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Selective ABO immunoadsorption in hematopoietic stem cell transplantation with major ABO incompatibility

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Abstract

Objective: ABO mismatch between donor and recipient occurs in 40% of allogeneic hematopoietic stem cell transplantations (HCT). Different strategies have been described to reduce isohemagglutinins (IHA) before HCT. We describe the effect of selective ABO immunoadsorption (ABO IA) on erythrocyte transfusion rate and the development of post-transplant pure red cell aplasia (ptPRCA).

Methods: 63 patients with major ABO incompatibility were retrospectively analyzed. Nine patients with major ABO incompatibility and high-IHA titer were treated by ABO IA before HCT. We analyzed the need for transfusion and the occurrence of ptPRCA. We compared the outcome with patients treated by other methods to reduce IHA.

Results: In all nine patients treated by ABO IA, IHA decreased in a median four times. PtPRCA occurred in one patient. The median number of transfusions was 8 (range: 0-36) between d0 and d100. In 25 patients with high-IHA titer without treatment or treated by other methods to reduce IHA, the need for transfusions was comparable. No difference in the incidence of ptPRCA was observed.

Conclusions: Selective ABO IA is a feasible, safe, and effective method to reduce IHA before HCT in major ABO incompatibility. No effect on transfusion rate or ptPRCA compared to other strategies could be observed.

KEYWORDS

ABO major mismatch, allogeneic stem cell transplantation, isohemagglutinins, post-transplant pure red cell aplasia, selective ABO immunoadsorption, therapeutic plasma exchange, transfusion need

Novelty Statements: Major ABO incompatibility is a frequent situation encountered in allogeneic stem cell transplantation. No evidence-based recommendations exist about the best strategy to decrease isoagglutinin titers before or after transplantation. We applied for the first time selective ABO immunoadsorption in patients with major ABO incompatibility and high isoagglutinin titers before allogeneic stem cell transplantation in a series of patients and compared the results to other strategies. Selective ABO immunoadsorption was feasible without any major side effects. However, the occurrence of pure red cell aplasia or need for transfusion was not strikingly different from other strategies.

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1 | INTRODUCTION

Hematopoietic stem cell transplantation (HCT) is a routine procedure for treatment of many patients affected by malignant, non-malignant, or inborn hematological disorders.[1] The choice of the stem cell donor is largely based on HLA compatibility.[2] Other factors influencing the selection of the donor are CMV status, sex of the donor ABO blood group mismatch as well as the age of the donor, KIR mismatch, or presence of HLA antibodies in case of an HLA unmatched donor.[3] In contrast to solid organ transplantation,[4] ABO incompatibility is not a major obstacle for HCT.[5,6] ABO incompatibility between donor and recipient is a frequent situation and occurs in about 40% of patients treated by HCT.

In ABO-incompatible HCT, the patient and/or the recipient present antibodies, so-called isohemagglutinins (IHA), in the serum against the antigens not expressed on their own red blood cell surface (RBC).[7] Major incompatibility is defined as the presence of antibodies against the RBC of the donor in the recipient while minor mismatch reflects the presence of IHA against the RBC of the recipient in the blood of the donor. Incompatibility can also be bidirectional. The minor or major IHA titer of the donor or the recipient can be very variable and is determined before HCT in the blood of the recipient, or the donor according to the mismatch situation.

In patients treated by HCT, ABO mismatch is not correlated with reduced overall survival.[8,9] However, complication rates in major incompatibility are higher when IHA are detected and non-relapse mortality is increased.[5,10] Especially in patients receiving a reduced-intensity conditioning regimen (RIC), non-relapse mortality related to ABO mismatch is reported to be increased.[11,12] This may be explained by a higher proportion of IHA producing B lymphocytes and plasma cells surviving RIC. Existing data on prophylactic clearance of major IHA before conditioning suggest that they may decrease the incidence of severe complications.[13] HCT with major or minor ABO mismatch can cause different problems.[14] IHA can induce acute hemolysis of the RBC of the donor at the infusion of the stem cell product or delayed hemolysis in minor ABO mismatch.[2,5,7,15] The amount of RBC is vastly different between peripheral stem cell (PBSC) collection with a low hematocrit and a total volume of RBC of less than 20 mL in most cases and a bone marrow product with a high hematocrit. Consequently, RBC must be removed from a bone marrow product before infusion when a high-IHA titer is detected before HCT.[2,7] The transfusion strategy for the recipient is adapted to ABO mismatch situation.[6,16] Nevertheless, a major ABO mismatch correlates with a delay of multi-lineage engraftment, that is, not only of RBC but also of platelets and neutrophils.[17] The incidence of graft failure is significantly higher in patients with a major ABO mismatch.[18] The need for transfusion during the first months after transplantation is higher in the group of patients with a major ABO mismatch independent of an IHA reducing strategy.[5,19] A further problem of ABO major mismatch is the occurrence of a secondary, post-transplant pure red cell aplasia (ptPRCA) weeks or even months after HCT.[20]

A ptPRCA occurs in approximately 7.5% of cases[20] after ABO-incompatible bone marrow or stem cell transplant and is observed most commonly with the combination of a blood group A donor and a blood group O recipient.

Although there is a high frequency of spontaneous resolution after a period of transfusion support (sometimes lasting months), 30%-40% of cases will result in chronic PRCA requiring additional measures. In these patients persistent, high-IHA titers can be detected.[5] If anti-donor isohemagglutinins persist longer than 2 months after transplant, the likelihood of spontaneous remission is reported to be low and the incidence of ptPRCA is high.[7]

In primary or most secondary PRCAs, the therapeutic approach typically aims to involve immunosuppression. In ptPRCA adjustments in immunosuppression regimens or other treatments like rituximab,[21] erythropoietin,[22] daratumumab,[23,24] or anti-thymocyte globulins[25] tapering of immunosuppressive drugs,[20,26] donor lymphocyte infusions (DLI)[27] are included after allogeneic stem cell transplantation. To avoid ptPRCA therapeutic plasma exchange (TPE),[28] semi-selective and selective immunoadsorption (IA),[29] have been used to eliminate high IHA before HCT.

Reducing the volume of RBC in the stem cell product may be indicated if the recipient has a high titer of IHA against the RBC of the donor. The cut-off for a significantly high-IHA titer is not well-defined in most recommendations, but 1:128 seems the most accepted value.[6,7] IHA can be removed before HCT prophylactically to avoid immediate hemolysis as well as delayed engraftment, high-transfusion need, and ptPRCA.[13] As an alternative strategy, the IHA is only removed pre-emptively after day 60 when IHA titer remains high to avoid occurrence of ptPRCA.[30] Alternatively, in some centers, IHA is only being removed when clinically relevant ptPRCA occurs.

Here, we retrospectively report on the use of selective IA with Glycosorb® columns[31] as a prophylactic strategy before HCT as part of our routine algorithm at the Uniklinik RWTH Aachen and compared the outcome with other methods or no specific treatment to reduce IHA before HCT in patients with a major ABO mismatch and a high-IHA titer. Glycosorb ABO columns eliminate specifically anti-A, anti-B, or both IHA according to the mismatch situation between donor and recipient.

2 | MATERIAL AND METHODS

2.1 | Patients

Adult patients from three German transplant centers (patients from University Hospital Bonn, patients from University Hospital Cologne, and patients from University Hospital Aachen) with an underlying hematological malignant disease treated between 2013 and 2019 as well as a major ABO incompatibility and measurable IHA were included in this retrospective study (Table 1). Significant differences between groups were only found for conditioning regimens ($P = .033$) and immunosuppression ($P = .001$). All patients received a stem cell product obtained by apheresis of peripheral blood after G-CSF stimulation (PBSC). ABO blood group was determined for all recipients and donors during pretransplantation work-up. In patients with a donor-recipient major and minor ABO mismatch, IHA titer was measured routinely with serum and RBC of the donor and recipient, respectively, by NaCl-ICT gel cart system (Biorad®). Major, minor, and bidirectional mismatch were defined according to standard criteria. Cut-off for a higher titer of IHA in major ABO incompatibility was defined as 1:128.

Five groups of patients were defined for comparison of transfusion need: Nine patients with an IHA titer (defined as equal to or higher than 1:128) were treated by selective ABO IA before the start of conditioning (group 1). A further group of 11 patients and a high-IHA titer received plasma products or thrombocytes directed against the donor blood group to absorb the IHA before transplantation and 5 patients were treated by TPE to reduce IHA titer before the start of conditioning (group 2). The third group of 14 patients with a high-IHA titer received no treatment to reduce IHA before HCT (group 3). Patients with an IHA titer of 1:64 or lower received no treatment to decrease the titer

TABLE 1 Patient characteristics

	With ABO MM	HMIA	HMNI	HMOI	LMNI	No ABO MM
Patients (n)	63	9	14	11	29	28
MRD/MUD/mMUD/Haplo	14/38/9/2	1/8/0/0	4/5/3/2	3/7/1/0	6/18/5/0	7/19/2/0
Age at transplantation (years)	58.3	56.1	54.4	57.0	58.9	59.1
Gender male/female	43/20	8/1	7/7	8/3	20/9	15/13
Diagnosis (n)						
AML	36	6	11	7	12	14
ALL	8	1	1	1	5	2
MDS	6	1	1	0	4	4
MPN	9	1	1	2	5	6
NHL	3	0	0	1	2	1
Multiple myeloma	1	0	0	0	1	0
Stem cell source PBSC/BM (n)	63/0	9/0	14/0	11/0	29/0	27/1
Conditioning regimen (n)						
Myeloablative (MA)	16	0	5	3	8	4
Reduced intensity conditioning (RIC)	35	8	3	6	18	22
Non-myeloablative	2	0	1	1	0	0
FLAMSA oder Melphalan-RIC	10	1	5	1	3	2
ATG in conditioning (y/n)	47/16	8/1	8/6	8/3	23/6	23/7
Immunosuppression						
CsA, MTX	31	8	2	6	15	23
CsA, MMF	24	1	8	4	11	4
Tacrolimus, MMF	6	0	4	0	1	0
Other or missing data	2	0	0	1	2	1
Type of ABO mismatch (r/d)						
Major (0/A, 0/B, 0/AB, A/B, B/A)	37/ 8/7/2/2	7/2/0/0/0	7/2/4/0/1	7/0/3/1/0	16/4/0/5/4	0

Note: HM vs LMNI indicates high major AB0 titer vs low major AB0 titer and no intervention; HMIA, high major AB0 titer and immunoadsorption; HMNI, high major AB0 titer and no intervention; HMOI, high major AB0 titer and other intervention, MM mismatch.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, anti-thymocyte globulin; BM, bone marrow; CsA, cyclosporine A; FLAMSA, fludarabine, amsacrine, cytarabine conditioning; haplo, haploidentical donor; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; mMUD, mismatched unrelate donor; MPN, myeloproliferative neoplasm; MRD, matched related donor; MTX, methotrexate; MUD, matched unrelated donor; NHL, Non-Hodgkin lymphoma; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioning.

before HCT (group 4). Transfusion rate of patients with ABO mismatch was compared to a group of 28 patients with an ABO-match constellation (group 5). Patient characteristics are summarized in Table 1. We analyzed retrospectively the feasibility, safety, and effects of selective ABO IA and the occurrence of ptPRCA as well as the need for transfusion. Patients treated by IA were all transplanted in Aachen.

Diagnostic criteria for ptPRCA were reticulocytes <30 G/L for more than 60 days after HCT, absence of or very few erythroblasts in the bone marrow (<1% erythroblasts), major or bidirectional ABO mismatch HCT, no graft failure defined by neutrophiles >0.5 G/L and exclusion of other causes for anemia (eg, disease relapse, CMV reactivation, hematotoxic medication).

Written informed consent was obtained for IA and TPA from all patients. All blood examination tests were part of the routine work-up. We obtained a positive statement from the ethical committee of the ethical board of the University Hospital Aachen for retrospective analysis of the patient cohort.

2.2 | Selective ABO immunoadsorption (ABO IA)

Patients received indwelling central double-lumen high-flux catheters (13F) as vascular access (Joline GmbH, Hechingen, Germany). To avoid allergic reactions to the absorber membrane, any ACE inhibitors were stopped in advance. Coagulation parameters were checked before and in between treatment sessions. Citrate was used for anticoagulation. Patient plasma was separated from whole blood by membrane separation technique using a separator made from polyethylene fibers, pore size 0.3 μm, sieving coefficient for IgG and IgM > 0.9 (Plasmaflo OP-08W, Asahi KASEI Corp. Tokyo, Japan). The plasma filtrate was then passed through the antigen-specific affinity purification column/adsorber for the elimination of targeted anti-A/B antibodies. The total plasma volume per treatment was 8000-14 000 mL (three times the calculated plasma volume of the patient), mean was 10 870 ml. Single-use devices and single-use bioactive carbohydrate-based affinity purification columns were used (Glycosorb®-AB0, Glycorex, Lund, Sweden). The purified plasma was returned to the patient without addition of any replacement fluids. Patients received 1 treatment daily, up to 3 days. All treatments were performed with an Octo Nova® apheresis device (Diamed Medizintechnik GmbH, Cologne, Germany).

2.3 | Therapeutic plasma exchange (TPE)

Patients received indwelling central double-lumen high-flux catheters (13F) as vascular access (Joline GmbH, Hechingen, Germany). Coagulation parameters were checked before and in between treatment sessions. A fibrinogen level <150 mg/dL was used as cut-off for fresh frozen plasma as replacement fluid. Anticoagulation was achieved using unfractionated heparin. Patient plasma (2500 mL in men, 2000 mL in women) was separated from whole blood by membrane separation technique using a separator made from polyethylene fibers, pore size 0.3 μm, sieving coefficient for IgG, IgA, and IgM > 0.9 (Plasmaflo OP-08W, Asahi KASEI Corp. Tokyo, Japan). The plasma filtrate was discarded and replaced by an equal volume of replacement fluid. In cases with fibrinogen levels >150 mg/dL prior to treatment, human albumin (5%) was used. In patients with fibrinogen levels <150 mg/dL or bleeding prior to treatment, all separated plasma was replaced by fresh frozen plasma.

2.4 | Statistical methods

Data are presented as frequencies or median and were analyzed using Pearson's chi-squared test/Fisher's exact test or Kruskal-Wallis test/Wilcoxon-Mann Whitney test, as appropriate. Spearman's correlation was applied to investigate the degree of association between PCRA frequency and transfusion rate. The impact of ABO incompatibility on overall survival (OS) was estimated according to Kaplan-Meier and assessed by log-rank testing and Cox regression models. Kaplan-Meier curves are presented and hazard ratios (HR) including 95% confidence intervals (95% CI), resp., are reported.

The data analysis was generated using SAS software 9.4. Statistical significance was indicated with a two-tailed $P < .05$ and multiple comparisons were adjusted by Bonferroni correction.

3 | RESULTS

3.1 | Reduction of IHA titer by immunoadsorption

Nine patients with a high-IHA titer were treated by selective Glycosorb® ABO IA. No Grade three or four toxicity classified as at least possibly related to the IA was observed during or after the procedure. Two or three IA sessions were operated before the start of the conditioning regimen to obtain a 4-fold decrease in IHA titer. Measurement before and after IA showed a decrease of IA titer in all patients. The median decline in IHA was factor 4 (Figure 1). In all but one patient, the titer of IHA could be decreased to <1:128 by 2-3 procedures the days before the start of conditioning. One patient had a decrease of 1:1024-1:256. In this group of 9 patients, WBC count >1 G/L was obtained after a median of 21 days (range 14-28 days) and PLT > 50 G/L after a median of 22 days (range 13-38 days except for 1 patient who never reached PLT > 50 G/L). In 7 of the 9 patients, a reticulocyte count was measured around d60 (median 65 G/L, range 2-167 G/L). All but one had reticulocytes ≥30 G/L except one patient who fulfilled the criteria for ptPRCA.

3.2 | Red blood cell transfusion

Transfusion rate was collected separately between d0 and d30, d30 and d60 as well as d60 and d100. In the selective ABO IA treated group of patients, the median number of erythrocyte transfusion

between d0 and d30, d30 and d60 or d60 and d100 was 6 (range 0-15), 0 (range 0-8), and 0 (range 0-13), respectively. Transfusion need for the three other groups with an ABO major mismatch was comparable, transfusion rate for patients without an ABO mismatch was significantly lower (Table 2). High transfusion needs after d30 correlated with the occurrence of ptPRCA (Table 3).

Median time to engraftment of white blood cells was significantly different between the five patients groups, however, the range of WBC > 1 G/L was as expected (Table 2). Platelet recovery was similar in all groups and no primary graft failure occurred.

3.3 | Incidence of ptPRCA

A ptPRCA occurred in one of the selective ABO IA treated patients and was successfully treated with rituximab. This patient had an 8-fold decrease of his IHA titer from 1:512 to 1:64 by IA before the start of conditioning. His IHA titer at d60 was unchanged when ptPRCA was diagnosed.

Two of the patients in the group with a high-IHA titer but without any prophylactic treatment developed ptPRCA but finally resolved with transfusion alone and one of the 29 patients in the low IHA titer group developed ptPRCA. However, 4 of these 14 patients received rituximab before d180 after transplantation, 3 for EBV reactivation, and one for immune thrombocytopenia. Three ptPRCAs were observed in the group of 11 patients with a high-IHA titer who received other methods than selective ABO IA before transplantation, including plasmapheresis. All patients with ptPRCA had low reticulocyte counts after d60. The difference in the incidence of ptPRCA in the selective ABO IA group was statistically not significant to the other treatment modalities. A trend to a higher frequency of ptPRCA was observed for the whole group of patients with a high-IHA titer compared to the patients with a low or no IHA titer (7/34 vs 1/29, $P = .112$) (Table 2).

3.4 | Survival analysis

In order to evaluate the association of ABO incompatibility and patients' survival, we analyzed the survival time between HCT and date of death and alive at the date of censoring, respectively, in the five groups.

Overall survival differed significantly between MM compared to no MM in general ($P = .016$) (Figure 2A) and when stratified for the 5 subgroups, a borderline significance ($P = .070$) was found for HMIA compared to no MM (Figure 2B). Accordingly, Cox regression identified a higher risk of death in HMIA compared to no MM (HR = 3.2, 95% CI [1.0-10.1], $P = .043$), LMNI compared to no MM (HR = 3.1, 95% CI [1.2-8.0], $P = .019$), and all MM compared to no MM (HR = 2.8, 95% CI [1.2-6.7], $P = .022$). No differences were found between the remaining groups.

4 | DISCUSSION

Despite the high frequency of HCT with a minor or major ABO mismatch, no randomized studies about the best strategy to adopt, to prevent, or to treat ptPRCA have been realized so far. Existing recommendations are essentially based on best available therapy, expert opinion, and registry data.[2,6] Most guidelines recommend a reduction of a high-IHA titer in recipients with a major ABO mismatch,[2,5,6,10] however, there is no consensus about the method. The most frequently used methods to reduce the IHA are TPE, donor secretor plasma transfusion, or small volumes of ABO-incompatible donor type RBC transfusion. The expected benefits of a decrease in IHA are a lower erythrocyte transfusion rate and a decrease in incidence of ptPRCA. A high consumption of erythrocyte concentrates remains still a major issue even in modern medicine and ptPRCA causes morbidity and high costs of treatment.

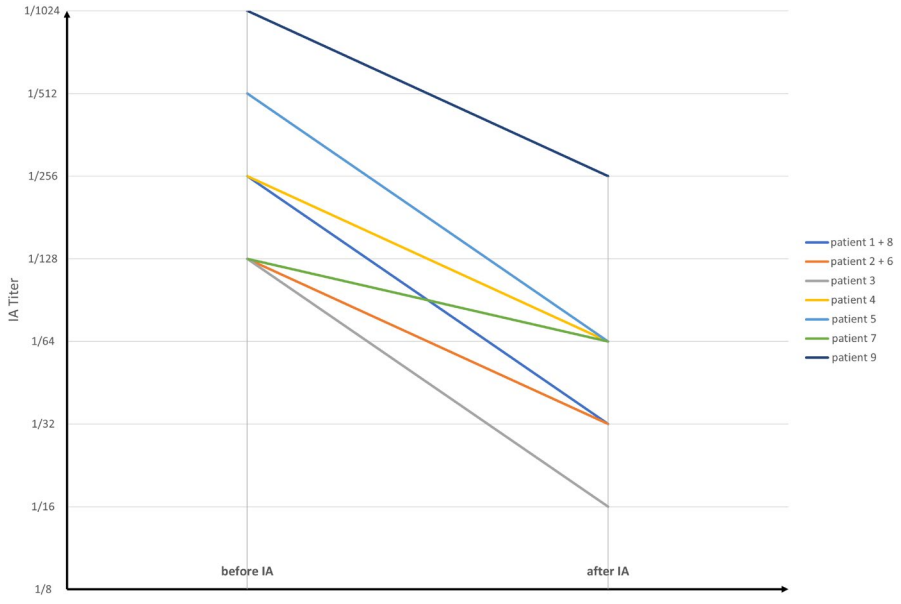

FIGURE 1 Decrease in IHA titer in 9 patients treated by IA before the start and after 2-3 selective ABO IA procedures

TABLE 2 Transfusion rate and PRCA incidence

	Total with ABO MM	HMIA	HMNI	HMOI	LMNI	No AB0 MM	*P*
Patients (n, %)	63 (100)	9 (14.3)	14 (22.2)	11 (17.5)	29 (46.0)	28	
AB0 major titer (mean)		1:256	1:256	1:512	01:32	0	
Transfusion rate*							
n (%) patients with transfusion							
Median (range) transfusions							
d0-d30	59 (93.7%)	8 (88.9%)	13 (92.9%)	9 (81.2%)	29 (100%)	27 (96.4%)	.655
	6 (0-24)	6 (0-15)	8 (0-14)	6 (0-10)	6 (1-24)	5 (0-17)	
d30-d60	26 (41.3%)	3 (33.3%)	3 (21.4%)	8 (72.7%)	12 (41.4%)	5 (17.9%)	.164
	0 (0-10)	0 (0-8)	0 (0-6)	2 (0-8)	0 (0-10)	0 (0-2)	
d60-d100	18 (28.6%)	3 (33.3%)	3 (21.4%)	6 (54.6%)	6 (20.7%)	3 (10.7%)	.327
	0 (0-17)	0 (0-13)	0 (0-8)	1 (0-7)	0 (0-17)	0 (0-10)	
d0-d100	60 (95.2%)	8 (88.9%)	13 (92.9%)	10 (90.9%)	29 (100%)	27 (96.4%)	.941
	8 (0-36)	8 (0-36)	9 (0-28)	8 (0-21)	7 (1-35)	6 (0-18)	
PRCA occurrence (n, %)†	7 (11.1)	1 (11.1)	2 (14.3)	3 (27.3)	1 (3.5)	0	
WBC > 1 G/L (median day)	17 (9-28)	21 (11-28)	12 (9-22)	20 (10-28)	15 (9-28)	20 (14-26)	.004

Note: HM vs LMNI indicates high major AB0 titer vs low major AB0 titer and no intervention; HMIA, high major AB0 titer and immunoadsorption; HMNI, high major AB0 titer and no intervention; HMOI, high major AB0 titer and other intervention; and MM, mismatch.

*Kruskal-Wallis test.

†Pearson's chi-squared test/Fisher's exact test, as appropriate.

TABLE 3 Spearman correlation (rho) between transfusion rates and PRCA occurrence

Period of transfusion/PRCA occurrence	rho	*P*
EK_d0_d30	0.23	.068
EK_d30_d60	0.51	<.001
EK_d60_d100	0.57	<.001
EK_d1_d100	0.43	<.001

We observed also worse overall survival in patients with major ABO mismatch compared to patients without major mismatch but no difference between the different strategies to proceed in case of major ABO mismatch.

Another strategy would be to accept the higher transfusion rate during the early phase of HCT and to monitor whether ptPRCA occurs. However, even if ptPRCA is not often life-threatening, treatment with erythrocyte concentrates, erythropoietin, or antibodies like rituximab or daratumumab are associated with side effects and may, for example, increase iron overload or cause infectious complications or a delay in vaccination.[32,33]

The majority of applications of selective IA are found in neurology, nephrology, and dermatology to eliminate disease-specific antibodies.[34,35] Selective ABO IA by Glycosorb® columns is widely used for reduction of IHA titer in solid organ transplantation, for example, kidney transplantation for related donors with a major ABO mismatch.[36] Efficacy of IA for these patients to reduce acute rejection of the transplanted organ has been proven.[37,38] Semi-selective IA can also be used to reduce HLA antibodies in solid organ transplantation as well as in HCT.[39]

To the best of our knowledge, no series of patients treated by selective ABO IA before HCT to reduce high titer IHA with an ABO major mismatch has been published so far. We have shown that selective ABO IA is feasible, safe, and efficient to reduce IHA. However, there was no difference in transfusion rate compared to the other treatment modalities or to patients without specific treatment for IHA reduction. PtPRCA occurred in one patient treated by IA with a high anti-A-titer before transplantation despite an effective lowering of IHA from 1:256 to 1:64. However, ptPRCA occurred also in the other groups and transfusion rates were also comparable. Advantages of selective ABO IA compared to plasmapheresis are reduced elimination of plasma proteins and immunoglobulins from the blood of the patient as well as an unimpaired humoral immune response.[37,38] In addition, selective ABO IA can be continued after the start of the conditioning regimen if necessary, since chemotherapeutic agents and ATG will not be eliminated in contrast to TPE or semi-selective IA with, for example, Therasorb®. Selective ABO IA is also more efficient to eliminate blood group-specific IgM compared to other methods.[37,38] Handisurya et al[29] recently published a series of 6 patients with PRCA after HCT treated by selective Glycosorb® ABO IA. The procedure was well-tolerated and effective with a

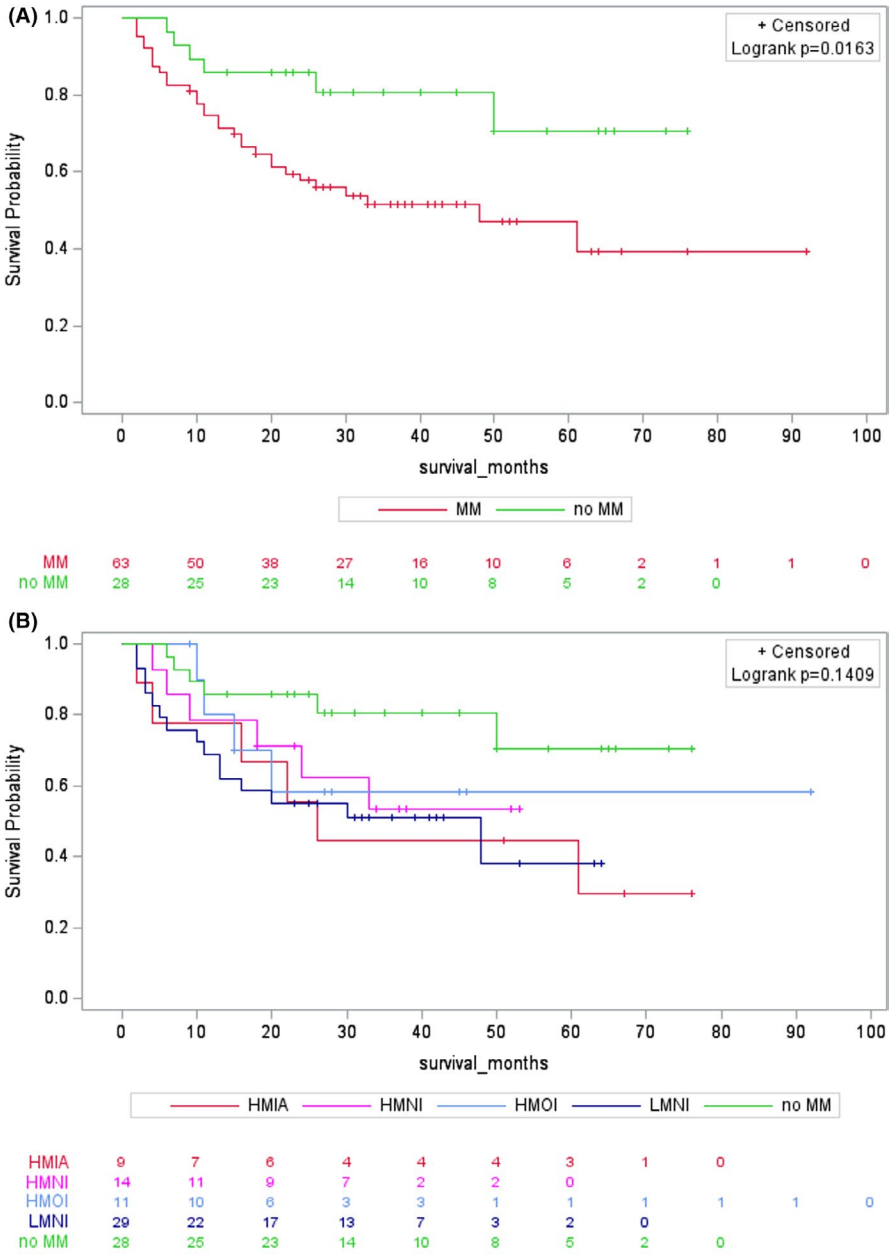

FIGURE 2 (A) Overall survival of patients with major ABO mismatch compared to patients without ABO mismatch. (B) Overall survival of subgroups of patients with major ABO mismatch compared to patients without ABO mismatch. HM vs LMNI indicates high major AB0 titer vs low major AB0 titer and no intervention; HMIA, high major AB0 titer and immunoadsorption; HMNI, high major AB0 titer and no intervention; HMOI, high major AB0 titer and other intervention; and MM, mismatch

decrease in IHA titer and finally resolution of PRCA. However, the median number of 24 IA sessions in 33 days to control PRCA was remarkably high.

Even if a difference in transfusion rate and occurrence of ptPRCA could not be observed in the analysis, feasibility of selective ABO IA in the setting of HCT and exclusion of frequent side effects were demonstrated. A difference in the occurrence of ptPRCA was not observed. However, in the group of patients treated by other methods than IA, ptPRCA was eventually covered by the use of rituximab. A low reticulocyte count at d60 after HCT as a predictor of ptPRCA was confirmed.

Despite the high frequency of ABO major mismatch[5,30] and a high frequency of ptPRCA in major ABO mismatch HCT,[5,40] no evidence-based recommendation about the best strategy to adopt is available. There is even no clear evidence if elimination of a high-IHA titer in a major ABO incompatibility before HCT is useful or if a specific approach to eliminate the IHA only when PRCA occurs after transplantation is a better strategy.

At least a direct comparison of selective ABO IA with other methods on a higher number of patients to determine safety and efficacy for elimination of IHA and clinical outcome is necessary. Studies must include effects on IHA titer but also complications, transfusions rate, occurrence of ptPRCA and graft failure as well as morbidity and non-relapse mortality. Alternatively, a more detailed analysis of registry data can be a useful tool to obtain more evidence for recommendations.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Contribution: conception and design: MC and EJo, provision of study materials or patients: EJe, HS, UH, MM, MW, SR, FB and GS, IHA analysis: MW, immunoadsorption: UK, data analysis: JG, SW and Ejo, data interpretation: SW, EJ, MC and THB, manuscript writing: MC, EJ, final approval of manuscript: all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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