Review Article

Immunoserologic and hemotherapy considerations in patients undergoing hematopoietic progenitor cell transplantation

Sajjad Hassan[1], Chester Andrzejewski Jr[2]

[1]Department of Transfusion Medicine, NIH Clinical Center, National Institutes of Health, Bethesda, MD, USA; [2]Department of Pathology, Baystate Medical Center, University of Massachusetts, Chan Medical School-Baystate, Springfield, MA, USA

Contributions: (I) Conception and design: S Hassan; (II) Administrative support: C Andrzejewski; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: S Hassan; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Sajjad Hassan, MD. Department of Laboratory Medicine, Yale-New Haven Hospital, New Haven, CT 06510, USA.
Email: sajjad.hassan@yale.edu; drsajjaad@hotmail.com.

Abstract: With increasing evidence of the success of hematopoietic progenitor cell (HPC) transplantation in the cure of many benign and malignant diseases, such interventions have been performed at increasing rates for the past several years. Due to myelosuppression caused by the conditioning and graft-versus-host disease (GVHD) prophylaxis regimens, blood component transfusions are almost inevitably needed. During transplantation, patient's hematopoietic lineages reconstitute to the HPC donor's progenitor cell types. Therefore, specific immunoserologic and hemotherapeutic aspects need to be considered for the selection of blood components during different phases of transplantation for successful outcomes. Those considerations include but are not limited to ABO and human leucocyte antigen (HLA) compatibility of the transfused blood components with either or both the patient and the HPC donor according to the particular phase of transplantation, and the special blood component processing to reduce the risk of transfusion associated graft-versus-host disease (TA-GVHD), cytomegalovirus (CMV) transmission in CMV seronegative patients and immune mediated platelets refractoriness. Complications may still arise, particularly in major, minor, or bidirectional ABO mismatched transplantations and/or due to the HLA mismatch and alloimmunization. Here we discuss the indications, immunoserologic considerations and the special component processing of red blood cells (RBCs), platelets, granulocytes, and plasma transfusions, based upon the current evidence and describe the prevention and management of salient, pertinent complications.

Keywords: Transfusion support; hematopoietic progenitor cell transplantation; hemotherapy

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Introduction

In the therapeutic arsenal of cellular therapies today, transplantation with hematopoietic progenitor cells (HPCs) not only occupies a historically important therapeutic, but a continuing clinically relevant one in the treatment and management of neoplastic and non-neoplastic disorders. Underpinning the support of this treatment option, and critical to successful patient outcomes from it, have been advances in the clinical care of the patient not the least of which have been the judicious and targeted use of ancillary therapeutics including biopharmaceutical agents and blood transfusions. The latter of these modalities has been and continues as a critical lynchpin in patient care. An understanding of the pertinent applications of hemotherapies during the various stages of HPC transplantation remains a key element in helping provide successful clinical outcomes.

HPC transplantation has been increasingly performed as increasing indications and success for various benign and

malignant diseases has been achieved (1). Conditioning regimens used for transplantation, either reduced intensity or myeloablative, result in cytopenia in preparation for the donor's HPCs to engraft. During the cytopenia before the engraftment, patients need red blood cells (RBCs) and platelet transfusions, until the donor's HPCs engraft. During the course of transplantation, the patient's blood type changes to the HPC donor's blood type. Therefore, special guidelines need to be followed while selecting the blood components, with regards to ABO RhD compatibility, human leucocyte antigen (HLA) compatibility and blood component processing.

HLA matching between the HPC donor and the recipient is highly important with regards to engraftment and the risk of post-transplantation acute or chronic graft-versus-host-disease (GVHD) (2-10). ABO matching between the HPC donor and the recipient is not required for a successful transplantation. Hence, transplantations with major, minor or bidirectional ABO incompatibility are commonly performed (11). Major incompatibility is defined as transplantation from a donor having A and/or B antigens to a recipient having the corresponding isohemagglutinins. Minor ABO incompatibility is defined as transplantation from a donor with A and/or B isohemagglutinins to a recipient having the corresponding A and/or B antigens. Bidirectional ABO incompatibility is defined as transplantation from a group A donor to a group B recipient or vice versa. In this case, the HPC donor has both an ABO antigen and an isohemagglutinin corresponding to the recipient's isohemagglutinin and ABO antigen, respectively.

Patients undergoing HPC transplantation remain dependent upon transfusion of RBCs and platelets until engraftment. Platelet engraftment is defined as the first day out of the 7 consecutive days of platelet count >20,000/mm^3 without any platelet transfusion. Neutrophil engraftment is defined as the first day out of the 3 consecutive days of absolute neutrophil count of >500/mm^3. Erythroid engraftment is difficult to define and RBC independence may be defined as the first day out of the 30 consecutive days of no RBC transfusion or appearance of 1% reticulocytes in the peripheral blood of the patient (11-13). Patients generally do not need granulocyte transfusions, since the neutropenia is usually treated with granulocyte-colony stimulating factor (G-CSF) infusion post-transplantation, unless indicated in some unusual circumstances.

A key to successful management of HPC transplantation patients is the essential communication amongst transfusion services and the clinical transplantation team and also importantly between the involved institutions (14). In cases of referral of patients from another hospital to the transplantation facility, robust communication is required by the transfusion services to obtain a detailed transfusion history of patients from the referral hospital. In this review we will examine some of the facets of and issues with hemotherapy and associated immunoserologic diagnostics pertinent to HPC transplantation and highlight some of the continuing challenges in supporting the delivery of this life-saving cellular therapeutic intervention. Due to space limitations, not all aspects can be addressed in detail and the reader will be referred to other resources for a more in-depth discussion of these areas.

Phases of transplantation

Whether HPC are derived from autologous or allogeneic sources, pharmacological conditioning regimens used in patient preparation for HPC engraftment are either reduced intensity or myeloablative protocols and typically result in trilineage cytopenia in the recipient during the phases of transplantation. From the transfusion medicine and cellular therapy perspectives, the process of HPC transplantation can be viewed as occurring in three phases, as follows:

(I) Pre-transplantation phase;
(II) Peri-transplantation phase;
(III) Post-transplantation phase.

Pre-transplantation phase

Pre-transplantation phase may be defined as the time during which the patient should be transfused with original, native blood ABO RhD type and it typically ends with the beginning of administration of the conditioning regimen (*Figure 1*) (15). However, in cases with ABO RhD incompatibility, blood components should be transfused considering both the HPC donor's ABO RhD type and the patient's ABO RhD type as early as possible, since RBCs remain in the blood circulation for days to weeks (16). Similarly, in many institutions a patient is transfused with irradiated, cytomegalovirus (CMV)-seronegative RBCs and platelets (if CMV seronegative) and leukoreduced blood components (to reduce febrile non-hemolytic reactions and HLA alloimmunization) as soon as the patient is identified as a candidate for HPC transplantation (15,16). Other institutions and physicians provide leukoreduced cellular components for reducing CMV transmission risk as well as for the other indications.

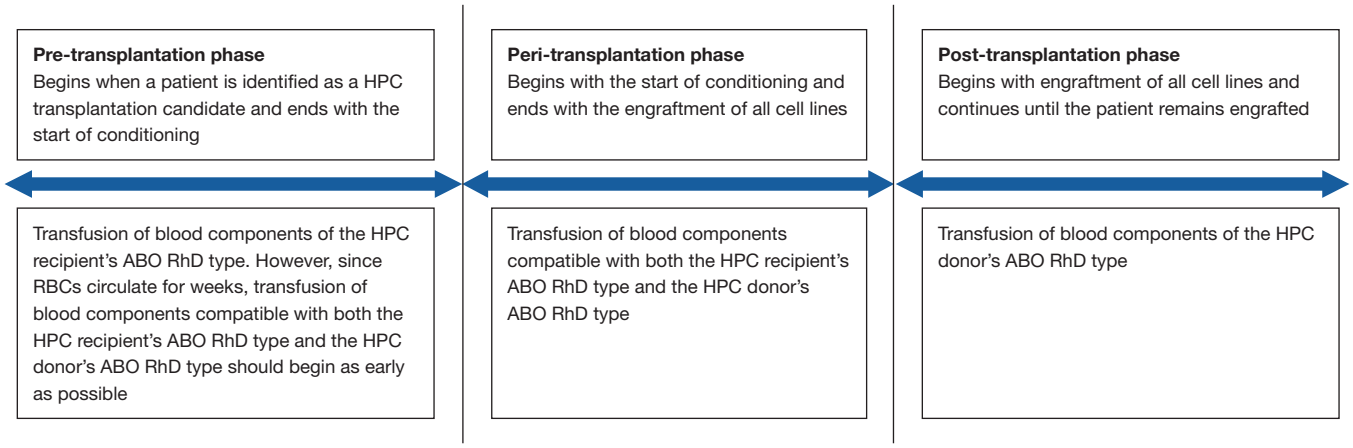

Figure 1 Phases of HPC transplantation. See text for details (15). HPC, hematopoietic progenitor cell.

Patients with benign hematologic disorders, such as sickle cell disease are not immunocompromised until the start of conditioning. Such patients are more prone to have HLA alloimmunization due to transfusions. Numerous studies have demonstrated that HLA alloimmunization is associated with a risk of graft failure (17-20). Hence, a restrictive transfusion strategy is followed in order to minimize the donor exposure and the risk of HLA alloimmunization (11). Although, patients with malignant hematologic diseases are immunocompromised due to the underlying malignancy or chemotherapy, they may also develop HLA alloimmunization and hence, should also be transfused RBCs and platelets based upon the transfusion thresholds of a restrictive strategy, as described later.

Peri-transplantation phase

Peri-transplantation phase can be defined as the period that begins with the start of administration of the conditioning regimen, continues through the infusion of HPC product in the recipient and ends with the engraftment of all cell lines. Erythroid engraftment is difficult to define, and RBCs independence may be defined as the first day out of the 30 consecutive days of no RBCs transfusion (11). Platelets and granulocytes engraft earlier (i.e., after 2–3 weeks or may be longer, after the infusion of HPC product; apheresis derived HPCs engraft earlier than marrow derived HPCs) (21). During this phase, patients are generally administered the conditioning and GVHD prophylaxis regimens and require transfusion of platelets and RBCs.

Specific immunoserologic prerequisites for selecting blood components, considering both the patient's blood ABO RhD type and the HPC donor's ABO RhD type must be followed during this phase (*Table 1*). Sometimes, isohemagglutinins may not be detected on RBCs back typing due to the immunosuppression caused by the conditioning regimen and later, by the GVHD prophylaxis regimen. Any ABO RhD discordance between the forward typing and the back typing and any disagreement between the current blood type and the historic blood type should be investigated and explained before transfusing any blood products. Although HLA matched platelets are preferred, they may not be available depending upon the inventory. If the HPC donor is HLA mismatched or haploidentical, platelet products should be selected avoiding the HPC donor's HLA class I antigens. If the patient has developed HLA class I antibodies, platelet products should be selected avoiding the cognate antigens, to avoid platelet refractoriness. Platelet crossmatching may be employed, as well.

For transplantations with major ABO incompatibility, red cell depletion of the HPC product is performed before infusion (22-24). In patients having minor ABO incompatibility with the HPC donor or if the donor has clinically significant red cell antibodies against the patient's red cell antigens, plasma reduction of the HPC product results in prevention of acute hemolytic reactions (25). Many HPC products that are not scheduled to be infused fresh after collection, are cryopreserved and stored. Dimethyl sulfoxide (DMSO) is used as a cryoprotective agent and results in significant improvement of post-thaw viability on the day of infusion. However, it can be associated with a mild to severe infusion reaction, called DMSO toxicity. To prevent its toxicity, AABB recommends the volume of DMSO infusion not to exceed 1 mL per kg of

Table 1 Blood group of the components to be transfused during the peri-transplantation phase

HPC transplantation	HPC donor	HPC recipient	Transfusion RBCs	Transfusion platelets*/plasma
Major	A	O	O	A, AB
	B	O	O	B, AB
	AB	O	O	AB
	AB	A	A, O	AB
	AB	B	B, O	AB
Minor	O	A	O	A, AB
	O	B	O	B, AB
	O	AB	O	AB
	A	AB	A, O	AB
	B	AB	B, O	AB
Bidirectional	A	B	O	AB
	B	A	O	AB

*, blood type for platelet transfusions describes the preferred ABO type. In case of limited inventory and non-availability of the preferred type, platelet products of other blood types may be transfused after following institutional limitation of isohemagglutinins in the product. HPC, hematopoietic progenitor cell; RBC, red blood cell.

the patient's weight per 24 hours (100 mL of a 10% DMSO solution contains 10 mL of DMSO) (26).

For sickle cell disease patients undergoing transplantation, many institutions perform serologic phenotyping and/or red cell genotyping of both the patient and the HPC donor. Determination of red cell phenotype of the patient and the HPC donor helps to predict which clinically significant red cell antibodies the patient may develop in the future.

After infusion of the HPC product, the patient typically remains cytopenic for about 2–3 weeks or longer, because of conditioning and GVHD prophylaxis, until the patient engrafts. The indications, immunoserologic considerations and special blood product considerations for RBCs and platelet transfusion remain the same as before HPC infusion, until erythroid and platelet engraftment, as described later.

Post-transplantation phase

Post-transplantation phase starts with the engraftment of all cell lines. During this phase, the patient's ABO RhD type has transformed into the HPC donor's blood type. For selection of compatible ABO RhD type blood components, different institutions follow their own criteria in order to ensure the transformation of the patient's original blood type into the HPC donor's blood type. At the institution where one of the authors trained, patient's blood type is considered to have switched to the HPC donor's blood type if the patient's red cell forward-typing and back-typing result is twice consecutively the HPC donor's blood type, short tandem repeat (STR) chimerism shows myeloid and lymphoid cells exclusively of HPC donor's origin, and the patient has remained RBC transfusion independent for at least 3 months. Patients may not need blood components during this phase, unless they develop any transplantation related or unrelated complication or their peripheral blood or bone marrow aspirate STR chimerism shows declining HPC donor chimerism. Although there are no data to justify the permanent use of irradiated blood components, many physicians recommend continuing to transfuse irradiated, CMV antibody seronegative RBCs and platelets (in CMV antibody seronegative patients) and leukoreduced blood components, due to lack of availability of a test that confirms a patient's complete immunologic reconstitution, after the transplantation (16). As noted above, some institutions and physicians provide leukoreduced cellular components for reducing CMV transmission risk as well as for the other indications previously discussed.

Based upon the currently available evidence, we describe the indications, selection of compatible blood components and the special processing requirements for patients undergoing HPC transplantation.

Indications for transfusion in HPC transplantation

RBCs

Since there are no larger, prospective studies performed on patients undergoing HPC transplantation, patients are transfused based upon AABB guidelines for the general patient population. Restrictive transfusion strategy is usually defined as transfusing RBCs only if the patient has a hemoglobin level of ≤7.0 or ≤8.0 g/dL or has symptomatic anemia. Liberal transfusion strategy is defined as transfusion of RBCs when the hemoglobin is ≤10.0 g/dL (27). Studies have shown better results with a restrictive transfusion strategy than with a liberal transfusion strategy (27-29). Hence, a restrictive transfusion strategy should be followed before or after transplantation (30). In cases of minor ABO incompatibility, RBCs are generally transfused based upon an institutionally defined higher transfusion hemoglobin level threshold (generally ≤9.0 g/dL) during the second week after transplantation, because of the risk of acute hemolytic anemia due to passenger lymphocyte syndrome (PLS) (31-37).

Platelets

The indications of platelet transfusion during HPC transplantation are based upon two major studies performed on patients with hypoproliferative thrombocytopenia.

The first study included patients undergoing autologous or allogeneic HPC transplantation (83%) and patients on chemotherapy (17%) for hematologic malignancies (38). The study randomized the patients into 2 groups. Patients in group 1 had prophylactic platelet transfusions at a platelet count of <10,000/mm^3 while patients in group 2 had therapeutic platelet transfusions, only in case of a clinical bleeding event at a platelet count of <10,000/mm^3. The WHO grade 2–4 bleeding events and the days of bleeding were less in the patients with prophylactic platelet transfusions. However, the rates of bleeding in the patients having autologous transplantation (who were 70% of the total patients in the study) were similar between the two groups.

The second study included patients who had undergone autologous transplantation and patients with acute myeloid leukemia (39). All patients were receiving chemotherapy. The study compared the rates of bleeding between the patients treated with prophylactic platelet transfusions and the patients treated with therapeutic platelet transfusions. The number of days of WHO grade 2–4 bleeding at all platelet counts, were significantly higher in patients with therapeutic transfusions than with prophylactic transfusions. In patients with acute myeloid leukemia major bleeding events were increased with therapeutic transfusions than with prophylactic transfusions. However, patients having autologous transplantation did not have significantly increased major bleeding events with therapeutic transfusions compared to those with prophylactic transfusions. The number of platelet transfusions was significantly less in patients having therapeutic transfusions than in patients having prophylactic transfusions.

In order to determine the optimum dose of platelets to be transfused in patients with hypoproliferative thrombocytopenia, a clinical trial, Determination of the Optimal Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenic Patients (PLADO study), included patients undergoing HPC transplantation and patients on chemotherapy for hematologic malignancies or solid tumors (40). Patients were given low dose, medium dose or high dose platelets (1.1×10^{11}, 2.2×10^{11} and 4.4×10^{11} per m^2 of body surface area). No significantly different rates of WHO grade 2–4 bleeding events were observed in the three groups. However, the median number of platelet transfusions per patient was significantly higher in the low dose group (5 transfusions) as compared with either the medium dose group (3 transfusions) or the high dose group (3 transfusions).

Based upon the above-described trials, patients are generally transfused if the platelet count is <10,000/mm^3, if the platelet count is <20,000/mm^3 in a febrile patient or if the patient has clinical bleeding. In pediatric patients undergoing HPC transplantation, considerable variation exists about the threshold for transfusion (41). Platelets are usually transfused based upon volume of the platelet product per child's weight in kg (10 mL/kg), if the platelet count is <15,000–20,000/mm^3 (42). In a secondary analysis of PLADO study, bleeding risk was compared between patients of different age ranges. Pediatric patients (between 6–18 years of age) had increased risk of bleeding than adults (≥19 years of age), especially in the patient subgroup that underwent autologous/syngeneic HPC transplantation (43). A recent implementation study of a restrictive platelet transfusion strategy in neonates reduced the non-indicated transfusions with no change in bleeding events (44). In sickle cell adult or pediatric patients, many physicians may transfuse platelets if the platelet count is <50,000/mm^3, due to a higher risk of intracranial bleeding, as a result of sickle cell vasculopathy (45,46).

Granulocytes

In the controlled studies performed addressing the benefit of granulocyte transfusions in patients with bacterial or fungal infections, some degree of success was evident in the earlier studies. This was especially true when adequate number of granulocyte transfusions were collected and transfused. As a result, granulocyte transfusions were recommended for patients with antimicrobial resistant bacterial or fungal infections (47). One trial result did not have a significant difference with granulocyte transfusions and others had mixed results (48,49). A meta-analysis of the previous trials demonstrated that the two significant factors causing a lack of benefit from granulocyte transfusions in some trials were the dose of granulocytes and the survival rates of the controls in those trials (47). As a result, AABB Standards for Blood Banks and Transfusion Services require that 75% of granulocyte products must have a minimum dose of 1.0×10^{10} granulocytes but higher doses are preferred (50). Studies performed on neonates with sepsis provided inconclusive evidence but encouraged further controlled studies to explore any benefit (51). However, recommendations included adult patients with neutropenia who had antimicrobial resistant, life threatening bacterial or fungal infections and were anticipated to be neutropenic for at least 1 week (52).

Important considerations about the selection of blood components

RBCs and ABO RhD compatibility

Extreme care should be taken about the ABO type of RBCs, since they must be compatible with the patient's isohemagglutinins. In cases of ABO incompatibility (major, minor or bidirectional) between the HPC donor and the recipient, the isohemagglutinins of the recipient change after engraftment, according to the HPC donor's blood type. Hence, the transfused RBCs must lack the ABO antigens corresponding to the isohemagglutinins of the patient and the HPC donor during the peri-transplantation phase. In patients having RhD incompatibility with the HPC donor, the RhD type also changes after engraftment, according to the HPC donor's RhD type. As a result, RhD negative RBCs are transfused during the peri-transplantation phase. Of course, patients with history of RBC alloantibodies must receive RBCs lacking the corresponding red cell antigens. For sickle cell patients undergoing transplantation, institutions have developed specific protocols about the degree of RBC antigen matching, for transfusions.

In addition, many blood centers and transfusion services have implemented universal leukoreduction of RBCs, and since RBCs themselves, only sometimes carry weaker HLA class I antigens (often called Bg antigens) as compared to those expressed on leucocytes and do not carry HLA class II antigens (53), HLA compatibility of the RBCs units with the patient is not required.

Platelets and HLA compatibility

The most important consideration while selecting platelets for patients undergoing HPC transplantation is HLA compatibility. If the patient has HLA class I antibodies, the goal is to select HLA matched platelets and if not available, to select the platelets from a donor lacking the corresponding HLA class I antigens, in order to prevent HLA antibodies mediated platelet refractoriness (54). Some institutions perform platelet crossmatching. If the patient does not have expected platelet increments despite HLA or crossmatch compatible platelet transfusions and does not have other non-immune cause of refractoriness, platelets with ABO type compatible with the recipients isohemagglutinins are selected.

The second goal of selecting HLA compatible platelets is to prevent HLA alloimmunization against the HPC donor's mismatched HLA class I antigens, in those patients who undergo HLA mismatched, related or unrelated, donor transplantation. Since donor specific HLA antibodies have been described to result in graft failure, HLA compatible platelets, missing the mismatched HLA class I antigens of the HPC donor, are selected. If the patient has a mismatched related donor or haploidentical donor, relatives should not donate blood products due to the risk of HLA alloimmunization against the related HPC donor's HLA antigens, since donor specific HLA antibodies have a higher risk of graft rejection (55).

For platelet transfusions of patients undergoing HPC transplantation, the requirement of ABO compatibility of isohemagglutinins in the platelet product with the ABO type of the patient is not different from that of non-transplantation patients. When isohemagglutinins in the platelet component is a concern, platelets in platelet additive solution (PAS) may be preferred, since they contain only about 35% of the plasma as compared to conventional platelets (56). Per AABB Standards for Blood Banks and Transfusion Services, all blood banks should have a process of limiting the transfusion of isohemagglutinins and red

cell antibodies in the plasma volume of platelet products, in patients with incompatible ABO blood type (50). However, ABO incompatible platelets may still be transfused, though not preferred, if the inventory is limited. In such a situation, the blood bank should follow a process of limiting the exposure of isohemagglutinins to the patient. Though less commonly observed, RhD positive platelets can result in RhD alloimmunization in RhD negative patients who undergo HPC transplantation (57,58). According to some reports, anti-D in the patient before transplantation or anti-D alloimmunization after transplantation may cause morbidity during transplantation with an RhD positive HPC donor (59-61), that may not only be limited to an increased number of RBC transfusions and a requirement for special procedures, e.g., plasma exchange (62). Administration of Rh immunoglobulin (RhIg) or anti-D during the peri-transplantation period may also cause morbidity, though there are no adequate studies describing the effect of RhIg administration upon erythroid engraftment and morbidity. Hence, many physicians may not administer prophylactic RhIg to a RhD negative patient after transplantation with a RhD positive HPC donor and after an RhD positive platelet transfusion during the peri-transplantation phase, though there are no specific guidelines addressing this.

Granulocytes

Granulocyte transfusions are indicated in patients undergoing HPC transplantation if they have life threatening, antimicrobial resistant bacterial or fungal infection, during a temporary period of severe neutropenia, in anticipation of marrow recovery. They are collected from healthy volunteer donors, after donor simulation with G-CSF, with or without steroids. Since hydroxy-ethyl starch (HES) is used as a sedimenting agent during the apheresis collection, donor's creatinine clearance should be tested prior to G-CSF administration, in order to minimize the risk of nephrotoxicity due to HES exposure during the collection. Also, donor's fundoscopy should be performed prior to dexamethasone administration, in order to minimize the risk of posterior subcapsular cataract development by the dexamethasone. After collection, granulocytes are stored at room temperature without agitation. They should be transfused within 24 hours of collection, but the earliest possible transfusion during the 24-hour shelf life is preferred (50).

ABO compatibility

Significant RBCs are present in the granulocyte product, so RBCs are removed by sedimentation in case of ABO incompatible donors. Also, products should be crossmatched before transfusion (50). Since granulocytes are transfused as soon as possible after collection and within 24 hours after the collection, close coordination between the donor center and the blood bank is required, allowing sufficient time for RBC sedimentation before transfusion. Granulocyte donors having minor ABO incompatibility with the recipient may be transfused without further manipulation, after testing the isohemagglutinins titer of the product is not above the institutional threshold, as described in AABB Standards for Blood Banks and Transfusion Services (50).

HLA compatibility

For HLA compatibility in patients with HLA class I or class II antibodies, granulocyte donors lacking the corresponding HLA antigens are selected, in order to avoid further increase in titer of the antibodies by the exposure and to prevent reverse-transfusion-related acute lung injury (TRALI) (63-65). Granulocytes from donors with the corresponding HLA antigens have also been described to have decreased migration to the site of infection, due to HLA antibodies of the patient (66,67). A second important consideration while selecting a granulocyte donor is the absence of mismatched HLA class I and/or class II antigens of the HPC donor. Transfusion of granulocytes carrying the mismatched HLA class I and/or class II antigens may result in HLA alloimmunization against those HLA antigens of the HPC donor. Since donor specific HLA antibodies are associated with increased risk of graft rejection, granulocyte donors lacking the mismatched HLA antigens of the HPC donor, are selected (2).

CMV serostatus of the donor

In granulocyte transfusions for CMV antibody seronegative recipients, CMV status of the donor is important, since, obviously, granulocytes cannot be leukoreduced. As granulocyte transfusions have been studied to result in CMV transmission, CMV seronegative donors should be selected for CMV seronegative patients (68,69).

Plasma

Generally, HPC transplantation does not result in deficiency of coagulation factors or coagulopathy. However, not rarely plasma transfusion may be indicated in patients due to the complications of transplantation. Sometimes, patients develop bleeding secondary to acute or chronic GVHD

involving the liver, veno-occlusive disease of the liver or transplantation associated thrombotic microangiopathy. The complications may result in bleeding or may cause an international normalized ratio (INR) of >1.7 or >1.5 before a surgical procedure. In case of major, minor or bidirectional ABO incompatibility, plasma components must be compatible with both the patient's and HPC donor's ABO type, before engraftment (*Table 1*).

COVID-19 convalescent plasma (CCP)

Since the beginning of the year 2020, COVID-19 pandemic has affected every aspect of human life and studies have demonstrated that immunocompromised patients, including the patients undergoing HPC transplantation are the most likely to develop severe disease. COVID-19 CCP was considered a potential treatment and after the preliminary results of clinical trials (70-72), US Food and Drugs Administration (FDA) granted emergency use authorization to CCP in August 2020 and updated it to the use of high-titer units only in February 2021 (73,74). However, the trials have mixed results to date (72,75-78), and an important criticism is the lack of randomization (79). Although there are few reports only about the use of CCP in HPC transplantation patients (80,81), some studies about its use in immunocompromised patients have suggested favorable results (81-84). Hence, CCP might prove to be efficacious, as the evidence continue to evolve. Apart from anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody testing, the guidelines about the collection, storage, immunoserologic compatibility and transfusion of CCP for patients undergoing HPC transplantation are the same as any other plasma component.

Complications

Complications due to major ABO incompatibility

ABO incompatibility (major, minor, or bidirectional) between the HPC donor and the recipient has not been found to be associated with complications, if appropriately managed (*Table 2*). As a result, transplantations with ABO incompatibility are commonly performed and managed.

Acute or delayed hemolytic reaction

If the donor-recipient pair has a major ABO incompatibility, the patient can have an acute or a delayed hemolytic reaction after the infusion of HPC product. To prevent a hemolytic reaction in cases with major ABO incompatibility, red cell depletion of the HPC product may be performed before infusion (22,85,86), especially in marrow-derived HPC transplantation because those products have higher number of RBCs (25–35% hematocrit) as compared to apheresis derived HPC (2–5% hematocrit and approximately ≤22 mL) (85) or cord-derived HPC products (acute hemolysis after cord derived HPC infusion is rare, since they are usually washed to remove excess RBCs, before or after cryopreservation) (87). This is particularly important for the recipients whose isohemagglutinins titers are ≥1:32, though the safe isohemagglutinins titers are not strictly defined and individual transplantation programs should define their policies for ABO incompatible transplantation (88).

Pure red cell aplasia (PRCA) and delayed erythroid engraftment

Also associated with major ABO incompatibility are delayed erythroid engraftment and/or PRCA (89). The cause of the delay is recipient's isohemagglutinins and hence this is more often seen in transplantation with reduced intensity conditioning than with myeloablative conditioning (89). PRCA usually resolves without any intervention, but treatment is required to decrease its duration and limit the number of RBC transfusions, thus avoiding iron overload (90). Treatment includes plasma exchange, donor lymphocyte infusion to facilitate erythroid engraftment, erythropoietin, rituximab, or a combination of these agents (11,91). Pre-transplantation transfusion of donor's type RBCs has been studied to decrease the recipient's isohemagglutinins titers and it is performed at some European centers (85,92). It has been observed that patients whose GVHD prophylaxis includes only T cell inhibition without B cell inhibition (e.g., cyclosporine only) have an increased risk of PRCA (90).

Complications due to minor ABO incompatibility

PLS

A potentially life-threatening complication associated with minor or bidirectional ABO incompatibility is PLS (31-37). In PLS, donor's lymphocyte in the HPC product cause the production of isohemagglutinins in the recipient, resulting in rapid and severe hemolytic anemia, mostly during the second week after transplantation (between D+7 and D+14). PLS is treated supportively, with careful monitoring of hemoglobin and hemolytic parameters after transplantation and prompt RBC transfusions when needed (25,35). Some institutions have a hemoglobin threshold of

Table 2 Salient transfusion/infusion related complications in patients undergoing HPC transplantation

Complication	Prevention/treatment
ABO incompatibility	
Major	
Acute hemolytic reaction	RBC depletion of HPC product
Pure red cell aplasia/delayed engraftment	Therapeutic plasma exchange of the patient
Minor	
Passive hemolysis due to donor's isohemagglutinins	Plasma reduction of HPC product
Passenger lymphocyte syndrome	Monitoring and prompt transfusion support
HLA incompatibility	
Donor specific antibodies and graft failure	Selection of HPC donor without cognate HLA antigen
Transfusion related acute lung injury	Selection of blood component donors without HLA antibodies
HLA class I antibodies and platelet refractoriness	Recruiting HLA compatible platelet donors
	Platelet crossmatching
Transfusion associated graft versus host disease	Irradiation of blood components or pathogen reduction of platelets
CMV transmission	Transfusion of CMV reduced-risk blood components
DMSO toxicity	DMSO should not exceed the maximum limit according to the patient's weight*
Transfusion/infusion transmitted infection	Donor testing and HPC product sterility testing
Febrile reaction	Leukoreduction of blood components
Allergic/anaphylactic reaction	Using PAS platelets, using washed or volume-reduced platelets, using washed RBCs
Transfusion associated circulatory overload	Slow transfusion/infusion rate, use of volume-reduced platelets, fluid intake output monitoring and careful use of diuretics

*, per AABB circular of information for the use of cellular therapy products, DMSO should not exceed '1 mL/kg of patient's weight/24 hours of administration', if the thawed product is not washed. 100 mL of a 10% solution contains 10 mL of DMSO (26). CMV, cytomegalovirus; DMSO, dimethyl sulfoxide; HLA, human leucocyte antigen; HPC, hematopoietic progenitor cell; PAS, platelet additive solution; RBC, red blood cell.

9.0 g/dL (instead of 7.0 g/dL) for RBC transfusion, post-transplantation, for such patients. Robust monitoring and a higher hemoglobin threshold for RBC transfusion prevents the development of rapid and severe, life-threatening hemolytic anemia due to PLS (25,35).

Passive hemolysis

If the donor-recipient pair has minor ABO incompatibility, the risk of passive hemolysis due to isohemagglutinins in the HPC product is minimized by limiting the plasma volume in the HPC product (marrow derived, apheresis derived) to be infused. Passive hemolysis may be severe in HPC donors with high isoagglutinin titers or by HPC product infusion in pediatric patients. Each institution has set up its criterion for maximum isohemagglutinins titer and/or plasma volume of the HPC product to be infused (25).

Non-ABO RBC antigens alloimmunization

A small percentage of the transplantation recipients develop non-ABO red cell antigen alloimmunization through exposure to the HPC donor's RBCs in the HPC product (93,94). Red cell antibody screen of the HPC donor and the HPC recipient is performed before transplantation (25). RBC phenotyping of the donor and the recipient is recommended but not routinely performed at most institutions, except in transplantation of sickle cell disease patients or patients having clinically significant red cell antibodies (94). For

RhD negative patients with an RhD positive HPC donor, red cell reduction of HPC product may not be performed, owing to some degree of HPC loss with red cell reduction of the HPC product (25). Studies have shown very low rates of RhD alloimmunization in such patients and many physicians may not administer prophylactic RhIg to prevent RhD alloimmunization due to concerns about erythroid engraftment and morbidity, though there are no adequate studies about these risks to date (62,95).

Institutes have established specific policies for the evaluation of the HPC donor-recipient pair, if the patient has clinically significant non-ABO red cell antibodies (25). In such cases, HPC donor's RBC phenotyping is performed. If the donor's RBC phenotype is positive for the corresponding antigen and the product hematocrit is high, red cell depletion of the HPC product may be performed. Each institution should follow its specific protocol for performing red cell depletion in this regard, based upon the antibody titer of the patient and hematocrit of the HPC product. Cases of non-ABO alloimmune hemolysis, most likely due to HPC donor-derived passenger lymphocytes, have also been reported (96).

Transfusion associated graft versus host disease (TA-GVHD)

Since the patients undergoing autologous or allogeneic HPC transplantation receive a conditioning regimen that includes immunosuppressive drugs, all RBC, platelet and granulocyte products must be irradiated to prevent TA-GVHD. Fresh frozen plasma and cryoprecipitate are acellular and therefore, do need to be irradiated (11). However, plasma that is never frozen should be irradiated or be subjected to pathogen reduction, since viable lymphocytes may be present. If the platelets are pathogen reduced, irradiation is not required, since the treatment with psoralen compounds inhibits T cell replication in the platelet product.

CMV transmission

Since most blood centers follow universal leukoreduction, the risk of CMV transmission has considerably decreased compared to before this practice was implemented. Studies show that the risk of transmission by leukoreduced blood components is as low as the risk associated with transfusion of blood components collected from CMV IgG seronegative donors (97-100). AABB Standards for Blood Banks and Transfusion Services require an institutional policy to decrease the risk of CMV transmission (50). As a result, different institutions have different policies, where some only issue blood components collected form CMV IgG seronegative donors, others rely on leukoreduction of RBCs and platelets since it has been shown to be equally effective in reducing the transmission risk. Granulocytes obviously, cannot be leukoreduced. Therefore, for CMV IgG seronegative recipients, granulocytes must be collected from CMV IgG seronegative donors. Concerns, however, have been raised about CMV infectivity of CMV IgG seronegative donors with CMV specific IgM and CMV DNA being detected in some individuals, presumably because such individuals may be in the window period of CMV specific IgG production (101,102). As a result, testing for CMV DNA, CMV IgM or IgG avidity against CMV have been suggested (102).

Platelet refractoriness due to HLA alloimmunization

HPC transplantation patients may develop platelet refractoriness due to a number of immune, non-immune or mixed etiologies (103). Since these patients may require multiple transfusions during the course of transplantation, they may develop HLA class I or class II antibodies. In some institutions, patients are screened monthly for HLA antibodies post-transplantation. Due to HLA antibodies against HLA class I antigens (A and B alleles), they may develop immune mediated refractoriness. For such patients, HLA class I antigen matched platelets or platelets collected from the corresponding HLA class I antigen negative donors result in the pertinent expected corrected count increment (CCI) values. An expected post-transfusion platelet count performed on a blood specimen drawn 10- to 60-minute post-transfusion shows a favorable result (54). Some institutions perform platelet crossmatching. There is evidence that this procedure can predict good CCIs following transfusion of compatible platelets. For some patients who have a very high percentage of panel reactive antibody (PRA) reactivity in the HLA class I antibody screening, platelet donor selection may be challenging. Some institutions have specialized donor recruitment programs for such patients to recruit HLA compatible donors.

Summary and conclusions

Transfusion of blood components in patients undergoing HPC transplantation requires careful consideration of a multitude of critical factors, as identified in this review.

With appropriate management and selection of blood components, many serious complications associated with transfusion in HPC transplantation patients can be prevented and treated. Although, complications may still arise despite evidence-based advances in transfusion medicine and cellular therapy, essential knowledge of transfusion support in HPC transplantation can result in better treatment outcomes.

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