REVIEW ARTICLE

blood advances

Post–hematopoietic stem cell transplantation immune-mediated anemia: a literature review and novel therapeutics

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Anemia after allogeneic hematopoietic stem cell transplantation (HSCT) can be immune or non–immune mediated. Auto- or alloimmunity resulting from blood group incompatibility remains an important cause in post-HSCT immune-mediated anemia. ABO incompatibility is commonly encountered in HSCT and may lead to serious clinical complications, including acute hemolysis, pure red cell aplasia, and passenger lymphocyte syndrome. It remains controversial whether ABO incompatibility may affect HSCT outcomes, such as relapse, nonrelapse mortality, graft-versus-host disease, and survival. Non-ABO incompatibility is less frequently encountered but can have similar complications to ABO incompatibility, causing adverse clinical outcomes. It is crucial to identify the driving etiology of post-HSCT anemia in order to prevent and treat this condition. This requires a comprehensive understanding of the mechanism of anemia in blood group–incompatible HSCT and the temporal association between HSCT and anemia. In this review, we summarize the literature on post-HSCT immune-mediated anemia with a focus on ABO and non-ABO blood group incompatibility, describe the underlying mechanism of anemia, and outline preventive and treatment approaches.

Introduction

There are at least 43 recognized blood groups in humans involving 345 red blood cell (RBC) antigens.[1] Approximately 30% to 50% of hematopoietic stem cell transplantations (HSCTs) are performed across the ABO blood group barrier, and clinically significant hemolysis is encountered in 10% to 15% of cases.[2,3] Other complications of ABO-mismatched HSCT include hemolytic infusion reactions, delayed engraftment, and pure red cell aplasia (PRCA).[4,5] Compared with those of ABO-mismatched HSCT, complications of non-ABO blood group–mismatched HSCT are less well-characterized. Recipients and donors are not routinely checked for non-ABO blood group phenotypes unless clinically indicated, such as when there is a known history of alloantibodies or heavy transfusion requirement in the recipient before transplantation.[6] The incidence of non-ABO blood group mismatch–related immunohematologic complications after HSCT is reported to be $<$10%, which likely reflects underreporting.[7-10]

Auto- or alloimmunity against RBCs is an important etiology of immune-mediated anemia in blood group–mismatched HSCT. The source of auto- or alloimmunity may be donor or recipient related, including passive antibody transfusion, passenger lymphocyte syndrome (PLS), alloantibodies formed against engrafting hematopoietic cells, or new auto- or alloantibodies resulting from transfusions (Figures 1 and 2). Antibodies can mediate phagocytosis and cellular toxicity and activate the complement pathway, resulting in intra-

Submitted 20 October 2021; accepted 23 December 2021; prepublished online on *Blood Advances* First Edition 31 December 2021; final version published online 26 April 2022. DOI 10.1182/bloodadvances.2021006279.

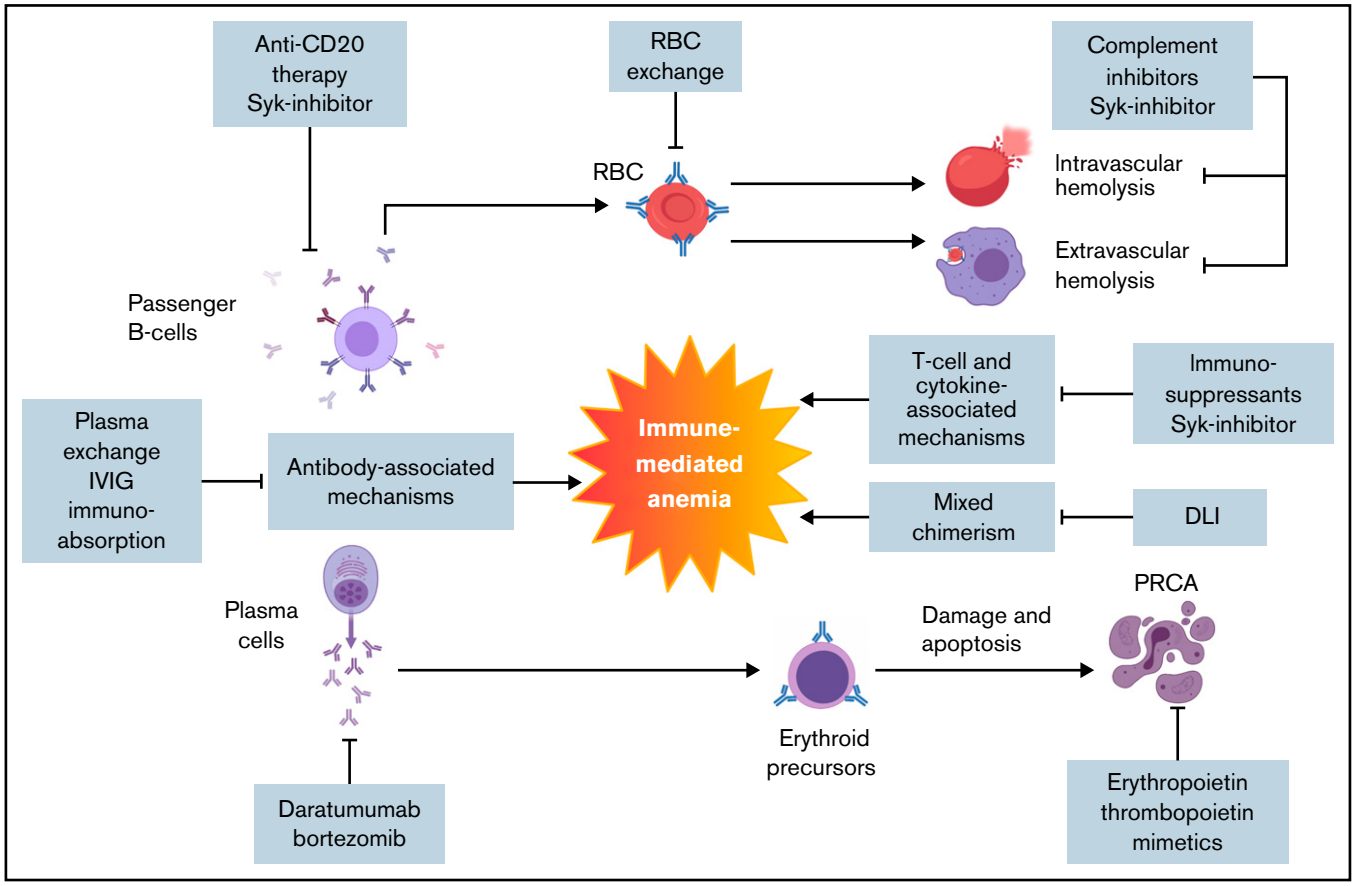


Figure 1. Pathophysiology and targeted therapy for post-HSCT immune-mediated anemia. Post-HSCT anemia is multifactorial as a result of new auto- or alloantibodies in combination with T cell– and cytokine-mediated inflammatory processes. There are no formal guidelines in management. Several therapeutic approaches that target different pathophysiologic aspects of post-HSCT immune-mediated anemia are outlined. DLI, donor lymphocyte infusion; IVIG, IV immunoglobulin; Syk, spleen tyrosine kinase.

and extravascular hemolysis.[11] Immune-mediated cytopenia can also occur as a manifestation of chronic graft-versus-host disease (GVHD).[12,13] The underlying mechanism of cytopenia in GVHD is unclear, but it is likely to result from altered T-cell immune reconstitution.[14]

The complexity of post-HSCT immune-mediated anemia requires close collaboration between transfusion medicine, hematology, and transplantation services. Detailed knowledge about recipient/donor blood group phenotypes and the temporal association between transplantation and hemolysis can help identify the underlying mechanism of hemolysis and direct appropriate management. This review summarizes the literature on post-HSCT immune-mediated anemia to provide insight into its pathophysiology, clinical manifestations, and preventive and proposed therapeutic strategies.

ABO mismatch

ABO mismatch is divided into major, minor, and bidirectional categories (Table 1).

Major ABO mismatch

Major ABO mismatch is characterized by the presence of naturally existing host isohemagglutinins against the corresponding carbohydrate ABO antigens of the donor RBCs. The most common scenario is when a group O recipient receives a non-O graft; less commonly, a group A or B recipient may receive a B or A graft, respectively, or an AB graft. The naturally occurring isohemagglutinins in recipients can attack donor RBC ABO antigens early after stem cell infusion or can affect erythroid precursors later in the post-HSCT course.

ABO isohemagglutinins are immunoglobulin M (IgM) antibodies that can robustly activate the classical complement pathway.[15] Through formation of the membrane attack complex, major ABO incompatibility may cause acute hemolytic transfusion reactions at the time of stem cell infusion, especially when the graft contains a significant volume of RBCs, such as in unmanipulated bone marrow (BM) grafts.[16] Furthermore, recipient isohemagglutinins against donor-derived erythroid precursor cells can lead to reticulocytopenia with subsequent PRCA, which is seen in 8% to 26% of major ABO-mismatched HSCTs.[17] PRCA usually occurs ~30 to 90 days post-HSCT and is characterized by an absence of erythroid precursors in otherwise normal BM.[18] Because a majority of recipients clear the donor-specific isohemagglutinins within 120 days, the development of PRCA has been attributed to residual recipient plasma cells that continue to produce isohemagglutinins (Figure 3).[4] Patients with PRCA can be transfusion dependent for months, become iron overloaded, and develop alloimmunization to other blood group antigens.[19] ABO antigens are also expressed on granulocytes and

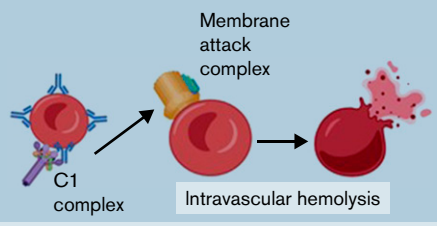
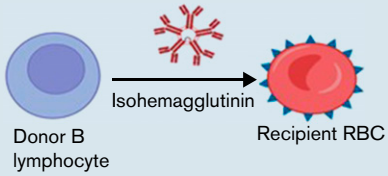
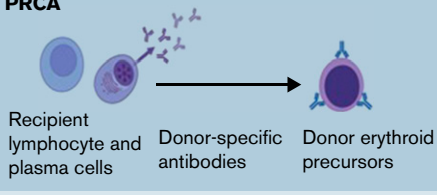
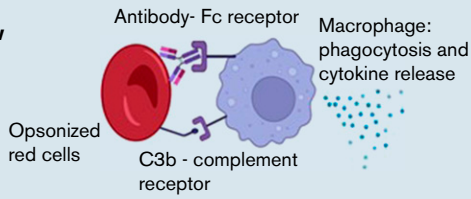
Cause	Condition	Onset	Prevention	Treatment
ABO mismatch	**Acute hemolytic reaction** 	**Day 0**, at the time of stem cell infusion	Red cell reduction of the graft in major ABO mismatch; plasma reduction of the graft in minor ABO mismatch	Supportive care; transfuse recipient-compatible red cell units in major ABO mismatch; transfuse donor-compatible red cell units in minor ABO mismatch
Minor ABO mismatch	**PLS** 	**Day +4–14**	Plasma reduction; in vivo or in vitro lymphodepletion	Supportive care; transfuse donor-compatible red cell units; RBC exchange
Residual recipient plasma cells; abnormal immune tolerance	**PRCA** 	**1–3 months**	Myeloablative conditioning when able	Supportive care; transfusion refractory cases: - Anti-B cell: rituximab - Donor lymphocyte infusion - Anti-plasma cell: daratumumab, bortezomib - Other immunosuppressants, IVIG, Syk inhibitor - Erythropoietin, TPO memetics
Development of new autoantibodies; abnormal immune tolerance; mixed chimerism	**Allo- and autoimmune hemolytic anemia** 	**>3 months**	Myeloablative conditioning when able	Supportive care Severe cases: treat as AIHA outside of the transplant setting - Common: corticosteroids, IVIG, rituximab - Others: erythropoietin, splenectomy, Syk inhibitor, anti-plasma cell, anti-complement, other immunosuppressants

Figure 2. General approach for posttransplantation immune-mediated hemolysis. The graph outlines underlying mechanisms of posttransplantation hemolysis, timing posttransplantation, preventive methods, and treatment strategies. Note there is no consensus or guideline on how to manage posttransplantation immune-mediated anemia. The management approaches listed are based on expert opinions and available literature. AIHA, autoimmune hemolytic anemia; IVIG, IV immunoglobulin; TPO, thrombopoietin.

platelets; therefore, major ABO mismatch can also lead to prolonged neutropenia and thrombocytopenia, resulting in severe infections and catastrophic bleeding.[20]

Whether major ABO mismatch can affect HSCT outcomes, such as survival, relapse, and GVHD, is controversial (Table 2). A single-center study of 1502 patients undergoing HSCT with different graft sources, including peripheral blood (PB), BM or cord blood, showed that ABO mismatch was not associated with neutrophil or platelet engraftment delay, incidence of acute or chronic GVHD, OS, or NRM, regardless of graft source.[21] A meta-analysis of 7 cohort studies showed that OS was not affected by ABO matching status.[22] In contrast, in a Center for International Blood and Marrow Transplant Research study that included 5179 patients, major ABO mismatch was associated with decreased OS (hazard ratio [HR], 1.19; 95% confidence interval [CI], 1.19-1.31; $P < .001$) and increased NRM (HR, 1.23; 95% CI, 1.08-1.4; $P = .002$).[23] In a European Blood and Marrow Transplant Acute Leukemia Working Group Registry study that included 837 patients who underwent haploidentical HSCT, major ABO mismatch was associated with an inferior day-100 engraftment rate, and in BM HSCT, it was associated with inferior OS.[24]

Patients with ABO mismatch may have lower rates of complications if they receive myeloablative (MA) conditioning.[25] One study showed that fludarabine/cyclophosphamide conditioning, compared with a total-body irradiation–based MA regimen, was associated with delayed full donor erythroid chimerism by a median of 74 days and increased risk of PRCA. The clearance of antidonor isohemagglutinins was faster in the latter.[25] Other studies have also shown impaired HSCT outcomes in ABO-mismatched HSCTs involving RIC.[26,27] ABO mismatch was associated with a 1.7-fold

Table 1. Directions of ABO mismatch

ABO mismatch	Recipient phenotype	Donor phenotype
Major	OAB	A, B, ABAB, BAB, A
Minor	ABAB	OOO, A, B
Bidirectional	AB	BA

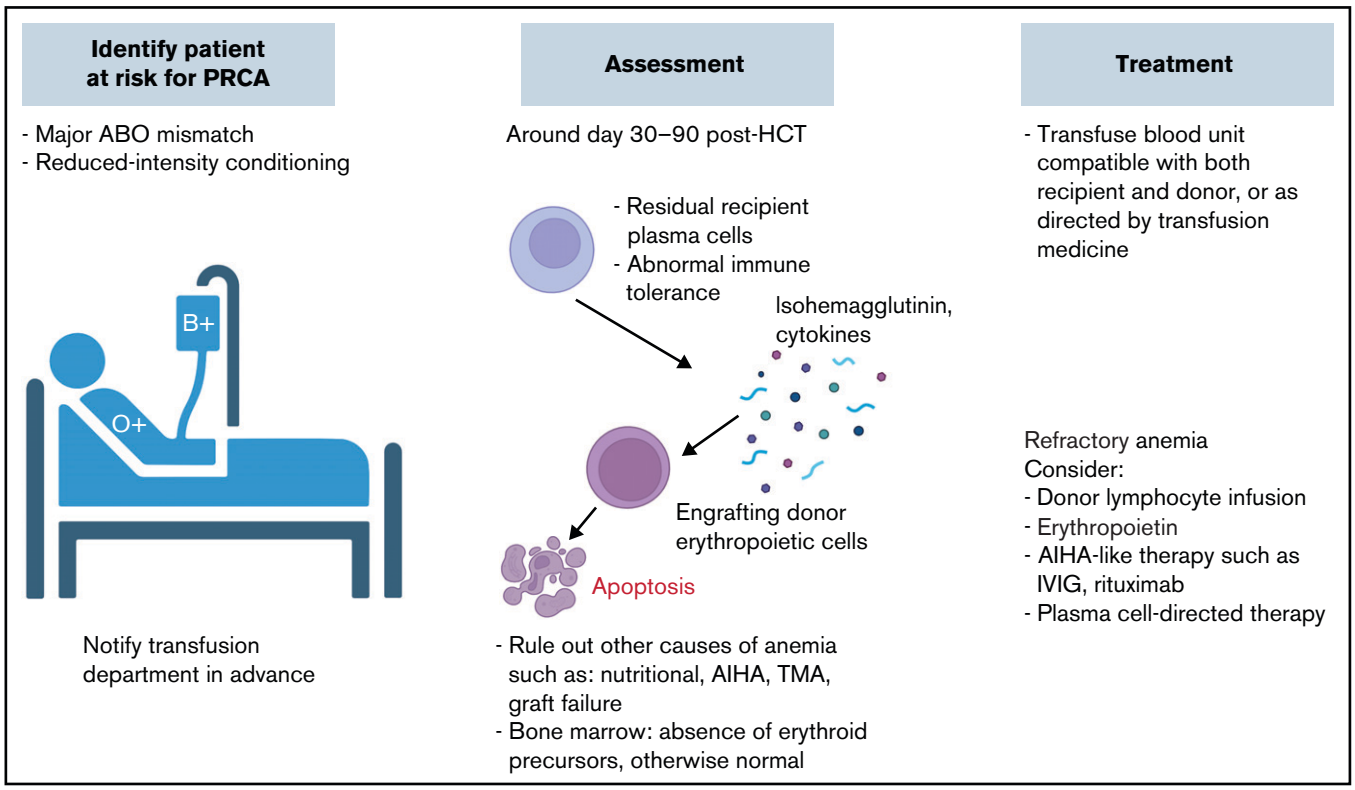


Figure 3. PRCA. PRCA is more frequently encountered in major ABO mismatch during the first 1 to 3 months posttransplantation. Management approach is similar to PLS, with frequent monitoring and RBC transfusion support. Other pharmacologic interventions can be considered in refractory cases. CBC, complete blood count; Hb, hemoglobin; IVIG, IV immunoglobulin; TMA, thrombotic microangiopathy.

increased risk of extensive chronic GVHD in a cohort of 594 patients who underwent alemtuzumab-based RIC HSCT.[27]

Preventive strategies for immunohematologic complications. Although ABO matching is not required for donor selection per current guidelines, it is worth taking into consideration when multiple suitable donors are available.[28] Besides using MA regimens when feasible, strategies to prevent complications in major ABO mismatch include graft RBC reduction and removal of host isohemagglutinins by therapeutic plasma exchange before HSCT.[29-31] In recipients with antidonor isohemagglutinin titers ≥1:32, RBC depletion should be performed to ensure infused RBCs <20 mL. When titers are ≤1:16, RBC depletion is generally not required.[3]

Because ABO antigens can be secreted into the plasma, pretransplantation immunoabsorption (ie, infusion of donor-type fresh frozen plasma [FFP] positive in A or B antigens to neutralize respective isohemagglutinins) is another approach to prevent complications. In a single-center study in Singapore, 79 of 99 major or bidirectional ABO-mismatched recipients were treated with donor FFP from day −5 to −2 before transplantation, including 70 patients with isohemagglutinin titers >1:32. Those with a titer level ≤1:32 at the time of stem cell infusion did not develop acute hemolysis. Three patients developed PRCA irrespective of pre- or post-FFP isohemagglutinin levels.[32] In another single-center study from Australia, 75 of 110 major or bidirectional ABO-mismatched recipients had isohemagglutinin titers >1:32 and received FFP with or without plasma exchange before HSCT. The incidence of PRCA was 5%. The risk of PRCA or delayed RBC engraftment was significantly higher in patients with pretransplantation isohemagglutinin titers ≥1:128.[17]

Donor-type RBC transfusion is another immunoabsorption method.[33,34] In a single-center study in thalassemia, 20 of 55 major or bidirectional ABO-mismatched recipients with isohemagglutinin titers ≥1:32 received small incremental doses of uncrossmatched donor RBCs during conditioning; 12 had mild hemolysis, and none had severe hemolysis or anaphylaxis. In patients who had no hemolytic reaction at the last transfusion or who had titers <1:32, BM grafts were infused without RBC depletion. No hemolytic reactions were observed post-HSCT, and all patients experienced engraftment without delay.[33] Despite these successes, immunoabsorption requires high expertise in transfusion medicine and close patient monitoring, and it remains to be validated in larger studies.

Minor ABO mismatch

Minor ABO mismatch is characterized by the interaction of donor-derived isohemagglutinins with corresponding recipient RBC antigens. These isohemagglutinins may be infused along with the stem cell products, causing acute hemolysis of recipient RBCs. Alternatively, passenger B-lymphocytes from the donor graft may proliferate and secrete isohemagglutinins and other RBC antibodies, causing clinically significantly delayed hemolysis called PLS (Figure 4).[35] PLS typically occurs 1 to 2 weeks post-HSCT, more frequently after PB than BM HSCT, because the former contains a higher concentration of lymphocytes.[35,36] RIC is associated with a higher risk of

Table 2. Selected studies evaluating ABO compatibility and transplantation outcomes (2000-2020)

Reference	Year	ABO match, n (%)*	RIC, n (%)	Related donor, n (%)	BM graft, n (%)*	GVHD prophylaxis	Engraftment	GVHD rate	Relapse rate	NRM	OS
16	2000	083 (53)65 (41)10 (6)	None	All related	−62 (74.7)46 (70.8)7 (70.0)	CNI + MTX	NS	No data	No data	No data	No data
118	2001	2860 (41)1670 (24)1802 (26)587 (8)	No data	All matched unrelated	All BM	Various regimens	NS	NS	No data	No data	NS
119	2005	2108 (68)451 (21)430 (14)114 (4)	258 (12)46 (10)54 (13)17 (15)	All related	All BM	CNI + MTX	Delayed engraftment in major ABO incompatibility	NS	NS	NS	NS
120	2007	121 (56)40 (19)40 (19)15 (7)	0.5% of all patients	86 (71)No data17 (43)No data	No data	CNI ± MTX; MTX alone	NS	NS	NS	NS	NS
121	2008	Major 205 (18.5)Minor 187 (17)	All patients	932 (84) of all patients	213 (19) of all patients	CNI only in 430 (39%)	No data	Higher in minor ABO incompatibility	No data	No data	Worse in minor ABO incompatibility
122	2008	2820 (47)1834 (31)1202 (20)143 (2)	348 (12)152 (8)136 (11)30 (21)	No data	No data	CNI + MTX	Delayed engraftment in major ABO incompatibility	Higher in major and minor ABO incompatibility	NS	Higher in major and minor ABO incompatibility	Worse in major and minor ABO incompatibility
43	2009	58 (38)30 (19)44 (29)22 (14)	17 (29)8 (27)15 (34)16 (73)	All matched unrelated	27 (47)8 (27)22 (50)9 (41)	CNI + MTX/MMF; 10% with CNI only	No data	Higher acute GVHD rate in minor ABO incompatibility	NS	NS	NS
23 (Stanford)	2015	1053 (61)297 (17)309 (18)78 (4)	526 (30) of all patients	1303 (75) of all patients	727 (42) of all patients	Various	No data	NS	NS	Higher in minor ABO incompatibility	Worse in minor ABO incompatibility, especially in BM grafts
CIBMTR(B-cell lymphoma)		240 (59)73 (18)73 (18)22 (5)	238 (55) of all patients	330 (76) of all patients	None	Various	No data	NS	NS	Higher in minor ABO incompatibility	Worse in minor ABO incompatibility
CIBMTR (AML or MDS)		2608 (50)1084 (21)977 (19)311 (6)	1448 (28) of all patients	2079 (40) of all patients	2333 (45) of all patients	Various	No data	NS	NS	Higher in major ABO incompatibility	Worse in major ABO incompatibility
42	2016	252 (49)105 (21)117 (23)38 (7)	192 (76)78 (74)86 (74)30 (79)	108 (43)25 (24)32 (27)7 (18)	None	No data	Delayed PLT engraftment in major ABO incompatibility	NS	NS	No data	NS
123(mismatched unrelated donor, AML)	2017	349 (40)215 (25)241 (28)71 (8)	193 (55)122 (57)154 (64)38 (54)	None	None	CNI-based in 87% of all patients	NS	Lower grade 2-4 acute GVHD rate in major ABO incompatibility	NS	NS	NS
24(haploidentical, AML)	2017	522 (63)127 (15)150 (18)38 (5)	215 (41)45 (35)68 (45)12 (32)	All haploidentical	279 (53)76 (60)83 (55)19 (55)	No data	Delayed engraftment in major ABO incompatibility	Higher grade 2-4 acute GVHD in bidirectional	NS	NS	Worse in major ABO incompatibility + BM graft

AML, acute myeloid leukemia; CIBMTR, Center for International Blood and Marrow Transplant Research; CNI, calcineurin inhibitor; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MTX, methotrexate; NRM, nonrelapse mortality; NS, not significant; OS, overall survival; PLT, platelets; RIC, reduced-intensity conditioning.

*Data given in the following order: matched, major, minor, bidirectional.

Table 2. (continued)

Reference	Year	ABO match, n (%)*	RIC, n (%)	Related donor, n (%)	BM graft, n (%)*	GVHD prophylaxis	Engraftment	GVHD rate	Relapse rate	NRM	OS
21	2017	704 (47)324 (22)372 (25)102 (7)	301 (43)128 (40)151 (41)54 (53)	372 (53)101 (31)88 (24)23 (23)	296 (42)87 (27)73 (17)19 (19)	No data	Delayed neutrophil engraftment only in bidirectional with umbilical cord blood graft	NS	NS	NS	NS
41(severe aplastic anemia)	2020	114 (57)47 (24)38 (19)0	All patients	All haploidentical	Both BM and PB in all patients	CNI + MMF	NS	Grade 3-4 acute GVHD more common in minor ABO incompatibility	No data	No data	NS
124	2020	590 (59.0)164 (16.4)191 (19.1)55 (5.5)	110 (17)32 (20)35 (18)18 (33)	531 (90)124 (76)145 (76)34 (62)	189 (32)33 (20)41 (22)8 (15)	CNI + MTX	Neutrophil engraftment delayed in mismatched groups	NS	NS	NS	NS

AML, acute myeloid leukemia; CIBMTR, Center for International Blood and Marrow Transplant Research; CNI, calcineurin inhibitor; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MTX, methotrexate; NRM, nonrelapse mortality; NS, not significant; OS, overall survival; PLT, platelets; RIC, reduced-intensity conditioning.

*Data given in the following order: matched, major, minor, bidirectional.

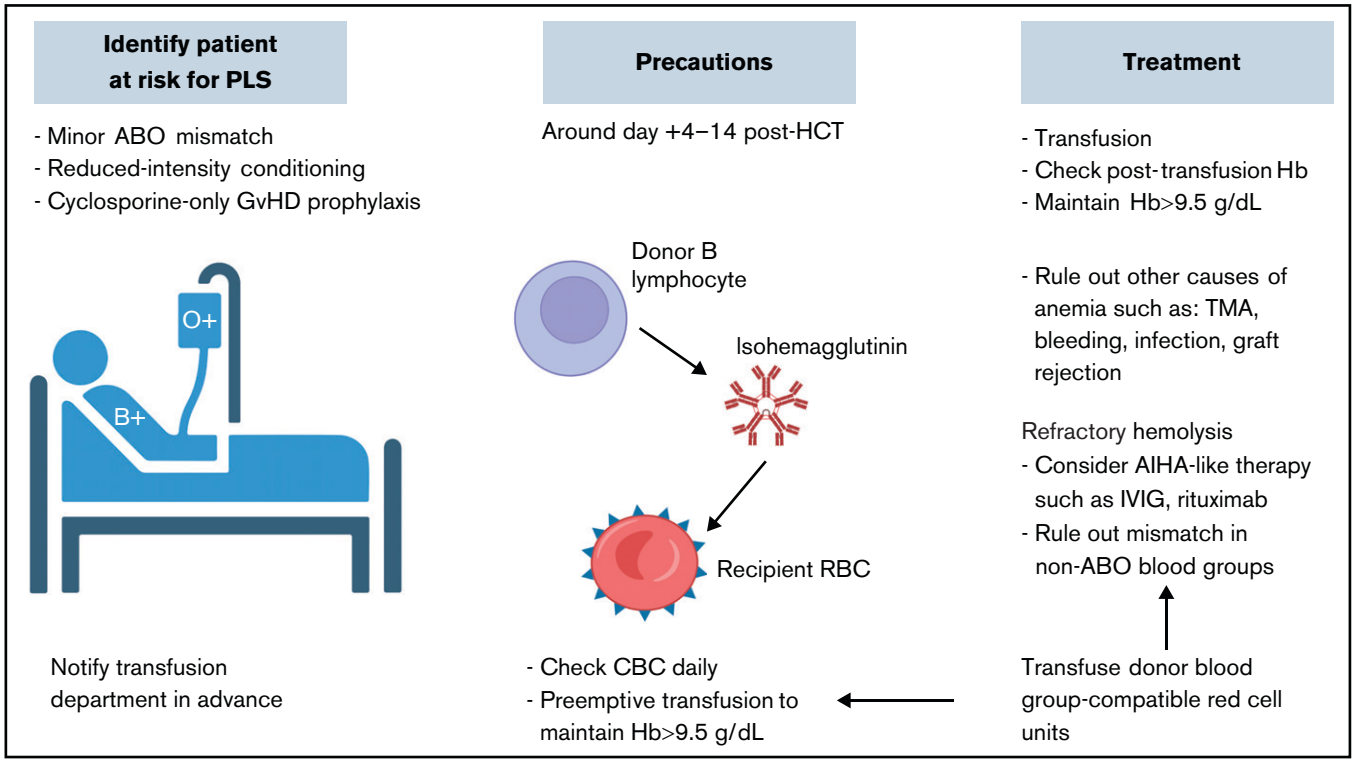


Figure 4. PLS. Proactive approach with identifying patients at risk before transplantation, alerting the blood bank service, conducting frequent count monitoring, and providing transfusion support in the first 2 weeks posttransplantation is key for better clinical outcomes. Hb, hemoglobin; IVIG, IV immunoglobulin; TMA, thrombotic microangiopathy.

PLS because recipient antigens may be left intact and subsequently stimulate donor B cells.[37,38] A cyclosporine-only GVHD prophylactic regimen has been associated with higher risks of immunohematologic complications because cyclosporine boosts B-cell antibody production.[2,39]

The impact of minor ABO mismatch on HSCT outcomes is also controversial (Table 1). Some studies suggest that minor ABO mismatch is a risk factor for acute GVHD, decreased OS, and increased NRM.[23,40-42] One study found it was associated with a threefold increased risk of grade 2 to 4 acute GVHD and fourfold increased risk of grade 3 to 4 acute GVHD.[43] In a 1737-patient cohort at Stanford University between 1986 and 2011, minor ABO mismatch was an independent risk factor for OS, with an HR of 1.56 (95% CI, 1.05-2.05; $P = .001$).[23] In a Center for International Blood and Marrow Transplant Research analysis of patients with lymphoma receiving PB grafts, minor ABO mismatch was associated with reduced OS and higher NRM (HR, 1.55 and 1.72; $P = .021$ and .03, respectively); however, these associations were not observed in patients with acute myeloid leukemia or myelodysplastic syndrome.[23]

Preventive strategies for immunohematologic complications. In minor ABO-mismatched HSCT, immediate hemolysis can be prevented by graft plasma volume reduction; this does not prevent PLS because it does not affect the B-cell component in the graft.[44] There is a scarcity of literature on how to prevent PLS. Patients need close monitoring for hemolysis, especially at ~1 to 2 weeks post-HSCT when PLS may occur. A direct antiglobulin test may assist in early detection of subclinical hemolysis. It is often checked once or twice weekly according to institutional protocols. Maintaining higher hemoglobin levels than the normal transfusion threshold is preferred, especially during the high-risk period, to avoid nadir in case severe or life-threatening PLS occurs. Collaborative efforts between transfusion and transplantation services to ensure the awareness of minor ABO mismatch and transfusion-compatible RBC components peritransplantation is critical.

Bidirectional ABO mismatch

Bidirectional mismatch occurs when the donor/recipient pair has both a major and minor ABO mismatch, such as type A donor/type B recipient or vice versa. The recipient is at risk of complications

Table 3. Non-ABO blood group systems with potential to cause clinically significant alloimmunization after HCT

RBC blood group system	Antibodies
Rh	Anti-D,[8,58,125] anti-C, anti-c,[58,126,127] anti-E[8,58,125,127,128]
Jk	Anti-Jk^{a},[8,128] anti-Jk^{b}
K	Anti-K,[50,58] anti-Js^{a}[58]
MNS	Anti-M,[50] anti-N,[7] anti-S, anti-s[8]
Lewis	Anti-Lu^{a},[129] anti-Le^{b}[7,58]
Diego	Anti-Di^{a}, anti-Di^{b}[128]
Other	Anti-McC,[58] anti-V,[58] anti-Knop[58]

associated with both directions of incompatibility (Table 1), and preventive methods should address both accordingly.

Non-ABO blood group incompatibility

Unlike ABO isohemagglutinins, which exist in the absence of previous exposure, alloimmunization to protein antigens occurs only after exposure. The incidence of alloimmunization after transfusion is 2% to 6% and most commonly involves the Rhesus (Rh), Kell (K), and Kidd (Jk) blood groups.[45-47] RhD antigen is the most potent non-ABO antigen, followed by K antigen. Patients with a history of alloimmunization are at higher risk of developing additional alloantibodies.[48] Although rare, non-ABO blood group alloantibodies may result in poor HSCT outcomes.[49,50] Complement cascade is implicated in immune-mediated anemia in some of the non-ABO–mismatched HSCT. For example, the IgG or IgM antibodies against Jk antigens are able to fix complements and induce intra- or extravascular hemolysis.[51] Mismatch of the Jk antigen system has been reported to cause severe hemolytic anemia or PLS.[8,52]

RBC alloimmunization resulting from non-ABO mismatch could originate from the donor, recipient, or both, depending on the temporal relationship between antibody development and chimerism status. Donor-derived alloantibodies include the preexisting antibodies in the graft and new antibodies produced by passenger or engrafted lymphocytes. Recipient-derived alloantibodies include preexisting antibodies and antibodies produced by residual lymphocytes and plasma cells.

Post-HSCT, a majority of the de novo non-ABO alloantibodies develop within the first month.[8] PLS can also occur in non-ABO blood group–mismatched HSCT, usually involving RhD, E, s, Jk^b, or Jk^a.[52-54] Table 3 outlines previously described clinically significant non-ABO blood group systems associated with alloimmunization after HSCT.

Patients receiving chronic transfusion therapy before HSCT are generally at higher risk of developing auto- and alloimmunization. Patients with sickle cell disease have high rates of RBC alloimmunization (23.8% to 45.7%) despite leukoreduction and prophylactic antigen matching.[55,56] Frequent transfusions, lack of phenotypically matched products, inadequate alloantibody testing, and presence of antigen variations, especially in donors of African descent, increase the risk of alloimmunization.[57] In 1 cohort, RBC antibodies were detected in 9 (15%) of 61 patients post-HSCT, including 3 patients with preformed and 6 with new antibodies, and 4 patients developed reticulocytopenia or hemolysis.[58] In a cohort of patients undergoing matched-sibling HSCT without MA conditioning, 31% (11 of 31) had a history of RBC alloantibodies, which was correlated with decreased donor T-cell chimerism at 1 year compared with patients without alloimmunization (median, 24% vs 55%; $P = .035$).[59] As the number of HSCTs in sickle cell disease is increasing, it remains a challenge to prevent and treat RBC alloimmunization peri-HSCT.

Thalassemia is another hemoglobinopathy that requires chronic transfusion therapy. Alloantibodies occur in 5% to 30% of patients with thalassemia and are more common after splenectomy, long duration of treatment, and frequent transfusions.[60-63] The dominant antibodies are against the Rh and K groups, each comprising 20% to 30% of the antibodies.[63] When prophylactically transfusing Rh (D, C, and E) antigen– and K antigen–matched RBC units, alloantibodies were still detected in 32.5% of patients, with an alloimmunization rate of 0.26 antibodies per 100 units, and 72.5% of antibodies were directed against Rh.[62] There are limited data on how non-ABO alloantibodies affect HSCT outcomes in patients with thalassemia.

Chronic granulomatous disease can coexist with the McLeod phenotype (ie, reduced expression of K blood group antigens and absence of XK protein on RBCs). This is due to the genetic proximity between the cytochrome B β subunit gene and the XK gene. Hönig et al[64] reported a case of successful HSCT in a patient with chronic granulomatous disease/McLeod phenotype with anti-K and anti-Kx alloantibodies. The patient received rituximab, antithymoglobin, MA conditioning, and a K^- HLA-matched unrelated graft. The patient had an uneventful HSCT course with prompt engraftment. The anti-K alloantibodies remained detectable until 20 months post-HCT.[64] Another patient received MA conditioning with busulfan, cyclophosphamide, and antithymoglobin, followed by a K^- BM graft. He developed refractory severe hemolytic anemia after day +100 as a result of anti-Kx and anti-K and was found to have low donor T-cell chimerism, despite B-cell and erythroid conversion. His hemolytic anemia resolved after 3 DLI.[65]

Outside of the chronically transfused population, the rate of non-ABO alloimmunization is reportedly low.[7,8,10] De la Rubia et al[10] reported a rate of 3.7% (8 of 217) of patients developing new non-ABO alloantibodies post-HCT, 2 of whom developed severe immune hemolytic anemia early after HCT; recipient age and ABO incompatibility were associated with the development of non-ABO alloantibodies. Ting et al[7] reported a rate of 8.7% (13 of 150) of patients experiencing new RBC alloantibody production from 12 days to 11 months post-HCT. In another retrospective study, the incidence of alloimmune hemolysis post-HCT involving non-ABO antigens was 1% (5 of 427 patients).[8] When alloantibodies are detected promptly, these complications may be prevented.[8,66] In 1 case, a recipient with anti-Jk^a antibodies received fludarabine/melphalan conditioning with rituximab, followed by Jk^{a+} donor PB stem cells without adverse events.[66] Complications related to non-ABO antigen incompatibility are expected to increase given the progressive success in HSCT and its wide use in malignant and nonmalignant diseases.[67]

Laboratory investigations in non-ABO blood group–mismatched HSCT

Immunohematologic complications caused by non-ABO blood group mismatch can be underdiagnosed because of inadequate phenotyping of the donor-recipient RBCs. In the absence of known preexisting alloantibodies in the recipient, testing beyond the ABO and Rh blood groups is generally not considered before transplantation. Some alloantibodies may be not detected, such as the Jk^a/Jk^b antibodies, because of fluctuation of the titers.[8] Jk antibodies are known to have an amnestic response such that a patient may test negative initially but have a subsequent reemergence of antibodies later in the post-HSCT course.

Extended serologic RBC phenotype matching is being performed for patients receiving frequent transfusions in order to provide appropriate antigen-negative blood products. Despite this, alloantibodies can still form and lead to additional challenges in transfusion.[68] Extended genotype RBC matching can detect and predict minor variations in RBC antigens that are hard to identify serologically; it is increasingly used in clinical practice.[69,70] Real-time

polymerase chain reaction is another method for quick RBC phenotyping in HSCT, especially when donor-recipient myeloid chimerism status is dynamically changing.[71]

Anemia resulting from autoimmunity

AIHA occurs in 4% to 6% of those undergoing HSCT.[72,73] In 1 study of T cell–depleted haploidentical HSCT in patients with severe combined immunodeficiency, the incidence of AIHA was 19.5%.[74] Patients post–second HSCT have higher incidence and earlier presentation of AIHA than those post–first HSCT.[75] AIHA may occur alone or in conjunction with other immune-mediated cytopenias.[73] RBC phenotyping of the donor and recipient, determined before HSCT, can help differentiate autoimmune-mediated anemia from alloimmunity.[76] In different reports, median time of onset ranges from 4 to 10 months post-HSCT.[75] Transplantation for nonmalignant disease is the most consistent risk factor for post-HSCT AIHA in the literature; other factors, such as unrelated donor, acute or chronic GVHD, cytomegalovirus activation, and alemtuzumab-containing conditioning regimen, have been reported, but reports are inconsistent.[72,76-78]

The pathophysiology of AIHA post-HSCT has not been fully elucidated, but it may be related to preformed autoantibodies and dysregulated immune tolerance. In the chronically transfused population, autoantibodies against RBCs have been reported in 7% to 25% of patients; a majority of the autoantibodies are transient, but some may lead to clinically significant hemolysis.[79] Patients who develop AIHA are severely lymphopenic, with low numbers of regulatory T cells; delayed T-cell immune reconstitution, resulting from either in vivo or ex vivo T-cell depletion, may allow autoreactive B cells to activate and expand without regulation.[74,80] In contrast, flowcytometry and cytokine analysis of patients with AIHA post-HSCT identified a decreased $CD3^+CD8^+$ T-cell ratio and a T-helper cell 2–related cytokine profile compared with control patients.[76] Patients who develop AIHA are at a higher risk for developing alloimmunity.

Treatment

Mild to moderate cases of hemolytic anemia, including PLS, are self-limited and are usually treated with simple transfusions of antigen-negative RBCs; however, finding the appropriate RBC unit can be challenging when multiple alloantibodies or antibodies to high-frequency antigens are present.[81] Approximately 50% of PRCA cases resolve spontaneously within 100 to 200 days post-HSCT, but in cases of prolonged anemia dependent on chronic frequent transfusions, treatment is necessary to prevent complications such as iron overload.[18,82-84]

Most of the therapeutic options for post-HSCT immune-mediated anemia are derived from AIHA, which does not have a licensed treatment itself (Figure 2).[80] Based on mechanism of action, the options can be categorized into immunosuppression, which includes the use of systemic steroids, IV immunoglobulin, rituximab, cyclophosphamide, azathioprine, and splenectomy in the severe cases; immunoabsorption; RBC or plasma exchange; and stimulation of erythropoiesis using erythropoietin or thrombopoietin mimetics (Figure 1).[85-89] For PRCA, the most commonly used therapies are rituximab, erythropoietin, and DLI (Figure 3).[90]

There are reports of efficacy using anti-CD20 monoclonal antibodies such as rituximab to treat PRCA.[91] Because B cells are responsible for isohemagglutinins or alloantibody production in PLS, rituximab can also be used in severe cases of PLS (Figure 4).[92] Other immunosuppressive treatments reported to work in refractory cases include abatacept, a fusion protein that blocks interaction between T cells and antigen-presenting cells.[93]

Erythropoietin-stimulating agents can increase RBC production and can be used as a therapeutic option in severe hemolytic anemia or PRCA post-HSCT.[88,94] Eltrombopag is a thrombopoietin receptor agonist approved for the treatment of aplastic anemia. It has shown efficacy in refractory acquired PRCA outside the HSCT setting.[95] Busca et al[89] reported 2 cases of PRCA that were refractory to erythropoietin, plasma exchange, rituximab, and bortezomib; these patients achieved sustained PRCA remission with eltrombopag.

DLI and tapering of immunosuppressants represent unique therapeutic options in the HSCT setting. These methods may improve donor chimerism, eliminate recipient plasma cells, and reduce alloreactivity from either the donor or recipient direction. The efficacy of both methods in PRCA is ~50% in case reports.[83] In 1 case report, a patient with PRCA received DLI with a $CD34^+$ stem cell boost and achieved normal blood counts after 2 months.[96] However, in a recent multicenter retrospective study, rituximab, DLI, and erythropoietin had no impact on the resolution of PRCA.[90] Mesenchymal stem cell infusion has also been used in refractory PRCA cases, with promising results.[97,98]

Plasma cells are a viable target for therapy because they may contribute to antibody production, especially in refractory hemolytic anemia and PRCA. Bortezomib was reported to be effective in 40% of cases in the literature.[83] Compared with other plasma cell–targeted therapy, daratumumab has a more appealing safety profile and mechanism of action.[99,100] A few case reports have noted its efficacy in refractory post-HSCT AIHA and PRCA.[101-103] Daratumumab may have efficacy in other forms of post-HCT immune-mediated cytopenia, such as thrombocytopenia or Evan's syndrome.[104] We previously reported durable response after daratumumab in a patient with posttransplantation thrombocytopenia.[105] Daratumumab impairs RBC crossmatch testing, which necessitates transfusing K^- units posttreatment, unless the RBC phenotype is identified pretreatment.[106] However, daratumumab is not always effective in post-HSCT immune-mediated cytopenia, likely because of the suppressive effect of daratumumab on $CD38^+$ regulatory T cells.[107,108]

A novel modulatory therapy that is worth testing is the Syk inhibitor fostamatinib. Its active metabolite, R406, was shown to reduce antibody-mediated platelet destruction. It was US Food and Drug Administration approved in April 2018 for patients with chronic immune thrombocytopenia for whom 1 line of therapy failed. Additionally, it is currently being studied in a phase 3 clinical trial for patients with warm AIHA (registered at www.clinicaltrials.gov as #NCT03764618) and in an early-phase chronic GVHD trial (#NCT02611063). The Syk pathway is critical for B-cell activation and proliferation; activated B cells may trigger T-cell activation and cytokine production.[109,110] Preclinical reports in xenograft models using PB mononuclear cells from patients with active chronic GVHD showed that the Syk inhibitor augments B-cell apoptosis while not affecting normal T-cell function.[111]

Therapies targeting the complement pathway are being more frequently used in immune-mediated cytopenia. Vo et al[112] used

eculizumab, a complement C5 inhibitor, to treat heavily alloimmunized patients with platelet transfusion refractoriness. Four of the 10 patients enrolled overcame platelet transfusion refractoriness with 1 dose of eculizumab. Eculizumab has shown efficacy in warm antibody AIHA and cold agglutinin disease.[113,114] In post-HSCT AIHA, eculizumab was effective in 1 of the 3 cases reported in the literature.[72] Several other complement inhibitors, such as pegcetacoplan and sutimlimab, are actively being investigated in complement-mediated hemolytic anemia.[115,116] These agents may be viable options for refractory hemolytic anemia post-HSCT.

Therapies carry their own risks. Infection is the most concerning complication in patients receiving immunosuppression. In 1 study analyzing the outcome of 46 patients with PRCA, 22 received treatment other than supportive care, and 7 died as a result of infection.[18] IV immunoglobulin, rituximab, and plasma exchange may cause anaphylactic reactions. DLI may lead to higher incidence of GVHD.[117] Therefore, careful evaluation of the risks and benefits before initiation of therapy is crucial, requiring multidisciplinary collaboration between transfusion medicine, hematology, and HSCT providers.

Conclusions

Donor-recipient RBC antigen mismatch is commonly encountered and results in clinically significant immunohematologic events, complicating the posttransplantation course. ABO phenotype is part of the donor-recipient pretransplantation workup to plan transfusion needs, clinical laboratory monitoring, and possible graft manipulations. Donor-recipient extended phenotyping for non-ABO antigens, such as Rh, K, and Jk, should be considered in high-risk groups, especially those receiving chronic transfusion therapy. HSCT across the barrier of RBC antigen mismatch may lead to acute hemolysis, PLS, and PRCA. Early detection of hemolysis, supportive care with antigen-negative or matched RBC transfusion, and appropriate interventions such as immunosuppression are necessary to improve clinical outcomes. Active collaboration between transfusion and transplantation services might help with early identification of clinically significant antibodies and prompt necessary treatment interventions.

Acknowledgments

The authors extend their gratitude to the patients reported in this review and thank Charles Bolan for his contribution and review of this manuscript.

Authorship

Contribution: Y.M. and Y.P. provided conception and design and wrote, reviewed, and/or revised the manuscript; S.S.K. reviewed and revised the manuscript; and S.A. and R.C. wrote and revised the manuscript and provided expert guidance.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References

1. International Society of Blood Transfusion. Red cell immunogenetics and blood group terminology. Available at: https://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology. Accessed 1 October 2021
2. Hows J, Beddow K, Gordon-Smith E, et al. Donor-derived red blood cell antibodies and immune hemolysis after allogeneic bone marrow transplantation. *Blood.* 1986;67(1):177-181.
3. Rowley SD, Donato ML, Bhattacharyya P. Red blood cell-incompatible allogeneic hematopoietic progenitor cell transplantation. *Bone Marrow Transplant.* 2011;46(9):1167-1185.
4. Griffith LM, McCoy JP Jr, Bolan CD, et al. Persistence of recipient plasma cells and anti-donor isohaemagglutinins in patients with delayed donor erythropoiesis after major ABO incompatible non-myeloablative haematopoietic cell transplantation. *Br J Haematol.* 2005;128(5):668-675.
5. Stussi G, Muntwyler J, Passweg JR, et al. Consequences of ABO incompatibility in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2002;30(2):87-93.
6. Allen ES, Nelson RC, Flegel WA. How we evaluate red blood cell compatibility and transfusion support for patients with sickle cell disease undergoing hematopoietic progenitor cell transplantation. *Transfusion.* 2018;58(11):2483-2489.
7. Ting A, Pun A, Dodds AJ, Atkinson K, Biggs JC. Red cell alloantibodies produced after bone marrow transplantation. *Transfusion.* 1987;27(2):145-147.
8. Young PP, Goodnough LT, Westervelt P, Diersio JF. Immune hemolysis involving non-ABO/RhD alloantibodies following hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2001;27(12):1305-1310.
9. Abou-Elella AA, Camarillo TA, Allen MB, et al. Low incidence of red cell and HLA antibody formation by bone marrow transplant patients. *Transfusion.* 1995;35(11):931-935.
10. de La Rubia J, Arriaga F, Andreu R, et al. Development of non-ABO RBC alloantibodies in patients undergoing allogeneic HPC transplantation. Is ABO incompatibility a predisposing factor? *Transfusion.* 2001;41(1):106-110.
11. Flegel WA. Pathogenesis and mechanisms of antibody-mediated hemolysis. *Transfusion.* 2015;55(suppl 2):S47-S58.
12. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant.* 2005;11(12):945-956.

13. Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group report. *Biol Blood Marrow Transplant.* 2006;12(4):375-396.

14. Szanto CL, Langenhorst J, de Koning C, et al. Predictors for autoimmune cytopenias after allogeneic hematopoietic cell transplantation in children. *Biol Blood Marrow Transplant.* 2020;26(1):114-122.

15. Stowell SR, Winkler AM, Maier CL, et al. Initiation and regulation of complement during hemolytic transfusion reactions. *Clin Dev Immunol.* 2012; 2012:307093.

16. Rowley SD, Liang PS, Ulz L. Transplantation of ABO-incompatible bone marrow and peripheral blood stem cell components. *Bone Marrow Transplant.* 2000;26(7):749-757.

17. Curley C, Pillai E, Mudie K, 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):291-297.

18. Hirokawa M, Fukuda T, Ohashi K, et al; PRCA Collaborative Study Group. Efficacy and long-term outcome of treatment for pure red cell aplasia after allogeneic stem cell transplantation from major ABO-incompatible donors. *Biol Blood Marrow Transplant.* 2013;19(7):1026-1032.

19. Gmür JP, Burger J, Schaffner A, et al. Pure red cell aplasia of long duration complicating major ABO-incompatible bone marrow transplantation. *Blood.* 1990;75(1):290-295.

20. Worel N, Greinix HT, Schneider B, et al. Regeneration of erythropoiesis after related- and unrelated-donor BMT or peripheral blood HPC transplantation: a major ABO mismatch means problems. *Transfusion.* 2000;40(5):543-550.

21. 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.

22. Kanda J, Ichinohe T, Matsuo K, 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):624-635.

23. Logan AC, Wang Z, Alimoghaddam K, et al; Center for International Blood and Marrow Transplantation. ABO mismatch is associated with increased nonrelapse mortality after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2015;21(4):746-754.

24. Canaani J, Savani BN, Labopin M, 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): 1066-1074.

25. Bolan CD, Leitman SF, Griffith LM, et al. Delayed donor red cell chimerism and pure red cell aplasia following major ABO-incompatible nonmyeloablative hematopoietic stem cell transplantation. *Blood.* 2001;98(6):1687-1694.

26. Worel N, Kalhs P, Keil F, et al. ABO mismatch increases transplant-related morbidity and mortality in patients given nonmyeloablative allogeneic HPC transplantation. *Transfusion.* 2003;43(8):1153-1161.

27. Brierley CK, Littlewood TJ, Peniket AJ, et al. Impact of ABO blood group mismatch in alemtuzumab-based reduced-intensity conditioned haematopoietic SCT. *Bone Marrow Transplant.* 2015;50(7):931-938.

28. Dehn J, Spellman S, Hurley CK, et al. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. *Blood.* 2019;134(12):924-934.

29. Buckner CD, Clift RA, Sanders JE, et al. ABO-incompatible marrow transplants. *Transplantation.* 1978;26(4):233-238.

30. Bensinger WI, Buckner CD, Thomas ED, Clift RA. ABO-incompatible marrow transplants. *Transplantation.* 1982;33(4):427-429.

31. 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):179-187.

32. Quek J, Lee JJ, Lim FL, et al. Donor-type fresh frozen plasma is effective in preventing hemolytic reaction in major ABO incompatible allogeneic stem cell transplant. *Transfusion.* 2019;59(1):335-339.

33. Mehta P, Ramprakash S, Raghuram CP, et al. Pre-transplant donor-type red cell transfusion is a safe and effective strategy to reduce isohemagglutinin titers and prevent donor marrow infusion reactions in major ABO-mismatched transplants. *Ann Hematol.* 2021;100(8):2071-2078.

34. Scholl S, Klink A, Mügge LO, Schilling K, Höffken K, Sayer HG. Safety and impact of donor-type red blood cell transfusion before allogeneic peripheral blood progenitor cell transplantation with major ABO mismatch. *Transfusion.* 2005;45(10):1676-1683.

35. Bolan CD, Childs RW, Procter JL, Barrett AJ, Leitman SF. Massive immune haemolysis after allogeneic peripheral blood stem cell transplantation with minor ABO incompatibility. *Br J Haematol.* 2001;112(3):787-795.

36. Toren A, Dacosta Y, Manny N, Varadi G, Or R, Nagler A. Passenger B-lymphocyte-induced severe hemolytic disease after allogeneic peripheral blood stem cell transplantation. *Blood.* 1996;87(2):843-844.

37. Noborio K, Muroi K, Izumi T, et al. Massive immune hemolysis after non-myeloablative allogeneic peripheral blood stem cell transplantation with minor ABO-incompatibility. *Leuk Lymphoma.* 2003;44(2):357-359.

38. Worel N, Greinix HT, Keil F, et al. Severe immune hemolysis after minor ABO-mismatched allogeneic peripheral blood progenitor cell transplantation occurs more frequently after nonmyeloablative than myeloablative conditioning. *Transfusion.* 2002;42(10):1293-1301.

39. Rosenthal GJ, Weigand GW, Germolec DR, Blank JA, Luster MI. Suppression of B cell function by methotrexate and trimetrexate. Evidence for inhibition of purine biosynthesis as a major mechanism of action. *J Immunol.* 1988;141(2):410-416.

40. Vaezi M, Oulad Dameshghi D, 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):139-147.

41. Ma YR, Wang WJ, Cheng YF, et al. Impact of ABO incompatibility on outcomes after haploidentical hematopoietic stem cell transplantation for severe aplastic anemia. *Bone Marrow Transplant.* 2020;55(6):1068-1075.

42. Grube M, Wolff D, Ahrens N, Herzberg PY, Herr W, Holler E. ABO blood group antigen mismatch has an impact on outcome after allogeneic peripheral blood stem cell transplantation. *Clin Transplant.* 2016;30(11):1457-1465.

43. Ludajic K, Balavarca Y, Bickeböller H, et al. Minor ABO-mismatches are risk factors for acute graft-versus-host disease in hematopoietic stem cell transplant patients. *Biol Blood Marrow Transplant.* 2009;15(11):1400-1406.

44. Booth GS, Gehrie EA, Bolan CD, Savani BN. Clinical guide to ABO-incompatible allogeneic stem cell transplantation. *Biol Blood Marrow Transplant.* 2013;19(8):1152-1158.

45. Heddle NM, Soutar RL, O'Hoski PL, et al. A prospective study to determine the frequency and clinical significance of alloimmunization post-transfusion. *Br J Haematol.* 1995;91(4):1000-1005.

46. Hoeltge GA, Domen RE, Rybicki LA, Schaffer PA. Multiple red cell transfusions and alloimmunization. Experience with 6996 antibodies detected in a total of 159,262 patients from 1985 to 1993. *Arch Pathol Lab Med.* 1995;119(1):42-45.

47. Seyfried H, Walewska I. Analysis of immune response to red blood cell antigens in multitransfused patients with different diseases. *Mater Med Pol.* 1990;22(1):21-25.

48. Higgins JM, Sloan SR. Stochastic modeling of human RBC alloimmunization: evidence for a distinct population of immunologic responders. *Blood.* 2008;112(6):2546-2553.

49. Klumpp TR. Immunohematologic complications of bone marrow transplantation. *Bone Marrow Transplant.* 1991;8(3):159-170.

50. López A, de la Rubia J, Arriaga F, et al. Severe hemolytic anemia due to multiple red cell alloantibodies after an ABO-incompatible allogeneic bone marrow transplant. *Transfusion.* 1998;38(3):247-251.

51. Kay B, Poisson JL, Tuma CW, Shulman IA. Anti-Jk^{a} that are detected by solid-phase red blood cell adherence but missed by gel testing can cause hemolytic transfusion reactions. *Transfusion.* 2016;56(12):2973-2979.

52. Leo A, Mytilineos J, Voso MT, et al. Passenger lymphocyte syndrome with severe hemolytic anemia due to an anti-Jk(a) after allogeneic PBPC transplantation. *Transfusion.* 2000;40(6):632-636.

53. Petz LD. Immune hemolysis associated with transplantation. *Semin Hematol.* 2005;42(3):145-155.

54. Franchini M, Gandini G, Aprili G. Non-ABO red blood cell alloantibodies following allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2004;33(12):1169-1172.

55. Campbell-Lee SA, Gvozdjan K, Choi KM, et al. Red blood cell alloimmunization in sickle cell disease: assessment of transfusion protocols during two time periods. *Transfusion.* 2018;58(7):1588-1596.

56. Hindawi S, Badawi M, Elfayoumi R, et al. The value of transfusion of phenotyped blood units for thalassemia and sickle cell anemia patients at an academic center. *Transfusion.* 2020;60(suppl 1):S15-S21.

57. Chou ST, Jackson T, Vege S, Smith-Whitley K, Friedman DF, Westhoff CM. High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. *Blood.* 2013;122(6):1062-1071.

58. Allen ES, Srivastava K, Hsieh MM, et al. Immunohaematological complications in patients with sickle cell disease after haemopoietic progenitor cell transplantation: a prospective, single-centre, observational study. *Lancet Haematol.* 2017;4(11):e553-e561.

59. Nickel RS, Flegel WA, Adams SD, et al. The impact of pre-existing HLA and red blood cell antibodies on transfusion support and engraftment in sickle cell disease after nonmyeloablative hematopoietic stem cell transplantation from HLA-matched sibling donors: a prospective, single-center, observational study. *EClinicalMedicine.* 2020;24:100432.

60. Thompson AA, Cunningham MJ, Singer ST, et al; Thalassemia Clinical Research Network Investigators. Red cell alloimmunization in a diverse population of transfused patients with thalassaemia. *Br J Haematol.* 2011;153(1):121-128.

61. Datta SS, Mukherjee S, Talukder B, Bhattacharya P, Mukherjee K. Frequency of red cell alloimmunization and autoimmunization in thalassemia patients: a report from eastern India. *Adv Hematol.* 2015;2015:610931.

62. Waldis SJ, Uter S, Kavitsky D, et al. Rh alloimmunization in chronically transfused patients with thalassemia receiving RhD, C, E, and K matched transfusions. *Blood Adv.* 2021;5(3):737-744.

63. El-Beshlawy A, Salama AA, El-Masry MR, El Husseiny NM, Abdelhameed AM. A study of red blood cell alloimmunization and autoimmunization among 200 multitransfused Egyptian β thalassemia patients. *Sci Rep.* 2020;10(1):21079.

64. Hönig M, Flegel WA, Schwarz K, et al. Successful hematopoietic stem-cell transplantation in a patient with chronic granulomatous disease and McLeod phenotype sensitized to Kx and K antigens. *Bone Marrow Transplant.* 2010;45(1):209-211.

65. Kordes U, Binder TM, Eiermann TH, et al. Successful donor-lymphocyte infusion for extreme immune-hemolysis following unrelated BMT in a patient with X-linked chronic granulomatous disease and McLeod phenotype. *Bone Marrow Transplant.* 2008;42(3):219-220.

66. Kim MY, Chaudhary P, Shulman IA, Pullarkat V. Major non-ABO incompatibility caused by anti-Jk(a) in a patient before allogeneic hematopoietic stem cell transplantation. *Immunohematology.* 2013;29(1):11-14.

67. Passweg JR, Baldomero H, Bader P, et al; European Society for Blood and Marrow Transplantation (EBMT). Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants. *Bone Marrow Transplant.* 2015;50(4):476-482.

68. Lasalle-Williams M, Nuss R, Le T, et al. Extended red blood cell antigen matching for transfusions in sickle cell disease: a review of a 14-year experience from a single center (CME). *Transfusion.* 2011;51(8):1732-1739.

69. Casas J, Friedman DF, Jackson T, Vege S, Westhoff CM, Chou ST. Changing practice: red blood cell typing by molecular methods for patients with sickle cell disease. *Transfusion.* 2015;55(6 Pt 2):1388-1393.

70. Fasano RM, Chou ST. Red blood cell antigen genotyping for sickle cell disease, thalassemia, and other transfusion complications. *Transfus Med Rev.* 2016;30(4):197-201.

71. Liu F, Li G, Mao X, Hu L. ABO chimerism determined by real-time polymerase chain reaction analysis after ABO-incompatible haematopoietic stem cell transplantation. *Blood Transfus.* 2013;11(1):43-52.

72. Barcellini W, Fattizzo B, Zaninoni A. Management of refractory autoimmune hemolytic anemia after allogeneic hematopoietic stem cell transplantation: current perspectives. *J Blood Med.* 2019;10:265-278.

73. Miller PDE, Snowden JA, De Latour RP, et al. Autoimmune cytopenias (AIC) following allogeneic haematopoietic stem cell transplant for acquired aplastic anaemia: a joint study of the Autoimmune Diseases and Severe Aplastic Anaemia Working Parties (ADWP/SAAWP) of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant.* 2020;55(2):441-451.

74. Horn B, Viele M, Mentzer W, Mogck N, DeSantes K, Cowan M. Autoimmune hemolytic anemia in patients with SCID after T cell-depleted BM and PBSC transplantation. *Bone Marrow Transplant.* 1999;24(9):1009-1013.

75. Ahmed I, Teruya J, Murray-Krezan C, Krance R. The incidence of autoimmune hemolytic anemia in pediatric hematopoietic stem cell recipients post-first and post-second hematopoietic stem cell transplant. *Pediatr Transplant.* 2015;19(4):391-398.

76. Kruizinga MD, van Tol MJD, Bekker V, et al. Risk factors, treatment, and immune dysregulation in autoimmune cytopenia after allogeneic hematopoietic stem cell transplantation in pediatric patients. *Biol Blood Marrow Transplant.* 2018;24(4):772-778.

77. O'Brien TA, Eastlund T, Peters C, et al. Autoimmune haemolytic anaemia complicating haematopoietic cell transplantation in paediatric patients: high incidence and significant mortality in unrelated donor transplants for non-malignant diseases. *Br J Haematol.* 2004;127(1):67-75.

78. Faraci M, Zecca M, Pillon M, et al; Italian Association of Paediatric Haematology and Oncology. Autoimmune hematological diseases after allogeneic hematopoietic stem cell transplantation in children: an Italian multicenter experience. *Biol Blood Marrow Transplant.* 2014;20(2):272-278.

79. Garratty G. Autoantibodies induced by blood transfusion. *Transfusion.* 2004;44(1):5-9.

80. González-Vicent M, Sanz J, Fuster JL, et al. Autoimmune hemolytic anemia (AIHA) following allogeneic hematopoietic stem cell transplantation (HSCT): a retrospective analysis and a proposal of treatment on behalf of the Grupo Español De Trasplante de Medula Osea en Niños (GETMON) and the Grupo Español de Trasplante Hematopoyetico (GETH) [published online ahead of print on 3 March 2018]. *Transfus Med Rev.* doi: 10.1016/j.tmrv.2018.02.005.

81. Adams BR, Miller AN, Costa LJ. Self-limited hemolysis due to anti-D passenger lymphocyte syndrome in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2010;45(4):772-773.

82. Aung FM, Lichtiger B, Bassett R, et al. Incidence and natural history of pure red cell aplasia in major ABO-mismatched haematopoietic cell transplantation. *Br J Haematol.* 2013;160(6):798-805.

83. Marco-Ayala J, Gómez-Seguí I, Sanz G, Solves P. Pure red cell aplasia after major or bidirectional ABO incompatible hematopoietic stem cell transplantation: to treat or not to treat, that is the question. *Bone Marrow Transplant.* 2021;56(4):769-778.

84. Stussi G, Halter J, Bucheli E, et al. Prevention of pure red cell aplasia after major or bidirectional ABO blood group incompatible hematopoietic stem cell transplantation by pretransplant reduction of host anti-donor isoagglutinins. *Haematologica.* 2009;94(2):239-248.

85. Holbro A, Passweg JR. Management of hemolytic anemia following allogeneic stem cell transplantation. *Hematology Am Soc Hematol Educ Program.* 2015;2015:378-384.

86. Hill QA, Stamps R, Massey E, Grainger JD, Provan D, Hill A; British Society for Haematology Guidelines. Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anaemia. *Br J Haematol.* 2017;177(2):208-220.

87. Silva VA, Seder RH, Weintraub LR. Synchronization of plasma exchange and cyclophosphamide in severe and refractory autoimmune hemolytic anemia. *J Clin Apher.* 1994;9(2):120-123.

88. Santamaría A, Sureda A, Martino R, Domingo-Albós A, Muñiz-Díaz E, Brunet S. Successful treatment of pure red cell aplasia after major ABO-incompatible T cell-depleted bone marrow transplantation with erythropoietin. *Bone Marrow Transplant.* 1997;20(12):1105-1107.

89. Busca A, Dellacasa C, Giaccone L, et al. Eltrombopag for the treatment of refractory pure RBC aplasia after major ABO incompatible hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2018;24(8):1765-1770.

90. Longval T, Galimard JE, Leprêtre AC, et al. Treatment for pure red cell aplasia after major ABO-incompatible allogeneic stem cell transplantation: a multicentre study. *Br J Haematol.* 2021;193(4):814-826.

91. Helbig G, Stella-Holowiecka B, Krawczyk-Kulis M, et al. Successful treatment of pure red cell aplasia with repeated, low doses of rituximab in two patients after ABO-incompatible allogeneic haematopoietic stem cell transplantation for acute myeloid leukaemia. *Haematologica.* 2005;90(suppl):ECR33.

92. Audet M, Panaro F, Piardi T, et al. Passenger lymphocyte syndrome and liver transplantation. *Clin Dev Immunol.* 2008;2008:715769.

93. Hess J, Su L, Nizzi F, et al. Successful treatment of severe refractory autoimmune hemolytic anemia after hematopoietic stem cell transplant with abatacept. *Transfusion.* 2018;58(9):2122-2127.

94. Taniguchi S, Yamasaki K, Shibuya T, Asayama R, Harada M, Niho Y. Recombinant human erythropoietin for long-term persistent anemia after major ABO-incompatible bone marrow transplantation. *Bone Marrow Transplant.* 1993;12(4):423.

95. Liu X, Cheng L, He Y, et al. Eltrombopag restores erythropoiesis in refractory adult acquired pure red cell aplasia. *Int J Hematol.* 2021;114(1):124-128.

96. Selleri C, Raiola A, De Rosa G, et al. CD34+-enriched donor lymphocyte infusions in a case of pure red cell aplasia and late graft failure after major ABO-incompatible bone marrow transplantation. *Bone Marrow Transplant.* 1998;22(6):605-607.

97. Fang B, Song Y, Li N, Li J, Han Q, Zhao RC. Mesenchymal stem cells for the treatment of refractory pure red cell aplasia after major ABO-incompatible hematopoietic stem cell transplantation. *Ann Hematol.* 2009;88(3):261-266.

98. Sergeevicheva V, Kruchkova I, Chernykh E, et al. Rapid recovery from chronic PRCA by MSC infusion in patient after major ABO-mismatched alloSCT. *Case Rep Med.* 2012;2012:862721.

99. Sackett K, Cohn CS, Fahey-Ahrndt K, Smith AR, Johnson AD. Successful treatment of pure red cell aplasia because of ABO major mismatched stem cell transplant. *J Clin Apher.* 2018;33(1):108-112.

100. Poon LM, Koh LP. Successful treatment of isohemagglutinin-mediated pure red cell aplasia after ABO-mismatched allogeneic hematopoietic cell transplant using bortezomib. *Bone Marrow Transplant.* 2012;47(6):870-871.

101. Tolbert VP, Goldsby R, Huang J, et al. Daratumumab is effective in the treatment of refractory post-transplant autoimmune hemolytic anemia: a pediatric case report [abstract]. *Blood.* 2016;128(22):XXX. Abstract 128.

102. Chapuy CI, Kaufman RM, Alyea EP, Connors JM. Daratumumab for delayed red-cell engraftment after allogeneic transplantation. *N Engl J Med.* 2018;379(19):1846-1850.

103. Schuetz C, Hoenig M, Moshous D, et al. Daratumumab in life-threatening autoimmune hemolytic anemia following hematopoietic stem cell transplantation. *Blood Adv.* 2018;2(19):2550-2553.

104. Blennerhassett R, Sudini L, Gottlieb D, Bhattacharyya A. Post-allogeneic transplant Evans syndrome successfully treated with daratumumab. *Br J Haematol.* 2019;187(2):e48-e51.

105. Migdady Y, Ediriwickrema A, Jackson RP, et al. Successful treatment of thrombocytopenia with daratumumab after allogeneic transplant: a case report and literature review. *Blood Adv.* 2020;4(5):815-818.

106. Chapuy CI, Nicholson RT, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. *Transfusion.* 2015;55(6 Pt 2):1545-1554.

107. van de Donk NWCJ. Reprint of "Immunomodulatory effects of CD38-targeting antibodies". *Immunol Lett.* 2019;205:71-77.

108. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood.* 2016;128(3):384-394.

109. Mócsai A, Ruland J, Tybulewicz VL. The SYK tyrosine kinase: a crucial player in diverse biological functions. *Nat Rev Immunol.* 2010;10(6):387-402.

110. Kaur M, Singh M, Silakari O. Inhibitors of switch kinase 'spleen tyrosine kinase' in inflammation and immune-mediated disorders: a review. *Eur J Med Chem.* 2013;67:434-446.

111. Poe JC, Jia W, Di Paolo JA, et al. SYK inhibitor entospletinib prevents ocular and skin GVHD in mice. *JCI Insight.* 2018;3(19):e122430.

112. Vo P, Purev E, West KA, et al. A pilot trial of complement inhibition using eculizumab to overcome platelet transfusion refractoriness in human leukocyte antigen allo-immunized patients. *Br J Haematol.* 2020;189(3):551-558.

113. Gauchy AC, Hentzien M, Wynckel A, et al. Efficacy of eculizumab in refractory life-threatening warm autoimmune hemolytic anemia associated with chronic myelomonocytic leukemia. *Clin Case Rep.* 2020;8(12):2641-2644.

114. Röth A, Bommer M, Hüttmann A, et al. Eculizumab in cold agglutinin disease (DECADE): an open-label, prospective, bicentric, nonrandomized phase 2 trial. *Blood Adv.* 2018;2(19):2543-2549.

115. Röth A, Barcellini W, D'Sa S, et al. Sutimlimab in cold agglutinin disease. *N Engl J Med.* 2021;384(14):1323-1334.

116. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med.* 2021;384(11):1028-1037.

117. Frey NV, Porter DL. Graft-versus-host disease after donor leukocyte infusions: presentation and management. *Best Pract Res Clin Haematol.* 2008;21(2):205-222.

118. Kollman C, Howe CWS, Anasetti C, et al. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. *Blood.* 2001;98(7):2043-2051.

119. Seebach JD, Stussi G, Passweg JR, et al; GVHD Working Committee of Center for International Blood and Marrow Transplant Research. ABO blood group barrier in allogeneic bone marrow transplantation revisited. *Biol Blood Marrow Transplant.* 2005;11(12):1006-1013.

120. Helming AM, Brand A, Wolterbeek R, van Tol MJD, Egeler RM, Ball LM. ABO incompatible stem cell transplantation in children does not influence outcome. *Pediatr Blood Cancer.* 2007;49(3):313-317.

121. Michallet M, Le QH, Mohty M, et al. Predictive factors for outcomes after reduced intensity conditioning hematopoietic stem cell transplantation for hematological malignancies: a 10-year retrospective analysis from the Société Française de Greffe de Moelle et de Thérapie Cellulaire. *Exp Hematol.* 2008;36(5):535-544.

122. Kimura F, Sato K, Kobayashi S, et al; Japan Marrow Donor Program. Impact of AB0-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):1686-1693.

123. Canaani J, Savani BN, Labopin M, et al. ABO incompatibility in mismatched unrelated donor allogeneic hematopoietic cell transplantation for acute myeloid leukemia: a report from the Acute Leukemia Working Party of the EBMT. *Am J Hematol.* 2017;92(8):789-796.

124. Ataca Atilla P, Akkus E, Atilla E, et al. Effects of ABO incompatibility in allogeneic hematopoietic stem cell transplantation. *Transfus Clin Biol.* 2020; 27(3):115-121.

125. Heim MU, Schleuning M, Eckstein R, et al. Rh antibodies against the pretransplant red cells following Rh-incompatible bone marrow transplantation. *Transfusion.* 1988;28(3):272-275.

126. Tasaki T, Sasaki S, Gotoh K, Itoh C, Itoh S, Kuriya S. Multiple red blood cell antibodies produced by donor B lymphocytes after ABO-matched allogeneic bone marrow transplantation. *Transfus Sci.* 1999;20(2):121-127.

127. Izumi N, Fuse I, Furukawa T, et al. Long-term production of pre-existing alloantibodies to E and c after allogenic BMT in a patient with aplastic anemia resulting in delayed hemolytic anemia. *Transfusion.* 2003;43(2):241-245.

128. Zupańska B, Zaucha JM, Michalewska B, Malinowska A, Brojer E, Hellmann A. Multiple red cell alloantibodies, including anti-Dib, after allogeneic ABO-matched peripheral blood progenitor cell transplantation. *Transfusion.* 2005;45(1):16-20.

129. Myser T, Steedman M, Hunt K, Strohm P, Williams M, Kennedy M. A bone marrow transplant with an acquired anti-Le(a): a case study. *Hum Immunol.* 1986;17(2):102-106.