible allogeneic BMT lasting > 230 days. Serum epo was increased (360 mU/mL).	Erythroid engraftment was observed soon after the initiation of rHuEpo at a dose of 50 U/kg daily. Complete correction of anemia was achieved in 3 weeks and was maintained after discontinuation of rHuEPO.
Taniguchi et al (9)	PRCA after major ABO-incompatible allogeneic BMT lasting > 200 days. Serum epo was markedly increased (720 mU/mL).	rHuEpo at a dose of 4,500 U sc daily was ineffective. The dose was increased to 9,000 U daily and an erythropoietic response was soon observed. Complete correction of anemia was achieved in 3 weeks and was maintained after discontinuation of rHuEPO.
Present report	PRCA after peripheral stem cell transplantation lasting 120 days. Serum epo was markedly increased (420 mU/mL).	Erythroid engraftment was observed soon after the initiation of rHuEpo at a dose of 10,000 U sc daily, 5 days weekly. Complete correction of anemia was achieved in 8 weeks and was maintained after discontinuation of rHuEPO.

donors. It has been proposed that circulating isoagglutinins may inhibit erythroid progenitor proliferation in these patients. High doses of rHuEpo would overcome such inhibition and allow erythroid precursor proliferation; this, in turn, would neutralize the circulating inhibitors and result in effective red cell production.[8]

Our patient was autotransplanted with autologous peripheral stem cells so that no ABO-incompatibility was involved in the pathogenesis of his PRCA. A working hypothesis is that excessive apoptosis of erythroid progenitors may occur in some patients following BMT.[3] This prevents erythroid engraftment since most CFU-Es die and few or no erythroblasts are formed. Erythropoietin has been demonstrated to be a survival factor for erythroid cells that expands erythropoiesis by preventing the apoptosis of erythroid progenitors and proerythroblasts.[12]

Thus, administration of rHuEpo may overcome the excessive death of erythroid progenitors in PRCA and allow sufficient production of erythroid precursors and erythroid engraftment.

A word of caution, however, must be spent about the interpretation of serum erythropoietin levels in PRCA. A relationship does exist between red cell precursor mass and erythropoietin clearance.[5] The latter must be somewhat slower in patients with PRCA, who completely lack erythroid precursors; in this case, the observed serum levels would overestimate endogenous erythropoietin production.

Therefore the possibility exists that the beneficial effects of rHuEpo reflect a condition of inadequate endogenous erythropoietin production in spite of high serum levels.

From a practical point of view, the present study and previous reports suggest that any patient with PRCA unresponsive to conventional therapy, especially following BMT, deserves treatment with a short course of high-dose rHuEpo.

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