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Blood and Genomics

2023, 7(1): 1−12

B & G

Review Article

ABO-incompatible allogeneic hematopoietic stem cell transplantation

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ABSTRACT

ABO blood group incompatibility is not a contraindication for allogeneic hematopoietic stem cell transplantation (allo-HSCT). An increasing number of ABO-incompatible HSCT (ABOi-HSCT) procedures have been performed along with advances in donor selection over the years. Currently, whether the recipient-donor ABO incompatibility has detrimental effects on post-HSCT outcomes is a matter of debate. Discrepancies across studies referring to various graft sources, donor types, conditioning regimens, and the use of immunomodulators complicate interpretations of the clinical outcomes of ABOi-HSCT, such as transfusion requirements, graft-versus-host disease (GVHD), disease relapse, overall survival (OS), and non-relapse mortality (NRM). Isohemagglutinins (ISO) targeting red blood cell (RBC) antigens are associated with post-HSCT immunohematological complications, including hemolysis, passenger lymphocyte syndrome (PLS), and pure red cell aplasia (PRCA). Immunohematological events occur frequently and are sometimes difficult to handle in clinical practice. Therefore, it is necessary to form a deeper understanding on the mechanism and a comprehensive management scheme for recipients of ABOi-HSCT. In this review, we summarized literature of the impact of ABO incompatibility on post-HSCT outcomes and outlined important immune-mediated hematological events.

Keywords: ABO blood group incompatibility, hematopoietic stem cell transplantation, immunohematological complication, hemolysis, pure red cell aplasia, passenger lymphocyte syndrome

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative option for a wide variety of hematological disorders. Human leukocyte antigen (HLA) compatibility is of primary concern when choosing a suitable donor for a transplantation recipient[1]. The major histocompatibility complex (MHC) which encodes HLA is located on chromosome 6 (6p21), while the MHC encoding carbohydrate glycosyltransferases which determine ABO blood group is located on chromosome 9 (9q34)[2–3]. This means the inheritance of the ABO blood system is independent of the HLA system,

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Conflict of interests: The authors declared no conflict of interests.

https://doi.org/10.46701/BG.2023012022036

leading to approximately 40%–50% of cases with ABO-incompatible HSCT (ABOi-HSCT)[4–5]. The ABO blood system was first discovered by Karl Landsteiner and is the most clinically significant one among the 43 recognized blood groups[6]. ABO blood antigens are known to be widely expressed on the membranes of multiple blood and tissue cells[7–8]. However, ABO blood antigens may also exist in a soluble form in patients with secretor genes (*FUT2*)[9].

Since more donor sources have become available for allo-HSCT, more donor-related parameter precautions need to be taken to ensure the HSCT success[10]. The clinical impact of donor-recipient ABO blood group or non-ABO blood group status on post-HSCT outcomes has become more attractive with the development of allo-HSCT[11–12]. Moreover, ABOi-HSCT can be complicated by immuno-hematological events, including hemolytic transfusion reactions, passenger lymphocyte syndrome (PLS), and pure red cell aplasia (PRCA) (***Fig. 1***)[13–14]. Immunohematological events following ABOi-HSCT result from red blood cell (RBC) alloimmunization due to the interaction between isohemagglutinins (ISO) and ABO antigens[15]. Subsequently, cells carrying ABO blood antigens are at a risk of destruction by either a complement-mediated pathway or opsonization, and clinically significant immuno-hematological complications may occur thereafter[15–16]. Generally, adverse consequences following ABOi-HSCT could be mitigated in a number of cases through the implementation of appropriate allograft procedures[9,11].

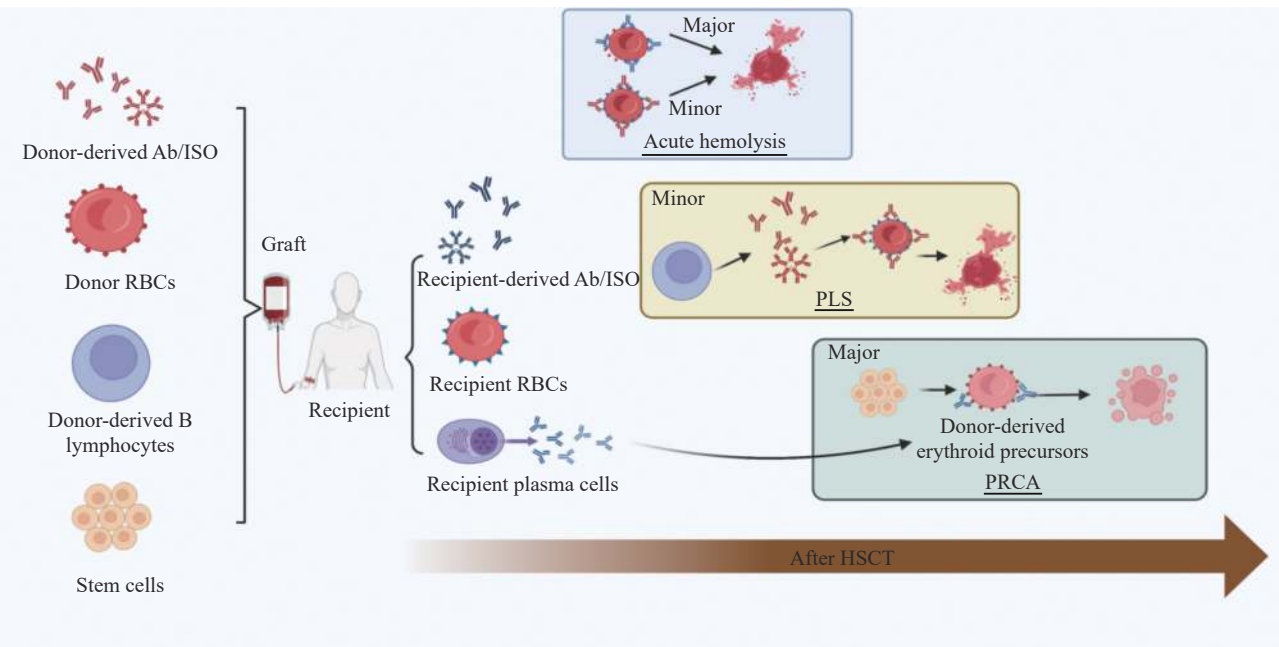

Fig. 1 **Overview of complications following ABO-incompatible HSCT.** Following ABOi-HSCT, acute hemolysis occurs in the context of major or minor ABOi-HSCT due to the interaction between ABO antigens on RBCs and Ab/ISO existing in plasma; PLS occurs in the context of minor ABOi-HSCT due to the interaction between donor-derived Ab/ISO and recipient RBCs; PRCA occurs in the context of major ABOi-HSCT due to the interaction between recipient-derived Ab/ISO and donor-derived erythroid precursors. ABOi-HSCT: ABO-incompatible hematopoietic stem cell transplantation; RBCs: red blood cells; Ab/ISO: antibodies or isohemagglutinins; PLS: passenger lymphocyte syndrome; PRCA: pure red cell aplasia.

ABO-INCOMPATIBLE ALLO-HSCT

ABO blood group incompatibility

ABO blood group incompatibility is characterized as major, minor, or bidirectional (***Table 1***). Major ABO incompatibility occurs when the recipient has ISO targeting the corresponding donor's RBC antigens. Minor ABO incompatibility refers to the presence of donor-derived ISO against the corresponding recipient's RBC antigens. Bidirectional ABO incompatibility is characterized by the presence of both recipient-derived and donor-derived ISO in the recipient/donor pair.

ABO blood group conversion and the change of ISO

Recipients without disease relapse inevitably experience dynamic ABO blood group conversion and

Table 1 **Transfusion strategies and pre-emptive procedures of grafts**

ABO incompatibility	ABO blood group		Transfusion strategy during blood group conversion		Procedures of grafts	
	Donor	Recipient	RBC transfusion	Platelet/Plasma transfusion	ISO titer	Pre-emptive procedures of grafts
Major	A	O	O	A	• Anti-donor ISO titer (≥1:32) • Anti-donor ISO titer (≤1:16)	• Red cell contamination in PBSC grafts <20 mL; RBC depletion of BM grafts • No manipulation of the PBSC grafts; RBC depletion of a BM graft might be considered in this situation but is not mandatory.
	B	O	O	B		
	AB	O	O	AB		
	AB	A	O or A	AB		
	AB	B	O or B	AB		
Minor	O	A	O	A	• Anti-recipient ISO titer (≥1:256) • Anti-recipient ISO titer (≤1:128)	• Plasma depletion of both PBSC and BM grafts; • No manipulation of the PBSC grafts; Plasma depletion of a BM graft might be considered in this situation but is not mandatory.
	O	B	O	B		
	O	AB	O	AB		
	A	AB	O or A	AB		
	B	AB	O or B	AB		
Bidirectional	A	B	O	AB	• A high ISO titer	• Both RBC and plasma depletion are required
	B	A	O	AB		

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

the ISO change after ABOi-HSCT[17–18]. The definition of complete blood type conversion differs among the three categories of ABO incompatibility[19]. For major incompatibility, the determination of ABO blood type is consistent between the forward test (FT) and reverse test (RT), and anti-donor ISO is not detectable. For minor incompatibility, the full donor type in FT is required while the serotype 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 FT is required, while the reverse stereotype to AB type is required. Complete reconstitution of the ABO blood type occurs within 90–110 days[19–20]. The time for complete blood type conversion is not affected by the ABO-incompatible status[19]. Nevertheless, there is a possibility of persistent recipient-type ABO antigen expression in peripheral blood after ABOi-HSCT under the circumstances of complete chimerism of donor white blood cells[21]. 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[22–23].

Following ABOi-HSCT, changes in ISO result in immunohematological consequences (***Table 2***)[24–25]. In the context of major/bidirectional ABOi-HSCT, a proportion of ABOi-HSCT cases undergo an increase in ISO at the outset, and a gradual decrease thereafter[24]. Gmür *et al*. observed that a rebound of recipient-derived ISO occurred in the first 4 weeks and remained elevated for 19–28 weeks in a few major ABO-incompatible cases[26]. Moreover, the disappearance of anti-A ISO is slower than that of anti-B ISO[24,27]. There is a correlation between the disappearance of anti-donor ISO and the appearance of donor-derived ABO antigens[27–28]. The graft-versus-plasma cell effect owing to a degree of genetic disparity between donors and recipients, was proven to have the potential for the disappearance of ISO to some extent[29]. However, Lemaire *et al*. did not observe a significant difference in the disappearance of ISO A according to the HLA compatibility status[24]. In cases of minor/bidirectional ABOi-HSCT, the anti-recipient ISO occurs at a possibility of 9%–27.7%[17,30], and is significantly more frequent in the minor group than in the bidirectional group (12% versus 2%)[30]. The anti-recipient ISO is associated with the development of acute graft-versus-host disease (GVHD)[30–31]. Additionally, cord blood transplantation seems to be associated with a relatively low risk of anti-recipient increase[30,32].

THE CLINICAL EFFECTS OF ABO INCOMPATIBILITY

Engraftment

Graft failure is commonly reported in a proportion of patients with HSCT. ABO incompatibility has been confirmed to have no influence on the rate of graft failure[33–35]. To date, there is a gap in standards for

Table 2 **Clinical features of immunohematological complications after ABO-incompatible HSCT**

ABO incompatibility	ABO-incompatible	Minor	Major	Bidirectional
Complications	Acute hemolysis	PLS	PRCA	Synthesize the above
Onset	The time of graft transfusion	1–3 weeks	1–4 months	
Risk factors	• Major: high level of anti-donor ISO, RBC in grafts>16 mL • Minor: high level of anti-recipient ISO in grafts	• Unrelated donor • Recipient of blood group A • Absence of methotrexate in GVHD prophylaxis • Reduced-intensity conditioning regimen • Peripheral blood grafts	• Pre-HSCT anti-donor ISO ≥1:64 • Type A anti-donor ISO • Non-myeloablative conditioning (fludarabine/busulfan) • An HLA-matched related donor and an unrelated donor (compared to a haploidentical donor)	Synthesize the above
Preventive intervention	• Reduction of anti-donor ISO in recipient (major): immunoadsorption, pre-HSCT donor type red cell transfusion • RBC depletion in grafts (major) • Plasma depletion in grafts (minor)	• Pre-HSCT RBC exchange • Plasma reduction in grafts	• Pre-HSCT reduction of anti-donor ISO: immunoadsorption, plasma exchange	Synthesize the above
Treatments	• Supportive care • corticosteroids • IVIG • TPE	• Supportive care • Rituximab • TPE	• Supportive care • Erythropoiesis stimulation • Reduction of post-HSCT anti-donor ISO (TPE) • Enhance of graft-versus-plasma cell effect (DLI) • Plasma cells/ B lymphocytes-directed: daratumumab, bortezomib, and rituximab	Synthesize the above

HSCT: hematopoietic stem cell transplantation; PLS: passenger lymphocyte syndrome; PRCA: pure red cell aplasia; ISO: isohemagglutinins; RBC: red blood cell; IVIG: intravenous immunogloblin; TPE: therapeutic plasma exchange; GVHD: graft-versus-host disease; DLI: donor lymphocyte infusion.

erythrocyte engraftment. Briefly, the criteria for erythrocyte engraftment involve reticulocyte recovery[35–38], RBC transfusion independence[39], and the ABO blood conversion[20,40]. Reticulocyte recovery is the most commonly used method for erythrocyte engraftment, which is defined as peripheral reticulocytes >1% (or 2%) for 3 consecutive days[36,38]. In this regard, major ABO incompatibility has a detrimental effect on red cell engraftment because of the persistence of host-derived anti-donor ISO[35,41].

However, no clear effects of ABO incompatibility on neutrophil and platelet engraftment were determined. A range of previous studies revealed no impact of ABO incompatibility on neutrophil and platelet engraftment[33,35,42]. Wu *et al*. indicated no significant influence of ABO blood group on the blood recovery[33]. This is similar to cases where patients with lymphoma and severe aplastic anemia were treated with ABO-incompatible haploidentical donors[43–44]. Nevertheless, the results regarding neutrophil and platelet engraftment were equivocal. In patients with acute leukemia, as opposed to those with HLA-mismatched unrelated HSCT using peripheral blood grafts[45], the cases with haploidentical HSCT had a lower rate of engraftment following major ABOi-HSCT, especially with bone marrow grafts[46]. Kimura *et al*. also found an impaired effect of major incompatibility on engraftment in unrelated bone marrow transplantation (BMT)[5]. It is speculated that ABO antigens absorbed on the surface of neutrophils and platelets or their precursors become targets for anti-donor A/B antibodies, impeding the blood recovery[47].

Transfusion requirements

Previous studies reported controversial results regarding the influence of ABO incompatibility on transfusion requirements. A series of studies revealed that ABO incompatibility may have a significant impact on transfusion burden[4,35,48–49]. Yuan *et al.* conducted a study in a cohort of 1762 patients with HSCT and found that major ABO incompatibility increased RBC and platelet transfusion support during the first 100 days post-HSCT, especially during the first 30 days[49]. This result was consistent with the findings of 800 cases of matched sibling HSCT at the National Institute of Health Clinical Center[48]. According to a retrospective study consisting of 1000

patients with HSCT, Atilla *et al.* found that cases of ABOi-HSCT received more RBC concentrate and platelet concentrate compared to those with ABO-compatible HSCT; however, no significant differences were observed among major, minor, and bidirectional groups[4]. Meanwhile, a few studies confirmed that ABO incompatibility had no impact on transfusion burden[33,50–51]. Recently, a study on 510 haploidentical HSCT cases showed that there were no significant differences in RBC and platelet transfusion requirements at 30, 60, 90, 180, and 365 days post-HSCT[33]. The potential reason for these controversial results may be the different intensities of conditioning regimens among the studies. As reported, myeloablative conditioning was administered to the whole cohort of haploidentical HSCT[33], while more than half of the cases received nonmyeloablative or reduced-intensity conditioning in the other two large studies[48–49]. Of note, most research on cord blood transplantation indicated that ABO incompatibility was not a risk factor for transfusion burden after transplantation[36,52]. Apart from 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[35,48].

GVHD

To date, no clear correlation between ABO incompatibility and GVHD has been established. ABO incompatibility may play a role in the development of acute GVHD as a result of the fact that A and B glycosyltransferase enzymes are allogeneic and may act as minor histocompatibility antigens (mHags), eliciting T cell responses[53]. As widely indicated, minor ABO incompatibility may play an adverse role in the development of acute GVHD in ABOi-HSCT[54–57]. In a population of HLA-matched unrelated transplantations, Ludajic *et al*. found that minor incompatibility was an independent risk factor for grade Ⅱ–Ⅳ acute GVHD, especially grade Ⅲ–Ⅳ acute GVHD[55]. This finding is in accordance with the results of HLA-matched sibling transplantation[54]. However, Stussi *et al.* indicated that minor incompatibility had an impaired effect on grade Ⅰ–Ⅳ acute GVHD rather than grade Ⅱ–Ⅳ acute GVHD in a study of 562 patients, where HLA-matched sibling HSCT accounted for 87%[56]. Recently, a study on pediatric cases found that minor ABO incompatibility had no influence on the severity of acute GVHD[57].

In addition, major and minor incompatibility may significantly increase the risk of acute liver GVHD rather than skin or gut aGVHD[44,58]. ABO antigens expressed in endothelial and epithelial tissues (especially bile tract) may result in a high risk of acute liver GVHD[59–60]. Notably, a study of 1199 patients with acute leukemia following myeloablative HSCT using a combination of bone marrow grafts and peripheral blood grafts confirmed that major incompatibility was an independent risk factor for aGVHD[10]. Hefazi *et al*. reported consistent results in the context of peripheral blood HSCT with reduced-intensity conditioning[41]. However, many studies demonstrated controversial findings that donor-recipient ABO incompatibility had no effect on the development of acute GVHD[4,5,33,35]. Regarding cord blood transplantation, most studies consistently confirmed no significant influence of ABO incompatibility on acute GVHD[61–63]. In view of chronic GVHD, few studies showed any impacts of ABO incompatibility[5,33,35,62]. However, a previous study on alemtuzumab-based reduced-intensity HSCT conversely found that patients with minor and major ABO incompatibility were at a higher risk for extensive chronic GVHD[64].

Relapse, non-relapse mortality (NRM), and survival

Conflicting results regarding the impact of ABO blood group on underlying disease relapse were reported in previous studies. A large registered study by Bazarbachi *et al*. confirmed a higher incidence of relapse in bidirectional ABOi-HSCT patients with lymphoma using haploidentical donors[43]. However, a previous study by Logan *et al.* did not reveal a significantly different incidence of relapse in lymphoma cases using peripheral blood graft[65] . In cases of acute myeloid leukemia (AML), Canaani *et al.* did not observe an increased risk of ABO incompatibility for relapse, regardless of the use of haploidentical donors or mismatched unrelated donors[45–46]. In addition, several large registered studies consistently demonstrated that ABO incompatibility had no effect on disease relapse after HSCT[5,58].

As previously published, the impact of ABO blood group on NRM was unclear. ABO incompatibility was reported to significantly increase the risk of NRM in the context of matched-related HSCT using peripheral blood grafts[42]. Kimura *et al.* found that major and minor incompatibilities increased the risk of NRM after unrelated BMT[58]. While major ABO incompatibility may increase the risk for NRM[10,35], Logan *et al.* found that minor incompatibility had an unfavorable impact on NRM based on two different

datasets: the Stanford dataset and the Center for International Blood and Marrow Transplant Research (CIBMTR) dataset[65]. In contrast, a series of studies illustrated that donor-recipient ABO blood groups had no impact on the incidence of NRM[4,43,66]. To date, the mechanism of ABO incompatibility on NRM remains unclear.

The impact of ABO blood group on survival has changed over time. In 2008, Kimura *et al*. found that major and minor ABO incompatibility had a detrimental impact on the survival of patients with unrelated BMT, using a registered dataset from Japan[58]. Moreover, a large study by Logan *et al.* revealed that minor incompatibility was a risk factor for survival in both the Stanford and CIBMTR datasets[65]. However, Kimura *et al.* subsequently confirmed that the ABO blood group lost its unfavorable effects on prognosis following unrelated BMT over time, according to a registered report in 2019[5]. In addition, Canaani *et al.* found that ABO incompatibility had no impact on survival in patients using unrelated or haploidentical related grafts[45–46]. Furthermore, in 2021, Valentini *et al.* illustrated that ABO incompatibility and graft sources had no effect on overall survival (OS) in a multivariate analysis[35].

THE IMMUNOHEMATOLOGICAL CONSEQUENCES

Acute hemolytic transfusion reaction

Anti-A and anti-B ISO 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 (***Fig. 2***)[16]. Clinically significant hemolysis or laboratory signs of hemolysis can be encountered in 10%–16.7% of the cases with ABOi-HSCT[37,67]. Acute hemolytic transfusion reactions may occur when grafts contain enough RBC volumes or a high level of anti-donor ISO in the major group (especially for bone marrow grafts) or a high level of anti-recipient ISO in the minor group[68]. Tomac *et al*. found that patients with post-HSCT hemolysis were characterized by IgM ≥ 1:8 and received >16 mL of RBCs in the context of major and bidirectional HSCT (***Table 2***)[69]. Preventive interventions for acute hemolysis include reduction of anti-donor ISO in recipients and RBC depletion in grafts for major ABOi-HSCT through apheresis or simple sedimentation[70]. Recently, pre-HSCT donor-type red cell transfusion has been considered a safe and effective strategy to prevent acute hemolysis when using major ABO-incompatible bone marrow grafts, if the anti-donor ISO is 1:32 or higher[71].

PLS

PLS results from *de novo* ISO or alloantibodies through passenger B lymphocytes from grafts, rather than a passive transfer of antibodies (***Fig. 2***)[67]. IgM anti-recipient ABO antibodies may serve as an early predictor of PLS after minor ABOi-HSCT[72]. Generally, post-HSCT PLS in the form of delayed immune hemolysis occurs 1–3 weeks after minor ABOi-HSCT, with a positive DAT (***Table 2***)[73–74]. PLS occurs more frequently in solid organ transplantations than in HSCTs[75]. According to previous reports, clinically significant hemolysis appeared in 10%–15% of cases of minor ABOi-HSCT[67]. The cases of severe and fatal PLS were reported[76–77], and patients with post-HSCT PLS may have an inferior survival rate compared to those without PLS[72]. Notably, no significant association was found between the severity of hemolysis and level of anti-recipient isohemagglutinin titers[72,78]. Risk factors for post-HSCT PLS included unrelated donor[34], recipient of blood group A[77], absence of methotrexate in GVHD prophylaxis[79], reduced-intensity conditioning regimen[78], and peripheral blood stem cells[80]. Remarkably, no guidelines exist for the prevention of post-HSCT PLS. Prophylactic RBC exchange is a controversial strategy. Worel *et al*. found that patients with prophylactic RBC exchange had a lower risk of severe hemolysis after minor ABOi-HSCT with reduced-intensity conditioning[81]. However, Cunard *et al*. failed to confirm the advantages of prophylactic RBC exchange[82]. Bolan *et al*. also postulated the inability of prophylactic RBC exchange to prevent severe hemolysis owing to technical impossibility[80]. Rituximab is an effective therapy for patients with severe post-HSCT PLS[83]. It is recommended that meticulous clinical monitoring, vigorous donor-compatible RBC transfusion, and timely therapeutic RBC exchange should be practiced during minor ABOi-HSCT procedure[77].

PRCA

PRCA after major ABOi-HSCT was established if persistently severe normocytic anemia, reticulocytopenia, and an absence of erythroblasts from otherwise normal bone marrow occurred for more than 60 days post-HSCT, in the absence of leukemia relapse, drug toxicity, or infection (***Table 2***)[38,84]. The persistence of peri-HSCT anti-donor ISO produced by recipient-derived plasma cells

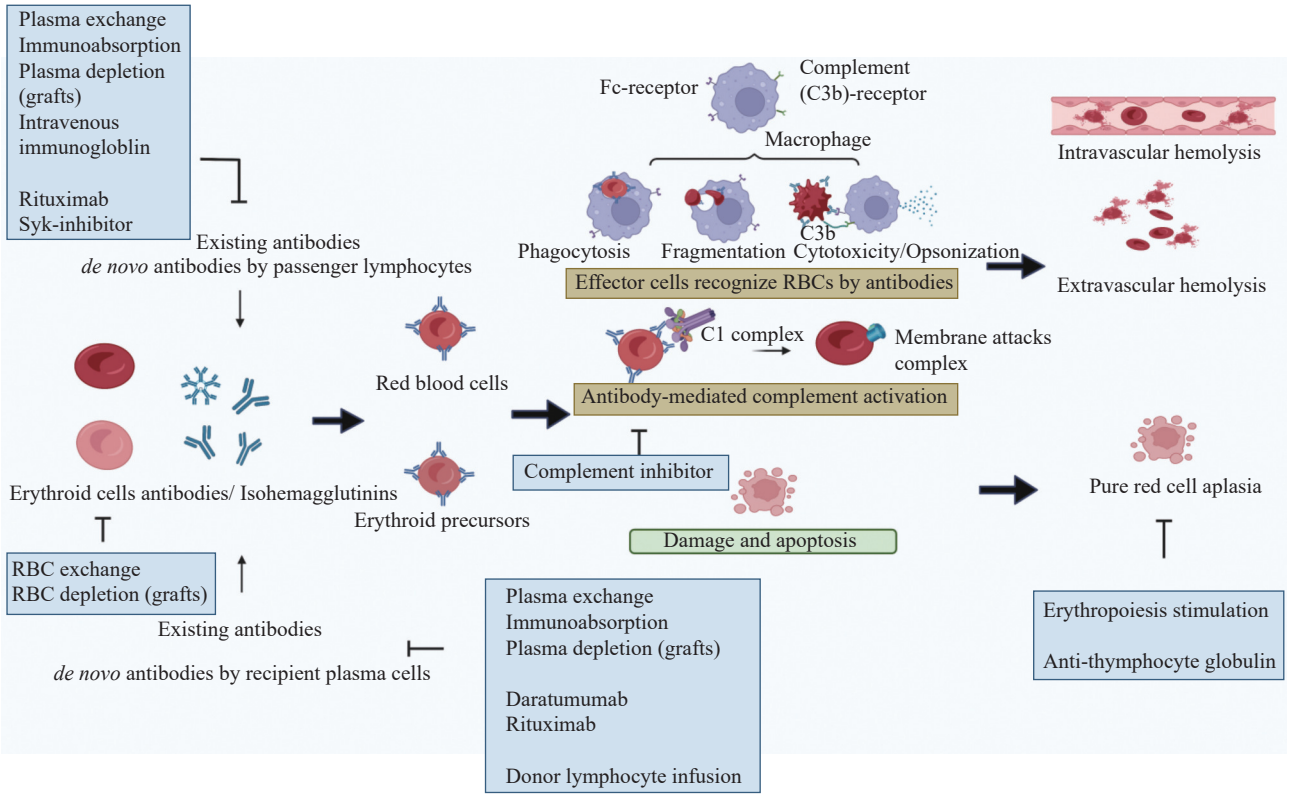

***Fig. 2* Mechanism of complications following ABO-incompatible HSCT.** The hemolysis following ABOi-HSCT results from destruction of RBCs *via* phagocytosis or fragmentation by macrophages and cytotoxicity by activation of complement pathway. Damage and apoptosis of erythroid precursors by peri-HSCT donor-derived ISO contributes to post-ABOi-HSCT PRCA. Procedures of RBC depletion, antibodies depletion (for example RBC exchange, plasma exchange, and rituximab), and complement inhibitor are beneficial to preventing immunological complications following ABOi-HSCT. ABOi-HSCT: ABO incompatible hematopoietic stem cell transplantation; RBCs: red blood cells; ISO: isohemagglutinins; PRCA: pure red cell aplasia.

was responsible for the development of PRCA (***Fig. 2***)[29,85]. Complement-mediated destruction of erythroid precursors by anti-donor ISO was recognized as the primary cause of post-HSCT PRCA[86], although the exact mechanism remains unclear. The disappearance of anti-donor ISO was significantly associated with the recovery of donor-derived reticulocytes[27–28], or the resolution of post-HSCT PRCA[26,38]. It was confirmed that the pre-HSCT ISO titer more than 1:64 was a predominant indicator of post-HSCT PRCA[87–88]. Additionally, *de novo* anti-donor ISO after major ABOi-HSCT contributed to some cases of post-HSCT PRCA with low ISO titers before HSCT[26], especially secondary post-HSCT PRCA[38]. Usually, post-HSCT PRCA was resolved when the anti-donor ISO titer declined to 1:16[26]. The graft-versus-plasma cell effect may play an important role in clearing donor-directed ISO after major ABOi-HSCT[38].

The incidence of post-HSCT PRCA ranges from 7% to 30% according to previous studies[38–39,88]. The risk factors for post-HSCT PRCA may include recipients with type A anti-donor ISO[27], the non-myeloablative conditioning regimen[89] or the use of a fludarabine/busulfan conditioning regimen[39,88], and unrelated donors or HLA-matched related donors (compared to haploidentical donors)[38]. Notably, major ABOi-HSCT using cord blood grafts may overcome the concern of post-HSCT PRCA[90].

PRCA had no impairing influence on clinical outcomes concerning OS, disease relapse, and NRM[38–39]. The majority of patients with post-HSCT PRCA showed self limitations[38–39]. However, refractory PRCA is an incapacitating complication in patients with major ABO-HSCT, which increases the burden of long-term transfusion, and thereafter leads to a high risk of iron overload and impaired quality of life[39,91]. Therapeutic options for post-HSCT consist of erythropoiesis stimulation, reduction of anti-donor ISO titers, and a strategy inducing the graft-versus-plasma cell effect[87]. However, there is no standard management for post-HSCT PRCA[87,92]. In view of the resolution of post-HSCT PRCA, neither Longval *et al*. nor Hirokawa *et al*. observed a significant

benefit in the treated group compared to the untreated group[84,88]. Recently, eltrombopag[93], ibrutinib[94], bortezomib[95], and anti-thymocyte globulin (ATG)[96] were reported as effective therapeutic treatments for refractory post-HSCT PRCA. Remarkably, a series of reports on daratumumab (a human IgG1κ anti-CD38 monoclonal antibody targeting plasma cells) achieved excellent treatment responses[97–100].

PRE-TRANSPLANTATION PROCEDURE AND TRANSFUSION STRATEGY

To avoid severe immediate hemolysis, delayed hemolysis, or PRCA following ABOi-SHCT, pre-HSCT graft manipulation was recommended according to the protocol described by Worel *et al.* (***Table 1***)[101]. In cases of major ABOi-HSCT with an anti-donor ISO titer of ≥1:32, the volume of RBCs in peripheral blood grafts should be <20 mL, and RBCs in bone marrow grafts should be depleted. In cases of minor ABOi-HSCT with an anti-recipient ISO titer of ≥1:256, plasma depletion of both peripheral blood grafts and bone marrow grafts is necessary.

Dynamic ABO blood group chimerism requires caution regarding blood transfusion safety until complete engraftment[40,102]. It is mandatory that RBCs should be compatible with both ABOi-HSCT donors and recipients (***Table 1***). In brief, type-O RBCs are recommended, regardless of the type of ABO incompatibility. Plasma or platelet concentrates of the donor type or recipient type are recommended for major or minor ABOi-HSCT, respectively. Type AB plasma or platelet concentrates should be selected for patients with bidirectional ABOi-HSCT.

SUMMARY

ABO incompatibility is common in patients undergoing HSCT. No consistent results have been reported concerning the impact of ABO incompatibility on the outcomes of HSCT. To some degree, ABOi-HSCT has specific effects on clinical outcomes including engraftment, GVHD, and NRM. This detrimental impact on the survival of patients with ABOi-HSCT was eliminated over the past few years. Additionally, immune-mediated hematological events after HSCT using ABO-incompatible grafts are common and occasionally life-threatening. It is necessary to consider the types of conditioning regimens, donor types, graft sources, and GVHD prophylaxis to investigate the exact impact of ABO incompatibility on outcomes following ABOi-HSCT. Meticulous clinical monitoring and vigorous interventions play a pivotal role in the successful management of ABOi-HSCT patients.

Acknowledgments

This work was supported by the grant from the National Natural Science Foundation of China (82170205).

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Received 28 November 2022, Revised 17 April 2023, Accepted 25 May 2023