

ABO-Mismatched Allogeneic Hematopoietic Stem Cell Transplantation

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Keywords

ABO-incompatible · Hematopoietic stem cells · Transplantation

Summary

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative option for a variety of malignant and non-malignant hematological and congenital diseases. Due to the fact that the human leukocyte antigen system is inherited independently of the blood group system, approximately 40–50% of all HSCTs are performed across the ABO blood group barrier. The expected immune-hematological consequences after transplantation of an ABO-mismatched stem cell graft are immediate and delayed hemolytic complications due to presence of isohemagglutinins or passenger lymphocyte syndrome. The risks of these complications can partially be prevented by graft manipulation and appropriate transfusion support. Dependent on the kind of ABO mismatch, different effects on engraftment have been observed, e.g. delayed red blood cell recovery and pure red cell aplasia. Data on incidence of acute graft-versus-host disease (GVHD), non-relapse mortality, relapse, and overall survival are inconsistent as most studies include limited patient numbers, various graft sources, and different conditioning and GVHD prophylaxis regimens. This makes it difficult to detect a consistent effect of ABO-mismatched transplantation in the literature. However, knowledge of expectable complications and close monitoring of patients helps to detect problems early and to treat patients efficiently, thus reducing the number of fatal or life-threatening events caused by ABO-mismatched HSCT.

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Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is widely used to treat patients with malignant and non-malignant hematological and congenital diseases [1]. A prerequisite for a successful HSCT is the availability of a human leukocyte antigen (HLA) identical stem cell donor, which is different to solid-organ transplantation where ABO compatibility between the donor and recipient is critical [2].

Due to the fact that the HLA system is inherited independently of the blood group system, approximately 40–50% of all HSCTs are performed across the ABO blood group barrier [3, 4]. Although the transplantation of an ABO-mismatched graft is feasible immune-hematological problems have to be considered, and special precautions should be taken in order to allow a safe HSCT. The clinical impact of ABO-disparate transplantations in terms of neutrophil or platelet engraftment, incidence of acute and chronic graft-versus-host disease (GVHD), non-relapse mortality (NRM), disease-free survival and overall survival is uncertain [4–8]. Moreover, besides bone marrow (BM) grafts which have been used since more than two decades other hematopoietic stem cell sources like peripheral blood stem cells (PBSC) and cord blood (CB) are currently available [9, 10] and non-myeloablative (NMA) or reduced-intensity conditioning (RIC) regimens have been introduced for stem cell transplantation [11]. ABO-mismatched transplantation may have different effects if G-CSF-primed PBSC or CB grafts or new conditioning regimens are used [11]. Besides the ABO blood group system, Rhesus (Rh) antigens, especially the D antigen, are clinically the most significant factors for alloimmunization that usually occur after exposure of RhD-negative individuals to RhD-positive blood components [12]. Studies in HSCT recipients have shown an incidence of 10% of anti-D alloimmunization in RhD-positive patients with a RhD-negative donor [13, 14].

Table 1. Standard procedures for ABO-mismatched transplants

ABO mismatch	PBSC/BM graft manipulation	Therapeutic apheresis
<i>Major</i> Recipient anti-donor isohemagglutinins $\geq 1:32$	<i>PBSC:</i> <20 ml RBC: no manipulation; ≥ 20 ml RBC: RBC depletion <i>BM:</i> RBC depletion	plasma exchange with AB plasma or albumin/sodium [26]
<i>Major</i> Recipient anti-donor isohemagglutinins $\leq 1:16$	<i>PBSC:</i> no manipulation <i>BM:</i> infusion without modification possible [11]; to be on the safe side: RBC depletion	plasma exchange with AB plasma or albumin/sodium
<i>Minor</i> Donor anti-recipient isohemagglutinins $\geq 1:256$	<i>PBSC + BM:</i> plasma depletion	experimental: RBC exchange with group O RBCs [17]
<i>Minor</i> Donor anti-recipient isohemagglutinins $\leq 1:128$	<i>PBSC:</i> no manipulation <i>BM:</i> infusion without modification possible [11]; to be on the safe side: plasma depletion	experimental: RBC exchange with group O RBCs [17]
<i>Bi-directional</i>	RBC depletion and plasma depletion (when anti-recipient isohemagglutinins are $> 1:128$)	

Definition of ABO Mismatch

Three groups of ABO mismatch can be defined. Minor ABO mismatch (20–25% of transplants) is characterized by the ability of donor B lymphocytes to produce anti-recipient antibodies (e.g. group O donor to a group A recipient). In major ABO mismatch cases (20–25% of transplants) anti-donor ABO antibodies are present in the recipient (e.g. group A donor to a group O recipient). Bi-directional ABO mismatch (up to 5% of transplants) occurs if both donor and recipient have antibodies directed against ABO blood group antigens of each other (e.g. group A donor to a group B recipient).

Immune-Hematologic Consequences of ABO-Mismatched HSCT

Immediate and Delayed Hemolysis

Due to the immunological incompatibility between donor and recipient, hemolytic transfusion reactions can appear. 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 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 PBSC grafts [3]. Therefore, in ABO-mismatched bone marrow transplant (BMT) it is clinical routine either to remove isohemagglutinins (in case of minor ABO mismatch) or incompatible RBCs (in case of major ABO mismatch) from the graft or to reduce anti-donor RBC antibodies or residual RBCs in the recipient by various techniques (table 1) [15–17]. 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 (table 1) [3].

With the introduction of RIC regimens an increased incidence of severe delayed immune hemolysis in minor ABO-mismatched HSCT (up to 30%) has been observed, which typically presents 7–14 days after transplantation [5, 8, 18]. The reason for this complication is thought to be on the one hand a higher amount of remaining recipient RBCs due to the reduced dose of chemo-/radiotherapy and the enhanced isohemagglutinin production by donor B lymphocytes (passenger lymphocyte syndrome), especially if PBSC grafts are used. In addition, the post-grafting immunosuppression which comprises of a calcineurin inhibitor (CNI) and an antimetabolite is different after RIC compared to myeloablative regimens. The majority of GVHD protocols for myeloablative transplant consist of CNI and methotrexate (MTX), whereas in RIC protocols CNI and mycophenolate mofetil (MMF) are used. Antimetabolites like MTX or MMF inhibit proliferation of T and B lymphocytes and also antibody production. In contrast to MTX, the circulating half-life of MMF is only 3.6 h, and the bond to inosine monophosphate dehydrogenase is rapidly reversible. This may permit antigen-primed B cells to escape T-cell control and to produce high numbers of anti-recipient RBC antibodies leading to immune hemolytic complications especially in the RIC setting [17]. Laboratory signs of intravascular hemolysis (e.g. drop in hematocrit and haptoglobin; elevated levels of free hemoglobin and lactate dehydrogenase) should be monitored in patients at risk, and patients should be screened for occurrence of anti-recipient RBC antibodies. In most cases, laboratory test results on a direct antiglobulin test will remain positive unless all antibody-bound RBCs have been lysed [8, 19].

Rhesus Mismatch

Besides immunological reactions due to an ABO mismatch in rare cases, a de novo anti-D immunization can occur. In case of a RhD-positive patient receiving a RhD-negative graft, donor lymphocytes are exposed to antigen-bearing recipient RBCs possibly leading to de novo D immunization in the post-transplantation period. The development of anti-D normally does not impair the transplant outcome and is not of clinical relevance in the post-transplant course of adults. Since RIC has also been demonstrated a feasible and safe procedure in children, the development of D antibodies after D-mismatched HSCT may become of clinical importance in the childbearing age of these individuals [20]. So far, data on the risk of de novo D immunization after RIC HSCT in children and adolescents are lacking. Thus, antibody screening in young patients after HSCT seems advisable to avoid complications during pregnancy. If signs of extravascular hemolysis occur in the post-transplant course after D-mismatched HSCT, one should consider de novo D immunization and apply supportive care accordingly.

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) is a complication after major ABO-mismatched HSCT and occurs in up to 29% of patients with a major ABO-mismatched donor [21, 22]. It is more frequently observed in the constellation of group A donors in group O recipients and results from the presence of recipient-derived residual B lymphocytes or plasma cells which produce isohemagglutinins directed against donor RBCs. The risk of PRCA increases with the use of RIC [22], sibling donors [23], and presence of high anti-A isohemagglutinins [24, 25]. Pre-transplant reduction of host anti-donor isohemagglutinins either by plasma exchange or immunoadsorption, or application of donor type packed RBCs, is reported to reduce the risk of PRCA [16, 26]. Since the incidence of PRCA is relatively low and spontaneous remissions are observed in a number of patients, a post-transplant prophylactic treatment of all major ABO-mismatched allogeneic HSCT recipients is not recommended [27]. If anti-donor isohemagglutinins persist for more than 60 days after HSCT, the probability of spontaneous clearance is low. In such cases various treatment modalities to remove persisting isohemagglutinins have been described [28]. Those may include erythropoietin [29], plasma exchange or immunoadsorption [21], taper of immunosuppressive drugs, or administration of donor leukocyte infusions (DLI) [22, 30]. In addition, the use of rituximab, a monoclonal antibody directed against CD20-positive B cells, has been shown to be effective in some case reports [31].

Engraftment

Several registry and cohort studies demonstrate that the presence of anti-donor isohemagglutinins (e.g. in major ABO mismatch) can delay RBC recovery and increase post-transplant RBC transfusion requirements [6, 21, 23, 32].

Despite it is known that ABO blood group antigens are also expressed on lymphocytes and platelets, no clear influence of ABO

mismatch with regard to leukocyte and platelet recovery has been found [33, 34]. Although registry studies of the Japan Marrow Donor Program (JMDP; 5,549 patients included) and the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC; 1,108 patients included) found a correlation of slower neutrophil engraftment with major ABO mismatch, a study of the National Marrow Donor Program (NMDP; 6,978 patients included) could not observe any difference in engraftment with respect to ABO match [6, 35, 36] (table 2).

In terms of platelet engraftment a meta-analysis of 7 cohort studies, the report for the JMDP, and other studies showed a delay in recovery for recipients of major ABO-incompatible grafts [6, 37, 38]. This phenomenon has previously been reported by other authors to be limited to major ABO-incompatible transplantation, who speculated that anti-donor isohemagglutinins bind to A or B antigens absorbed on the surface of neutrophils, platelets, or their precursors [32].

Graft Failure

Remberger et al. [39] observed an increased risk of graft failure after major ABO-mismatched transplantation (7.5 vs. 0.6%) in an analysis of 224 patients. In this study, 6 patients with graft failure were detected, including 4 of 67 major ABO mismatch and 2 of 16 bi-directional ABO mismatch cases. However, in this analysis, HLA-A, HLA-B, HLA-DR allele level mismatch was also a factor significantly associated with graft failure. Five of 6 patients with graft failure had at least one HLA allele-mismatched donor, making it difficult to precisely ascribe the definitive role of ABO mismatch in this setting. In the report of the JMDP an increased risk for secondary graft failure was observed in univariate analysis for patients receiving any kind of ABO-mismatched graft but these findings could not be confirmed in multivariate analysis [6]. In contrast to the results above, other studies have not found a higher risk of secondary graft failure in combination with ABO-mismatched transplantation, leading to the assumption that additional factors may have an influence on sustained engraftment [40–42].

Graft-versus-Host Disease

As ABO antigens are not only expressed on blood cells but also on non-hematopoietic structures and tissue (e.g. endothelial and epithelial cells, von Willebrand factor) donor ABO-type isohemagglutinins can also bind to those host cells, and some authors raise the question whether ABO antigens and isohemagglutinins are also involved in the pathogenesis of GVHD [7]. However, results of published studies are conflicting (table 2).

Kimura et al. [6] reported a higher incidence of acute GVHD grade III–IV in both the major and minor ABO mismatch but not in the bi-directional ABO-incompatible group. Interestingly, the incidence of liver GVHD was higher in minor ABO-mismatched transplantation. Their hypothesis is that epithelial cells of the large

Table 2. Studies focusing on clinical outcomes after ABO-mismatched stem cell transplantation^{a,b}

Author	ABO match (N) Identical Minor Major Bi-directional	Donor	Conditioning regimen GVHD prophylaxis	Graft source	Engraftment ANC	Acute GVHD Grade II-IV	Chronic GVHD	Relapse	NRM	OS
Bacigalupo et al. [43]	124 27 23 excluded	RD	MA CNI or MTX or CNI + MoAb	BM	no data no data	0.003 (higher minor) no data	no data	no data	no data	no data
Benjamin et al. [50]	153 55 62 22	RD, URD	MA CNI + MTX ± steroids	BM	NS NS	no data no data	no data	no data	no data	0.003 (lower major) 0.05 (lower minor) (AML only)
Blin et al. [52]	395 0 337 77	RD, URD	MA + RIC CNI+MTX or MMF	BM PBSC cord blood	NS NS	0.05 PBSC only no data	NS	NS	No data	NS
Canals et al. [37]	52 15 8 2	RD	RIC CNI + MTX	PBSC	NS 0.005 (major slower)	NS	NS	NS	NS	NS
Erker et al. [48]	79 32 21 11	RD, URD	MA + RIC CNI+MTX	BM PBSC	NS NS	NS NS	NS	0.002 (higher minor/bid)	no data	0.006 (higher minor/ bid)
Gutiérrez-Aguirre et al. [46]	88 20 13 0	RD	RIC CNI + MTX	PBSC	NS NS	NS (higher minor) NS	NS	no data	NS	NS
Kanda et al. [38] Meta-analysis	697 228 202 81	RD, URD	MA + RIC CNI + others	BM PBSC	RD: NS URD: 0.01 (minor slower) 0.012 (bid slower)	no data	no data	no data	GVHD-related 0.001 (higher bid)	RD: NS URD: lower minor/bid
Keever-Taylor et al. [44]	266 96 90 29	RD, URD	MA CNI + MP ± ATG	BM	no data no data	0.001 (higher minor) no data	NS	no data	no data	NS

Table 2. continued on next page

Table 2. Continued

Author	ABO match (N)	Donor	Conditioning regimen	Graft source	Engraftment	Acute GVHD	Chronic GVHD	Relapse	NRM	OS
	Identical		GVHD prophylaxis		ANC	Grade II-IV	GVHD			
	Minor				Platelets	Grade III+IV				
	Major									
	Bi-directional									
Kim et al. [41]	49	RD	MA + RIC	PBSC	NS	NS	NS	NS	NS	NS
	15									
	20		CNI ± MTX or MMF		NS	no data				
	5									
Kimura et al. [6]	2,820	URD	MA + RIC	BM	0.004 (major slower)	no data	no data	no data	0.0001 (major higher)	0.016 (major lower)
Registry study	1,202									
JMDP	1,384		CNI + MTX		0.001 (major slower)	0.001 (major or minor higher)			0.009 (minor higher)	
	143									
Kollman et al. [35]	2,860	URD	MA + RIC	BM	NS	no data	NS	NS	NS	NS
Registry study	1,802									
NMDP	1,670		various		no data	NS				
	587									
Mehta et al. [47]	76	RD	MA	BM	no data	NS	NS	0.039 (lower ABO-mm)	0.048 (lower ABO-mm)	0.004 (higher ABO-mm)
	27 minor/bid									
	16 major		CNI ± MTX		no data	no data	no data			
Michallet et al. [36]	716	RD, URD	RIC	BM	no data	NS	NS	no data	0.01 (minor higher)	0.001 (lower minor vs. id)
Registry study	205			Cord blood						
(SFGM-TC)	187		CNI ± MTX/MMF + other agents	PBSC	no data	no data			NS for major	NS for major
	not stated									
Mielcarek et al. [23]	960	RD, URD	MA	BM	NS	NS	no data	no data	no data	NS
	299									
	314		CNI + MTX		NS	no data				
	103									
Ozkurt et al. [53]	80	RD, URD	MA + RIC	BM	NS	NS	NS	NS	0.01 (higher minor)	0.02 (lower minor)
	30			PBSC						
	25				NS	0.04 (higher minor)				
	12									
Resnick et al. [49]	127	RD, URD	RIC	BM	NS	NS	NS	NS	0.045 (minor higher)	NS
	38			PBSC						
	56 major/bid		CNI		NS	NS			0.023 (major higher)	

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Table 2. Continued

Author	ABO match (N) Identical Minor Major Bi-directional	Donor	Conditioning regimen GVHD prophylaxis	Graft source	Engraftment ANC	Acute GVHD Grade II-IV Grade III+IV	Chronic GVHD	Relapse	NRM	OS
Seebach et al. [32] Registry study (CIBMTR)	2,108 451 430 114	RD	MA CNI + MTX	BM	0.001 (major slower) no data	NS 0.006 (bid only)	NS	NS	NS	NS
Stussi et al. [7]	361 98 86 17	RD, URD	MA + RIC	BM PBSC	NS NS	NS no data	no data	NS	no data	0.0009 (lower bid) NS (major or minor)
Worel et al. [42]	21 9 8 2	RD, URD	RIC CNI + MMF	PBSC	NS NS	NS no data	NS	0.056 (lower for ABO-mm)	0.05 (higher for ABO-mm)	NS

ABO-mm = ABO-mismatched; AML = acute myelogenous leukemia; ANC = absolute neutrophil cells; ATG = antithymocyte globulin; bid = bidirectional; BM = bone marrow; CIBMTR = Center of International Blood and Marrow Transplant Research; CNI = calcineurin inhibitors; id = identical; JMDFP = Japan Marrow Donor Program; MA = myeloablative; MMF = mycophenolate mofetil; MoAB = monoclonal antibodies; MP = methylprednisolone; MTX = methotrexate; N = number; NMDFP = National Marrow Donor Program; NRM = non relapse mortality; NS = not significant; OS = overall survival; PBSC = peripheral blood stem cells; RD = related donor; RIC = reduced intensity conditioning; SFGM-TC = Société Française de Greffe de Moelle et Thérapie Cellulaire; URD = unrelated donor.

^aAdapted from Rowley et al. [11].

^bP value is given where a significant correlation was found.

bile tract expressing ABO blood group antigens may be injured by donor-derived isohemagglutinins, thereby possibly increasing the incidence and severity of liver GVHD. On the contrary Seebach et al. [32] observed severe acute GVHD (grade III–IV) of the liver limited to recipients of bi-directional ABO-incompatible grafts. In a study of Bacigalupo et al. [43], 174 patients receiving an HLA-identical allogeneic BMT were analyzed for factors associated with acute GVHD. In this study, minor ABO mismatch was associated with a significantly higher risk of severe acute GVHD when compared with ABO-matched and major ABO-mismatched pairs. Besides the ABO match, donors of group O, older recipients, rapid engraftment, and older donors were also associated with a higher risk of GVHD. The cumulative incidence of GVHD \geq grade II was 39% for ABO-matched, 54% for major ABO-mismatched, and 82% for minor ABO-mismatched pairs. Keever-Taylor et al. [44] analyzed risk factors for the development of GVHD in 481 recipients of T-cell-depleted marrow allografts. The results showed an increased relative risk of acute GVHD for patients with a ≥ 2 HLA antigen-mismatched donor and for recipients of minor but not of major or bi-directional ABO-mismatched grafts compared to ABO-identical pairs. Ludajic et al. [45] observed that a minor ABO-mismatch represents a significant risk factor for acute GVHD (grade II–IV) with an estimated risk increase of almost 3-fold, and even 4-fold for severe acute GVHD (grade III–IV). Recently, Gutiérrez-Aguirre et al. [46] analyzed a cohort of patients exclusively receiving RIC and found the highest rate of acute GVHD in minor ABO-mismatched transplant recipients (25%) compared with ABO-identical (20.5%) and major ABO-mismatched cases (15.4%). Other publications did not observe any influence of ABO mismatch on the incidence of clinically significant acute GVHD [8, 23, 37].

All but one of the studies reporting on the incidence of GVHD showed no influence of ABO-mismatched transplantation on development or severity of chronic GVHD. Gutiérrez-Aguirre et al. [46] observed a higher incidence of chronic GVHD in the context of minor ABO mismatch (35%), in contrast to ABO-identical (30.8%) and major ABO-mismatched transplants.

Risk of Relapse

None of the four large register studies which included RIC cases reported an effect of ABO mismatch on risk of malignant disease relapse [6, 32, 35, 36]. In two of these studies data regarding relapse were even not reported as did most of the cohort studies (table 2). Three studies showed an influence but with conflicting results. Mehta et al. [47] found that donor-recipient ABO match in his patient cohort of myeloablatively treated patients was the only factor independently associated with a higher risk of relapse as it was found in the study of Worel et al. [42]. The latter study included only RIC cases. In contrast Erker et al. [48] who analyzed myeloablative and RIC cases showed that the risk for relapse was higher in minor and bi-directional ABO-mismatched cases.

Some authors assume that by using RIC regimens, any graft-versus-tumor effect may be more evident, resulting in different

findings compared to myeloablative treatment protocols [11, 42] (table 2).

Non-Relapse Mortality

As already discussed, the transplantation of ABO-mismatched grafts can cause severe immediate or delayed immune hemolytic reactions, leading to the death of the patient in the worst case. Besides this complication which can be avoided by prophylactic actions in nearly all cases, no other consistent effect on transplant-related mortality has been found (table 2). After the introduction of RIC regimens, some authors found an increased mortality for patients receiving ABO-mismatched grafts [6, 36, 42, 49]. One possible reason is that myeloablative conditioning could obscure such an effect due to the higher toxicity [11]. However, results of cohort and registry studies are conflicting. Two registry studies found a higher risk for NRM in the RIC cohort, one of those also for major ABO-mismatched cases if myeloablative conditioning was applied [6, 36], whereas some cohort studies observed an increased risk for patients after minor, major or bi-directional ABO-mismatched transplants [4, 8, 46] (table 2).

Overall Survival

As overall survival reflects the observations for non-relapse mortality especially in the early post-transplantation period, it is not amazing that some authors found ABO mismatch as a cause for decreased survival rates. Kimura et al. [6] observed a shorter overall survival for patients receiving a major ABO-mismatched graft compared to minor or bi-directional ABO-mismatched transplantation, whereas Michallet et al. [36] found a lower survival rate for minor ABO-mismatched versus ABO-matched cases. Besides these large registry reports, various cohort studies including lower numbers of patients reported on conflicting results. The majority of authors did not observe an influence of ABO mismatch on survival. Benjamin et al. [50] revealed a significantly decreased survival in ABO-mismatched BM graft recipients in the first 100 days after transplantation. Multivariate analyses showed that the effect was significant for both minor and major ABO mismatches only in patients with acute myelogenous leukemia and myelodysplastic syndrome. Stussi et al. [7] showed a lower overall survival only for bi-directional ABO-mismatched cases. In contrast, Mehta et al. [47] found that ABO-mismatch was associated with superior overall and disease-free survival as did Erker et al. [48] for patients receiving minor and bi-directional ABO-mismatched grafts (table 2).

Standard Procedures and Transfusion Strategy for ABO-Mismatched HSCT

To avoid immediate or delayed complications of ABO-mismatched stem cell grafts several manipulation steps have been de-

Table 3. Transfusion strategy

ABO mismatch	Recipient	Donor	RBC support from start of conditioning regimen	Platelets ^b and plasma
Major	O	A	O ^a	A, AB
	O	B	O ^a	B, AB
	O	AB	O ^a	AB
	A	AB	A, O ^a	AB
	B	AB	B, O ^a	AB
Minor	A	O	O	A, AB
	B	O	O	B, AB
	AB	O	O	AB
	AB	A	A, O	AB
	AB	B	B, O	AB
Bi-directional	A	B	O ^a	AB
	B	A	O ^a	AB
Rhesus D mismatch	Recipient	Donor	RBC and platelet support from start of conditioning regimen	RBC and platelet support after HSCT
Rh D	positive	negative	positive	negative
	negative	positive	negative	positive
^a Group O RBC until anti-donor isohemagglutinins are undetectable, additionally RBCs of donor type blood group should be present while signs of relapse or graft failure are absent, then switch to donor blood group. ^b First choice for platelet support given. Platelets stored in additive solution reduce the volume of incompatible plasma. Otherwise ABO-incompatible platelet components should be plasma reduced.				

scribed. It is either possible to remove incompatible cells or isohemagglutinins from the graft by various techniques or to remove or adsorb incompatible cells or isohemagglutinins from the recipient by apheresis devices [3, 15–17] (table 1).

The transfusion strategy in ABO-mismatched cases must consider both the blood group systems of the recipient and the donor [11, 19]. In case of major or bi-directional ABO-mismatched transplants, transfusions of blood group O RBCs and blood group AB platelets or plasma are necessary. The decision when to switch to donor type blood group varies from center to center. We would recommend transfusing blood group O RBCs until anti-donor isohemagglutinins are undetectable in two consecutive blood samples of the recipient; additionally, RBCs of donor type blood group should be present while signs of relapse or graft failure are absent (table 3). As ABO blood group antigens are also expressed on the surface of platelets, not only the blood group of the product which is considered to be transfused but also the natural blood group antibodies of the recipient and stem cell donor have to be taken into account. Especially in group O patients with high anti-A isohemagglutinins, platelets of group A1 donors should be avoided. If platelet components stored in additive solution are used, the remaining donor plasma concentration is only 35%. Therefore, transfusion of minor ABO-mismatched platelets can be performed without further plasma removal [19].

Conclusion

ABO-mismatched HSCT has specific effects on transplant-associated morbidity, mostly due to immune hematologic events, de-

velopment of acute GVHD, risk for relapse, NRM, and overall survival. However, outcome of patients after ABO-mismatched HSCT reported in the literature are not consistent, and several other factors, e.g. kind of conditioning regimen, donor and graft source and GVHD prophylaxis, have to be taken into account to be able to compare the studies properly. Recently, major ABO mismatch in CB transplantations has been described to be associated with decreased survival and disease free survival rates and higher transplant-related mortality in adults with hematological malignancies. Therefore when several CB units are available, the use of a unit that is ABO-identical or with minor ABO mismatch should be taken into consideration [51].

To implement standard procedures and transfusion strategy for ABO-mismatched transplants, besides conditioning regimen, donor and graft source, also the availability of different technologies (graft manipulation, apheresis techniques) and the competence of the staff should be considered before a decision is made.

Despite advances in knowledge, development of new technologies, and closed monitoring of patients at risk, complications after ABO-mismatched stem cell transplantation may still occur. But knowledge of these complications and close monitoring of patients can help to detect problems early and to treat the patient efficiently, thus reducing the number of fatal or life-threatening events.

Disclosure Statement

The author declares no conflict of interest.

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