Transfusion Support for ABO-Incompatible Progenitor Cell Transplantation

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ABO-incompatible transplant · Transfusion · Platelet transfusion

Summary

ABO-incompatible transplants comprise up to 50% of allogeneic progenitor cell transplants. Major, minor and bidirectional ABO-incompatible transplants each have unique complications that can occur, including hemolysis at the time of progenitor cell infusion, hemolysis during donor engraftment, passenger lymphocyte syndrome, delayed red blood cell engraftment, and pure red cell aplasia. Appropriate transfusion support during the different phases of the allogeneic progenitor cell transplant process is an important part of ABO-incompatible transplantation.

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Introduction

The ABO antigens are oligosaccharides that are formed by the addition of sugars to a precursor substance located on the surface of cells. They are present on a number of cells other than red blood cells, including vascular endothelial cells. ABO antigens can also be present as soluble substances in body fluids. Individuals who do not express the A or B antigens will make antibodies or isoagglutinins to the antigen(s) they do not express [1]. By contrast, Rh antigens are only present on red blood cells. Rh antibodies only form after exposure to the Rh antigen through transfusion or pregnancy [2]. Because the HLA genes are located on the short arm of chromosome 6, the ABO genes are located on the long arm of chromosome 9 and the Rh genes are located on the short arm of chromosome 1, even HLA-matched siblings will often be ABO-incompati-

ble. The only guarantee of finding two siblings who are ABO-, Rh-, and HLA-matched is in syngeneic twins. If an ABO-matched progenitor cell donor is available, the donor is considered to be preferable to a non-ABO-matched donor. However, other considerations, including the HLA type, donor age and CMV status, are considered more important in progenitor cell donor selection than ABO match. In approximately 40–50% of progenitor cell transplants, the donor and recipient are ABO-incompatible. ABO-incompatible progenitor cell transplants can be classified as major ABO-incompatible, minor ABO-incompatible or bidirectional ABO-incompatible [3]. Transfusion during progenitor cell transplantation can be separated into three phases, with phase I occurring during the preparative regimen, phase II during engraftment, and phase III post-engraftment. How to safely transfuse patients who receive ABO-incompatible progenitor cell grafts is an important part of the transplant process.

Major ABO Incompatibility

A progenitor cell graft is classified as major ABO-incompatible if the recipient possesses preformed antibodies or isoagglutinins directed against the red blood cells of the graft. This occurs in all blood group O patients who received a non-group O graft. It also occurs in blood group A and B patients who receive a group AB graft (table 1). Significant transfusion-related complications can happen in recipients of major ABO-incompatible progenitor cell grafts. The first complication that can occur is hemolysis at the time of infusion, because the graft contains incompatible red blood cells and the recipient has pre-formed antibodies directed against these cells [4]. The reaction is identical to a hemolytic transfusion reaction that can occur from transfusion of an incompatible unit of red blood cells. Studies have shown that the risk of hemolysis increases with an increase in the volume of incompatible cells transfused. However, there is no volume of incompatible red blood cells that can be considered completely safe to infuse [5]. The quantity of red

Table 1. Types of ABO-incompatible progenitor cell transplants

Blood type of recipient	Blood type of donor
<i>Major incompatibility</i>	
O	A
O	B
O	AB
A	AB
B	AB
<i>Minor incompatibility</i>	
A	O
B	O
AB	O
AB	A
AB	B
<i>Bidirectional incompatibility</i>	
A	B
B	A

blood cells present in a progenitor cell graft varies by the type of collection. Apheresis products typically contain less than 20 ml of red blood cells. Apheresis products can typically be infused into adult patients without need to reduce the amount of red blood cells in the product. However, reduction of red blood cells in the product may be needed for pediatric patients and small adults. Bone marrow products typically have a hematocrit of 25–35%, meaning that 1 l of bone marrow can contain up to 350 ml of red blood cells, which is more than a unit of packed red blood cells. Thus, bone marrow products which are ABO-incompatible will usually need to be manipulated to reduce the number of red blood cells prior to infusion. Cord blood products have a similar hematocrit, but removal of red blood cells prior to product storage limits the number of incompatible red blood cells that are present in most components. The volume of red blood cells present in any progenitor cell product can be significantly decreased by the use of a cell processing device and an agent that aids in cell sedimentation [6]. However, reduction of red blood cells will also result in loss of progenitor cells. An alternative to reduction of the number of red blood cells present in the graft is the reduction of isoagglutinins in the recipient. However, this is not often performed in the USA. Therapeutic apheresis to prevent hemolysis in a major ABO-incompatible transplant has been classified as a category II indication (disorders for which apheresis is accepted as second line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment) for plasma exchange by the American Society for Apheresis [7].

The second potential complication that can occur after major ABO-incompatible progenitor cell transplantation is delayed red blood cell engraftment or pure red cell aplasia (PRCA) [8]. PRCA is defined as reticulocytopenia (<1%) lasting more than 60 days post-transplant and absence of erythroid precursors in the marrow with engraftment of platelets, lymphocytes, and myeloid cells. It is caused by the continued presence of isoagglutinins in the patient after transplantation, which can continue to be produced by residual recipient B cells and plasma cells [3]. The risk of PRCA is in-

creased with blood group A donors and in non-myeloablative transplants [9]. In recipients of major ABO-incompatible progenitor cell transplants, PRCA can result in being red blood cell transfusion-dependent for months to years. In addition, these patients can develop hemochromatosis secondary to transfusion.

The concerns for transfusion in major ABO-incompatible progenitor cell transplants are the compatibility of red blood cells transfused and restricting transfusion of additional donor-incompatible isoagglutinins. During phase I of the transplant process, the recipient can safely receive blood components of recipient type. During phase II, the compatibility of red blood cells can be addressed by transfusion of cells of recipient type. This is safe because recipient red blood cells will always be compatible in a major ABO-incompatible progenitor cell transplant. In order to reduce additional transfusion of isoagglutinins directed against the engrafting red blood cells, platelets and plasma of donor type are typically transfused in phase II. For example, if the recipient is blood type O and the donor is blood type A, transfusion would be with type O red blood cells and type A platelets and plasma. In practice, it may not be possible to always provide the preferred type of platelets due to supply limitations. For this reason, transfusion services that support progenitor cell transplantation should define which type of platelets should be administered if the first choice of platelets is not available. Table 2 lists which platelets should be administered, in order of preference, if platelets of donor type are not available. Additional information regarding platelet transfusion in progenitor cell transplantation is provided in the platelet transfusion section.

During phase III of the transplantation, donor red blood cells have engrafted, and incompatible recipient isoagglutinins are no longer present. The recipient can receive red blood cells, platelets, and plasma of donor type.

Minor ABO Incompatibility

A progenitor cell transplant is classified as minor ABO-incompatible when the donor's plasma contains isoagglutinins directed against ABO antigen(s) present on the recipient's red blood cells. This occurs when a recipient who is blood group A, B, or AB receives a progenitor cell graft from a group O donor or when a group AB recipient receives a graft from a donor who is blood group A or B (table 1).

Significant complications that can be associated with a minor ABO-incompatible progenitor cell transplant include hemolysis of recipient's red blood cells at the time of infusion and delayed hemolysis of recipient's red blood cells secondary to stimulation of donor B cells. Immediate hemolysis secondary to passive infusion of donor isoagglutinins, directed against recipient red blood cells, is not common. The risk is increased with components that contain large volumes of plasma, in donors with high-titer isoagglutinins, and in recipients with relatively small blood volumes [10]. This risk can be decreased by reducing the volume of plasma present in the progenitor cell product. In general, this is most likely to be needed in bone marrow products, which can contain significant quantities of donor plasma.

Recipient	Donor	Phase I, all products	Phase II		Phase III, donor-compatible, all products				Phase III, donor- and recipient-compatible			
			RBCs	platelets 1st choice	platelets 2nd choice	plasma 1st choice	plasma 2nd choice	RBCs	platelets 1st choice	platelets 2nd choice	plasma	
Major incompatibility												
O	A	R	O	A	AB,B,O	A	AB	D	D	A	AB,B,O	A,AB
O	B	R	O	B	AB,A,O	B	AB	D	D	B	AB,A,O	B,AB
O	AB	R	O	AB	A,B,O	AB	NA	D	D	AB	A,B,O	AB
A	AB	R	A	AB	A,B,O	AB	NA	D	D	AB	A,B,O	AB
B	AB	R	B	AB	B,A,O	AB	NA	D	D	AB	B,A,O	AB
Minor incompatibility												
A	O	R	O	A	AB,B,O	A	AB	D	D	A	AB,B,O	A,AB
B	O	R	O	B	AB,A,O	B	AB	D	D	B	AB,A,O	B,AB
AB	O	R	O	AB	A,B,O	AB	NA	D	D	AB	A,B,O	AB
AB	A	R	A	AB	A,B,O	AB	NA	D	D	AB	A,B,O	AB
AB	B	R	B	AB	B,A,O	AB	NA	D	D	AB	B,A,O	AB
Bidirectional incompatibility												
A	B	R	O	AB	B,A,O	AB	NA	D	D	AB	B,A,O	AB
B	A	R	O	AB	A,B,O	AB	NA	D	D	AB	A,B,O	AB
D = Donor; R = recipient; NA = not applicable.												

Delayed hemolysis after minor ABO-incompatible transplantation may be fatal and typically begins within 7–10 days after transplantation. The hemolysis is secondary to antibodies, directed against the recipient's native red blood cells, formed by B lymphocytes that are contained within the progenitor cell graft, and is referred to as passenger lymphocyte syndrome. This complication has not been reported after transplantation of cord blood, which is most likely explained by the fact that B lymphocytes within cord blood would not have previously been sensitized to ABO antigens. Isoagglutinins to ABO antigens do not begin to develop until several months after birth [1].

Transfusion needs should focus on the transfusion of red blood cells that are compatible with both the donor and the recipient, while avoiding transfusion of isoagglutinins directed against the residual red blood cells of recipient origin. It would seem logical that reducing the amount of incompatible red blood cells that are present in the recipient, prior to transplant, would reduce the risk of passenger lymphocyte syndrome. Thus, some have suggested that prophylactic red blood cell exchange prior to minor ABO-incompatible progenitor cell transplantation should routinely be performed [11]. However, a recent study of red blood cell exchange prior to ABO-incompatible transplantation at the author's own institution suggested that this practice does not decrease severe hemolysis. Additionally, it did not improve 1-year survival, the number of red blood cell units transfused after transplant, or the length of hospitalization [12]. The American Society for Apheresis assigns prophylactic red blood cell exchange prior to minor ABO-incompatible progenitor cell transplant a classification of category III (Optimum role of apheresis therapy is not established. Decision making should be individualized) [7].

In phase I of the transplant process, all of the blood components received by the recipient can be of recipient type. However, in some centers, it is practice to transfuse red blood cells of donor type as soon as it is known that the patient is likely to receive a minor ABO-incompatible progenitor cell transplant. The reasoning behind this is similar to the reasoning behind prophylactic red blood cell exchange and is to reduce the amount of recipient type red blood cells that can be hemolyzed if passenger lymphocyte syndrome develops. Although this may seem logical, there are no controlled clinical trials to support this practice. Additionally, the volume of hemolysis experienced in cases of passenger lymphocyte syndrome can greatly exceed the red blood cell volume of the recipient [13]. It has been hypothesized that ABO antigens from destroyed red blood cells adhere to transfused red blood cells of donor type which can cause hemolysis of transfused red blood cells in addition to hemolysis of the cells of recipient type.

In phase II of the transplant process, the patient should receive red blood cells of donor type. Platelets and plasma should ideally not contain isoagglutinins directed against the recipient's red blood cells. Platelets and plasma of the recipient's blood type are considered to be the first choice. For example, if the recipient is blood group A and the donor is blood group O, transfusion should be with group O red blood cells and with group A platelets and fresh frozen plasma. In phase III of the process, many centers transfuse

red blood cells, platelets, and plasma of donor type. An alternate approach to platelet and plasma transfusion which considers isoagglutinin compatibility with both the donor and recipient is preferred by some transplant centers [14]. The ABO antigens are expressed on many other cells, including endothelial cells. Cells, other than red blood cells, continue to express ABO antigens of recipient type after progenitor cell transplantation [15]. Selection of platelet and plasma products that are compatible with both the donor and recipient in phase III of the transplant will minimize the transfusion of isoagglutinins directed against the ABO antigens of the recipient's native endothelial cells. Centers favoring this approach would transfuse red blood cells of donor type but continue to transfuse platelets and plasma of recipient type (first choice) in phase III (table 2), since the isoagglutinins in platelets and plasma of donor type would be incompatible with ABO antigens expressed on endothelial cell of the recipient.

Bidirectional ABO Incompatibility

Bidirectional ABO incompatibility occurs when both major ABO incompatibility and minor ABO incompatibility are present in the same transplant. This occurs when a group A recipient receives a progenitor cell transplant from a group B donor and when a group B recipient receives a graft from a group A donor (table 1). All of the previously described complications associated with major and minor ABO-incompatible progenitor cell transplantation are associated with bidirectional ABO-incompatible transplantation, including hemolysis of donor cells at the time of infusion, hemolysis of recipient cells at the time of infusion, delayed engraftment, PRCA, and passenger lymphocyte syndrome. Progenitor cell products, particularly bone marrow, may need to have red blood cells and plasma removed prior to administration.

In phase I of the transplant, the patient can receive all products of the recipient's blood type. During phase II of the transplant, only group O red blood cells can be transfused because all other types of red blood cells would be incompatible with the donor, the recipient, or both. The first choice of platelets and plasma is group AB. All other types of platelets and plasma will contain isoagglutinins that will be incompatible. If the first choice of platelets is not available, the order of preference for platelets is listed in table 2. In phase III of the transplant, transfusion of all products can be of donor type. Alternatively, if isoagglutinin compatibility with both the donor and the recipient is preferred, red blood cell transfusion can be of donor type while the first choice of platelets and plasma remains group AB.

Additional ABO-Incompatible Transplants

Performing an additional transplant after failure of the first graft or after disease recurrence has become more common. In the case of failure of the first progenitor cell graft, there is often no evidence of the first graft, and only two blood types need to be considered, the patient's native blood type and the blood type of the second progenitor cell donor. In cases where the patient is being

transplanted for disease recurrence, there may be three blood types involved; the patient's original blood type, the first donor's blood type and the second donor's blood type. In these cases, the simplest way to transfuse the patient after infusion of the second graft is to provide group O red blood cells and group AB platelets and plasma until engraftment of the second donor is established. If group AB platelets are not available, transfusion of platelets that protect engraftment of the second donor are preferred.

Platelet Transfusion

In an ideal world the first choice of platelet transfusion would be available for all patients, including progenitor cell transplant patients. In reality, because platelets in the USA only have a shelf life of 5 days, the first choice of platelets is not always available, and the patient cannot wait for transfusion until the first choice becomes available. Table 2 lists, in order of preference, the blood group of platelets that should be used if the first choice is not available. The preferences are determined based upon minimizing the transfusion of incompatible isoagglutinins to protect engraftment. Thus, if incompatible platelets must be transfused, it is preferable to administer platelets with incompatible isoagglutinins directed against the recipient's ABO antigens. Other means of minimizing the transfusion of incompatible isoagglutinins should also be considered. Some donor centers and transfusion services limit exposure to incompatible isoagglutinins by limiting donation of apheresis platelets by donors with high-titer isoagglutinins or limiting transfusion of units collected from these donors to compatible recipients [16]. For example, at the author's institution, apheresis platelets that have a positive titer at a 1:100 dilution for anti-A or anti-B can only be transfused to compatible recipients. Another means of limiting exposure to incompatible isoagglutinins is the use of platelets stored in a platelet-additive solution (PAS). The current PAS platelets approved in for use in the USA have 65% less plasma than conventional apheresis platelets, and presumably 65% less isoagglutinins. Additionally, PAS platelets have been shown to reduce the incidence of allergic transfusion reactions by 45% [17]. Although allergic transfusion reactions are often mild, they can cause significant patient discomfort and are best avoided, if possible.

Processes and Policies

Organizations that perform progenitor cell transplants must have policies and procedures in place to address many aspects related to transfusion medicine. The transfusion service needs to be informed that the transplant is going to take place. Ideally this should happen as soon as possible in the process. The transfusion service needs to have a method to determine what blood components the patient should receive in each phase of the transplant. In addition to ABO, the policy should address transfusion practice if the donor and recipient are Rh-incompatible. Many facilities choose to transfuse Rh-negative red blood cells until phase III of the transplant, switching to Rh-positive red blood cells at this time, if the donor is Rh-positive.

Transfusion practices can be formalized in a standard operating procedure (SOP) that is followed for every transplant. Alternatively, a transfusion service physician can perform a consult that is placed in the patient's medical record and used in the transfusion service. This option has the benefit of having a transfusion medicine physician review every bone marrow transplant case prior to transplant and individualize transfusion therapy for each patient. If the consult is placed in the patient's medical record, it will also be available to members of the clinical team.

Another policy that needs to be established is how to determine when phase III of the transplant begins. There are no absolute rules that govern this decision, and practice is varied [18]. Thus most transfusion services will need to establish their own policies in the area. At a minimum, the patient's forward blood type (antigens expressed on the red blood cells) must be of donor type, and recipient's isoagglutinins directed against the donor's red blood cells must have disappeared. Other factors that may be considered in making the determination to switch to donor type red blood cells for transfusion include ongoing transfusion requirements and results of chimerism studies. Individual review of each patient's red blood cell transfusion requirements and stability of donor chimerism can assist in making the decision to switch to transfusion of donor-type red blood cells. At the author's institution, there is a minimum requirement that the patient's forward type is of donor type and there are no incompatible isoagglutinins present in two consecutive samples drawn at least a week apart in order to consider changing the patient's blood type. The case is then reviewed by a transfusion medicine physician who considers the patient's clinical status, transfusion requirements, and chimerism results before deciding whether it is appropriate to switch the patient's blood type. In general, we tend to be more conservative regarding switching the patient's blood type in cases of major ABO incompatibility than in cases of minor ABO incompatibility. Additionally, we require an order written and signed by a transfusion medicine physician to change the patient's blood type in our blood bank computer system.

A policy regarding progenitor cell transplantation and irradiation of blood components to prevent transfusion-associated graft versus disease (TAGVHD) should be established. Irradiation of cellular blood components must commence by the time the conditioning regimen begins. Plasma and cryoprecipitate do not need to be irradiated because they are acellular. Transfusion services need to establish how long after transplant the patient will continue to receive irradiated cellular blood components. The AABB (formerly American Association of Blood Banks) recommends that a transfusion service shall have a policy regarding the transfusion of irradiated components and that cellular blood components shall be irradiated when a patient is identified as being at risk of TAGVHD [19]. In practice, many centers continue to provide irradiated products for this group of patients for the rest of their lives.

Disclosure Statement

The author has no conflicts of interest to report.

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