EXPERT VIEW/REVIEW PAPER

ABO Type of Granulocytes Transfused during ABO Mismatch Hematopoietic Stem Cell Transplants

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Abstract

With increasing resistance to antimicrobial agents, the use of granulocyte transfusions (GTX) are showing promising results and may lead to early clearance of infections in neutropenic patients. In this review article, we describe the potential role of GTX in hematopoietic stem cell transplantation (HSCT) in the setting of ABO-incompatible transplants. Apart from the antimicrobial effect of GTX, there is growing interest in assessing the immunomodulatory effect and potential antitumor role of GTX.

A granulocyte product containing red blood cells (RBCs), white blood cells (WBCs), and platelets with a significant amount of plasma can resemble "*whole blood*." The ABO type of the granulocyte during phase II (from infusion of stem cells till engraftment) neutropenic period in ABO-incompatible HSCT is the most challenging. Most commonly, group "O" type of granulocytes are used in this phase. One of the main challenges is the presence of both anti-A and anti-B types of isohemagglutinins in group O granulocytes. Alternatively, group AB granulocytes—free of isohemagglutinins but expressing both A and B antigens—may offer a safer option under certain circumstances.

With recent renewed interest in using granulocyte transfusions in managing the neutropenic phase of HSCT, one should keep in mind the ABO type of granulocyte being used during phase II and its possible effect on the hemolytic complications. In this article, we explore the practical considerations, risk of hemolysis, and transfusion strategies for ABO-incompatible GTX in the HSCT setting and highlight the lack of data on the same.

Keywords: ABO blood type, Granulocyte transfusion, Stem cell transplant.

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Introduction

Bacterial and fungal infections are one of the major causes of mortality and morbidity in recipients of hematopoietic stem cell transplants (HSCT) with treatment-related neutropenia. Multidrug-resistant organisms (MDROs) are increasingly responsible for infections in HSCT recipients. One of the institutional studies from India showed the prevalence of MDRO (carbapenem-resistant Enterobacteriaceae) as high as 60% in pediatric oncology patients, causing significant mortality.[1] With increasing resistance to antimicrobial agents, the use of granulocyte transfusions (GTX) is being increasingly utilized for the early clearance of infections in these neutropenic patients.[2,3] Apart from the antimicrobial effect of GTX, there is growing interest in assessing the immunomodulatory effect and potential antitumor effects.[4,5]

The standard volume of granulocyte apheresis products ranges around 300 mL with a hematocrit of 15–40% depending on the blood volume processed, use of a sedimenting agent (e.g., Hydroxyethyl starch—HES), and type of cell separator used.[6,7] In the presence of red blood cells (RBCs), white blood cells (WBCs), and platelets with a significant amount of plasma, a granulocyte product usually acts similarly to "*whole blood*." As per the Association for the Advancement of Blood and Biotherapies (AABB) recommendations, granulocyte products should be of the same ABO type and cross-match compatible with the patient.[8] Provision of a similar ABO type of granulocyte product becomes a challenge when supporting patients undergoing ABO-mismatched HSCT. We aim to present a short report on the possible influence of using ABO-mismatch granulocyte transfusion in HSCT settings and measures that can be taken to reduce the risk.

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Basics of Granulocyte Transfusions

Mobilization is achieved using single- or double-dose corticosteroids (Dexamethasone 8–12 mg or prednisolone) with or without granulocyte colony-stimulating factor (G-CSF, 5–10 µg/kg subcutaneously). A commonly used fixed-dose regimen includes dexamethasone 8 mg and G-CSF 450 µg given 12 hours prior to apheresis.[9–11] A study conducted on 20 donors showed that G-CSF alone yields more granulocytes than dexamethasone alone ($41.1 \pm 20.4 \times 10^9$ vs $21.0 \pm 10.0 \times 10^9$; $p < 0.001$), but the combination of G-CSF and dexamethasone results in the highest yield ($67.1 \pm 22.0 \times 10^9$; $p < 0.002$).[12] In a 5-week crossover study done on five participants who received various single-dose regimens of G-CSF and dexamethasone, peak absolute neutrophil count (ANC)

was observed at 12 hours across all regimens. The combination of subcutaneous G-CSF 450 µg and oral Dexamethasone 8 mg increased ANC from 2800/µL to 37900/µL and was well tolerated, supporting its use as an optimal single-dose mobilization strategy.[13] Once initiated, granulocyte transfusion therapy should be administered at least daily and continued until clinical resolution of infection, defervescence, recovery of the ANC to ≥0.5 × 10^9/L, or as determined by the treating physician as recommended by AABB.[6]

The AABB[6] and Directorate General of Health Services (DGHS), India[14] recommend transfusing granulocyte doses of ≥1 × 10^9 cells/kg/day until infection resolves or neutrophil recovery occurs. The European Directorate for the Quality of Medicines and HealthCare (EDQM)[15] advises that apheresis units should contain 1.5 to 3 × 10^8 granulocytes/kg recipient body weight (or 0.9 to 1.8 × 10^{10} per full apheresis unit), while pooled buffy coat units (from up to 12 donations) should yield >5 × 10^9 granulocytes; children are dosed at 0.3 × 10^9/kg in pooled buffy coat. The UK National Health Service (NHS)[16] follows a similar approach for pooled buffy coat granulocytes: 1–2 units daily for adults, and 10–20 mL/kg for children. Components must be irradiated, not agitated, and ideally transfused within 24 hours.

Content of Granulocytes

Granulocyte transfusion dosing and quality specifications vary across major guidelines. Apheresis granulocyte concentrates, per AABB, typically contain >1 × 10^{10} granulocytes in 200–300 mL volume, along with 20–50 mL of red cells and a variable number of platelets. DGHS aligns with this, stating that apheresis units contain 200–400 mL with >1 × 10^{10} granulocytes, 2 to 10 × 10^{11} platelets, 5–50 mL of red cells, and uniquely mentions 0.1–0.7 × 10^9 other leukocytes. EDQM also recommends the dose of granulocytes, 1.5 to 3 × 10^8/kg recipient body weight per apheresis unit, and notes significant red cell and platelet content.

For pooled buffy coat-derived granulocytes, EDQM and NHS guidelines converge on a target granulocyte yield of >5 × 10^9 per unit, usually prepared by pooling 10–12 buffy coats suspended in plasma or platelet additive solution. The NHS specifies a final volume of 175–250 mL, and recommends dosing adults with 1–2 packs daily, while children under 50 kg receive 10–20 mL/kg. DGHS mentions a lower granulocyte content (0.5 to 1 × 10^9) in pooled units, with a plasma volume of 200–250 mL.[6,14–16]

Preferred and Potential Donors for Granulocytes in Nontransplant and Transplant Recipients and the Utility of ABO/RH Matches

ABO mismatch between donor and recipient during HSCT is known to influence the outcome of the transplants due to pre-existing antibodies or antigens present in the donor graft (RBC content), which are not compatible.[17] The risk of immediate hemolysis (at the time of HSCT product infusion) is higher in major mismatch HSCT as compared to delayed hemolysis in minor mismatch cases.[18] An ABO-mismatched HSCT also possesses the risk of delayed engraftment, pure red cell aplasia, etc.[17] There is no data on the influence of transfusion of mismatched or "O" blood type granulocytes in ABO-incompatible HSCT settings.

Table 1: Various ABO types of granulocytes to be used in ABO-mismatched HSCT

Mismatch type	*Recipient ABO*	*Donor ABO*	*Potential clinical consequence (granulocyte transfusion)*	*Etiology (granulocyte-relevant)*	*Potential interventions (granulocyte-specific)*
Major	O	A, B, AB	Acute hemolysis, delayed engraftment	Recipient anti-A/B lyse donor RBCs in granulocyte product	Use group O granulocytes (preferably low-titer) or plasma reduction of granulocyte product; reduction of isoagglutinin titers of recipient by plasma exchange using AB plasma; AB granulocytes with RBC reduction may be considered
Major	A	AB	Same as above	Recipient anti-B lyse donor RBC in product	Use group A granulocytes—with possible plasma reduction of granulocyte product or selecting a low-titer anti-B donor
Major	B	AB	Same as above	Recipient anti-A lyse donor RBC in product	Use group B granulocytes—with possible plasma reduction of granulocyte product or selecting a low-titer anti-A donor
Minor	A	O	Delayed hemolysis (passenger lymphocyte syndrome)	Donor anti-A in product plasma	Prefer low-titer group O donor; plasma reduction of granulocyte product; second choice: group A granulocytes
Minor	B	O	Same as above	Donor anti-B in product plasma	Prefer low-titer group O donor; plasma reduction of granulocyte product; second choice: group B granulocytes
Minor	AB	O, A, B	Same as above	Donor anti-A/anti-B in product plasma	AB granulocytes with RBC reduction may be considered
Bidirectional	A	B	Major + minor hemolysis risk, engraftment delay	Recipient anti-B + donor anti-A	First choice: group O granulocytes (low-titer) or plasma-reduced granulocytes; second choice: AB granulocytes with RBC reduction
Bidirectional	B	A	Same as above	Recipient anti-A + donor anti-B	First choice: group O granulocytes (low-titer) or plasma-reduced granulocytes; second choice: AB granulocytes with RBC reduction

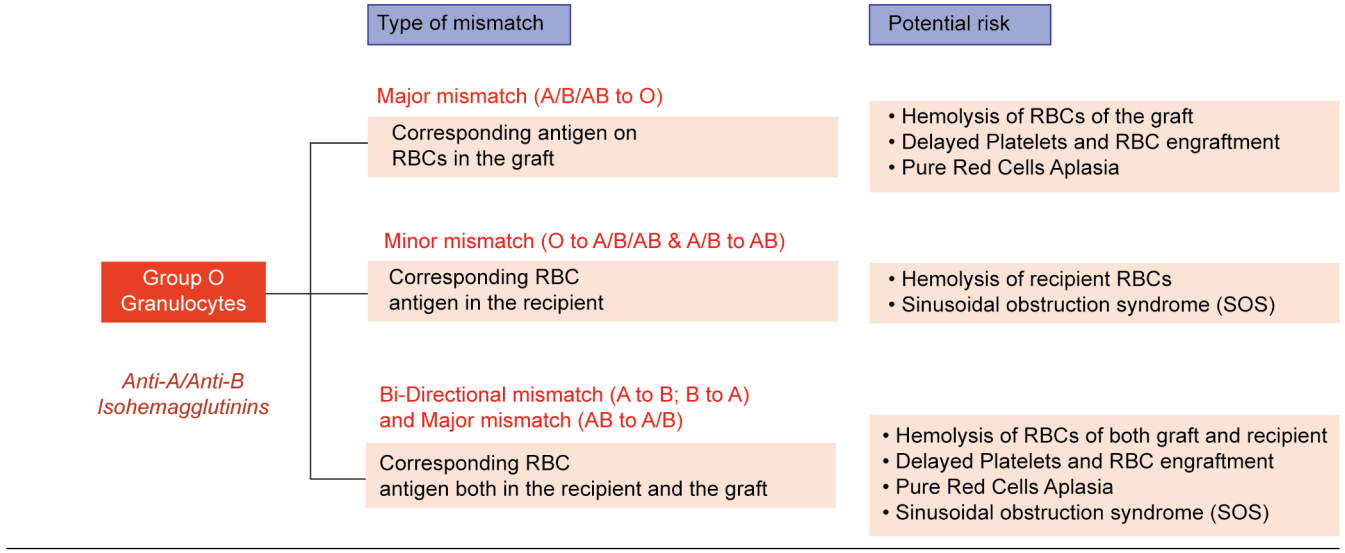

Fig. 1: Impact of group "O" granulocyte transfusions during the phase II of ABO-mismatched HSCT

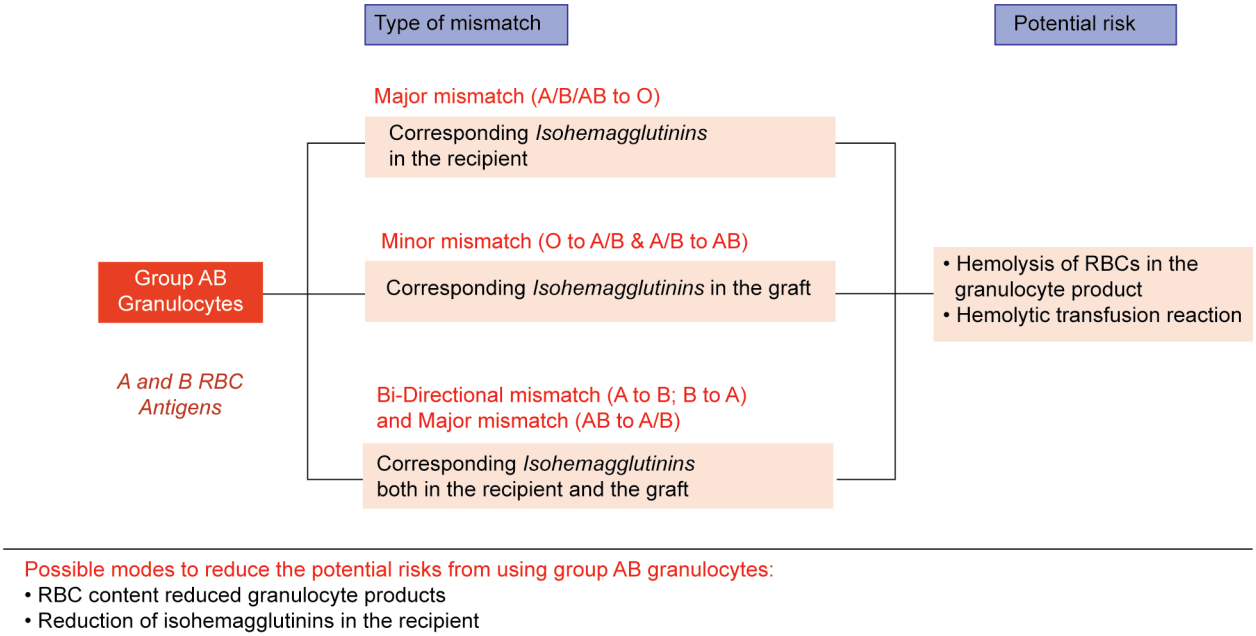

Fig. 2: Impact of group "AB" granulocyte transfusions during the phase II of ABO-mismatched HSCT

Phases of Transplant and Anticipated Challenges

There are three types of ABO-mismatched HSCT: Major (graft with the RBC antigen and recipient with the corresponding antibody); Minor (graft with the antibody and recipient with the corresponding RBC antigen); and Bidirectional (both major and minor). There are three phases of ABO-mismatched HSCT that possess special challenges (with regard to the ABO type) when offering transfusions. Phase I is during the preparative regimen (pretransplant), phase II is following stem cell infusion till engraftment, and phase III is after complete engraftment. While supporting transfusion of granulocytes, the ABO type during phase I should be of the recipient ABO type, whereas during phase III it should be the donor (CD34 cell donor) ABO type (after engraftment).

The ABO type of the granulocyte during phase II of the ABO-incompatible HSCT is the most challenging (Table 1). Most commonly, group "O" type of granulocytes are used in this phase. One of the main challenges is due to the presence of both anti-A and anti-B types of isohemagglutinins in group O granulocytes. These isohemagglutinins may react or cause hemolysis due to the corresponding antigen either in RBCs of the graft (mainly major mismatch), recipient (mainly minor mismatch), or both (bidirectional mismatch) (Fig. 1). This is a major challenge when transfusing high-volume granulocyte products. However, in adults, this may be significant if the donor has high antibody titers or in pediatric recipients, where volume per weight

(kg) may be higher. Selecting a low-titer group "O" granulocyte donor or collecting granulocytes from platforms like MCS9000 may help in collecting more concentrated low-volume products.

Transfusing anti-A and anti-B isohemagglutinins poses a risk of hemolysis of the corresponding antigens in the recipient (in case of minor mismatch between granulocyte product and recipient) and even in the RBC antigen present in the graft (major mismatch; between granulocyte product and graft). These antibodies can also cause delayed engraftment of platelets and red cells, as well as pure red cell aplasia (PRCA) due to the inhibition of the reconstituting marrow, as well as disruption of the bone marrow maturation (medullary precursors) by the persistent exposure of the isohemagglutinins (from the granulocyte products).[17] In cases of a minor mismatch, the exposure of the isohemagglutinins may also cause sinusoidal obstruction syndrome (SOS) due to the presence of the ABO antigens on the sinusoidal endothelial cells.[17,19]

The risk of complications due to isohemagglutinins may be greater if the volume of the plasma is high in the granulocyte product, if the total volume transfused (mL/kg) is more (in pediatric patients), if the titer of isohemagglutinins is higher, and due to repeated transfusions resulting in greater exposure (since granulocyte may be given daily). Selecting donors with low-titer group O blood donors for granulocyte donation or volume reduction of the granulocyte product may reduce the risk.[20]

The use of "AB" blood-type granulocytes in phase II of the ABO-incompatible HSCT can also be an option. The "AB" blood type granulocytes offer the advantage that they do not contain any isohemagglutinins; however, they possess both types of A and B antigens. The only risk with using "AB" blood-type granulocytes is hemolysis of the A and B antigens on the RBCs due to isohemagglutinins present, either in the recipient or the graft (Fig. 2). These can be managed with a reduction in the RBC content in the granulocytes by using sedimenting agents or centrifugation.[21] The titer of isohemagglutinins may also be less in some of the recipients, which can further reduce the risk of hemolysis.

These complications can be monitored by regular clinical assessment with evaluation of direct antiglobulin test, lactate dehydrogenase levels, haptoglobin, reticulocyte counts, and peripheral smear. Although no published data is support our hypothesis, however, the same has also not been excluded in the studies analyzing the effect of ABO incompatibility and the outcome of HSCT. There is a need to establish the safety of the use of either "AB" or "O" blood type (low-titer) of granulocyte transfusion during phase II of ABO-mismatched HSCT. With recent renewed interest in using granulocyte transfusions in managing the neutropenic phase of HSCT, one should keep in mind the ABO type of granulocyte being used during phase II and its possible effect on the hemolytic complications.

Key Idea

Granulocyte transfusions are increasingly being used for managing the neutropenic phase during HSCT.

Use of group "O" or "AB" type granulocytes in phase II of the bidirectional HSCT may possess certain hemolytic risks and complications.

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Author Contributions

SA, KB and RS wrote the manuscript, SD and NR reviewed the manusctript and approved it.

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No AI tool was used to write this manuscript.

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