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.

(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 m², 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)
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 daunorubicin (DNR), 6-mercaptopurine (6-MP) and cytarabine (Ara-C), followed by three courses of consolidation therapy with etoposide (ET) and aclarubicin (ACR). Although her AML relapsed in May 1994, the second remission was obtained after treatment with mitoxantrone (Mit), cytarabine (Ara-C), BHAC, etoposide (ET) and aclarubicin (ACR). She tolerated the DFPP well and manifested no complications or during or after apheresis.

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 lysed by persistent host’s anti-A or anti-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 reticulocyosis requiring 170 days or more after BMT. The present cases did not show evidence of reticulocyosis at 100 days after BMT, probably because of high titers of anti-A or anti-B 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 reticulocyosis 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 for ABO-Mismatched BMT

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 immunoabsorption followed by DFPP for delayed RBC recovery since we were not able to repeat immunoabsorption due to the extensive cost of the procedure. DFPP is generally thought to be more effective than immunoabsorption in the removal of antibodies from the blood. However, immunoabsorption 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 immunoabsorption greatly reduced the anti-A ab titer. Thus, immunoabsorption may be more recommended than DFPP for the treatment of prolonged red cell aplasia.

Conclusion

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

References