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Clinical Guide to ABO-Incompatible Allogeneic Stem Cell Transplantation

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The independent genomic inheritance of the human leukocyte antigen (HLA) and the ABO-blood group system allows for HLA-matched hematopoietic progenitor cell transplantation (HCT) to occur in donors who are not matched for ABO blood groups. In fact, nearly one-half of all HCT will involve recipient–donor ABO incompatibility. This places the recipient at increased risk for acute and delayed hemolytic reactions, delayed RBC engraftment, and pure red blood cell aplasia. Additionally, clinical and laboratory evaluation for potential non-ABO, minor RBC antigen-antibody discrepancies may be beneficial to facilitate safe transfusions before, during, and after transplantation. In addition to posing potential clinical risks, analyses of outcomes in ABO-incompatible HCT have yielded inconsistent results with respect to overall survival, relapse risk, incidence of acute or chronic graft-versus-host disease, and engraftment of platelets and granulocytes. As such, pretransplantation donor–recipient evaluation and management for ABO-incompatible HCT requires adopting unique strategies when major, minor, and bidirectional differences exist. These strategies have the potential to improve patient outcomes and allow for effective management of the blood bank inventory. The purpose of this article is to describe practical approaches to screening for and managing ABO-incompatible HCT, with the goal of reducing preventable morbidity and mortality after transplantation.

INTRODUCTION

The human major histocompatibility complex, also termed human leukocyte antigens (HLA), has been divided into 3 regions on chromosome 6p21: class I (telomeric), class II (centromeric), and class III [1-2]. This genomic region is critical to engraftment, prediction of clinical outcomes, and balancing the potential harm from graft-versus-host disease (GVHD) and the benefit from the graft-versus-leukemia effect. In contrast to HLA, mismatching of the ABO blood group system is not an impediment to hematopoietic progenitor cell transplantation (HCT) [3]. The genes encoding ABO carbohydrate glycosyltransferases are located on chromosome 9q34, far from the genes encoding HLA, and are, therefore, inherited independently [4,5]. As a consequence, HLA-matched allogeneic stem cell donors have some degree of ABO incompatibility in approximately 25% to 50% of transplantations [6,7]. Although not as significant as the degree of HLA match, graft source, risk of infection, and donor age and gender, clinical outcomes in ABO-incompatible HCT are generally considered inferior to those in ABO-compatible HCT, with mixed or undefined results in overall survival, relapse rates, acute and chronic GVHD, and engraftment of platelets and granulocytes [8-19]. Given that both ABO-identical and ABO-incompatible HSCT require extensive transfusion support, it is essential to have a working understanding of the inherent risks and benefits of the differing transfusion policies and procedures.

ABO compatibility has important consequences for clinical outcomes as well as blood management in the pretransplantation (phase I), transplantation (phase II), and postengraftment (phase III) time periods [20]. The ABO blood group antigens are immunodominant sugars that are expressed throughout the body on the surface of RBCs, platelets, white blood cells, vascular and organ endothelium, and in plasma [21-23]. In the clinical laboratory, blood typing is determined by the presence of blood group antigens on the surface of RBCs (forward typing) as well as by the presence of blood group antibodies in the plasma (reverse typing). These antibodies, termed isohemagglutinins, are directed against the ABO antigens lacking on the patient's cells, and are not present at birth but appear during the first year of life. Adjunctive molecular testing can also be performed to clarify complex serologic evaluations [22]. The expected expression of blood group antigens and antibodies in individuals of various blood groups is displayed in Table 1.

In contrast to HCT, one significant barrier to solid organ transplantation is major ABO incompatibility between donor and recipient, which can be associated with humoral rejection of the graft and a high rate of recipient mortality. This type of rejection is mediated by preformed recipient antibodies cross-reacting with incompatible alloantigen expressed on the graft, resulting in complement activation and damage to the graft including catastrophic thrombosis [24]. The so-called ABO barrier has been crossed in renal and liver transplantation by utilizing plasmapheresis, intravenous immune globulin, and rituximab, as well as other therapies to curtail recipient anti-A and anti-B titers, although antibody titering itself is highly institution and operator dependent [25-28]. Adult cardiac transplantation across the ABO barrier is not a generally accepted medical practice [23,29].

In hematopoietic progenitor cell transplantation, the complications associated with ABO-incompatible transplantation are distinct from those associated with solid organ

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Table 1
Types of Donor–Recipient ABO Incompatibilities

Mismatch Type	ABO Blood Type		Potential Clinical Consequence	Etiology	Potential Interventions
	Recipient	Donor			
Major	O	A, B, AB	• Acute hemolytic episode • Delayed RBC engraftment	• Transfusion of incompatible red blood cells • Recipient anti-donor isohemagglutinins	• Red blood cell reduction of stem cell product
Major	A	AB	• Pure red blood cell aplasia	• Loss of immature stem cells from processing with ABO antigens expressed on granulocytes and platelets	• Therapeutic plasma exchange in recipient to reduce isohemagglutinins before transplantation (uncommon in United States) • Promote donor erythropoiesis via erythropoietin administration
Major	B	AB	• Delayed granulocyte and platelet engraftment		
Minor	A	O	• Acute hemolytic episode	• Donor plasma with elevated isohemagglutinin titers/small blood volume recipient • Passenger lymphocytes producing isohemagglutinins	• Plasma reduction • Continual clinical monitoring between days +5 and 15 for signs/symptoms of hemolysis (including laboratory monitoring with LDH, bilirubin, CBC, DAT)
Minor	B	O	• Delayed hemolysis secondary to passenger lymphocyte syndrome		
Minor	AB	O, A, B			
Bidirectional	A	B	• Combination of major and minor consequences	• Combination of major and minor etiologies	• Combination of major and minor interventions
Bidirectional	B	A			

LDH indicates lactate dehydrogenase; DAT, direct antiglobulin test.

transplantation. ABO incompatibility is classified as either major, minor, or bidirectional. Major ABO-incompatible HSCT (eg, from a type A, type AB, or type B donor to a type O recipient) is characterized by the presence of antidonor blood group antibodies in recipient plasma. Minor ABO incompatibility (eg, from a type O donor to a type A, type B, or type AB recipient) is characterized by the passive transfer of incompatible blood group antibodies from the donor to the recipient. In bidirectional ABO incompatibility (eg, type A donor to a type B recipient), both major and minor incompatibilities are present. In HCT, complications due to ABO mismatch arise from incompatibility due to antibodies and antigens present in the graft and recipient blood, as well as other cells of the donor and recipient immune system.

The clinical and blood management consequences of these incompatibilities are discussed below.

MAJOR ABO INCOMPATIBILITY

A major ABO incompatibility exists when a novel immunodominant sugar moiety (A: N-acetylgalactosamine; B: galactose) from a donor is transfused into a recipient with the corresponding blood group antibodies (anti-A, anti-B, and/or anti-A, B). This clinical scenario occurs most frequently in group O patients who are receiving stem cell transplantations (SCTs) from group A, group B, or group AB donors. Less frequently, major incompatibility is encountered when group A and group B recipients receive grafts from group AB donors.

Clinical Manifestations

The major complications of major ABO-incompatible transplantation are hemolysis of red cells at the time of graft infusion, delayed red cell engraftment, and pure red cell aplasia (PRCA). All of these complications occur because of cross-reactivity between donor blood group antigens and recipient antibodies (isohemagglutinins). Stem cell products, collected from either peripheral blood apheresis collection, bone marrow, or cord blood, contain varying quantities of donor red blood cells that can potentially be bound and destroyed by conjugate blood group antibodies produced by the recipient immune system. The quantity of infused red cells depends on the graft source and cell processing issues, such as cryopreservation, and may result in an acute hemolytic transfusion reaction during transplantation [30]. Moreover, major incompatibilities may result in delayed RBC engraftment, clinically characterized by diminished reticulocyte counts and a corresponding increase in RBC transfusion requirements. In PRCA [31], conversion to donor hematopoietic progenitor cells (HPC) RBC production takes place, but the reconstituting marrow is inhibited by the persistence of isohemagglutinins secreted by recipient plasma cells [32]. The recipient isohemagglutinins disrupt normal bone marrow maturation of medullary precursors at the colony-forming units-erythroid stage, which is the earliest point of ABO antigen presentation [33]. Recovery of erythropoiesis in the setting of a major ABO-incompatible transplantation is dependent on the pretransplantation quantity (titer) of antidonor isohemagglutinins, quantity of target antigen available, rate of clearance of isohemagglutinins, presence of GVHD, transplantation conditioning regimen, and the native recipient erythropoeitic function [34-36]. PRCA often resolves within a few weeks to months; however, there are documented cases of PRCA persisting beyond 5 years [37]. Within the literature, the incidence of post-HCT PRCA may vary according to the conditioning regimen and reportedly varies between 6% and 30% [15].

Resolution of PRCA often occurs following tapering of immunosuppression; however, erythropoietin, steroids, plasma exchange, rituximab, and donor lymphocyte infusions have also been employed [38-41]. All of these measures, especially tapering of immunosuppression and use of donor lymphocyte infusions, should be undertaken in a manner consistent with the overall transplantation objectives.

Immunodeficiency in the post-transplantation period combined with lamivudine may facilitate the development of PRCA in the context of a major ABO mismatch [42].

Preventive Measures

It is important to note that there are no regulations regarding the volume of RBCs allowed in an HPC product. One strategy to prevent hemolysis of an SCT graft is to deplete RBCs from HPC products before transplantation [8,18]. Unfortunately, this process can also reduce the overall progenitor cell content of the HPC product, making this strategy less appealing in circumstances where there are few progenitor cells to spare, as may occur with cord blood transplantation [8].

Another approach to prevent complications of major ABO-incompatible SCT is to reduce the titer of incompatible recipient isohemagglutinins. This can be accomplished by plasma exchange or, if available, the use of immunoadsorption columns [17,43]. Although pretransplantation (recipient) isohemagglutinin reduction may be associated with decreased immunohematologic complications in this setting, there is no consensus in the literature with respect to the most efficient strategy for isohemagglutinin reduction in major ABO-mismatched HCT, especially in the era of peripheral blood progenitor cell transplantation. In some studies, patients with PRCA had significantly higher pretransplantation isohemagglutinin titers compared with those who did not develop PRCA.

Studies have shown the successful use of donor-type secretor plasma for the purpose of isohemagglutinin reduction before HCT. Although use of donor-type nonsecretor plasma has been previously used for this purpose, use of secretor plasma donors (ie, donors who secrete A/B antigens into plasma and other body fluids) maximizes the chance for (recipient) anti-A and/or B isohemagglutinin reduction after infusion in comparison to nonsecretor plasma. This is because the A/B antigens present in secretor plasma will deplete anti-A/B isohemagglutinins directly by antigen-antibody binding, as opposed to nonsecretor plasma, which is reliant on plasma expansion for dilution of anti-A/B isohemagglutinin titers [44,45].

Slow infusion of donor-type RBCs to deplete (recipient) anti-A and/or B isohemagglutinins before HCT has also been used for this purpose, although even with concurrent rigorous hydration and pre-administration of antihistamine medication, significant RBC-related transfusion reactions may still occur, including fever, rigors, hematuria, and frank hemolysis [46]. Risk of hemolytic-type reactions can be avoided with use of secretor plasma rather than RBC transfusions.

Of course, especially in patients at high risk for delayed engraftment (eg, those with myelofibrosis) and those who have received multiple RBC transfusions, selection of ABO-compatible HCT donors is optimal. However, ABO incompatibility generally exerts less impact on outcome than other donor–recipient relationships, such as graft source, degree of HLA matching, status of exposure to CMV and other infectious disease, and most likely, donor age, gender, and parity. Overall, major ABO mismatch does not seem to have a consistent effect on other major outcomes after allogeneic HSCT, such as incidence of acute or chronic GVHD, relapse rate, and overall survival, regardless of the stem cell source [8-19] (Table 2).

MINOR ABO INCOMPATIBILITY

Anti-A and anti-B are naturally occurring antibodies that begin to appear as the gut flora matures and are present in clinically significant levels by 12 to 14 months of life [47]. Once these ABO blood group antibodies are identified in the plasma, they persist indefinitely, although the titer of these antibodies varies from person to person [48]. All of the major sources of HPC, including marrow, peripheral blood, and cord blood contain plasma, with marrow specimens containing up to 1500 mL [49]. Minor ABO incompatibility occurs in one of the following circumstances: (1) when a group AB recipient receives a stem cell transplantation from a non-AB donor, which contain anti-A, anti-B, or both; (2) when a group A recipient receives a B or an O transplantation, which contain anti-A; or (3) when a group B recipient receives an A or O transplantation, which contain anti-B. The incidence of minor incompatibility depends on the relative frequency of ABO blood groups in the donor and recipient populations.

Clinical Manifestations and Management of Minor ABO-Incompatible HCT

The most significant complication of minor ABO incompatibility is massive hemolysis of recipient erythrocytes, which generally occurs 7 to 14 days after transplantation and is associated with production of isohemagglutinins by antibody-producing immune cells contained in the donor graft [50,51]. In cases where avoiding minor ABO incompatibility is not feasible, reduction of donor isohemagglutinin content in the graft to prevent immediate hemolytic reactions may be attempted by reducing the volume of plasma in the stem cell infusion [49,51]. However, similar to the transfusion of ABO-incompatible platelets, there is not a strong association between donor ABO blood group antibody titer and hemolysis [49,50,52]. Carefully monitoring the patient for signs and laboratory evidence of RBC hemolysis and providing appropriate transfusion support if hemolysis is detected is needed at the time of graft infusion in instances of minor ABO incompatibility.

Of most clinical significance is passenger lymphocyte syndrome (PLS), which occurs when transplanted B lymphocytes produce incompatible blood group antibodies after transplantation [51,53]. Hemolysis associated with PLS is delayed 5 to 15 days post-transplantation [50,51,54,55] and is rare after 6 to 8 weeks. PLS can be underestimated or overlooked; thus, measurements of antibodies against the recipient's RBC antigens may provide a useful hallmark of PLS occurring in mild-to-moderate immune hemolysis. In particular, direct antiglobulin testing (direct Coombs) may

Table 2
Effect of ABO Incompatibility on Recipient Survival and Incidence of Graft-versus-Host Disease

Study Authors	Year	Survival after ABO-Incompatible HCT Transplantation			Risk of Graft-versus-Host Disease
		Major	Minor	Bidirectional	
Kimura et al. [3]	2008	Decreased	Decreased	No difference	Increased with minor or major ABO mismatch
Helming et al. [13]	2007	No difference*	No difference*	No difference*	No difference*
Erker et al. [15]	2005	No difference	Decreased	Decreased	No difference
Kim JG et al. [12]	2005	No difference	No difference	No difference	No difference
Stussi et al. [14]	2002	Decreased	No difference	No difference	Increased with minor ABO mismatch
Benjamin et al. [18]	1999	Decreased†	Decreased†	No difference	No difference with minor or major mismatch
Bacigalupo et al. [19]	1988	—	—	—	Increased with minor ABO mismatch
Benisnger et al. [41]	1982	No difference	—	—	No difference with major ABO mismatch
Buckner et al. [17]	1978	—	No difference	—	No difference with minor ABO mismatch

RR indicates relative risk.

* Pediatric patients.

† Only in patients being treated for acute myeloid leukemia or myelodysplastic syndrome. A difference was not observed in a larger subset of patients who were treated for chronic myelogeneous leukemia.

provide an extremely useful laboratory assessment of potential PLS-induced hemolysis in conjunction with routine hemolytic laboratory analysis [56].

In cases of minor ABO mismatch HSCT, almost all the donor lymphocytes produce antibodies against the recipient's red cell antigens, yet the frequency of clinically significant hemolysis is only 10% to 15% (detected by antibodies directed against recipient RBC). Several risk factors for the development of PLS have been reported and include the following: (1) pairing group A or group AB recipients with group B donors; (2) using peripheral blood stem cells (higher donor $CD19^+$ B-lymphocytes than bone marrow grafts and possible conversion to a TH2 profile following granulocyte colony-stimulating factor mobilization) as the source of HSC; (3) employing calcineurin inhibitors (immunosuppressive effects on T cells) without methotrexate for GVHD prophylaxis; and (4) using non-HLA matched sibling donors. Clinically significant PLS has not been described after minor ABO-incompatible HCT using cord blood grafts.

Sinusoidal obstruction syndrome (SOS) is reportedly more common in patients with minor ABO-mismatched grafts. Because blood group antigens are presented in hepatic sinusoidal endothelial cells, Lapierre et al. have suggested that isohemagglutinins of donor origin in the minor ABO-mismatched HSCT might attack sinusoidal endothelial cells contributing to the development of SOS [57]; however, the association of SOS with minor ABO-incompatible transplantations has not been observed at levels reaching statistical significance [42]. Selecting ABO-compatible donors, when possible, is recommended, especially in patients at high risk for veno-occlusive disease. Similar to studies of major ABO mismatched HSCT, studies of minor ABO mismatched HSCTs have shown inconsistent results with regard to survival and GVHD risk [8-19] (Table 2).

Management and Preventive Strategies

Plasma reduction does not reduce the B lymphocyte content of marrow transplantations and, therefore, does not affect the incidence of PLS. Using rituximab to prevent GVHD reportedly reduces the incidence of PLS [58]. Of note, PLS also occurs in solid organ transplantation if competent donor B lymphocytes are present in the graft, with the risk of hemolysis increasing with higher graft lymphocyte content and when post-transplantation immunosuppression does not include an antiproliferative agent [59,60]. Some centers have advocated the use of pretransplantation red cell exchange to reduce the volume of donor-incompatible RBCs in the recipient before infusion [31]; however, this strategy has not found wide acceptance because red cell exchange procedures are inefficient and are associated with a relatively large fraction of residual recipient red cells [50,61].

BIDIRECTIONAL ABO INCOMPATIBILITY

Bidirectional incompatibility is the simultaneous presence of both of a major and a minor incompatibility. For example, if a group B recipient receives a transplant from a group A donor, the anti-A in the recipient is incompatible with the A antigen on the donor cells (major incompatibility) and the anti-B in the donor plasma is incompatible with the B antigen expressed on the recipient's cells (minor incompatibility). In these instances, the transplantation team and the transfusion service must be prepared to address complications of both types of incompatibilities. Selection of blood products in this circumstance is important and requires AB plasma products and group O RBCs. The impact of bidirectional ABO incompatibility on survival and incidence of GVHD has also not been consistently established [8-19] (Table 2).

NON-ABO/RH ANTIBODIES

Although infrequently encountered, antibodies to RBC antigens other than ABO in the HPC setting can be clinically significant [62-65]. Antibodies to minor RBC antigens have been reported in HPC transplantation at a rate of ~1% [66,67] to 8.6% [63], with varying clinical implications. Various antibodies (anti-Jk^b, anti-M, anti-Le^b, anti-Di^b, anti-E, anti-Jk^a, and anti-K) have been identified, with a mean time to detection of approximately 1 month, although some may appear much later [68]. This observation demonstrates that transplantation alloantibody formation is still possible in the peritransplant period, despite profound immunosuppression. The mean number of RBC units transfused is similar in patients who developed alloantibodies compared with those who did not, suggesting that the production of RBC antibodies was not strictly correlated with the number of RBC transfusions administered. Multiple potential immunizing factors exist for the formation of minor RBC antigen alloimmunization, including donor-derived lymphocytes infused with the HPC graft, recipient lymphocytes resistant to the conditioning regimen, donor-derived lymphocytes that engraft after the transplantation, and the secretor status of the donor and recipient. The age of the recipient, along with the conditioning regimen, may also contribute to non-ABO antibody formation in HPC transplantation [68]. The clinical impact of non-ABO antibodies is generally insignificant; however, severe hemolysis from antibodies to the Kidd (Jk) blood group system have been identified. In these cases, the donor was previously sensitized to the Kidd antigen, but the pretransplantation antibody screen did not detect the antibody. This phenomenon is common in patients with antibodies to the Kidd blood group system, and when re-exposed to the corresponding antigen, may result in an anamnestic response with concomitant hemolysis [69,70].

RhD incompatibilities are also encountered. When a D- recipient is transplanted from a D+ donor (D-major mismatch), clinically one may consider depleting RBCs from the graft. When a minor mismatch is evident, the recipient should be transfused with D- RBCs. Hemolysis may be more significant and occur earlier when the donor has preformed anti-D present at the time of transplantation [20].

MONITORING AND TRANSFUSION SUPPORT IN ABO-MISMATCHED STEM CELL TRANSPLANTATION

We acknowledge that there are many acceptable ways to monitor and provide transfusion support for ABO mismatched HSCT patients. One strategy is to closely follow hemoglobin levels and reticulocyte counts while monitoring post-transplantation anti-A and anti-B isohemagglutinins IgG and IgM titers weekly beginning from day +4 post-HSCT. For patients with an anti-A and/or anti-B titer >1:128 during pretransplantation assessment, IgG and IgM may be evaluated twice weekly after transplantation until achievement of titers below 1:16, then weekly until their complete disappearance. Hemagglutinin titer quantification is followed until it is undetectable for 2 consecutive weeks, except in patients with persistent RBC transfusion requirements. Other strategies include transfusion with donor-compatible blood in minor ABO mismatched HCT patients.

Table 3
Transfusion Support Recommendations for ABO-Incompatible HPC Transplantation

Recipient	Donor	Phase I*	Phase II†					Phase III‡				
		All Products	RBCs	Platelets		Plasma		RBCs	Platelets		Plasma	
				First Choice	Second Choices	First Choice	Second Choices		First Choice	Second Choices	First Choice	Second Choices
O	A	Recipient	O	A	AB, B, O	A	AB	Donor	A	AB, B, O	A	AB
O	B	Recipient	O	B	AB, A, O	B	AB	Donor	B	AB, A, O	B	AB
O	AB	Recipient	O	AB	A, B, O	AB	NA	Donor	AB	A, B, O	AB	NA
A	AB	Recipient	A	AB	A, B, O	AB	NA	Donor	AB	A, B, O	AB	NA
B	AB	Recipient	B	AB	B, A, O	AB	NA	Donor	AB	B, A, O	AB	NA
A	O	Recipient	O	A	AB, B, O	A	AB	Donor	A	AB, B, O	A	AB
B	O	Recipient	O	B	AB, A, O	B	AB	Donor	B	AB, A, O	B	AB
AB	O	Recipient	O	AB	A, B, O	AB	NA	Donor	AB	A, B, O	AB	NA
AB	A	Recipient	A	AB	A, B, O	AB	NA	Donor	AB	A, B, O	AB	NA
AB	B	Recipient	B	AB	B, A, O	AB	NA	Donor	AB	B, A, O	AB	NA
A	B	Recipient	O	AB	B, A, O	AB	NA	Donor	AB	B, A, O	AB	NA
B	A	Recipient	O	AB	O, A, B	AB	NA	Donor	AB	A, B, O	AB	NA

NA indicates not applicable.
* Time period from diagnosis to transplantation.
† Time period from transplantation to RBC engraftment.
‡ Engraftment established, as indicated by direct antiglobulin testing being negative, along with 2 consecutive independent samples with the forward and reverse typing showing donor ABO status.

Management of platelet transfusions in ABO-mismatched HSCT patients can be challenging. When available, ABO-compatible platelet transfusions are preferred because they are associated with improved corrected count increments [71], including patients undergoing bone marrow transplantation [72]. In addition, patients receiving ABO-incompatible plasma via platelet transfusion are occasionally reported to have hemolytic reactions [73,74]. Patients with major ABO incompatibility receive platelet and plasma transfusions of donor type and RBC transfusions of recipient type during the first period after the transplantation and switch over to donor blood type when conversion of the ABO blood group is observed and antidonor alloantibody titers are undetectable. Platelets and plasma of recipient type and RBC of donor blood type are transfused after the transplantation in patients with minor ABO incompatibility.

For patients with bidirectional incompatibility, the first choice of blood groups is AB for platelet and plasma infusions, and type O for RBC transfusions. In the case of ABO-incompatible platelet transfusions, pooled random platelets suspended in additive solution are used to minimize the dose of alloantibodies contained in the plasma.

Following reduced-intensity conditioning regimens, hematopoietic and immune function are both host and donor in

Table 4
Suggested Approach to ABO-Incompatible HPC Transplantation

Evaluation
Phase I, pretransplantation conditioning
Donor and recipient laboratory analysis
Evaluate ABO/Rh status, presence or absence of antibodies
1. Two independent peripheral blood samples for ABO/Rh typing and antibody screen
   a. Determination of clinical significance or insignificance of all non-ABO minor RBC antibodies (eg, anti-K versus anti-N)
   b. Determination of ABO-incompatibility type: major, minor, bidirectional, or none
2. Communication with clinical teams regarding transfusion support and risk for hemolysis

HPC acquisition and potential manipulation
Confirmation of ABO-incompatibility and stem cell dose. If product contains transplant dose (or approximate dose), HPC product manipulation may not be warranted given anticipated CD34 loss with product modification.
1. Major mismatch: RBC depletion
2. Minor mismatch: plasma depletion
3. Bidirectional: consider both product modifications in appropriate clinical context

Management
If donor–recipient ABO-discrepancy is identified, immediate notification and documentation with clinical team, transfusion medicine service, and stem cell processing laboratory. Transplant conditioning and post-transplant immunosuppression regimen will determine risk profile for persistence of recipient plasma cell isohemagglutinin production.
Major mismatch:
1. Monitor for acute RBC hemolysis (DAT, LDH, haptoglobin, reticulocyte count, isohemagglutinin titers, AST/ALT, bilirubin, peripheral blood smear)
   a. Evaluation for potential pure red blood cell aplasia

Minor mismatch:
1. Based on product modification (plasma reduction), risk stratify potential for acute and delayed hemolysis
   a. Day +5 to 15, monitor for passenger lymphocyte syndrome with daily CBC
   b. Keep hemoglobin level at least 9 g/dL, with donor compatible RBC transfusions

Bidirectional:
1. Monitor for both major and minor incompatibility-related adverse events
2. Ensure adequate supply of blood type AB plasma products and O RBCs

HPC indicates hematopoietic progenitor cells; DAT, direct antiglobulin test; LDH, lactate dehydrogenase; AST/ALT, aspartate aminotransferase/alanine aminotransferase ratio.

origin for variable periods after transplantation, with a delayed disappearance of host alloantibody-producing plasma cells. Thus, the risks of hemolytic reactions and delayed RBC engraftment may be higher in cases of donor–recipient major ABO-incompatibility when nonmyeloablative regimens are used.

Transfusion support recommendations for ABO-incompatible HSCT are summarized in Table 3.

SUMMARY

The overall clinical and laboratory management of ABO-incompatible HPC transplantation is complex (Table 4). During the initial transplantation evaluation, potential ABO discrepancies between the recipient and donor require a systematic approach. Although the Foundation for the Accreditation of Cellular Therapies requires ABO typing of both the donor and recipient, there is ultimately no selection guidance, other than requiring resolution and documentation before issuing the HPC product [75]. As a result, a concise transfusion policy, conditioning regimen, cellular processing protocol, and post-transplantation immunosuppression treatment plan needs to be established by the individual institution to address major, minor, and bidirectional mismatching. It is very important that the clinical teams and blood bank remain in communication to collectively anticipate and manage post-transplantation immunohematologic events, and especially to correctly manage potentially catastrophic immune hemolysis and avoid the inappropriate transfusion of donor incompatible RBCs in patients with PLS due to minor ABO incompatibility. Establishing electronic notification systems between the transplantation team and the corresponding blood bank are critical in this pursuit.

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