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ABO Isoagglutinin Levels in Management of ABO Incompatibility in Allogeneic Hematopoietic Cell Transplantation

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Abstract

Background: Despite renewed interest in ABO isoagglutinin levels post allogeneic Hematopoietic Cell Transplantation (alloHCT), relevant studies are scarce. We investigated the impact of ABO isoagglutinins on management of ABO incompatibility.

Materials and Methods: We prospectively enrolled consecutive alloHCT recipients since we started ABO isoagglutinin measurement (2014-2019) and compared them with a historical control group (2001-2013).

Results: Among 645 alloHCT recipients, 147 (23%) had ABO incompatibility. Incidence of ABO incompatibility did not differ between treatment periods (21% *vs*. 26%). PRCA developed in 29 patients at a median of 32 (24-115) post-transplant day; 23 in the early and 6 in the late period (p=0.012). Among pre-transplant factors, treatment period (p=0.003) and major incompatibility (p<0.001) independently predicted higher rates of PRCA. Isoagglutinin titers of 512 or higher were associated with the development of PRCA (p<0.001) that required plasma exchange in all, but one cases (p=0.023). With a follow-up of 184 months (5-228) in surviving patients, our real-world data in a large cohort of HCT recipients confirm previous reports that ABO incompatibility does not affect outcomes, irrespectively of transplant characteristics.

Discussion: ABO incompatibility is not a risk factor for adverse outcomes. ABO isoagglutinin levels emerge as a helpful tool in guiding proper diagnosis and management in these patients.

Keywords: Isoagglutinin, ABO incompatibility, Pure red cell aplasia; alloHCT

Introduction

A successful allogeneic Hematopoietic Cell Transplantation (alloHCT) program requires a close collaboration between transfusion and transplant experts. Transfusion of alloHCT recipients depends on ABO incompatibility, the need for irradiated products, and appropriate use of CMV negative and HLA-matched products. Since stem cells do not express ABO antigens, alloHCT is feasible across ABO barriers [1].

ABO incompatibility between donor and recipient is encountered in up to 50% of alloHCTs [1]. Some studies have suggested that ABO incompatibility is associated with poor Overall Survival (OS) and increased Treatment-Related Mortality (TRM) indicating adverse risk groups such as patients with reduced intensity conditioning, unrelated donor or bone marrow graft [2-6]. In 2009, a meta-analysis showed marginally lower overall survival in patients with minor or bidirectional mismatched grafts from unrelated donors, highlighting the need of further studies [7]. On the contrary, our group has presented that ABO incompatibility does not compromise alloHCT outcomes [8]. Further studies confirmed these results [9-13]. Recent studies focusing on the haploidentical setting are in agreement with these results, only in patients transplanted with peripheral grafts [14,15].

ABO incompatibility classified into major (recipient's plasma contains ABO isoagglutinins against donor red blood cells/RBC antigens), minor (graft contains the isoagglutinins targeting

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the recipient's A and/or B antigen), and bidirectional (both major and minor). Patients with Major ABO incompatibility may develop: 1) immediate hemolysis of the RBCs infused with the graft, 2) delayed hemolysis of the RBCs produced by graft, or 3) Pure Red Cell Aplasia (PRCA). Severe hemolytic transfusion reaction at the time of transplant can be successfully eliminated by *ex-vivo* RBC removal from the donor marrow. Regarding PRCA, monitoring by immunohematological testing has been suggested. Nevertheless, there are no established criteria for the maximum allowable RBC content in products and/or the critical isoagglutinin titer in the donor. Patients with minor ABO incompatibility are at risk of developing immediate hemolysis of the recipient RBCs or delayed hemolysis due to persistent production of isoagglutinin by the marrow lymphocytes. Other risks have been also postulated since blood group antigens expressed on recipient's cells may be bound by donor isoagglutinins. Such risks of endothelial injury syndromes have not been debated in recent studies [16]. The simultaneous occurrence of major and minor ABO incompatibility is rare; and causes hemolysis by the recipient, and/or donor isoagglutinins.

Despite renewed interest in the role of ABO isoagglutinin levels, relevant studies are scarce. In the present study we primarily aimed to investigate the impact of ABO isoagglutinin levels on guiding management of ABO incompatibility compared to our historic control group. Secondarily, we addressed the controversial issue of the impact of ABO incompatibility on alloHCT outcomes.

Methods

Study population

We prospectively enrolled consecutive alloHCT recipients treated at our JACIE-accredited Unit from January 2014 to June 2019. We also enrolled a historical control group of consecutive alloHCT recipients transplanted at our center from 2001 to 2013. Data were extracted from our prospectively acquired database, with an updated follow-up of patients until December 2019. Charts from patients with ABO incompatibility were re-reviewed to identify diagnostic and therapeutic features.

Patients were transplanted according to standard European Society for Blood and Marrow Transplantation (EBMT) indications [17] and standard operating procedures of our JACIE-accredited center, as previously published [18,19]. Assessment and grading of acute GVHD was performed according to criteria suggested by Glucksberg et al., while chronic GVHD was assessed and graded according to Sullivan et al criteria [20,21]. Disease phase at transplant was categorized in 3 groups: 1st complete remission (early), other complete remission (intermediate) or advanced stage. Unrelated and haploidentical transplant recipients received low dose of rabbit ATG (Thymoglobulin 5 mg/kg) as part of the conditioning, as previously described [18,19]. As recommended, blood products were irradiated according to our department protocol, so that no part of the component received a dose lower than 25 Gy and higher than 50 Gy (European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS) 2017).

Management of patients with ABO incompatibility

Complications are related to both major and minor incompatibilities. The following standard operation procedures were followed throughout the study period. In case of major ABO mismatch, the red cell contamination in Peripheral Blood Stem Cell (PBSC) graft was kept <20 mL, and RBC depletion of bone marrow grafts was performed, according to recommendations [22,23]. Prophylactic infusion of Rh-negative blood was preferred for Rh minor mismatches. Group O RBCs and donor type platelets were used until recipient change to donor ABO type.

An extensive work-up was performed in patients with signs and/or symptoms of anemia and ABO incompatibility. Diagnosis of PRCA was performed by an extended profile of tests to exclude other causes of anemia, as previously described [24]. Patients with erythroblasts lower than 10% in the bone marrow and exclusion of other causes were managed for suspected PRCA with erythropoietin initially and then, steroids or plasma exchange when necessary. During the current period, sequential measurements of ABO isoagglutinins guided decisions, in patients with a titer of 1:32 and higher.

ABO isoagglutinin measurement

Since 2014, our transfusion service standardized IgG ABO isoagglutinin measurements. Briefly, measurements are performed through our automated instrument (AutoVue Innova, Ortho, USA) using serial manual dilutions. Standardization of the method included titrating studies with the automated and manual method. Measurement was performed once in patients with ABO incompatibility and sequentially in patients with suspected PRCA.

Statistical analysis

Data were analyzed using the statistical program SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Continuous variables were described as median and range and categorical variables as frequencies. Patient-, disease-, and transplant-related variables were compared using chi-square statistics for categorical variables and Mann-Whitney for continuous variables. Studied factors in the whole transplant population included: age, gender, disease, phase at transplant, type of donor and graft, type of conditioning, ABO incompatibility, acute and chronic GVHD, relapse, survival. Probabilities for relapse, TRM and GVHD were calculated using the cumulative incidence estimator to accommodate competing risks [25]. Kaplan-Meier estimates were used to calculate the probability of Disease-Free (DFS) and Overall Survival (OS). A pre-planned sub-group analysis was performed according to donor, conditioning and graft source. Multivariate analysis was performed using Cox proportional hazards model for DFS and OS.

Results

Study population

We studied 645 alloHCT recipients, 410 transplanted in the early and 235 in the current time period. Table 1 summarizes patients' transplant characteristics. Differences between groups can be explained by changes in transplant policies over the years. Patients transplanted in the current period were characterized by significantly increased age and percentage of alternative donors, as well as lower percentage of advanced disease phase at transplant and myeloablative conditioning compared to the early period (Table 1).

ABO incompatibility

Among 645 alloHCT recipients, 147 (23%) had ABO incompatibility (144 major, 41 minor, 39 bidirectional). Of these, 86 were transplanted in the early, compared to 61 in the current period. Incidence of ABO incompatibility did not differ between treatment periods (21% *vs.* 26%, p=0.143). Acute or delayed hemolysis produced by the graft was not clinically significant. Prolonged transfusion requirements were observed only in patients with PRCA.

Table 1: Characteristics of patient population (n=645).

Characteristics	Early period (n=410)	Current period (n=235)	p-value
Age (median, range)	36, 4-66	39, 16-67	0.007
Male gender (n, %)	143 (35)	103 (44)	0.048
Disease (n, %)			
Acute myeloid leukemia	169 (41)	89 (38)	0.122
Acute lymphoblastic leukemia	151 (37)	80 (34)	
Other	90 (22)	66 (28)	
Phase at transplant (n, %)			
Early	197 (48)	132 (56)	0.032
Intermediate	78 (19)	49 (21)	
Advanced	135 (33)	54 (23)	
Myeloablative conditioning (n, %)	319 (78)	159 (68)	0.012
Peripheral blood graft (n, %)	274 (67)	212 (90)	<0.001
Donor (n, %)			
Sibling	175 (72)	109 (46)	<0.001
Unrelated	111 (27)	110 (47)	
Alternative	4 (1)	16 (7)	

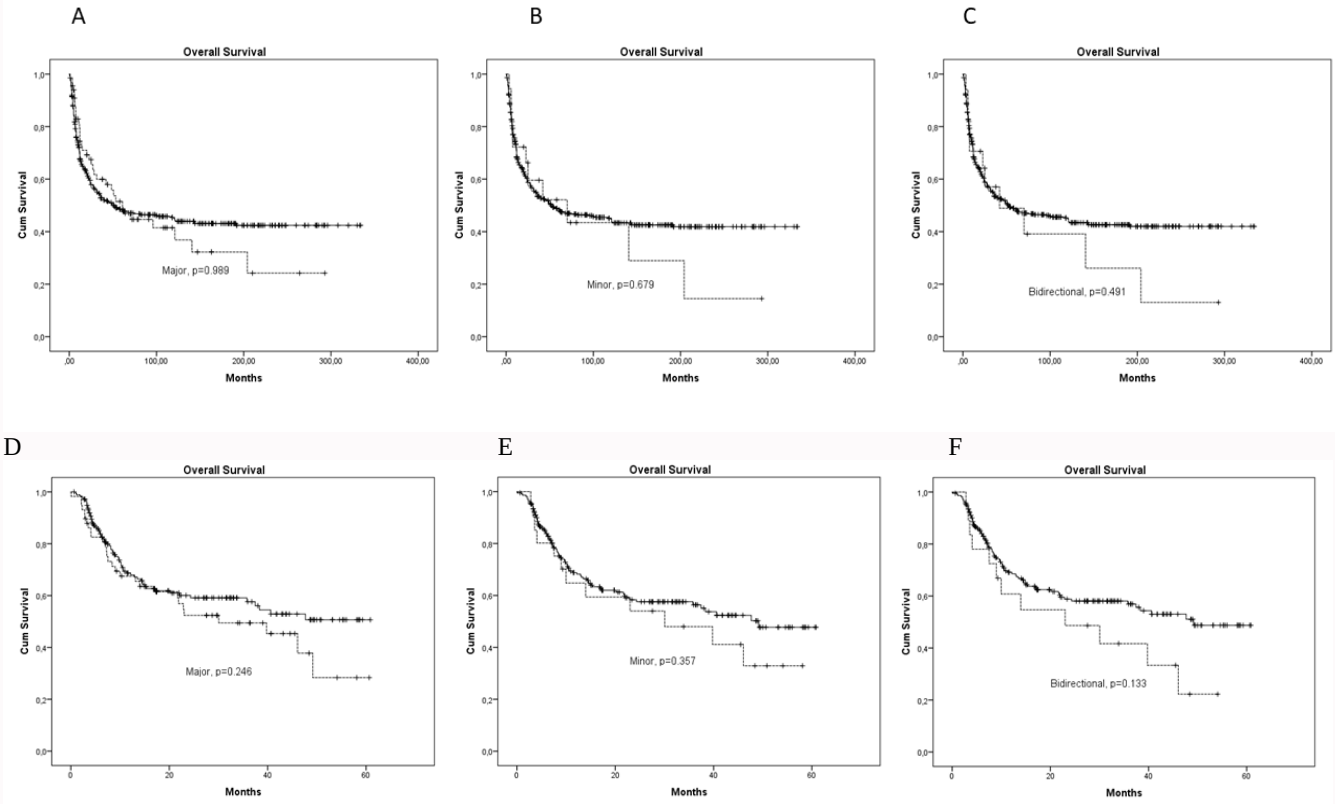

Figure 1: A-C: Similar overall survival in patients with major (A), minor (B), and bidirectional (C) incompatibility transplanted during the early period (2001-2013). D-F: Similar overall survival in patients with major (A), minor (B), and bidirectional (C) incompatibility transplanted during the current period (2014-2019). Dotted lines refer to patients with incompatibility as noted.

Pure red cell aplasia

In total, 29 patients developed PRCA at a median of 32 (24-115) post-transplant day; 23 in the early and 6 in the late period (p=0.012). Among pre-transplant factors, treatment period (p=0.003) and major incompatibility (p<0.001) independently predicted PRCA diagnosis. The effect of treatment period may be attributed to measurement of isoagglutinin levels. The latter guided management of non-hemolytic anemia leading to a reduced number of patients in need of intervention for PRCA.

Transfusion requirements were increased in patients treated for PRCA during the early with a median of 4 (range 1-89) compared to current period with a median of 1 (0-12). Erythropoietin was

administered in all PRCA patients, steroids in 15/29 and plasma exchange in 11/29 with a median of 9 (5-15 sessions). A titer of 512 or higher was associated with the development of PRCA (p<0.001), that required plasma exchange in all but one cases (p=0.023). One patient presented with PRCA due to Rhesus incompatibility with pre-existing anti-D alloimmunization that resolved with erythropoietin, corticosteroids and 9 plasma exchange sessions.

Outcomes in the whole cohort

The effect of ABO incompatibility (major, minor, and bidirectional) was studied in the early and current period. The median follow-up of surviving patients in the early period reached 107 months (range 73-228). OS was not different in patients with major, minor, and bidirectional incompatibility, as shown in Figure 1. With a follow-up of 27.6 months (5.9-61) in surviving patients of the current period, there was no difference in OS of patients with major, minor, and bidirectional (Figure 1). The results were similar in the sub-group analysis of patients with unrelated donors, reduced intensity conditioning and bone marrow graft source. It should be noted however that only 1 patient among 21 with haploidentical donors, and 24 patients receiving a marrow graft had ABO incompatibility during the current period. In both periods, ABO incompatibility (major, minor or bidirectional) was also not associated with acute and chronic GVHD or TRM.

Outcomes in patients with ABO incompatibility

With a follow-up of 184 months (5-228) in surviving patients, PRCA did not affect DFS and OS (Figure 2, p=0.351 and p=0.447). Among pre-transplant factors, favorable OS was predicted only by early disease phase at transplant (p=0.001), sibling donors (p=0.006), and total body irradiation at conditioning (p<0.001); these remained independent predictors in the multivariate analysis. Similarly, PRCA was not associated with acute and chronic GVHD or TRM. Despite differences in patient characteristics between time periods, neither reduced intensity conditioning nor transplant period had significant effects on HCT outcomes in patients with ABO incompatibility.

Discussion

Our findings confirm that ABO incompatibility is not associated with poor alloHCT outcomes. Interestingly, that was true for both treatment periods, despite differences in transplant characteristics. Furthermore, we have compared for the first time outcomes of ABO incompatibility in patients with measurements of ABO isoagglutinins compared to a historic control group. ABO isoagglutinin measurement has prospectively shown to be useful in guiding diagnosis and treatment of PRCA.

The impact of ABO incompatibility on alloHCT outcomes has been evaluated in heterogeneous transplant cohorts leading to conflicting results [2-4,6-15]. An earlier meta-analysis revealed that minor or bidirectional incompatibility leads to decreased OS in unrelated alloHCT [7]. Nevertheless, a large retrospective analysis by Damodar et al. [11] revealed that neither minor, nor bidirectional incompatibility had any effect on OS. The same was true for sibling, unrelated, and cord blood donors. Our results are in line with these findings, since ABO incompatibility did not affect transplant outcomes in both transplant periods. During the early period, the majority of donors were siblings; while, during the current period, the percentage of unrelated donors increased significantly. Regarding the graft source, results can be safely extracted only from the early period, showing no effect of the graft source.

Another debated issue in ABO incompatibility is the role of the reduced intensity conditioning. Hefazi et al. [5] indicated that major and bidirectional incompatibility is associated with poor outcomes in a certain group of patients with acute leukemia and myelodysplastic syndrome transplanted with reduced intensity conditioning. Similarly, analyses of outcomes in reduced intensity have identified ABO incompatibility as an independent predictor of poor TRM [3,26,27]. However, these data have not been confirmed by our analysis and other studies focusing on ABO incompatibility [9-13,28].

Taken together, these findings highlight that ABO incompatibility should not be considered as an adverse risk factor for alloHCT outcomes. This finding is of utmost importance for donor selection, especially in periods or areas with limited donor availability. Despite worldwide expansion of the donor pool with haploidentical donors, the latest COVID-19 pandemic has raised several obstacles in successful donor selection, including donor availability, cryopreservation and/or transfer of grafts. In accordance with current guidelines [29], ABO incompatibility should not be considered a reason for transplantation deferral. It should be kept however in mind that grafts manipulation,

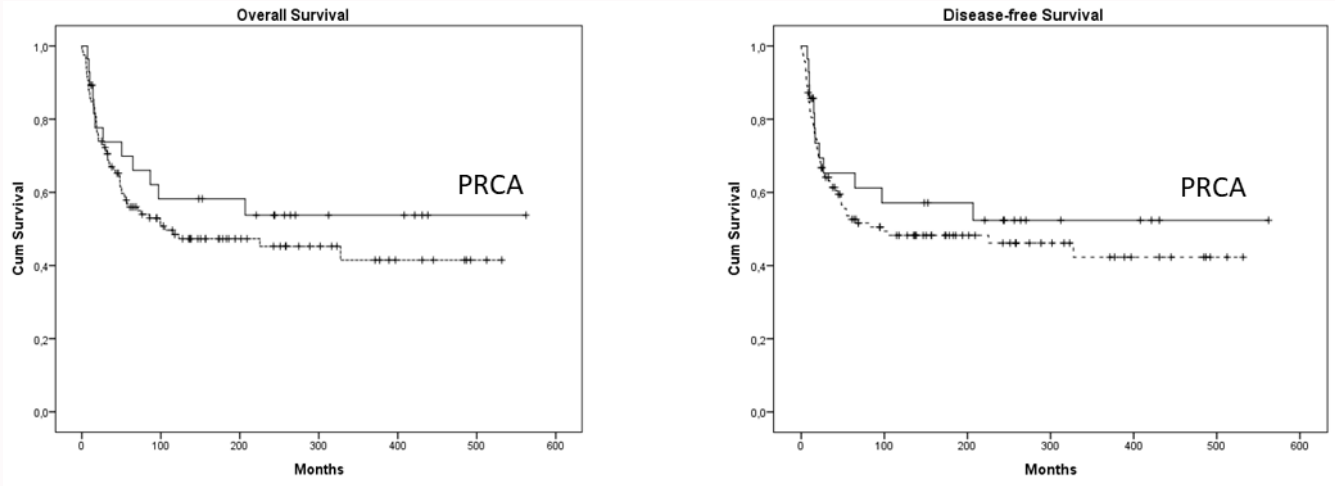

Figure 2: Similar overall survival (A, p=0.351) and disease-free survival (B, p=0.447) in patients with and without PRCA. PRCA: Pure Red Cell Aplasia. Black line refers to patients with PRCA; while the dotted one to patients without PRCA.

close monitoring and management through an effective blood bank and transfusion program may be essential for a successful alloHCT in these patients.

Regarding management of PRCA, our study has highlighted a useful role of isoagglutinin measurement. Although this seems reasonable, only a few small studies have presented relevant data, without studying a control patient population [30,31]. In addition, Curley et al. [32] have focused on pre-transplant measurements and guidance. Interestingly, there is no consensus guidance on post-transplant measurements. Our study shows excellent outcomes of graft-induced hemolysis using only graft manipulation techniques. In addition, measurement of ABO isoagglutinins was associated with lower incidence of PRCA and lower transfusion requirements. We were also able to confirm a cut-off titer, above which patients are to be considered for plasma exchange. In addition, our therapeutic strategy of plasma exchange was effective in all refractory patients, sparing them from further immunosuppression with ATG, or rituximab that have been administered in refractory patients [1,33].

Lastly, another interesting finding of our study concerns the report of patient that developed PRCA due to Rhesus incompatibility with pre-existing anti-D alloimmunization. Rhesus incompatibility is not because anti-D alloimmunization is infrequent in alloHCT recipient [34]. This patient however, with pre-existing anti-D alloimmunization, developed refractory PRCA. Even in this case, treatment with erythropoietin, corticosteroids and 9 plasma exchange sessions was effective.

Our study has several limitations. First, we have prospectively recruited our patients with ABO isoagglutinins, but the historic control group was recruited retrospectively. Second, our patient population does not include special groups, such as pediatric thalassemia patients, in whom ABO incompatibility has been associated with impaired outcomes [35]. Furthermore, our cohort was characterized by a small number of haploidentical donors that does not allow for safe conclusions regarding this donor population. Nevertheless, our large cohort is representative of the global indications for alloHCT and improvements in alloHCT practices over the years. Furthermore, our patients have been transplanted according to the standard operational procedures of a single center.

In conclusion, our real-world data in a large cohort of HCT recipients confirm previous reports that ABO incompatibility does not affect alloHCT outcomes. ABO isoagglutinin levels emerge as a helpful tool in prospectively guiding proper diagnosis and management in these patients. Given the lack of consensus guidance in ABO isoagglutinin measurements, future prospective studies will clarify their role in clinical practice.

References

1. Staley EM, Schwartz J, Pham HP. An update on ABO incompatible hematopoietic progenitor cell transplantation. Transfus Apher Sci. 2016;54(3):337-44.
2. Benjamin RJ, McGurk S, Ralston MS, Churchill WH, Antin JH. ABO incompatibility as an adverse risk factor for survival after allogeneic bone marrow transplantation. Transfusion. 1999;39(2):179-87.
3. Kimura F, Sato K, Kobayashi S, Ikeda T, Sao H, Okamoto S, et al. Impact of ABO-blood group incompatibility on the outcome of recipients of bone marrow transplants from unrelated donors in the Japan Marrow Donor Program. Haematologica. 2008;93(11):1686-93.
4. Logan AC, Wang Z, Alimoghaddam K, Wong RM, Lai T, Negrin RS, et al. ABO mismatch is associated with increased nonrelapse mortality after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2015;21(4):746-54.
5. Hefazi M, Litzow M, Hogan W, Gastineau D, Jacob E, Damlaj M, et al. ABO blood group incompatibility as an adverse risk factor for outcomes in patients with myelodysplastic syndromes and acute myeloid leukemia undergoing HLA-matched peripheral blood hematopoietic cell transplantation after reduced-intensity conditioning. Transfusion. 2016;56(2):518-27.
6. Vaezi M, Dameshghi DO, Souri M, Setarehdan SA, Alimoghaddam K, Ghavamzadeh A. ABO incompatibility and hematopoietic stem cell transplantation outcomes. Int J Hematol Oncol Stem Cell Res. 2017;11(2):139-47.
7. Kanda J, Ichinohe T, Matsuo K, Benjamin RJ, Klumpp TR, Rozman P, et al. Impact of ABO mismatching on the outcomes of allogeneic related and unrelated blood and marrow stem cell transplantations for hematologic malignancies: IPD-based meta-analysis of cohort studies. Transfusion. 2009;49(4):624-35.
8. Sakellari IB, Mallouri S, Abela DE, Kaloyannidis P, Apostolou A, Yannaki E, et al. Major and bidirectional ABO incompatibility related pure red cell aplasia does not compromise the outcome post allogeneic hematopoietic stem cell transplantation Bone Marrow Transplant. 2014;49:3.
9. Seebach JD, Stussi G, Passweg JR, Loberiza Jr FR, Gajewski JL, Keating A, et al. ABO blood group barrier in allogeneic bone marrow transplantation revisited. Biol Blood Marrow Transplant. 2005;11(12):1006-13.
10. Watz E, Remberger M, Ringden O, Lundahl J, Ljungman P, Mattsson J, et al. Analysis of donor and recipient ABO incompatibility and antibody-associated complications after allogeneic stem cell transplantation with reduced-intensity conditioning. Biol Blood Marrow Transplant. 2014;20(2):264-71.
11. Damodar S, Shanley R, MacMillan M, Ustun C, Weisdorf D. Donor-to-recipient ABO mismatch does not impact outcomes of allogeneic hematopoietic cell transplantation regardless of graft source. Biol Blood Marrow Transplant. 2017;23(5):795-804.
12. Junior JAS, Martinho GH, de Macedo AV, Verçosa MR, Nobre V, Teixeira GM. Assessing the impact of ABO incompatibility on major allogeneic hematopoietic stem cell transplant outcomes: A prospective, single-center, cohort study. Hematol Transfus Cell Ther. 2019;41(1):1-6.
13. Ciftciler R, Goker H, Buyukasık Y, Karaagac T, Aksu S, Tekin F, et al. Impact of ABO blood group incompatibility on the outcomes of allogeneic hematopoietic stem cell transplantation. Transfus Apher Sci. 2020;59(1):102597.
14. Canaani J, Savani BN, Labopin M, Huang XJ, Ciceri F, Arcese W, et al. Impact of ABO incompatibility on patients' outcome after haploidentical hematopoietic stem cell transplantation for acute myeloid leukemia - a report from the Acute Leukemia Working Party of the EBMT. Haematologica. 2017;102(6):1066-74.
15. Yang N, Guan L, Liu Z, Ding Y, Zhu C, Luo L, et al. ABO blood type incompatibility is not a risk factor of outcomes for Acute Myeloid Leukemia (AML) patients after unmanipulated haplo-identical peripheral blood hematopoietic stem cell transplantation. Ann Transplant. 2019;24:350-8.
16. Lapierre V, Mahe C, Aupérin A, Stambouli F, Oubouzar N, Tramalloni D, et al. Platelet transfusion containing ABO-incompatible plasma and hepatic veno-occlusive disease after hematopoietic transplantation in young children. Transplantation. 2005;80(3):314-9.
17. Duarte RF, Labopin M, Bader P, Basak GW, Bonini C, Chabannon C, et al. Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: Current practice in Europe, 2019. Bone Marrow Transplant. 2019;54(10):1525-52.
18. Sakellari I, Batsis I, Bousiou Z, Mallouri D, Constantinou V, Gavriilaki E, et al. The role of low-dose anti-thymocyte globulin as standard prophylaxis

in mismatched and matched unrelated hematopoietic peripheral stem cell transplantation for hematologic malignancies. Clin Lymphoma Myeloma Leuk. 2017;17(10):658-66.

19. Sakellari I, Mallouri D, Gavriilaki E, Batsis I, Kaliou M, Constantinou V, et al. Survival advantage and comparable toxicity in reduced-toxicity treosulfan-based versus reduced-intensity busulfan-based conditioning regimen in myelodysplastic syndrome and acute myeloid leukemia patients after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2017;23(3):445-51.

20. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-8.

21. Flowers ME, Kansu E, Sullivan KM. Pathophysiology and treatment of graft-versus-host disease. Hematol Oncol Clin North Am. 1999;13(5):1091-112, viii-ix.

22. Rowley SD, Donato ML, Bhattacharyya P. Red blood cell-incompatible allogeneic hematopoietic progenitor cell transplantation. Bone Marrow Transplant. 2011;46(9):1167-85.

23. Carreras E, Dufour C, Mohty M, Kröger N, editors. The EBMT handbook: Hematopoietic stem cell transplantation and cellular therapies. Springer International Publishing. 2019.

24. Gavriilaki E, Sakellari I, Batsis I, Mallouri D, Bousiou Z, Vardi A, et al. Transplant-associated thrombotic microangiopathy: Incidence, prognostic factors, morbidity, and mortality in allogeneic hematopoietic cell transplantation. Clin Transplant. 2018;32(9):e13371.

25. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452-8.

26. Michallet M, Le QH, Mohty M, Prébet T, Nicolini F, Boiron JM, et al. Predictive factors for outcomes after reduced intensity conditioning hematopoietic stem cell transplantation for hematological malignancies: A 10-year retrospective analysis from the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Exp Hematol. 2008;36(5):535-44.

27. Rio B, Chevret S, Vigouroux S, Chevallier P, Fürst S, Sirvent A, et al. Decreased nonrelapse mortality after unrelated cord blood transplantation for acute myeloid leukemia using reduced-intensity conditioning: A prospective phase II multicenter trial. Biol Blood Marrow Transplant. 2015;21(3):445-53.

28. Gutierrez-Aguirre CH, Gomez-De-Leon A, Alatorre-Ricardo J, Cantú-Rodríguez OG, González-Llano O, Jaime-Pérez JC, et al. Allogeneic peripheral blood stem cell transplantation using reduced-intensity conditioning in an outpatient setting in ABO-incompatible patients: are survival and graft-versus-host disease different? Transfusion. 2014;54(5):1269-77.

29. Ciurea SO, Cao K, Fernandez-Vina M, Kongtim P, Malki MA, Fuchs E, et al. The European Society for Blood and Marrow Transplantation (EBMT) consensus guidelines for the detection and treatment of Donor-Specific anti-HLA Antibodies (DSA) in haploidentical hematopoietic cell transplantation. Bone Marrow Transplant. 2018;53(5):521-34.

30. Chung HJ, Lee JH, Kwon SW. Significance of donor-derived isoagglutinins in ABO-Incompatible hematopoietic stem cell transplantation. J Clin Lab Anal. 2008;22(6):383-90.

31. Tomac G, Bojanic I, Mazić S, Vidović I, Raos M, Ćepulić BG, et al. Haemolysis, pure red cell aplasia and red cell antibody formation associated with major and bidirectional ABO incompatible haematopoietic stem cell transplantation. Blood Transfus. 2018;16(4):397-404.

32. Curley C, Pillai E, Mudie K, Western R, Hutchins C, Durrant S, et al. Outcomes after major or bidirectional ABO-mismatched allogeneic hematopoietic progenitor cell transplantation after pretransplant isoagglutinin reduction with donor-type secretor plasma with or without plasma exchange. Transfusion. 2012;52(2):291-7.

33. Gómez RV, Vázquez GV, Concepción VN, García AG, Saavedra CA. Successful treatment of pure red cell aplasia with high-dose dexamethasone after ABO-incompatible allogeneic hematopoietic stem cell transplantation. Hematol Oncol Stem Cell Ther. 2018;11(1):44-6.

34. Cid J, Lozano M, Fernández-Avilés F, Carreras E, Pereira A, Mazzara R, et al. Anti-D alloimmunization after D-mismatched allogeneic hematopoietic stem cell transplantation in patients with hematologic diseases. Transfusion. 2006;46(2):169-73.

35. Atay D, Erbey F, Akcay A, Ozturk G. Is ABO mismatch another risk factor for allogeneic hematopoietic stem cell transplantation in pediatric thalassemic patients? Pediatr Transplant. 2015;19(6):645-51.