Management of Minor ABO Incompatibility in Allogeneic Stem Cell Transplant by Plasma Reduction from the Graft: Case Report from A Tertiary Care Private Hospital in Dhaka

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ABSTRACT

Human Leukocyte Antigen (HLA) matching plays a crucial role in allogeneic SCT outcome and remains the single most important factor for donor selection. ABO blood group barrier is often crossed between patient and donor. ABO incompatibility may cause acute haemolysis due to transfer of high titre donor isohaemagglutinins contained in the graft or in paediatric patients with small blood volume. To overcome this obstacle, some amount of plasma present in progenitor cell product can be reduced. Plasma reduction can be done in many ways. For a financial constrain set up, we did the plasma reduction manually to overcome the complications and cost. Here we are presenting a case report from Bangladesh.

Key words: Plasma reduction, ABO incompatibility, allogeneic stem cell transplant, Immune haemolysis, Bangladesh.

Introduction

Allogeneic stem cell transplant (SCT) is a curative option for a variety of malignant and non-malignant haematological diseases. HLA matching is the most important predictor for transplant outcomes and rate of engraftment. SCT performed across ABO blood group barrier has proven to be effective. Both blood group system and HLA system inherited independently. HLA genes are located on short arm of chromosome 6 and the genes encoding ABO carbohydrate glycosyltransferase are located on long arm of chromosome 9, hence a potential donor could be fully HLA matched but ABO incompatible. Approximately 40-50% of all SCTs are ABO incompatible.1 ABO incompatibility in SCT is classified into three groups: major, minor and bi-directional. Major incompatibility is characterized by presence of preformed antibodies or isoagglutinins in recipient against red blood cells of the graft. In minor incompatibility the graft contains isoagglutinins directed against corresponding A or B antigens on
recipient’s red blood cells. Bidirectional shares features of both major and minor incompatibilities. Minor ABO incompatibility occurs in 20-25% of transplants due to one of the three following circumstances: (1) if AB recipient receives SCT from a non-AB donor with anti-A, anti-B, or both; (2) when a group A recipient receives SCT from group B or O, which contains anti-A; and, (3) if a group B recipient receives from group A or O, which contains anti-B. The expected immune-haematological consequences in this type of SCT could be immediate (during graft infusion) and delayed (during engraftment) haemolysis. If the graft contains large volumes of plasma with high titre isoagglutinins and recipient has relatively small blood volumes, the risk is increased which can be prevented by graft manipulation and appropriate transfusion support.

Allogeneic SCT was started in 2018 in Bangladesh and currently mostly done at private setting. Preventing complications due to ABO incompatible SCTs are a great challenge. Here we present country’s first successful plasma reduction from graft in minor ABO incompatible allogeneic SCT in a paediatric patient.

**Case report**

A 14-year-old boy diagnosed as acute myeloid leukaemia (Intermediate risk) was admitted in Evercare Hospital Dhaka (EHD) for allogeneic SCT. He was initially treated in another hospital with DAE chemotherapy protocol and transferred to this hospital with neutropenic sepsis with shock and right psoas myositis (creatinine phosphokinase was 7964 U/L, normal 38 to 175 U/L) which were managed accordingly. During this period, he developed covid infection and Decitabine started as bridging therapy. He was found MRD negative and received one cycle high dose cytarabine before allogeneic SCT. His 8 years old brother was found full HLA match with minor ABO incompatibility (Patient AB +ve and donor B +ve). Donor’s anti-A titre was 1:256 (IgM) and 1:512 (IgG) by master dilution. As titre was high plasma reduction was planned after stem cell collection. He was conditioned with fludarabine and busulfan in myeloablative dose. Sperm banking was done prior chemotherapy to overcome infertility.

Donor was given G-CSF to mobilize the stem cells and collected on day -1 using Spectra Optia. CD34+ cell count was 65.59/µl before collection and his total blood volume was 2336ml. One hundred and sixty three ml of graft was collected after 2 times total blood volume processing through right femoral vein catheter. After collection of 73 ml, plasma was reduced using refrigerated centrifuge machine following institutional protocol. The product bag was centrifuged at 1800 rpm (900 x g centrifugal force) for 10 minutes at 200C followed by manual expression using plasma extractor. To minimize buffy coat loss which contain the hematopoietic progenitor cells, we kept one inch of residual plasma in product bag. Post collection CD34+ cell count was 3004/µl and cell dose was 5.48 x 106/kg. Post plasma reduction volume (90ml) was transfused on day 0. Patient was closely monitored during transfusion for any signs of immediate haemolysis. Cyclosporin A and methotrexate were used as GVHD prophylaxis. He was routinely monitored for haemolysis, back pain, elevation of bilirubin, lactate dehydrogenase and serum creatinine. Direct antiglobulin test was negative. Post-transplant period was uneventful except culture negative febrile neutropenia and grade II oral mucositis which was managed accordingly. His neutrophil and platelet both engrafted on D+17. He was transfused with irradiated B RhD positive packed red blood cells (PRBC) with precaution and AB RhD positive platelets in his post-transplant period. He was discharged on D+24. Patient’s measurable residual disease (MRD) is negative, he
is off immnosuppressive therapy and in remission till last follow up 10 months after SCT.

**Discussion**

The ABO blood group antigens are oligosaccharides expressed on the surface of red blood cells, platelets, white blood cells, vascular and organ endothelium. As soluble substance they can also be present in body fluids like plasma. Isoagglutinins are naturally occurring antibodies directed against the ABO antigens lacking on the patient’s cells and absent during birth but appear during 12-14 months of life. These anti-A and anti-B antibodies persist in plasma indefinitely and their titre varies from person to person. If donor anti-recipient isoagglutinin titre is ≥ 1:256, plasma should be reduced from graft.4

Minor ABO incompatible SCT can cause acute haemolysis of recipient’s red blood cells at the time of transfusion due to passive transfer of isoagglutinins present in an unmanipulated graft. All the sources of hematopoietic progenitor cell like bone marrow, peripheral blood and umbilical cord blood contain plasma. Using simple centrifugation high titre isoagglutinin containing plasma can be reduced from graft. Automated Buffy coat enrichment techniques can be also used.

Another significant complication of minor ABO incompatibility is passenger lymphocyte syndrome (PLS), which occurs due to viable B lymphocytes in graft producing isoagglutinins directed against residual recipient ABO antigens present in RBCs. PLS involving non-ABO antibodies has also been reported.6 Haemolysis typically occurs after 5 to 15 days post-transplant and is rare after 6 to 8 weeks.7 Worel et al. noted clinically significant haemolysis occurs in 10-15% but brisk haemolysis may lead to death.8 It is frequently seen in non-myeloablative transplants. Other risk factor includes using peripheral blood stem cells as it carries greater lymphocyte load than bone marrow graft and use of cyclosporin without methotrexate for post-transplant graft versus host disease (GVHD) prophylaxis.

Methotrexate is more cytotoxic for B cells and it may prevent delayed hemolysis.9 To prevent it careful monitoring of the patient for signs of haemolysis and laboratory evidence of intravascular haemolysis like increased total bilirubin and indirect bilirubin, hemoglobinemia, haemoglobinuria, elevated lactate dehydrogenase or a sudden unexplained decrease in haematocrit is essential after appropriate transfusion. Myeloablative conditioning can be used. Positive direct antiglobulin test indicates presence of donor derived isoagglutinins. In rare instances, prophylactic red cell exchange prior to transplant is performed.

In the current minor ABO incompatible SCT, considering high donor isoagglutinin titre and small blood volume of the patient, plasma was reduced from PBSC product. Due to financial constraint we used simple centrifugation. Following transplant after myeloablative conditioning, the patient did well. His GVHD protocol also included both cyclosporin and methotrexate. Special precaution was maintained in transfusing PRBC to minimize the residual donor plasma in post-transplant phase. Rapid engraftment occurred and currently the patient is in remission.

From August 2018 to September 2021 total 15 allogeneic SCTs were successfully done in the EHD. We have encountered 4 cases of ABO incompatibility with successful plasma reduction in the graft and there was no delay in engraftment. Despite advances in knowledge and development of new technologies complications may still occur. Close monitoring of patients at risk, implementing standard procedures and competency of the staff helps to detect problems early, thus reducing the number of fatal or life-threatening events.
Carbohydrate glycosyltransferase are located on long independently. HLA genes are located on short arm group system and HLA system inherited haematological diseases. HLA matching is the most Allogeneic stem cell transplant (SCT) is a curative be fully HLA matched but ABO incompatible. Minor incompatibility the graft contains isoagglutinins in recipient against red blood cells of the graft. In classified into three groups: major, minor and transfusion support. Preventing complications due to ABO incompatible SCTs are a currently mostly done at private setting. Preventing immune-haematological consequences in this type transplants due to one of the three following.


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