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BRIEF REPORT

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Pure red cell aplasia after major ABO-incompatible bone marrow transplantation: two case reports of treatment with recombinant human erythropoietin

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Abstract A 34-year-old man with acute myelocytic leukemia (AML : MO) and a 32-year-old woman with AML : M2 developed pure red cell aplasia (PRCA) after receiving a major ABO-incompatible bone marrow transplant (BMT). The first patient responded to recombinant human erythropoietin (rhEPO) therapy, while the second did not. The second patient also received methylprednisolone (m-PSL) but developed reticulocytosis and hemolysis after the administration of m-PSL. Plasmapheresis was then performed and the patient promptly recovered from hemolysis and PRCA. We conclude that close attention must be paid when treating PRCA following major ABO-incompatible BMT with rhEPO and m-PSL, as there is always the potential for massive hemolysis.

Key words ABO-incompatible bone marrow transplantation · Bone marrow transplantation, ABO-incompatible · Red cell aplasia, bone marrow transplantation

Introduction

A delay in erythrocyte recovery after major ABO-incompatible bone marrow transplantation (BMT) is often documented [2, 4, 6, 11]. Patients may become dependent on red blood cell transfusions for a long period, a condition similar to pure red cell aplasia (PRCA) [2, 4, 6, 11]. The delay is assumed to be caused by the persistence of host-derived antibodies targeting erythrocyte antigens on late-stage erythroid precursors [2]. There have been a few reports of the spontaneous recovery of erythrocytes; in other cases, patients have required a variety of clinical interventions [5, 7–10]. Recently, Heyll et al. [5] reported a patient with PRCA after major ABO-incompatible BMT who was successfully treated with recombinant human erythropoietin (rhEPO). We describe two patients with PRCA following ABO-incompatible BMT, one who responded to rhEPO, and a second who developed massive hemolysis following rhEPO and methylprednisolone (m-PSL). The second patient recovered following plasmapheresis.

Case reports and results

Patient 1

A 34-year-old man with acute myelocytic leukemia (AML : MO) in first complete remission received a bone marrow transplant from his HLA-identical and MLC-negative brother. This transplant was performed following a conditioning regimen consisting of cytosine arabinoside (CA) 1.4 g/m^2, every 12 h on days 6 and 5 pre-BMT, cyclophosphamide (CY), 2250 mg/m^2, on days 4 and 3 pre-BMT, and total body irradiation (TBI) in fractionated doses (2.5 GY) twice daily for a total of 12.5 Gy on days ——2, ——1, and 0 in July 1990. There was a major ABO incompatibility. The blood group of the donor was A Rh-positive and that of the recipient was O Rh-positive, with anti-A and anti-B agglutinin titers of 1 : 256 and 1 : 128, respectively. Donor marrow cells were infused after erythrocyte depletion by centrifugation on Lymphoprep (Nycomed Pharma, Oslo, Norway). Cyclosporin A and short-term methotrexate were administered for prophylaxis of acute graft-versus-host disease (AGVHD). A neutrophil count of 0.5×10^9/l and a platelet count of 50×10^9/l were reached on days 24 and 30 following BMT, respectively. NO evidence of erythroid recovery was obtained.

Analyses of bone marrow aspirates on days 29, 64, 100, 162, and 265 revealed a morphological picture of PRCA, with less than 1 % erythroid precursors in an otherwise normal marrow. The patient's anti-A agglutinin titer remained 1 : 16 on day 265. Cyclosporin A had been tapered and was discontinued on day 150. Parvovirus B19 was not identified in the blood by dot-blot hybridization. Because the patient had received 100 units of red blood cell transfusions by this time, he received rhEPO after giving informed consent. The initial rhEPO dose was 3000 IU intravenously every other day from day 265 to day 285. The absolute reticulocyte count began to increase and reached 136×10^9/l on day 282. The rhEPO dose was then increased to 6000 IU every other day from day 287 to day 293, and 6000 IU daily from day 294 to day 308. On day 290, his anti-A agglutinin titer decreased to an undetectable level in his serum, and the appearance of blood group A erythrocytes was confirmed. On day 317, hemoglobin increased to 15.5 g/dl, with an absolute reticulocyte count of 639×10^9/l and 51.6 % erythroid precursors in his bone marrow. To date (4.5 years post-BMT), the patient has been in remission with normal blood counts and normal marrow findings.

Patient 2

A 32-year-old woman with AML (M2) in second remission received a bone marrow transplant from her HLA-identical and MLC-negative brother in September 1992. There was a major ABO incompatibility. The blood group of the donor was A Rh-positive while that of the recipient was O Rh-positive with anti-A and anti-B agglutinin titers of 1 : 32 and 1 : 16, respectively. Conditioning regimens, prophylaxis of AGVHD, and erythrocyte depletion were carried out as in patient 1. AGVHD grade I developed on day 27 but resolved without any additional treatment. A neutrophil count of 0.5×10^9/l and a platelet count of 50×10^9/l were reached on days 19 and 24 following BMT, respectively. The patient's blood showed a virtual absence of reticulocytes. Analyses of bone marrow aspirates on days 29, 69, 98, and 132 revealed normal myeloid and megakaryocytic maturation with less than 2 % erythroid precursors. Her anti-A agglutinin titer remained 1 : 4. Parvovirus B19 was not identified in the blood by polymerase chain reaction. Because the patient had received 46 units of red blood cell transfusions, shw was treated with rhEPO after giving informed consent. She received 6000 IU of rhEPO intravenously daily from day 132 to day 165, at which time treatment was discontinued. Cyclosporin A was stopped on day 153.

Analysis of a bone marrow aspirate on day 167 showed 0.6 % erythroid precursors, with an absolute reticulocyte count of 5.1×10^9/l. On day 167, m-PSL was administered intravenously at a dose of 1100 mg/day for 3 days and was then tapered and discontinued on day 173. The patient developed hypertension with a blood pressure of 172/122 mm Hg on day 174. Laboratory data were as follows: hemoglobin 7.0 g/dl, platelet count 66×10^9/l, absolute reticulocyte count 58.0×10^9/l, serum LDH 2261 mu/ml, total bilirubin 1.9 mg/dl, direct bilirubin 0.5 mg/dl, haptoglobin < 10 mg/dl, creatinine 0.99 mg/dl, fibrinogen 84 mg/dl, PT 14.0 s, APTT 26.5 s, FDP 0.2 mg/dl, negative direct and indirect antiglobulin test, anti-A agglutinin titer 1 : 4, and anti-B agglutinin titer 1 : 2. Urinalysis showed proteinuria (1000 mg/dl) and microscopic hemoglobinuria (RBC 5–8/hpf). A review of the peripheral blood smear revealed erythrocyte fragmentation.

Plasmaphereses with 1.5 l of fresh frozen plasma were performed on days 175 and 176. The patient's hypertension resolved on day 181. At that time, her hemoglobin increased to 9.6 g/dl with an absolute reticulocyte count of 348×10^9/l. Massive proteinuria decreased to 30 mg/dl. Analysis of a bone marrow aspirate showed 31.0 % erythroid precursors. On day 202, the patient's anti-A agglutinin titer decreased to an undetectable level in the serum, and the appearance of blood group A erythrocytes was confirmed. Since that time (3 years post-BMT), she has been in remission with normal blood counts and normal marrow findings.

Discussion

Erythrocyte engraftment is often delayed following major ABO-incompatible BMT but is usually observed spontaneously after 2–3 months with a decrease in agglutinin titers [11]. Treatment of PRCA is generally not required in the early post-transplant phase [4, 6, 11]. However, PRCA may persist for longer periods and require many erythrocyte transfusions [11]. As for the mechanism responsible for the delay of recovery after ABO-incompatible BMT, Gmur et al. have hypothesized that auto-erythrocyte antibodies produced by persistent functional B lymphocytes of recipient origin inhibit erythroid engraftment [4]. In fact, many reports have shown that recovery of erythrocyte production is associated with decreases in agglutinin titers. Barge et al. [1] have clearly demonstrated the presence of normal numbers of immature erythroid progenitors, BFU-E, in this setting that can form erythroid bursts in the absence of patient serum. Braine et al. [3] have also suggested that a delay in erythrocyte recovery after ABO-incompatible BMT can be attributed to high pretransplant agglutinin titers. In our patients, the anti-A agglutinin titer at the time of BMT was high (1 : 256) in patient 1 and 1 : 32 in patient 2.

Several therapeutic approaches, including the administration of rhEPO [5, 10], m-PSL [8], and antilymphocyte globulin [7] as well as plasmapheresis [9], have been reported to be effective in this setting. RhEPO stimulates the bone marrow to produce excess numbers

of erythroid precursors. The hypothesis behind this approach is that once production of erythrocytes exceeds a threshold agglutinin level that causes hemolysis of almost all erythrocytes produced, erythrocytes would increase and the titer of agglutinin would decrease with absorption of agglutinin. In our first patient, production of erythrocytes occurred without any massive hemolysis and the patient responded as predicted by this hypothesis. However, our second patient did not respond to rhEPO alone. Therefore, we began treatment with m-PSL at a dose of 1100 mg/day in an attempt to decrease agglutinin titers. Seven days after beginning m-PSL administration, hemolysis occurred simultaneously with the onset of reticulocytosis. The hemolysis resolved promptly after 2 days of plasmapheresis and the reticulocytosis progressed. Agglutinin titers decreased and remained at undetectable levels thereafter. Or et al. have reported that reducing the titers of erythrocyte antibodies may be necessary to shift the balance towards donor hematopoiesis [9]. The clinical symptoms and laboratory data exhibited by patient 2 were similar to those in patients who develop hemolytic uremic syndrome (HUS) following BMT. Plasmapheresis is known to be beneficial in HUS. However, we could not determine whether the hemolysis that occurred when the patient recovered from PRCA was, in fact, due to HUS since a renal biopsy was not performed.

We conclude that it may be beneficial to use rhEPO in the treatment of PRCA after ABO-incompatible BMT. In cases where rhEPO is not effective, treatment with m-PSL and plasmapheresis may be attempted. However, one must be cantious and bear in mind the potential for massive hemolysis.

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