Review

Immuno-Hematologic Complexity of ABO-Incompatible Allogeneic HSC Transplantation

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Review

Immuno-Hematologic Complexity of ABO-Incompatible Allogeneic HSC Transplantation

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Abstract: ABO incompatibility is not considered a contraindication for hematopoietic stem cell transplantation (HSCT). Approximately 30% of transplants from related donors and up to 50% of transplants from unrelated donors are ABO-incompatible. The immuno-hematologic investigationsmay evaluate donor/recipient ABO mismatch and anti-A/B isohemoagglutinins (IHAs) titration in pre-HSCT phase. Immediate hemolysis or delayed complications (passenger lymphocyte syndrome and pure red cell aplasia) can appear post-HSCT. Some preventive treatmentstake into consideration the manipulation of the product and decision-making algorithms based on the titration of IHAs in the recipient with clinical protocols for the removal/reduction of IHAs through plasma exchange or immunoadsorption procedures. Currently, the best approach in the managementof ABO-incompatibletransplant is not defined in expert consensus documents or with solid evidence. In addition, the methods for IHAs titration are not standardized. The transfusion strategy must consider both the blood group systems of the recipient and the donor until the RBC engraftment and the confirmed ABO conversion (forward and reverse typing) on two consecutive and independent samples. Therefore, ABO incompatibility in the HSCT is an important immuno-hematologic challenge and request all necessary preventive measures including the appropriate selection of ABO blood components for transfusion.

Keywords: HSCT; ABO-incompatibility; immuno-hematologic monitoring; anti-A/B titration

1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curable modality for hematological or non-hematological malignancies. ABO incompatibility is not considered a contraindication for HSCT [1].

On the surface of red blood cells (RBCs) there are 360 antigens expressed as proteins, glycoproteins or glycolipids. The International Society of Blood Transfusion (ISBT) [2] has classified forty-five blood group systems genetically determined by 50 genes; to these systems are currently attributed about 2,000 alleles.

The gene loci of the HLA and ABO systems are independent and located on different chromosomes [3], respectively on the short arm of chromosome 6 (6p21) and the long arm of chromosome 9 (9q34); it follows, therefore, that approximately 30% of transplants from related donors and up to 50% of transplants from unrelated donors are ABO incompatible [4].

Due to the immunological incompatibility between donor and recipient, hemolytic reactions can appear. Acute hemolytic transfusion reaction anti-A and anti-B isohemoagglutinins(IHAs) are immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies. Antibodies can mediate the destruction of RBCs through phagocytosis or fragmentation by macrophages and cytotoxicity by activation of the complement pathway, which eventually results in intravascular and extravascular hemolysis [5].

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The immunohematological consequences of red cell-incompatible transplantation lead to acute hemolytic reactions which may occur when grafts contain enough RBC volumes or a high level of anti-donor isohemoagglutinins(especially for bone marrow grafts) or a high level of anti-recipientisohemoagglutinins[6].

2. ABO-incompatibility and immuno-hematologic complications

Within the ABO system, three types of incompatibility [7] can be configured in the possible donor/recipient group combinations (Table 1):

- major incompatibility, when there are recipient's isohemoagglutininsagainst the donor's red blood cells are present (20-25%),
- minor incompatibility when there are donor isohemoagglutininsagainst the recipient's red blood cells (20-25%),
- bidirectional incompatibility when both conditions occur simultaneously (5%).

Clinically significant hemolysis is encountered in 10% to 15% of cases; the incidence of non-ABO blood group mismatch–related immuno-hematologic complications after HSCT is reported to be 10% [4].

This incompatibility becomes of clinical relevance in the transplantation of HSC from bone marrow, compared to transplantation from peripheral blood or cord blood, as the amount of incompatible red blood cells in the product significantly exceeds the amount of approximately 20-30ml, considered tolerable in common transfusion practice [1]. In fact, ABO incompatibility can lead to immediate or delayed immunological complications (Table 2), such as immediate and delayed hemolysis, Pure Red Cell Aplasia (PRCA), impact on engraftment and, according to some, also on the outcome of the transplanted patient, although there are conflicting opinions in this regard as also demonstrated by the results of the most important international registriesand by other authors in the literature [8–10].

Table 1. Type of ABO incompatibility.

INCOMPATIBILITY	RECIPIENT	DONOR
ABO MAJOR (recipient isohemoagglutinins incompatible with donor red blood cells)	O	A
	O	B
	O	AB
	A	AB
	B	AB
ABO MINOR (donor isohemoagglutinins incompatible with recipient red blood cells)	A	O
	B	O
	AB	O
	AB	A
	AB	B
ABO BIDIRECTIONAL (both the recipient's and the donor's isohemoagglutinins are present)	A	B
	B	A

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Table 2. Complications and preventive interventions in ABO incompatibility.

TYPE OF INCOMPATIBILITY	COMPLICATIONS	CAUSES	PREVENTIVE TREATMENTS
ABO MAJOR	Immediate haemolysis	Infusion of donor's incompatible red blood cells	- RBCs depletion of BM grafts (>20 ml) -No manipulation of red cell contamination in PBSC grafts (<20ml)
	Delayedhaemolysis	Anti-donor isoahemogglutinins by recipient residual B lymphocyte	-Anti-donor IHAs titer (≥1:32)
	Pure Red Cell Aplasia (PRCA)	Persistence of high titer isohemoagglutinins anti-donor	-Immunoadsorption, plasma exchange
ABO MINOR	Immediate haemolysis	High titer isohemoagglutinins in donor plasma	-Anti-recipient IHAs titer (≥1:256) -Plasma depletion of both PBSC and BM grafts
	Delayed hemolysis	Passenger Lymphocyte Syndrome (PLS) by donor lymphocyte (isohemoagglutinins anti-host)	
ABO BIDIRECTIONAL	Immediate haemolysis	Recipient and donor isohemoagglutinins	-Both RBCs and plasma depletion are required
	Delayed haemolysis	Isohemoagglutinins by recipient and donor B lymphocyte	

RBC: red blood cell; BM: bone marrow; PBSC: peripheral blood stem cells; IHAs; isohemagglutinins.

Approaches to overcoming the immunological barrier of the ABO-incompatibility.

To overcome the immunological barrier of the ABO system and avoid the known complications, the marrow product is generally subjected to manipulation, depending on the type of incompatibility: removal of the red blood cells in case of major incompatibility, removal of the plasma in case of minor incompatibility, both the procedures in case of bidirectional incompatibility [3].

According to the time of occurrence a distinction can be made between immediate (during graft infusion) and delayed (during engraftment) immune hemolysis. Immediate hemolysis is commonly seen when bone marrow (BM) grafts are used as they contain more red blood cells (RBCs; approximately 200–450 ml) and plasma (up to 1,000 ml or more) compared to peripheral blood stem cell (PBSC) grafts. Due to a lesser content of RBCs (approximately 8–15 ml) and plasma (approximately 200–500 ml) in PBSC grafts, it is usually not necessary to manipulate these products in case of ABO mismatch [1,7].

To avoid the immediate severe hemolytic reactions, it is necessary that the product to be transplanted (graft) does not contain a large quantity of incompatible red blood cells (RBCs). Some preventive procedures preparatory to the infusion involving the product are therefore essential (**TableII**). It is possible to eliminate the RBCs through erythrocyte depletion methods through

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centrifugation with cell separators or by immunomagnetic separation. The product to be subjected to these procedures is bone marrow due to the greater quantity of RBCs it contains compared to the product obtained from apheresis. The post manipulation product must contain a quantity of erythrocytes not exceeding 0.3 mL/kg recipient. Naturally, the erythrocyte depletion procedure must guarantee an absence of loss of CD34+ stem cells. Another possible approach is to reduce the recipient's anti-A/anti-B isohemagglutinins titre through so-called reductive plasmapheresis carried out close to the transplant. The antibody titer considered safe is below 1:32 [1,3]. Some adopt alternative and/or complementary approaches to manipulation, taking into consideration decision-making algorithms based on the titration of IHAs in the recipient and protocols for the removal/reduction of IHAs through plasma exchange/plasma or immunoadsorption procedures. Generally, a recipient IHAs titer of 1:32 is adopted as the threshold for the removal of red blood cells from the graft or the adoption of plasma exchange or immunoadsorption procedures, and the titer of 1:256 of the donor's IHAs as the threshold for plasma removal. Raimondi et al [11] conducted survey in 2004 at 34 Italian Transplant Units from which this emerged that in the case of major incompatibility, most centers (82.3%) always carried out erythrocyte depletion, while the remaining 17.6% intervened based on the titre of recipient IHAs, many centers also carried out plasma exchange, 55.8% based on the recipient's IHAs titre, 2.9% always. As regards minor incompatibility, 81.2% of the centers always removed the plasma from the bone marrow product, while the remaining 18.7% only based on the IHAs titer, which however had a very wide range, from 1:16 at 1:256. It should be noted that 6.6% of the centers that responded to the questionnaire adopted a residual dose of incompatible red cells in the graft of 50 ml as a threshold criterion. A recent survey conducted by Balduzzi et al. [12] in the pediatric setting with the contribution of 36 centers, reported that in the case of major incompatibility, most centers (82%) remove the red blood cells from the graft, the 14% the combination of red blood cell removal and plasma exchange procedures; in the event of minor incompatibility, in 52% of cases the plasma is removed, with a reference IHAs titre varying from 1:32 to 1:128; in 41% of cases no intervention is undertaken. These data largely underline how there is great heterogeneity in the global approach both in terms of product manipulation and indications for plasma exchange.

Given the minority use of the marrow source compared to peripheral blood, data in the literature from the last decade are performed and the best approach in the management of ABO incompatible marrow transplant is not defined in expert consensus documents or reference guidelines based on scientific evidence and on the evaluation of benefits and risks of alternative options. Therefore, the consolidated clinical experience, the available technology, the degree of collaboration among the Immunohematology Laboratory, Apheresis Service and Transplantation Unit represent the most important tools with which the clinical protocols are defined. Generally, it is an experience-based approach that the transplant team shares based on their results. In addition, the methods for IHAs titration are not standardized [13] and the decision-making algorithms adopted to intervene are very different, results that are difficult to compare and not universally shared. In fact, the titration is a semi-quantitative method to determine the strength of antibody reactivity in plasma or serum. There are multiple factors that can affect the determination of anti-A/B IHAs titres (IgM and IgG) including testing platform, diluents, incubation time, strength of reaction cut-off, testing phase, skills and experience of the operators [14]. Therefore, the wide inter-laboratory variation can be due to techniques used (tube, column or microplate technologies), process (manual or automated), incubation temperatures (room temperature or 37°C), methods (direct or indirect), red cell diluents, dithiothreitol (DTT) and titration endpoints used. Scheneider et al. [15] reported that the equivalency between the automated and manual titres can be low (62.2% for IgM and 60.6% for IgG), and in addition the benefits of automated ABO titration include more efficient use of time and resources, and superior reproducibility (more precision). Therefore, there was a wide variability in titre results between and within different technologies [16]. These findings demonstrate the need for an External Quality Assessment (EQA) program for ABO titration and the use of a standard technique that mayr educe the variability and enable to obtain equivalent results (for IgM and IgG IHAs across centers, with a homogeneous clinical interpretation and better outcomes for patients [17].

 doi:10.20944/preprints202402.0477.v1

Thorpe et al. [18] described the use of a lyophilized serum preparation, 14/300, as a World Health Organization (WHO) Reference Reagent for high titre anti-A and anti-B in serum, with nominal anti-A and anti-B titres of 128 for direct room temperature (DRT), and nominal anti-A and anti-B titres of 256 for indirect antiglobulin testing (IAT). It should allow the global standardization and control of hemagglutination titrations for anti-A and anti-B in patient samples.

Each transplant center defines management protocols for ABO incompatible transplants and periodically should monitor and evaluate their results with apheresis and blood transfusion services.

Immuno-hematologic investigations and monitoring

ABO antigens are present not only on hematopoietic stem cells (HSCs), but also on tissues, including the kidney and endothelium, in body fluids, bound to plasma proteins [19,20]. After HSCT, the expression of ABO antigens changes on hematopoietic stem cells and circulating hematopoietic cells, while the tissue expression remains that of the recipient. In the presence of minor incompatibility, a tolerance to the recipient's antigens will develop and antibodies directed against the recipient's ABO antigens will not be produced. For example, a group A recipient who receives HSCs from a O group donor will change the group after engraftment, becoming O, while he will not produce anti-A isohemoagglutinins due to the phenomenon of "immunological tolerance". It is not known whether the lymphocytes of the donor develop tolerance or the IHAs are absorbed from the plasma onto the endothelium making them undetectable or both [21]. In the phase immediately following the HSCs infusion, there will be the simultaneous presence of red blood cells from the recipient and the donor, sometimes making it difficult to determine the blood group for the presence of the mixed fields in forward typing also for the RBCs transfusions [22]. ABO incompatibility is not normally responsible for delayed engraftment of neutrophils and platelets, nor does it increase the risk of GvHD and has no effect on overall survival. However, the impact of ABO mismatch on outcomes following allo-HSCT remains controversial [23–25].

La Rocca et al. [26] reported that donor engraftment, graft failure or other complications did not differ between ABO compatible or incompatible patients. ABO incompatibility did not show a significant impact on graft-versus-host disease, overall survival or disease-free survival. Factors associated with the need for prolonged red blood cell support were ABO incompatibility (p=0.0395), HLA disparity between donor and recipient (p=0.004) and the onset of hemorrhagic cystitis (p=0.015). In multivariate analysis HLA disparity was the only statistically significant condition (p=0.004).

In the Table 3 are reported the immuno-hematologic investigations to perform and the timing in pre and post-HSCT phases.

The definition of complete blood type conversion differs among the three categories of ABO incompatibility with gradual ABO group shift. For major incompatibility, the determination of ABO blood type is consistent between the forward test and reverse test, and anti-donor isohemoagglutinins is not detectable [5]. For minor incompatibility, the full donor type in forward typing is required while the reverse remains the original type of the recipient, and the direct antiglobulin test (DAT) is negative, indicating the absence of anti-recipient antibodies. For bidirectional incompatibility, the full donor type in forward is required, while in the reverse AB type. Complete reconstitution of the ABO blood type occurs within 90–110 days [27]. Nevertheless, there is a possibility of persistent recipient-type ABO antigen expression in peripheral blood after HSCT with ABO incompatibility under the circumstances of complete chimerism of donor white blood cells. This phenomenon may be attributed to the fact that persistent recipient-derived mucous cells or gastrointestinal cells generate ABO antigens that may shed into the intestinal lumen, and then are digested, absorbed, and transported to the peripheral blood [28].

 doi:10.20944/preprints202402.0477.v1

Table 3. Immuno-hematologic approach monitoring and timing.

Pre-transplant phase -30 days
Major and minor incompatibility (recipient and donor) -ABO-RhD-Rh-Kell typing and other antigens, if possible -DAT (if positive, monospecific antiglobulin and eluate) and IAT (if positive, RBC antibody identification) -titration of anti-A/anti-B IHAs (IgM and IgG)
Major incompatibility (recipient) -IHAs titration (IgM and IgG) before and after plasmapheresis procedures
Post-transplant phase
*Major incompatibility***(recipient)** - perform anti-A/anti-B IHAs titration (IgM and IgG) (+1, +7, +14, +28; every 15 days up to the 100th day after transplant)
*Minor incompatibility***(recipient)** -DAT, IAT (once a week for 2-3 weeks) -If DAT positive, perform monospecific antiglobulin and eluate (once a week for 1 month until negative test)
-ABO/Rh typing (+30, every month) with a correct serological evaluation of mixed field in forward typing and RBC genotyping, where possible

DAT: direct antiglobulin testing; IAT: indirect antiglobulin testing; RBC: red blood cells; IHAs: isohemagglutinins.

Therefore, for ABO blood type conversion and database change some diagnostic and clinical aspects must be taken into consideration: complete serological ABO definition (forward and reverse typing) at two consecutive and independent blood samples, negative TAD, evaluation of the correct presence/absence of anti A/B isohemoagglutinins at room temperature and IAT, and transfusion independence.Genotyping for confirming the present ABO alleles may be helpful.

Transplant conditioning and post-transplant immunosuppression regimen will determine risk profile for persistence of recipient plasma cell isohemagglutinin production. There is a strong correlation between the titer of incompatible IHAs and the risk of post-transplantation immune-hematologic complications. In addition, the reappearance of IHAs after major ABO-incompatible allogeneic HSCT may be a sign of relapse. The conditioning protocol, the hematological disease, the use of anti-thymocyte globulin (ATG) and GVHD prophylaxis, the number of T lymphocytes contained in the graft, and the HLA mismatch might also have an impact on donor and recipient isohemoagglutinins [29–31].

While the disappearance of IHAs anti-A/-B in case of major or bidirectional incompatibility is frequent during the first year after allogeneic HSCT, respectively in 82% and 96% of cases, the appearance of minor or bidirectional incompatibility is much less frequent (11% for isoagglutinin A, or even non-existent for isoagglutinin B in one year). Disappearance of IHAs anti-A is significantly slower in patients with myeloid diseases compared to other diseases. A disappearance of these IHAs was observed in 75.0% (9/12) of patients with HLA-matched related HSCT, and in 84.2% (32/38) of patients with other types of HLA compatibility [32].

In case of ABO major mismatch, it would be necessary to monitor for acute RBC hemolysis (DAT, LDH, haptoglobin, reticulocyte count, isohemagglutinins titration, AST/ALT, bilirubin, peripheral blood smear) and to evaluate the potential pure red blood cell aplasia (PRCA) (Table 4) [4,5].

 doi:10.20944/preprints202402.0477.v1

Table 4. Delayed immune-hematologic complication after ABO-incompatible HSCT.

	ABO Incompatibility	Onset	Risk factors	Preventive interventions	Immuno-hematologic investigations	Treatment
PRCA	Major	+30-120 days -Rule out other causes of anemia: AIHA, TMA, graft failure -Bone marrow: absence of erythroid precursors (reticulocytopenia)	-Pre-HSCT anti-donor IHAs ≥1:64 -Type A anti-donor IHAs - Nonmyeloablative conditioning -HLA-matched related donor and unrelated donor	-Reduction of anti-donor IHAs (residual recipient lymphocyte and plasma cells, abnormal immune tolerance): immunoadsorption, plasma exchange	-DAT positive: IgG+, C3d+ or both -Eluate positive for the presence of anti-A/B IHAs -IHAs titration	-Supportive care: transfusion support -Donor lymphocyte infusion (DLI) -Erythropoietin -IVIG, rituximab -Reduction of anti-donor IHAs (plasma exchange) -Plasma cell-directed therapy: Daratumumab, bortezomib, rituximab
PLS	Minor	+5-21 days -Rule out other causes of anemia: TMA, bleeding, infection, graft rejection	-Unrelated donor -Recipient of blood group A -Absence of methotrexate in GVHD prophylaxis (cyclosporine only) -Reduced-intensity conditioning regimen -Peripheral blood grafts	Plasma reduction in grafts	-DAT positive: IgG+, C3d+ or both -Eluate positive for the presence of anti-A/B IHAs -IHAs titration	-Supportive care; transfuse donor compatible RBC units. -Rituximab -Plasma exchange

PRCA: pure red cell aplasia; PLS: passengerlymphocytesyndrome; AIHA: autoimmune hemolyticc anemia; TMA: thrombotic microangiopathy: GVHD:graft versus host disease; RBC: red blood cells; DAT: direct antiglobulin testing; IHAs: isohemagglutinins.

The incidence of PRCA after major ABO incompatibility HSCT ranges from 7% to 30% and shows severe normocytic anemia, reticulocytopenia, and an absence of erythroblasts from otherwise normal bone marrow occurred for more than 30 days post-HSCT, in the absence of leukemia relapse, drug toxicity, or infection. The persistence of anti-donor isohemoagglutinins due to recipient-derived plasma cells and the titer more than 1:64 is an indicator of PRCA [33]. The risk factors for PRCA (30-120 days post-HSCT) may include recipients with type A anti-donor IHAs, the nonmyeloablative conditioning regimen or the use of a fludarabine/busulfan conditioning regimen, and unrelated donors or HLA-matched related donors (compared to haploidentical donors) [5]. Regard to immune-hematologic testing, the DAT positive for IgG, C3d or both, with eluate positive for anti-A/B isohemoagglutinins and the suppression of erythropoiesis induced by anti-A/B IHAs represent the characteristic picture [34].

 doi:10.20944/preprints202402.0477.v1

Treatment of PRCA includes plasmapheresis, transfusion support, high-dose erythropoietin, donor lymphocyte infusion, anti-thymocyte globulin, rituximab, and steroids [35,36].

In case of ABO minor mismatch, it would be necessary to stratify the risk potential for acute and delayed hemolysis at 5 to 21 days post HSCT and to monitor for passenger lymphocyte syndrome (PLS) with daily complete blood count (Table 4) [4,5]. Regard the immune-hematologic testing must be performed the same of PRCA. GVHD prophylaxis by sole cyclosporine or reduced-intensity conditioning is common in PLS in patients with the A blood group receiving stem cells from the O blood group, more frequently after PB than BM HSCT, because the former contains a higher concentration of lymphocytes. A cyclosporine-only GVHD prophylactic regimen has been associated with higher risks of immune-hematologic complications because cyclosporine boosts B-cell antibody production With reduced-intensity conditioning an increased incidence of severe delayed immune hemolysis in minor ABO-mismatched HSCT (up to 30%) has been observed [37–39].

In case of bidirectional ABO-mismatch it would be necessary tomonitor for both major and minor incompatibility-related adverse events and toensure adequate supply of blood type AB plasma products and O RBCs [1].

Briefly, autoimmune hemolytic anemias (AIHAs) occur in 4% to 6% of HSCT and may occur alone or in conjunction with other immune-mediated cytopenias. Median time of onset ranges from 4 to 10 months post-HSCT. Several factor such as transplantation for nonmalignant, unrelated donor, acute or chronic GVHD, cytomegalovirus activation are the most consistent risk factor for post-HSCT AIHA. It may be related to dysregulated immune tolerance allowing autoreactive B cells to activate and expand without regulation [5,40].

Transfusion support

ABO incompatibility, graft sources, the intensity of conditioning regimens, doses of CD34+ cells in the graft, and pre-HSCT transfusion may affect post-HSCT transfusion requirements.

The transfusion strategy in ABO-mismatched cases must consider both the blood group systems of the recipient and the donor. Dynamic ABO blood group chimerism requires caution regarding blood transfusion safety until complete engraftment. The dynamic change of blood phenotype is not only related to the patient's status, but also the basis for the implementation of compatible blood transfusion. Often final decision to switch to the donor’s ABO type varies from center to center. It is mandatory not infuse the recipient isohemoagglutinins and donor ABO antigens until RBC engraftment. In ABO-incompatibility the main rule to apply is to guarantee that red blood cells, platelets and plasma are ABO compatible with both the patient's and donor's ABO antigens and IHAs [1,3,7].

Therefore, for major incompatibility, the RBC concentrates to be transfused must have the same group as the recipient until the IHAs disappear, while for platelet concentrates and fresh frozen plasma the donor group must be respected. For minor incompatibility the RBC concentrates must be of the same group as the donor, while for platelet concentrates and fresh frozen plasma the recipient's group must be respected regardless of the disappearance of the recipient's red blood cells. For bidirectional incompatibility, the RBCs must be group O, while for platelet concentrates and fresh frozen plasma, group AB must be transfused (Table 5). An increase in transfusion amount is noted for major and bidirectional incompatibilities compared to minor incompatibilities [40,41].

Platelet transfusion choices may be expanded by subgrouping the A antigen. Platelets from blood group A2 donors do not express A antigen. Hence, they are fully blood group O compatible with the further advantage of lacking anti-A antibodies. Such platelets have the advantages of lacking susceptibility to recipient isohemoagglutinins and of post transfusion corrected count increments that are improved over blood group A1 platelets [21].

Therefore, for transfusion support with red blood cells and platelets, which constitutes an important part of the treatments for patients undergoing ABO incompatible HSCT, it is necessary a serial control program by serological techniques and molecular biology methods, where possible.

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Table 5. Indications for the transfusion of blood components in ABO incompatibility.

ABO Type			RBC concentrates		Platelet concentrates		Fresh Frozen Plasma	
ABO incompatibility	Recipient	Donor	I choice	II choice*	I choice	II choice**	I choice	II choice
Major	O	A	O	A	A	AB, B, O	A	AB
	O	B	O	B	B	AB, A, O	B	AB
	O	AB	O	AB	AB	A, B, O	AB	-
	A	AB	A, O	AB	AB	A, B, O	AB	-
	B	AB	B, O	AB	AB	B, A, O	AB	-
Minor	A	O	O	-	A	O, B, AB	A	AB
	B	O	O	-	B	O, A, AB	B	AB
	AB	O	O	-	AB	A, B, O	AB	-
	AB	A	A, O	-	AB	A, B, O	AB	-
	AB	B	B, O	-	AB	B, A, O	AB	-
Bidirectional	A	B	O	B	AB	B, A, O	AB	-
	B	A	O	A	AB	A, B, O	AB	-

RBC: red blood cells; *After disappearance of IHAs towards ABO donor, negative TAD and two consecutive samples with the forward andreverse typing confirming donor ABO group; **Plasma-reduced platelet concentrates or suspended in additive solution.

Conclusion

ABO incompatibility is common in patients undergoing HSCT. The barrier of ABO antigen mismatch may lead to acute hemolysis or delayed complications such as PLS and PRCA. Active collaboration between Blood Transfusion Service and Transplants Unit may help to evaluate the immuno-hematologic picture and the clinical risk factors at donor-recipient pre-HSCT work-up.

Currently, the best approach in the management of ABO incompatible HSCT is not defined in expert consensus documents or reference guidelines evidence based.

Therefore, close immuno-hematologic monitoring with particular attention on a standardization of ABO titration results, specific recipient/graft treatments and appropriate transfusion strategy are the three suggested intervention pillars on which to elaborate shared clinical protocols to prevent the complications post-HSCT.

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