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Transfusion policy in allogeneic hematopoietic stem cell transplantation

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ABSTRACT

The incompatibility of ABO blood group between the recipient and the donor is not a barrier to perform allogeneic hematopoietic stem cell transplantation (Allo-HSCT). However, ABO incompatibility may lead to many complications during and after stem cell transplantation at the early or late period. Therefore, the typing of the blood group of the recipient and the donor should be done prior to the transplantation. In addition, the ABO/Rh group of blood products for transfusion should be determined according to the type of ABO-incompatibility. In this review, the subtypes of ABO blood group-incompatibility and transfusion policies will be discussed in detail.

The compatibility of human leukocyte antigen between the recipient and the donor in allo-HSCT setting is important but the incompatibility of ABO-blood group does not constitute a barrier to transplantation [1]. The genes encoding carbohydrate glycosyl transferase in the formation of ABO-blood group are located on chromosome 9q34 [2]. These genes do not have an association with genes encoding human leukocyte antigens on chromosome 6p21 [3].

However, it is important to know the transfusion policies and procedures well since extensive transfusion support is required in HSCT. Although the transfusion requirement of blood components is generally comparable according to the source of stem cells used in transplantation, this requirement may be increased by the fact that the engraftment period is late in bone marrow and cord blood transplantations [4]. In addition, the requirement of blood transfusion may change in association with the intensity of the conditioning regimens used for transplantation, and may also be higher especially in ablative regimens than in reduced intensity regimens [5].

At present, 40–50% of allo-HSCTs are ABO incompatible. Of this incompatibility, 20–25% is major, 20–25% minor and 5% bi-directional (major plus minor) [6]. The accreditation committees recommend that all donors shall be tested before the HSC collection for the ABO group and type D [7]. If there is no donor blood sample, it is absolutely necessary to determine the blood group before cryopreservation of the stem cell product. However, since the cord blood products are frozen, the blood group cannot be retested from the product.

In the condition of ABO incompatibility, the blood transfusion policy is evaluated in three distinct periods: a) before transplantation period (phase I); b) at transplantation period (phase II); and c) after engraftment period (phase III). Blood group typing is based on the identification of the antigens on the erythrocyte surface by the forward grouping and the isohemaglutinins (rearrangement) of the blood group antibodies in the plasma by the reverse grouping.

ABO incompatibility between the recipient and the donor is divided into three subtypes based on erythrocyte antigens and isohemaglutinins in both the recipient and the donor (Table 1). Especially ABO isohemoglutinins may cause various complications during stem cell infusion and post-transplantation period.

1. Major ABO incompatibility

There is isohemagglutinin in the recipient against donor-derived blood group antigens. For example; the transplantation of graft from a donor with A-blood group to the recipient with O blood group. The major problem that may be encountered in major ABO incompatibility is acute hemolysis during graft infusion [6–9]. In addition, delayed erythrocyte engraftment at the post-transplantation or late-onset complications such as pure red cell aplasia (PRCA) may be observed. The stem cell sources used in transplantation include erythrocytes at varying amount in peripheral blood, bone marrow, and cord blood, therefore the amount of hemolysis varies depending on the erythrocyte content of the stem cell product. In addition, cell processing processes, such as dimethylsulfoxide (DMSO), can cause acute hemolysis. Nevertheless, the major complication is the delayed erythrocyte engraftment associated with increased erythrocyte requirement in the major incompatibility. PRCA has been developed by the result of suppression of maturation in the bone marrow due to both isohemaglutinins produced by the patient's plasma cells and the consequence that donor-derived hematopoietic precursor cells cannot start erythrocyte production [9].

The depletion of the erythrocytes in the stem cell product can be performed to prevent hemolysis in major ABO incompatibility [6–8].

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Table 1
ABO incompatibility and clinical outcomes [7].

Type	ABO Blood Group		Potential Clinical Outcome	Etiology	Prevention/Management
	Recipient	Donor			
Major	O	A, B, AB	• Acute hemolytic reaction	• Transfusion with incompatible erythrocyte cells	• Erythrocytes depletion in the stem cell product
Major	A	AB	• Delayed erythrocyte engratment		• Therapeutic plasma exchange to reduce isohemagglutinins before transplantation
Major	B	AB	• Pure red cell aplasia • Delayed granulovcyte and thrombocyte engraftment	• Loss of immature stem cells producing ABO antigens expressed in granulocytes and platelets	• To provide erythropoiesis with erythropoietin administration
Minor	A	O	• Acute hemolytic reaction	• High isohemagglutinin titers in donor plasma	• Plasma reduction
Minor	B	O	• Delayed type hemolysis due to PLS in the stem cell graft		• Close follow-up for hemolysis symptoms / findings between + 5 and +15 days of transplantation for hemolysis
Minor	AB	O,A,B		• Isohemoglutinin-producing passenger lyphocytes	
Bidirectional	A	B	• Combination of those seen in major and minor incompatibility	• Combination of those seen in major and minor incompatibility	• The intervention as major and minor incompatible
Bidirectional	B	A			

This process is usually done in the product of bone marrow derived stem cells since the depletion will lead to the loss of hematopoietic stem and progenitor cells. The bone marrow product is approximately 1–2 liters and 25–35% of the product volume is erythrocytes. This refers to about 1 unit or more of the erythrocyte suspension. As the content of erythrocytes in the stem cell product collected with apheresis is generally very small (< 20 mL), there is no need for erythrocyte depletion. Another approach is to reduce the high amount of anti-donor isohemagglutinin in the recipient's plasma via plasma exchange or immunoadsorption in the recipient at pre-transplantation period. There is no consensus on reducing the amount of isohemagglutinin in the recipient, especially in peripheral stem cell transplantations. In the case of plasma exchanges, the use of donor type secretory plasma is shown to be successful. For example: Plasma secreting A/B antigens are more effective than non-secreting plasma in reducing anti-A/B isohemagglutinins.

Although there is no threshold for a safe infusion, the use of 10–40 mL or 0.2–0.4 mL / kg of erythrocytes in adults with the major incompatibility is generally well tolerated. If the erythrocyte content in the stem cell product is less than 15 mL, it does not lead to a clinically significant acute hemolysis. Some centers divide the product into two equal parts and infuse them in 6–8 h when the erythrocyte content in the HSC product is above the threshold. Some centers deplete erythrocytes if the isohemagglutinin titer in the recipient is equal to or more than 32.

There are several techniques for reducing erythrocytes in the product. These are the methods for cell separation; by manual erythrocyte sedimentation using hydroxyethyl starch or by automatic centrifugation with Ficoll-Hipaque density gradient or semi-automated and automatic cell washer with the apheresis method. In our center we are performing the cell separation by automatic cell washer.

Slow infusion of donor type erythrocytes prior to HSCT can reduce the anti-A and anti-B isohemaglutinins in the recipient. In addition, a pre-medication with good hydration and anti-histaminics should be given before the HSCT. Nonetheless, transfusion reactions such as fever, chills, hematuria and significant hemolysis can be seen at significant levels.

ABO incompatibility is important when choosing a donor for the delayed engraftment in high-risk patients such as myelofibrosis and/or the history of multiple transfusions. However, graft source, HLA incompatibility, donor age and gender, CMV status and other infectious conditions are more important than ABO blood group in the choice of donor. Major ABO incompatibility has no significant impact on the development of acute and chronic GVHD, recurrence rate of the underlying disease and survival [10,11].

Erythrocyte engraftment is generally defined as an absolute reticulocyte count more than 30×10^{12} / L (> 1%) and no need for erythrocyte transfusion. The evidence is the presence of 100% donor-type erythrocyte chimerism in the bone marrow of the patient and the disappearance of donor type isohemaglutinins in the recipient plasma. Delayed erythrocyte engraftment was reported in the patients transplanted with reduced-intensity conditioning regimen in some studies [12]. This was associated with a high number of patient's plasma cells producing isohemagglutinin against donor erythrocytes. It has been showed that disappearance of donor-type isohemagglutinins occurred in the shorter time in the patients transplanted from an HLA-identical unrelated donor compared to an HLA-identical related one and in the patients developing grade II-IV GvHD [13].

PRCA is defined as an extension of reticulocytopenia (< 1%) over 60 days with the absence of erythroid precursors, while there are megakaryocytes, lymphoid and myeloid precursors in bone marrow [9,14]. After the transplantation with major ABO incompatibility, the rate of PRCA varies between 6–30%. Generally, PRCA has observed during tapering the immunosuppressive treatment. In the major ABO incompatibility, the improvement of erythropoiesis depends on the amount of anti-donor isohemaglutinin in the recipient prior to the transplantation, the clearance time of these isohemagglutinin, the amount of target ABO antigen, the occurrence of GvHD, the conditioning regimen for the transplantation and natural erythropoietic function in the recipient. Several studies have been reported that the frequency of PRCA increased in the patients receiving reduced-intensive conditioning regimen or cyclosporine. Delays in erythrocyte engraftment and PRCA are more frequent when the patients with the blood group O receive stem cell products from the donors with the blood group A.

2. Minor ABO incompatibility

ABO blood group antibodies have been generated by intestinal bacteria 12–24 months after birth. Antibodies are usually permanent when they occur but their titrations may vary individually [14]. Minor incompatibility was defined as bellows [6–8,15]:

1) the patients with AB blood group received donor stem cell transplantation containing anti-A and/or anti-B isohemagglutinin;
2) the patients with A blood group underwent the transplantation from the donor with anti-A isohemagglutinin, or
3) the patients with B blood group was transplanted from the donor with anti-B isohemagglutinin.

In the case of minor incompatibility, plasma reduction in stem cell product has been recommended to prevent hemolysis that may be observed during infusion. Minor incompatibility may lead to mild or severe hemolysis in the patients 7–14 days after transplantation, which may extend to 6–8 weeks. This is because passenger lymphocytes in the stem cell products reconstitute in the patient to produce