□ CASE REPORT □

Apheresis Therapy for Prolonged Red Cell Aplasia after Major ABO-Mismatched Bone Marrow Transplantation

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Two cases of leukemia were treated successfully with apheresis for delayed recovery of erythropoiesis due to antibody-mediated red cell aplasia after ABO-mismatched bone marrow transplantation (BMT). A 25-year-old female (ABO group O) underwent BMT from her brother (group A). Immunoadsorption using Biosynsorb A performed on day 146 after BMT followed by double filtration plasma pheresis (DFPP) reduced anti-A antibody titers from 1:32 to 1:2. Anemia improved dramatically within 2 weeks. A 49-year-old female (group O) underwent BMT from her mother (group A). She was treated with DFPP on day 131 after BMT. Anti-A antibody titers dropped from 1:16 to 1:1 and anemia improved gradually.
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Key words: delayed red blood cell (RBC) recovery, double filtration plasma pheresis (DFPP), immunoadsorption

Introduction

Major ABO incompatibility between donor and recipient red blood cells exists in approximately 10% to 20% of HLA-matched bone marrow transplantation (BMT) and in 15% to 20% of HLA-mismatched BMT (1). In ABO-mismatched BMT, double filtration plasma pheresis (DFPP) or immunoadsorption using columns containing synthetic A or B antigens has been used successfully to remove anti-A or anti-B antibodies (ab) prior to marrow infusion (2, 3). However, the efficacy of blood apheresis for delayed red blood cell (RBC) recovery after ABO-mismatched BMT has not been documented well. We report here two cases of leukemia who were treated effectively with apheresis for persistent red cell aplasia after ABO-mismatched BMT.

Methods

Measurement of ABO antibodies

The IgM anti-A ab titer was measured by saline agglutination of major ABO-type specific red blood cells at room temperature. Heparinized plasma was clotted by the addition of protamine sulfate before testing. Blood chemistry and hematologic values were determined at the clinical laboratories with standard techniques.

Apheresis therapy

DFPP procedure

The patient's blood was drawn and separated into corpuscles and plasma via the first separator fiber (Plasmacure, 0.6 m^2, Kuraray Co., Ltd., Osaka). The separated plasma was then passed through a second filter which was made of ethylene vinyl alcohol (Evaflax 2A, Kuraray Co.). The total volume of separated plasma was 60 ml/kg for each treatment. The filtered plasma and separated blood cells were circuited back into the patient. A saline solution containing albumin replaced the drained plasma.

Immunoadsorption procedure

Immunoadsorption was also performed using the DFPP system, but the second filter was replaced with an immunoadsorbent (Biosynsorb A, Kawasumi Laboratories, Tokyo) which was a chemically synthesized human blood-group substance covalently linked to crystalline silica. The volume of separated plasma was 60 ml/kg for each treatment.

Case Reports

Patient 1

A 25-year-old female (ABO group O), who presented with general malaise and leukocytosis (white blood cells (WBC)

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$12.9\times10^9/l$), was diagnosed as having chronic myelogenous leukemia (CML) in July 1994. After treatment with interferon and hydroxyurea, leukocytosis improved (WBC $4\times10^9/l$). The patient underwent BMT from her HLA-identical brother whose blood type was A in October 1994. Her anti-A ab titer prior to BMT was 1:128. She was treated with 4 mg/kg of busulfan daily for 4 days followed by cyclophosphamide (CY) 60 mg/kg/day intravenously (IV) for two days before BMT. The patient received cyclosporin, 1.5 mg/kg IV in two divided daily doses starting from day-1. Engraftment, which was documented by rapid recovery of WBC and platelet counts occurred early. There was no evidence of graft-versus-host disease (GVHD) or hemolysis such as elevated serum indirect bilirubin or lactate dehydrogenase (LDH) levels. Nevertheless, she remained RBC transfusion-dependent without evidence for donor-derived erythropoiesis. Bone marrow examination showed marked hypoplasia of erythroid series at one month after BMT. She was administered two courses of methylprednisolone pulse therapy (1,000 mg daily for three days) on day 96 and 116 without appreciable effect. She underwent 1 course of immunoadsorption and DFPP because the anti-A titer remained high (1:32).

IgM anti-A titers decreased from 1:32 to 1:8 after immunoadsorption, then to 1:2 following these apheresis therapies on day 147, and was undetectable on day 187. Marked reticulocytosis occurred on day 20 after apheresis. The hemoglobin level increased from 6.8 g/dl to 9.9 g/dl on day 225 (Fig. 1). The patient tolerated the DFPP and immunoadsorption quite well and had no complications during or after apheresis.

Patient 2

A 49-year-old female (ABO group O), who presented with a fever and petechiae was diagnosed as having acute myelogenous leukemia (AML, M2) in November 1993. A complete remission was obtained following induction chemotherapy with enocitabine (BHAC), daunorubicin (DNR) and 6-mercaptopurine (6-MP) followed by three courses of consolidation therapy with mitoxantrone (Mit), cytarabine (Ara-C), BHAC, etoposide (ET) and aclarubicin (ACR). Although her AML relapsed in May 1994, the second remission was obtained after chemotherapy with Mit, ET, CY and prednisolone (PSL) (MEAP). After two additional courses of MEAP and BHAC-ACR-DMP (DNR, 6-MP, PSL) therapy, she underwent BMT from her mother whose blood type was A in December 1994. There was only one locus mismatch between the recipient and donor HLA. Mixed lymphocyte culture (MLC) was non-reactive. Before BMT she was conditioned with 4 mg/kg of busulfan daily for 4 days followed by CY, 60 mg/kg IV daily for two days and 2.5 mg/kg of rabbit anti-thymocyte globulin daily for four days. Her anti-A ab titer was 1:32. She received cyclosporin 3 mg/kg IV in two divided daily doses from day-1. The patient achieved early engraftment of the marrow graft that was documented by rapid recovery of WBC and platelet counts. There was no evidence of acute GVHD and hemolysis such as elevated serum indirect bilirubin or LDH levels and decreased haptoglobin levels. However, reticulocytes did not appear even 100 days after BMT. Bone marrow examination performed on days 60 and 95 after BMT revealed severe red cell aplasia. Because anti-A titers remained high (1:16) on day 111 after BMT, the patient proceeded to apheresis therapy.

Three sessions of DFPP starting from day 131 reduced the IgM anti-A ab titer from 1:16 to 1:2. However, the titer increased to 1:16 at 8 days after DFPP. Three sessions of DFPP was repeated on day 174 followed by methylprednisolone pulse therapy (1,000 mg daily for consecutive 3 days). The anti-A ab titer dropped to 1:1 and became undetectable on day 187. Reticulocytosis occurred at 8 days after DFPP. A type RBCs were documented on day 209 and sustained thereafter. The hemoglobin level increased from 6.8 g/dl to 9.4 g/dl on day 216. She tolerated the DFPP well and manifested no complication during or after the procedures. In association with the improvement of anemia, WBC and platelet counts also increased after the last DFPP (Fig. 2).

Comments

Recipients of a major ABO-mismatched marrow graft do not usually experience graft rejection (4), suggesting that hematopoietic stem cells do not seem to express appreciable amounts of cell surface ABO antigens (5). However, major ABO-incompatible transplants do carry the risk of a hemolytic transfusion reaction at the time of marrow infusion, due to the presence of incompatible donor RBC contained in the marrow inoculum. In addition, RBC precursors derived from the donor's stem cells may be lyzed by persistent host's anti-A or B ab, leading to the delay in the elevation of donor's RBC following BMT. Sniecinski et al (6) reported that 7.6% of patients undergoing ABO-mismatched BMT showed markedly delayed reticulocytosis requiring 170 days or more after BMT. The present cases did not show evidence of reticulocytosis at 100 days after BMT, probably because of high titers of anti-A ab. Fukuda et al (7) reported that high titers of pre-transplant anti-A or anti-B agglutinin are correlated with the delay in RBC recovery. Reviron et al (8) also reported that high residual hemagglutinin titers at day 20 post-BMT are positively correlated with the delay in RBC engraftment. Hemolysis and delayed reticulocytosis after BMT can be prevented by removing the isohemagglutinins from the marrow recipient prior to marrow infusion (3). Plasma exchange is effective (9), but uses large quantities of a valuable blood product and exposes the recipient to additional risks of allergic reaction and transmissible diseases. Hence, DFPP and/or immunoadsorption therapies have been applied to removal of the isohemagglutinins prior to major ABO-mismatched BMT (2, 3).

On the other hand, there have been a few reports of successful blood apheresis for delayed RBC recovery after major ABO-mismatched BMT. Or et al reported two cases of prolonged pure red cell aplasia following major ABO mismatched BMT that resolved immediately after one cycle of plasmapheresis (10). The present two cases with prolonged pure red cell aplasia after ABO-mismatched BMT also responded to DFPP and immunoadsorption and dramatically restored donor-derived erythropoiesis. These clinical courses indicate that

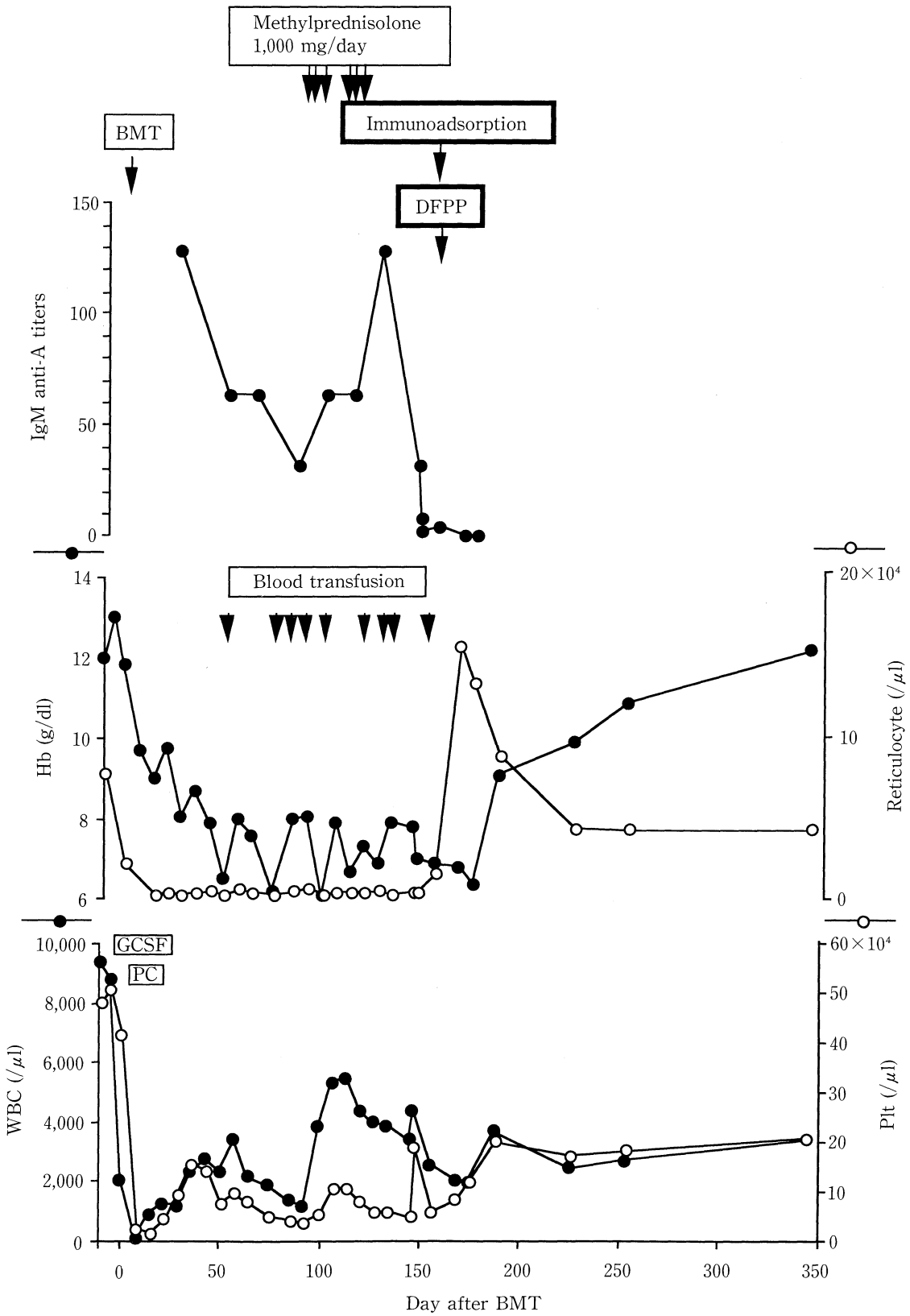

Figure 1. Clinical course of patient 1. After one session of immunoadsorption and DFPP, IgM anti-A titers were decreased and marked reticulocytosis occurred, followed by improvement of anemia.

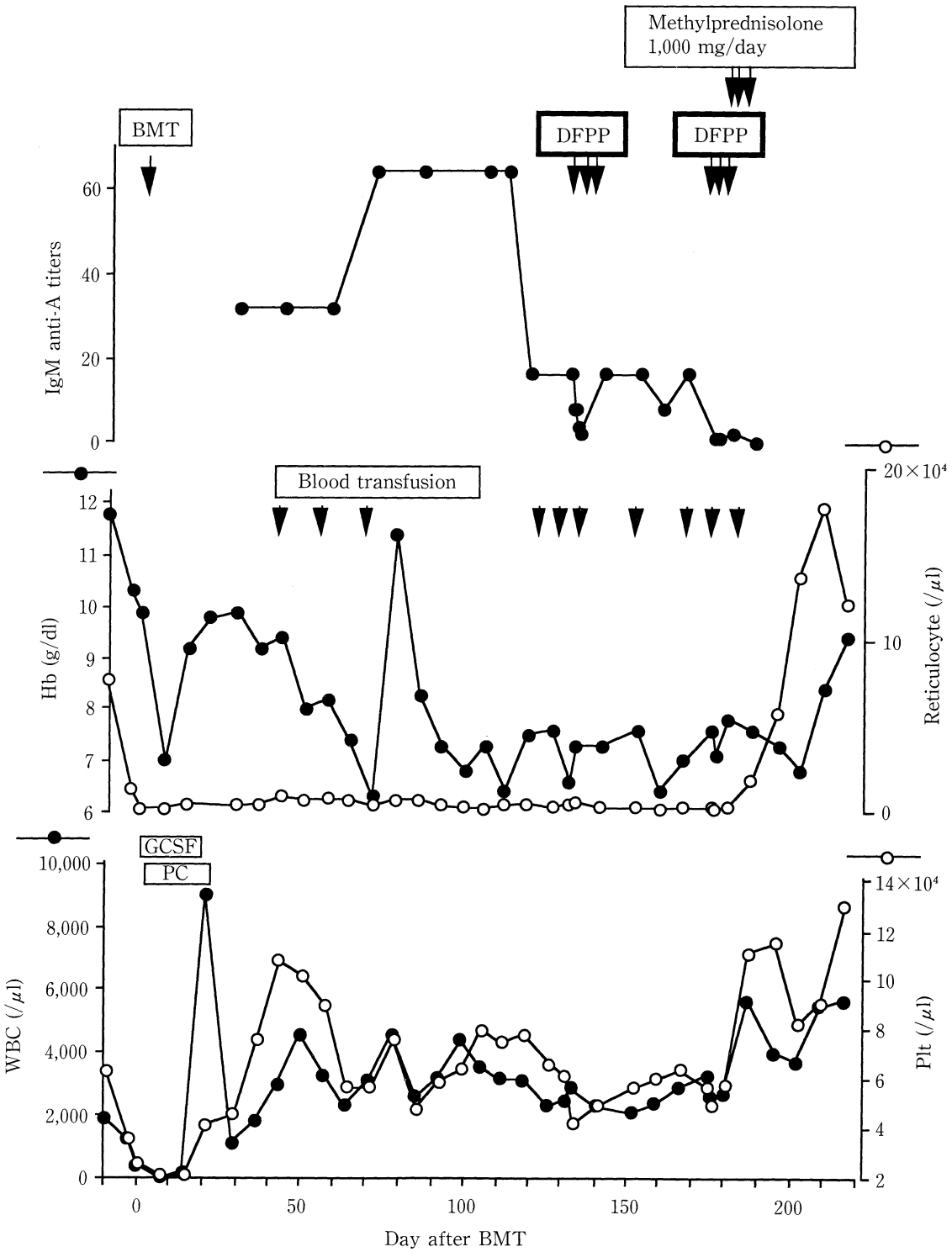

Figure 2. Clinical course of patient 2. After two courses of DFPP followed by one course of methylprednisolone pulse therapy (1,000 mg daily for consecutive three days), reticulocytosis immediately occurred in association with a decrease of IgM anti-A titers. Platelet and leukocyte counts also increased after these treatments.

apheresis therapy is useful not only for the prevention of both hemolysis and delayed RBC recovery, but also for the treatment of prolonged red cell aplasia in ABO-mismatched BMT.

In most ABO-mismatched BMT, the donor RBCs emerge in the peripheral blood within about one month after BMT and isohemagglutinin disappears from the serum due to its absorption by donor-derived RBC. Since the prevalence of delayed RBC recovery after ABO-mismatched BMT has been reported in about 20% (6), it is more useful to do the apheresis therapy after BMT for the case with a high isohemagglutinin titer or prolonged RBC recovery than doing it for all cases before BMT in point of fact.

Sniecinski et al (6) reported a case of prolonged red cell aplasia that was remitted 605 days after BMT following 13 plasma exchanges. Similarly, in patient 2, the first three sessions of DFPP failed to recover erythropoiesis, leading to rebound of anti-A ab titers. However, DFPP combined with methylprednisolone pulse therapy successfully reduced anti-A ab titers. It has been reported that steroid pulse therapy is useful for suppressing the rebound of antibody production after apheresis therapy (11). These findings suggest that corticosteroid therapy suppressed further production of isohemagglutinin by the residual host B cells and synergistically reduced the anti-A ab titers with DFPP. It is generally believed that the persistence of host-derived antibody-producing cells contributes to high titers of isohemagglutinin after BMT (4, 6). Non-TBI regimens used for preconditioning of our two patients may have favored the survival of host B cells, leading to the persistence of high anti-A ab titers. The combination of methylprednisolone pulse therapy with plasmapheresis may be useful for some cases with antibody-mediated red cell aplasia refractory to apheresis therapy.

We treated patient 1 with immunoadsorption followed by DFPP for delayed RBC recovery since we were not able to repeat immunoadsorption due to the extensive cost of the procedure. DFPP is generally thought to be more effective than immunoadsorption in the removal of antibodies from the blood. However, immunoadsorption has advantages over DFPP in selectivity for the removal of pathogenic antibodies and in the necessity for replacement of removed plasma. In patient 1 one round of immunoadsorption greatly reduced the anti-A ab titer. Thus, immunoadsorption may be more recommended than DFPP for the treatment of prolonged red cell aplasia.

Conclusion

Immunoadsorption and DFPP are useful in treating prolonged antibody-mediated red cell aplasia after major ABO-mismatched BMT.

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