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Review

Transfusion support for stem cell transplant recipients

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ABSTRACT

Hematopoietic stem cell patients regularly require transfusion support. Indications for transfusion in this population are similar to other patients being treated with chemoradiation; however, special considerations must be made in regards to pretransfusion testing, ABO compatibility, product modifications, and anticipated challenges while patients undergo engraftment. Additionally, infusion of hematopoietic stem cells requires acute understanding of product collection, modification, and potential side effects. As these patients often require numerous platelet transfusions, platelet refractoriness may be encountered and practice options are discussed. We review current indications and guidelines for transfusion in hematopoietic stem cell patients and make recommendations for best practice based on current literature.

Introduction

Patients undergoing hematopoietic stem cell transplant (HSCT) often require transfusion support secondary to ongoing chemotherapy and radiotherapy induced cytopenia [1]. The last 2 decades of medical advances have rapidly expanded the range of disease types for which HSCT can be considered. HSCT is now considered an option with curative potential for both neoplastic as well as non-neoplastic disorders. Furthermore, expansion into nonmalignant benign hematologic conditions like sickle cell disease and thalassemia, as well as hereditary disorders of the immune system are now routinely treated with HSCT. The indications for blood product transfusion mirror those in other oncology patients but include special considerations in the pretransplant, transplant, and post-transplant periods. Herein we review standards and provide background based on the currently available literature.

Stem cell infusion

The stem cell transplant process begins with conditioning or preparative regimens, tailored to optimize stem cell harvesting. Not all donors or patients are candidates for varying preparative chemotherapy or mobilizing agents, as such the total number and composition of the stem cell source has varied over time [2]. Whether a patient receives an autologous peripheral blood stem cell product, a matched unrelated allogeneic hematopoietic stem cell product, bone marrow, or umbilical cord blood product, there will always be clinical and product factors to consider at time of infusion.

Adverse reactions to HSC infusion are common and range in severity from mild to potentially life threatening [3]. Common reactions include gastrointestinal manifestations such as nausea or vomiting, flushing, fever, malodor, hypertension, and cough and more rarely respiratory compromise, neurologic abnormalities or fatal arrhythmia [3-6]. Frozen cells must be suspended in a cryoprotective agent, typically dimethyl sulfoxide (DMSO), which has been implicated as the cause for numerous adverse reactions and can cause malodor, histamine release, and nervous system abnormalities [7]. Though infused products generally contain less than 15% DMSO, further efforts have been made in certain conditions to remove DMSO prior to infusion, though this manipulation may lead to cell loss [7]. Of interest, HSC infusion products can contain lysed cells, debris, metabolites, and electrolytes which may induce symptoms associated with infusion, as evidenced by the persistence of reactions in DMSO-free or DMSO-depleted HSC [8]. Symptoms associated with infusion are likely multifactorial and related not only to DMSO or substances within the product but clinical circumstances in individual patients as well.

Numerous steps are taken to ensure sterility of HSC and regulations, exemplified by Foundation for the Accreditation of Cellular Therapy (FACT) standards that require microbiological cultures be

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performed on minimally manipulated HSC, despite this, contamination rates have been reported between 0.2% and 26.3% [9,10]. The suspected etiologic of this microbiologic contamination may be secondary to collection or transfer bag leaks or microfractures, inadvertent collection of skin plugs and associated skin commensal contaminants, subclinical donor bacteremia, or other etiologies [11,12]. Common organisms are Gram-positive skin commensal bacteria or rarely Gram negative or fungal pathogens [11,12].

Infusion of products containing known infectious pathogens is occasionally necessitated due to clinical circumstance. Patients generally receiving products with positive cultures are already undergoing a pretransplantation preparative regimen schedules and the transplant cannot be delayed, but with appropriate antimicrobial therapy these patients show no significant difference in outcomes [9,13]. Patients receiving contaminated stem cell products may develop positive blood cultures, paradoxically to different bacteria than that identified in the product, and develop neutropenic fever at similar times compared to those receiving uncontaminated stem cells [9,13]. Transplant recipients with viral illnesses such as hepatitis B or C and HIV require monitoring as well as prophylactic therapy for optimal outcomes; likewise, special considerations must be undertaken for processing and storage of HSC graft collected from donor with these viral illnesses [14,15].

Pretransfusion testing

HSCT patients continue to undergo routine pretransfusion testing as long as transfusion support is required. Donors must undergo ABO/Rh, human leukocyte antigen (HLA), and we recommend initial indirect antibody screen [16,17]. A recipient cross match should be performed in ABO compatible stem cell transplants [18]. Recipients will undergo initial type and screen and testing will be followed throughout the transplant course to identify emerging minor red blood cell antibodies or changing ABO blood types. ABO typing on both the donor and recipient must be performed in duplicate on two separate samples, with resolution and documentation of any discrepancies [19]. Incompatibilities in ABO blood types of HSCT donor and recipient will affect plasma, red blood cell (pRBC), and platelet (PLT) transfusions and as such, transfusion services should be made aware of HSCT patients.

Although HLA compatibility is key for successful outcomes in HSCT, ABO is inherited independently and as such, the ABO barrier has been crossed in HSCT. Transplants involving ABO compatible donor-recipient pairs are optimal, but outcomes are generally similar in terms of mortality, relapse, and GVHD, in the 25% to 50% allogeneic transplants that are ABO incompatible [17,18]. Incompatibilities are categorized as major with recipient antibodies against donor, minor with donor antibodies against recipient ABO, or bidirectional. The immediate concern for infusion of ABO incompatible stem cell products is hemolysis due to incompatible RBCs or ABO antibodies, isohemagglutinins, though there are other specific manifestations associated with each type of incompatibility.

Major incompatibility involves infusion of ABO incompatible red cells. Retrospective data exists showing <50 to 80 mL in accidental incompatible red cell transfusion was not associated with death and caused minor symptoms, and stem cell products contain significantly lower quantities of red cells [20,21]. Though no standards exist for red cell content, peripheral blood stem cell products generally contain <15 mL whereas bone marrow products contain much greater amounts [21-23]. Reduction in red cell mass may be performed with a target of less than <20 to 25 mL and can be accomplished by RBC sedimentation or density gradient separation [22]. This however can be associated with reduction in hematopoietic stem cells, which may be especially impactful in products containing a lower volume of stem cells, such as those collected from cord blood [22]. Preinfusion plasma exchange may also be performed in patients with high titers of isohemagglutinins, though again standardization is problematic, and we suggest slowing of infusion with continued monitoring for hemolysis [24]. Infusion of secretor plasma to bind ABO antibodies may also be considered as a means of mitigating high circulating isohemagglutinins [17]. Major ABO incompatible HSCT patients have delayed red cell engraftment which may manifest as pure red cell aplasia which will be detailed later [18].

In minor ABO incompatible transplants, incompatible donor isohemagglutinins and lymphocytes are infused into the recipient. As theoretically anticipated, there is hemolysis associated with infusion of incompatible isohemagglutinins and stem cell products may be modified prior to by centrifugation and plasma reduction, with minimal loss in stem cell mass. Reduction of recipient red cells by red cell exchange or transfusion of compatible red cells may be performed, though this is not extensively employed do to mixed results [22]. Though not well-described in the literature, immune tolerance with a lack of antibodies against recipient red cells is an anticipated outcome in a number of minor incompatible transplants [20,25,26]. However, donor lymphocytes may mount an immune response against recipient red cell antigens in passenger lymphocyte syndrome, which is detailed below.

(1) Bidirectional incompatibility is complicated by issues as described in major and minor incompatibility

HSCT results in a change for recipient to donor blood type change following engraftment of the erythroid lineage. Varying timelines for beginning to transfuse the recipient with donor type RBCs have been suggested, but the best timing for this change this corresponds to preparative regimen, source and type of ABO incompatibility. Cohn suggests presence of 1% reticulocytes or 30 days after last red cell transfusion [21]. A recent publication suggest that reticulocytes more accurately characterize red cell engraftment than does ABO typing, although practically identification of typing by blood bank staff is key [26]. Resolving recipient's blood type may also be difficult, as secretors may produce ABO antigens that adhere to type O cells, causing forward typing challenges or lack of back typing in some patients [18]. Until engraftment is complete, selecting products compatible with both the donor and recipient is necessary but places significant stress on product management within the blood bank since the transfusion of group O RBCs and group AB plasma is often required.

Product Modification

When preparing blood products for transfusion in HSCT patients, steps must be in place to ensure appropriate product preparation. Specifically, products must be modified in order to prevent infection as well as transfusion associated graft vs host disease in these relatively immune compromised patients.

HSCT patients are at increased risk for transfusion transmitted cytomegalovirus (CMV) [27]. CMV latently infects monocytes in asymptomatic blood donors with historic infection. As such leukoreduction serves to ameliorate this issue; however, there is viral shedding by endothelial cells into plasma during active infection [27]. Leukoreduced products from CMV serologically negative donors are also available. The watershed publication on this issue demonstrated no increase in CMV transmission between leukoreduced and CMV-seronegative blood in HSCT patients, and a recent survey reported that leukoreduction remains most prevalent means of preventing transfusion transmitted CMV [28,29]. Furthermore, donors acutely infected in the window period prior to detectable antibodies are known to have circulating CMV cell-free virus, and there is some interest in transfusion from long-term seropositive donors as they are less likely to have cell-free virus [27].

Pathogen reduced PLTs and plasma are licensed in both the European Union (EU) and the United States of America (US) [30-33]. These blood products significantly reduce the risk of CMV as well as HIV in addition to bacteria, viruses, and parasites [33]. Promising research has also demonstrated efficacy of pathogen reduction in preventing transfusion associated graft vs host disease (TA-GVHD) by inactivation of donor T lymphocytes [32]. However, pathogen reduced products are not widely in use at this time, and more traditional methods for product modification are still the norm.

Irradiation is the primary method for reducing the risk of TA-GVHD, and is indicated for all patients undergoing stem cell transplantation [33]. Product irradiation can lead to red cell membrane fragility and a resultant increase in the concentration of potassium in the product, which may be of concern low body weight patients [36]. Additionally, the shelf life of the product is reduced to 28 days after irradiation, or the original expiration date, whichever is the soonest temporally [33,34].

Indications for transfusion

Due to cytopenia induced by preparative chemo radiation and prior to marrow recovery, HSCT patients generally require transfusion support. Specifically, patients require transfusion prior to engraftment in order to maintain oxygen delivery and maintain hemostasis. However, the thresholds for transfusion are similar to those in other critically ill patient populations.

The AABB recommends restrictive red cell transfusion practice with a hemoglobin threshold of 7 g/dL in a majority of patients, with the caveat that there is insufficient evidence in patients with "severe thrombocytopenia (patients treated for hematological or oncological disorders who at risk of bleeding)" [35]. They attribute this to superior PLT transfusion response in bleeding patients with higher hemoglobin levels as support by a number of studies. Randomized controlled trials in oncology patients comparing liberal vs restricted transfusion strategies have identified that lower hemoglobin thresholds of 7 to 9 g/dL are no worse than liberal transfusion triggers of 10 g/dL or higher [36]. Our group currently recommends a restrictive red cell transfusion strategy in the absence of symptomatic anemia or hemorrhage.

The AABB recommends prophylactic transfusion at a threshold of 10,000/μL for all hospitalized patients [37]. The TOPPS trial demonstrated reduced bleeding with prophylactic transfusion in patients below this level [38]. A similar trial compared prophylactic transfusion at 10,000/μL vs PLT transfusion for symptomatic bleeding among acute myeloid leukemia and autologous HSCT patients: no increase in severe bleeds (WHO grade 3 or higher) with only therapeutic transfusion in autologous SCT patients [39]. Based on the literature and our experience, we recommend prophylaxis at 10,000/μL, with an exception that therapeutic PLT transfusion for autologous transplant patients is acceptable.

Granulocyte transfusions are available but not routinely utilized by many transplantation services [1]. In a randomized control trial of 104 neutropenic patients comparing high-dose granulocyte transfusion and standard antimicrobial therapy, there was no significant difference in survival or provable bacterial or fungal infections [40].

Delayed complications from ABO mismatched transplants

Case vignette 1

A 73-year-old male (O positive) underwent a reduced intensity transplant from a fully HLA-matched unrelated A positive donor for acute myeloid leukemia. He received single-agent targeted therapy prior to transplant and never received any pRBC or PLT transfusions. At 3 months post-transplant, hemoglobin began to decline. At 4 months post-transplant, he requires pRBC transfusions weekly. Sorted chimerism of peripheral blood CD3 and CD33 cells shows that he is fully donor chimeric. Blood group testing reveals O positive pRBCs. He does not have graft vs host disease and he is not on any myelosuppressive medications. No evidence of viral or bacterial infections. Bone marrow biopsy confirms remission of underlying cancer, and virtual absence of erythroid precursors. How would you manage this patient?

Pure red cell aplasia from Major ABO mismatched transplant

Allogeneic hematopoietic cell transplantation is a curative approach for benign and malignant hematologic conditions. Since HLA and ABO genes are inherited independently, ABO incompatibility can exist despite HLA matching [23]. Fig. 1 shows the different kinds of ABO mismatch in transplants.

Pure red cell aplasia occurs when there is a major ABO mismatch, such that the recipient has preformed antibodies in the recipient (O recipient, A or B donor) [17,41]. Since recipient plasma cells are likely the last to switch to donor chimerism, the recipient's plasma cells continue to make antibodies against donor RBC antigens. The result is intramedullary hemolysis; hence, the reticulocyte count is low or undetectable. This clinical presentation is in contrast to the usual hemolysis, in which a robust reticulocyte count is prominent. In addition, erythroid precursors are absent in the marrow, along with detection of high titers of antidonor isohemagglutinins. Other conditions such as disease relapse, drug toxicity and concomitant infections should be excluded. Red cell aplasia can delay RBC engraftment for several months. This condition is frustrating to both patient and provider, since patients require pRBCs every week, resulting in severe iron overload. Pure red cell aplasia (PRCA) risk is higher in O recipients from A donors [42].

There is no standard of care of management of PRCA due to major ABO mismatch transplants. Currently available therapies, used alone or in combination, include: tapering of immunosuppression [41], bortezomib [43], high dose steroids [44], plasma exchange, rituximab (anti-CD20) [45], erythropoiesis-stimulating agents (ESAs) [46], and donor lymphocyte infusions [47].

Often the first intervention is taper of immunosuppressive medications to promote an alloreactive effect against recipient plasma cells. Another approach to promote alloreactivity is to administer donor lymphocyte infusion. However, patients may have concomitant conditions such as graft-vs-host disease, which may preclude either of these strategies. Usually corticosteroids, ESAs or rituximab are employed. Rituximab acts against mature B-lymphocytes and spares CD20 negative plasma cells.

Effects of plasma exchange are usually transient and not effective long-term. Recent case reports have shown responses with daratumumab, hypothesizing that direct targeting of CD38 positive plasma cells would decrease antibody production removing the barrier for donor cell recovery [48,49].

Case vignette 2

A 45-year-old male (A positive) undergoes reduced intensity conditioning for myelodysplastic syndrome, following which he receives a peripheral blood stem cell graft from an O positive, matched unrelated donor. Around day 12, absolute neutrophil counts begin to rise. However, hemoglobin drops precipitously from 8 to 5 gm/dL in 24 hours. The sample is tagged as "hemolyzed," and the clinical team repeats testing to determine the hemoglobin level. Lactate dehydrogenase is elevated, haptoglobin is decreased, and the hemoglobin is even lower at 4 gms/dL upon repeat testing. How would you evaluate this patient?

	Blood group O	Blood group A	Blood Group B	Blood group AB
Antibodies (relevant for picking plasma products)	Anti-A, Anti-B	Anti-B	Anti-A	None
Antigens on red cells (relevant for choosing RBC products)	No antigens	A	B	A and B

Does patient have pre-formed antibodies? (i.e. O patient will have anti-A and anti-B)

Does donor have pre-formed antibodies? (i.e. O donor will have anti-A and anti-B)

Overarching rule: Identify a plasma product and pRBC product that is compatible with both donor and recipient

	Donor	Recipient	Plasma and Platelets	PRBC
			Choose a plasma product that will not have antibodies to both donor and recipient (AB plasma will not have any antibodies – hence universal plasma, platelet donor)	Choose a RBC product that will not have antigens corresponding o antibodies present in the donor and patient (O pRBC will not have any antigens – hence universal pRBC donor)
Donor has pre-formed antibodies (Minor ABO mismatched transplant)	O	A	A, AB	O, A
	O	B	B, AB	O,B
	O	AB	AB	O
Recipient has pre-formed antibodies (Major ABO mismatched transplant)	A	O	A, AB	O, A
	B	O	B, AB	O, B
	AB	O	AB	O
Bi-directional transplant	A	B	AB	O
	B	A	AB	O

Fig. 1. Rationale for blood product selection in ABO-mismatched transplantation.

Passenger lymphocyte syndrome from minor ABO mismatched transplant

Passenger lymphocyte syndrome is an immune-mediated hemolytic process caused by donor lymphocytes sensitized to patient red blood cells [50]. While plasma reduction of the stem cell graft is always performed prior to infusion, the viable donor B-lymphocytes infused along with the stem cell allograft develop antibodies against recipient red cell antigens. This syndrome also occurs with solid organ transplantation and if there is a discrepancy between donor and recipient minor RBC antigens (Kidd, Rh, and Fya) [51,52]. There may be massive, life-threatening hemolysis [53]. Transplant centers should have standard policies to monitor closely for passenger lymphocyte syndrome, between days +5 and +21 post-transplant. Since the transferred B-lymphocytes do not engraft, the syndrome is self-limited.

Several risk factors have been postulated, such as stem cell as allograft source and use of cyclosporine without methotrexate as GVHD prophylaxis [54]. In a review of over 17 publications involving 27 patients, the median duration of hemolysis was 8 days with a median pRBC transfusion requirement of nine units [55]. Rarely, rituximab has been utilized for severe hemolysis [55].

HLA alloimmunization and PLT transfusion-refractoriness

Case vignette 3

A 36-year-old multiparous woman received myeloablative conditioning for acute myeloid leukemia in first complete remission prior to 6/6 HLA matched peripheral blood stem cell transplant from her brother. Conditioning was with busulfan and fludarabine and graft-vs-host disease prophylaxis was tacrolimus and short-course methotrexate. At day +2, she is noted to have severe oral hemorrhagic mucositis with PLT count <10 K/μL requiring daily PLT transfusions. Post-transfusion PLT counts show poor responses to PLT transfusions; from a pretransfusion PLT count of 12K, she has a PLT count of 8 K after transfusion. Percentage reactive antibody for HLA antibodies shows 100% reactivity suggesting severe alloimmunization. Besides oral bleeding, she does not have any other bleeding symptoms. How would we support this patient through engraftment?

Issues

This patient has HLA alloimmunization resulting in transfusion-refractory thrombocytopenia. This condition may present with or without donor-specific antibodies. The reader is referred to comprehensive reviews for a detailed discussion of donor-specific antibodies, where the major issue is one of promoting engraftment [56]. Since she received a fully matched graft, she does not have donor-specific antibodies. HLA antibodies increase her risk of bleeding due to transfusion-refractory thrombocytopenia, pre-engraftment.

How prevalent is transfusion-refractory thrombocytopenia?

In a large prospective trial of prophylactic PLT, transfusions in 816 patients (PLADO study) showed that the incidence of HLA alloimmunization was 8%. [57] In this study HLA alloimmunization was defined as defined as (1) an increase in HLA Class I panel-reactive antibodies to ≥20%, and (2) clinical refractoriness, defined as 2 consecutive ≤4 hours post transfusion corrected PLT count increments (CCI) of <5000. Corrected PLTPLT CCI are calculated using patient's body surface area, Platelets (PLTPLT) count increment (calculated by using the 15 minutes - 1 hour post-transfusion PLT-PLT count).

The CCI $\times 10^9$/L (CCI) is calculated from the PLT Increment, patient's body surface area in m^2(BSA) and the dose of PLTs transfused $\times 10^{11}$(PD):-

$$CCI = PI \times BSA \times PD^{-1}$$

With a median follow up of 30 days in this study, Poor CCI was prevalent in 17% of recipients. Most providers taking care of transplant patients are unlikely to use this formula on a daily basis since they will likely not have access to the dose of PLTs transfused. Centers should collaborate closely with their transfusion medicine departments in such challenging patient scenarios to determine whether transfusion-refractoriness is immune-mediated and to determine the threshold for prophylactic PLTs transfusions in patients with severe HLA alloimmunization.

There can be both immune and nonimmune causes of poor response to PLT transfusions (Active bleeding, sepsis, medications, disseminated intravascular coagulation, Splenomegaly). Detection of high percentage of HLA antibodies and excluding nonimmune conditions increase the likelihood of a serologic etiology for transfusion-refractoriness.

Given lack of prospective studies of management, a recent review summarized clinical dilemmas and strategies for managing alloimmunization when definitive evidence based strategies do not exist [58,59]. Virtually all patients with hematological malignancies already receive apheresis PLTs, which lower the risk of HLA alloimmunization.

In patients with severe alloimmunization (multiparous females), HLA matching of PLTs can be performed. The transfusion medicine departments supporting transfusion management in the care of hematopoietic stem cell patients usually have policies for provision of HLA selected products using a strategy of antibody avoidance, or HLA matching or cross matching of PLTs.

Gavya et al. evaluated if there was a difference between using random apheresis PLTs vs HLA-selected PLTs vs pooled PLTs in HLA-sensitized patients in a single-institution retrospective study [60]. The success rates of random apheresis PLTs, HLA-selected PLTs and pooled PLTs was 31%, 80%, and 35%, respectively. They concluded that HLA-selected PLTs resulted in higher mean CCIs and more successful transfusions.

There is currently a threshold of 20K PLTs for patients with hematological malignancies. In inpatient settings where PLT counts are closely monitored, the PLT threshold is lower at 10K, with exceptions for active bleeding and procedures [59,61]. There is not a clear standard of care in the United States for PLT transfusion thresholds in patients with HLA alloimmunization. Most of the published data regarding treatment strategies comes from the NHS experience.

Other strategies reports as case series involve 24 hours continuous infusion of PLTs [62]. These are resource-intensive approaches that may be prohibitive in the setting of PLT shortages. Academic transplant centers work closely with their collaborating transfusion medicine departments to establish standard of care guidelines within each institution. Novel HLA matching strategies have been studied, mostly in single-center studies to help effectively utilize a precious resource [63].

In summary, transfusion medicine is critical important for optimal supportive care of the post-transplant patient, both in the immediate setting of transplant and later post-engraftment. While progress has been made in product selection and thresholds for transfusion, future studies are needed to develop evidence-based strategies or curative approaches for patients with one of the most vexing problems such as HLA alloimmunization and refractoriness to platelet transfusions. Close collaboration between transplant centers and transfusion medicine departments is vital to provide the best supportive and cost-effective care.

Conflicts of Interest

Dr. Vasu has consulted for Omeros Therapeutics, Johnson and Johnson. Kiadis Inc has an exclusive licensing agreement with Ohio State University for a cellular therapy product. No conflicts relevant to this article.

Dr. Booth and Dr. Adkins do not have any conflicts of interest.

References

[1] Elemary M, Seghatchian J, Stakiw J, Bosch M, Sabry W, Goubran H. Transfusion challenges in hematology oncology and hematopoietic stem cell transplant - literature review and local experience. Transfus Apher Sci 2017;56(3):317–21.

[2] Juric MK, Ghimire S, Ogonek J, et al. Milestones of hematopoietic stem cell transplantation - from first human studies to current developments. Front Immunol 2016;7:470.

[3] Ikeda K, Ohto H, Okuyama Y, et al. Adverse events associated with infusion of hematopoietic stem cell products: a prospective and multicenter surveillance study. Transfus Med Rev 2018;32(3):186–94.

[4] Benekli M, Anderson B, Wentling D, Bernstein S, Czuczman M, McCarthy P. Severe respiratory depression after dimethylsulphoxide-containing autologous stem cell infusion in a patient with AL amyloidosis. Bone Marrow Transplant 2000;25(12):1299–301.

[5] Truong TH, Moorjani R, Dewey D, Guilcher GM, Prokopishyn NL, Lewis VA. Adverse reactions during stem cell infusion in children treated with autologous and allogeneic stem cell transplantation. Bone Marrow Transplant 2016;51(5):680–6.

[6] Zenhausern R, Tobler A, Leoncini L, Hess OM, Ferrari P. Fatal cardiac arrhythmia after infusion of dimethyl sulfoxide-cryopreserved hematopoietic stem cells in a patient with severe primary cardiac amyloidosis and end-stage renal failure. Ann Hematol 2000;79(9):523–6.

[7] Shu Z, Heimfeld S, Gao D. Hematopoietic SCT with cryopreserved grafts: adverse reactions after transplantation and cryoprotectant removal before infusion. Bone Marrow Transplant 2014;49(4):469–76.

[8] Cordoba R, Arrieta R, Kerguelen A, Hernandez-Navarro F. The occurrence of adverse events during the infusion of autologous peripheral blood stem cells is related to the number of granulocytes in the leukapheresis product. Bone Marrow Transplant 2007;40(11):1063–7.

[9] Namdaroglu S, Tekgunduz E, Bozdag SC, et al. Microbial contamination of hematopoietic progenitor cell products. Transfus Apher Sci 2013;48(3):403–6.

[10] Foundation for the Accreditation of Cellular Therapy. Hematopoietic cellular therapy. 2018. https://www.ebmt.org/sites/default/files/2018-06/FACT-JACIE7thEditionStandards.pdf.

[11] Klein MA, Kadidlo D, McCullough J, McKenna DH, Burns LJ. Microbial contamination of hematopoietic stem cell products: incidence and clinical sequelae. Biol Blood Marrow Transplant 2006;12(11):1142–9.

[12] Sauer-Heilborn A, Kadidlo D, McCullough J. Patient care during infusion of hematopoietic progenitor cells. Transfusion 2004;44(6):907–16.

[13] Dal MS, Tekgunduz E, Cakar MK, et al. Does microbial contamination influence the success of the hematopoietic cell transplantation outcomes? Transfus Apher Sci 2016;55(1):125–8.

[14] Liang R. How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood 2009;113(14):3147–53.

[15] Krishnan A. Stem cell transplantation in HIV-infected patients. Curr Opin HIV AIDS 2009;4(1):11–15.

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

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

[18] Akkok CA, Seghatchian J. Immunohematologic issues in ABO-incompatible allogeneic hematopoietic stem cell transplantation. Transfus Apher Sci 2018;57(6):812–15.

[19] Foundation for the Accreditation of Cellular Therapy. Hematopoietic Cellular Therapy. 2018. https://www.ebmt.org/sites/default/files/2018-06/FACT-JACIE7thEditionStandards.pdf.

[20] Janatpour KA, Kalmin ND, Jensen HM, Holland PV. Clinical outcomes of ABO-incompatible RBC transfusions. Am J Clin Pathol 2008;129(2):276–81.

[21] Cohn CS. Transfusion support issues in hematopoietic stem cell transplantation. Cancer Control 2015;22(1):52–9.

[22] Holbro A, Passweg JR. Management of hemolytic anemia following allogeneic stem cell transplantation, Hematology/the Education Program of the American Society of Hematology. American Society of Hematology. Educ Program 2015;2015:378–84.

[23] Rowley SD. Hematopoietic stem cell transplantation between red cell incompatible donor-recipient pairs. Bone Marrow Transplant 2001;28(4):315–21.

[24] Booth GS, Gehrie EA, Savani BN. Response to "What is the optimal approach to major ABO-incompatible allogeneic stem cell transplantation". Biol Blood Marrow Transplant 2013;19(12):1760–1.

[25] Stussi G, Huggel K, Schanz U, Passweg JR, Seebach JD. Levels of anti-A/B antibodies after ABO-incompatible hematopoietic stem cell transplantation. Transplant Proc 2005;37(2):1385–7.

[26] Chen J, Liu F. Analysis of ABO chimera from peripheral red cells and reticulocytes by flow cytometry and micro gel column technique in patients post-ABO-incompatible HSCT. Clin Transplant 2018;32(2).

[27] Ziemann M, Thiele T. Transfusion-transmitted CMV infection - current knowledge and future perspectives. Transfus Med 2017;27(4):238–48.

[28] Bowden RA, Slichter SJ, Sayers M, et al. A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. Blood 1995;86(9):3598–603.
[29] Weisberg SP, Staley EM, Williams LA, et al. Survey on transfusion-transmitted cytomegalovirus and cytomegalovirus disease mitigation. Arch Pathol Lab Med 2017;141(12):1705–11.
[30] INTERCEPT® Blood System for Platelets [package insert]. Concord, CA: Cerus Corporation; 2018. https://intercept-usa.com/images/resources/Package_Inserts/INTERCEPT_Blood_System_INT2230B_LV_Package_Insert_May-2018.pdf.
[31] C. FDA, Implementation of pathogen reduction technology in the manufacture of blood components in blood establishments: questions and answers; draft guidance for industry., (2019).
[32] Cid J. Prevention of transfusion-associated graft-versus-host disease with pathogen-reduced PLTs with amotosalen and ultraviolet A light: a review. Vox Sang 2017;112(7):607–13.
[33] Bahar B, Tormey CA. Prevention of transfusion-associated graft-versus-host disease with blood product irradiation: the past, present, and future. Arch Pathol Lab Med 2018;142(5):662–7.
[34] Mark M, Fung K, Eder AF, Spitalnik SL, Westhoff CM. Technical Manual. In: 19th ed. Bethesda. MD: AABB; 2017.
[35] Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. JAMA 2016;316(19):2025–35.
[36] Estcourt LJ, Malouf R, Trivella M, Fergusson DA, Hopewell S, Murphy MF. Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support. Cochrane Database Syst Rev 2017;1:CD011305.
[37] Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Aabb, PLT transfusion: a clinical practice guideline from the AABB. Ann Int Med 2015;162(3):205–13.
[38] Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis PLT-transfusion strategy for hematologic cancers. New Engl J Med 2013;368(19):1771–80.
[39] Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic PLT transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. Lancet 2012;380(9850):1309–16.
[40] Price TH, Boeckh M, Harrison RW, et al. Efficacy of transfusion with granulocytes from G-CSF/dexamethasone-treated donors in neutropenic patients with infection. Blood 2015;126(18):2153–61.
[41] 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):1687–94.
[42] Schetelig J, Breitschaft A, Kroger N, et al. After major ABO-mismatched allogeneic hematopoietic progenitor cell transplantation, erythroid engraftment occurs later in patients with donor blood group A than donor blood group B. Transfusion 2005;45(5):779–87.
[43] 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):870–1.
[44] Yang X, Levis M. Pulsed-high-dose dexamethasone as a treatment for pure red cell aplasia following ABO-incompatible allogeneic stem cell transplantation. Transfus Med 2014;24(4):246–8.
[45] 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):108–12.
[46] Heyll A, Aul C, Runde V, Arning M, Schneider W, Wernet P. Treatment of pure red cell aplasia after major ABO-incompatible bone marrow transplantation with recombinant erythropoietin. Blood 1991;77(4):906.
[47] Verholen F, Stalder M, Helg C, Chalandon Y. Resistant pure red cell aplasia after allogeneic stem cell transplantation with major ABO mismatch treated by escalating dose donor leukocyte infusion. Eur J Haematol 2004;73(6):441–6.
[48] Chapuy CI, Kaufman RM, Alyea EP, Connors JM. Daratumumab for delayed red-cell engraftment after allogeneic transplantation. New Engl J Med 2018;379(19):1846–50.
[49] Salas MQ, Alahmari A, Lipton JH. Successful treatment of refractory red cell aplasia after allogeneic hematopoietic cell transplantation with daratumumab. Eur J Haematol 2020;104(2):145–7.
[50] Petz LD. Immune hemolysis associated with transplantation. Semin Hematol 2005;42(3):145–55. doi:10.1053/j.seminhematol.2005.05.017.
[51] Nadarajah L, Ashman N, Thuraisingham R, Barber C, Allard S, Green L. Literature review of passenger lymphocyte syndrome following renal transplantation and two case reports. Am J Transplant 2013;13(6):1594–600.
[52] Panaro F, DeChristopher PJ, Rondelli D, et al. Severe hemolytic anemia due to passenger lymphocytes after living-related bowel transplant. Clin Transplant 2004;18(3):332–5.
[53] Bornhauser M, Ordemann R, Paaz U, et al. Rapid engraftment after allogeneic ABO-incompatible peripheral blood progenitor cell transplantation complicated by severe hemolysis. Bone Marrow Transplant 1997;19(3):295–7.
[54] Gajewski JL, Petz LD, Calhoun L, et al. Hemolysis of transfused group O red blood cells in minor ABO-incompatible unrelated-donor bone marrow transplants in patients receiving cyclosporine without posttransplant methotrexate. Blood 1992;79(11):3076–85.
[55] Lee HJ, Gulbis A, De Padua Silva L, et al. Rituximab for passenger lymphocyte syndrome associated with allogeneic SCT. Bone Marrow Transplant 2008;42(1):67–9.
[56] Gladstone DE, Bettinotti MP. HLA donor-specific antibodies in allogeneic hematopoietic stem cell transplantation: challenges and opportunities, Hematology/the Education Program of the American Society of Hematology. American Society of Hematology. Educ Progr 2017;2017(1):645–50.
[57] Hess JR, Trachtenberg FL, Assmann SF, et al. Clinical and laboratory correlates of PLT alloimmunization and refractoriness in the PLADO trial. Vox Sang 2016;111(3):281–91.
[58] Stanworth SJ, Navarrete C, Estcourt L, Marsh J. PLT refractoriness–practical approaches and ongoing dilemmas in patient management. Brit J Haematol 2015;171(3):297–305.
[59] Prodger ARCF, Estcourt LJ, Stanworth SJ, Murphy MF. PLT transfusion: alloimmunization and refractoriness. Semin Hematol 2019 In Press.
[60] Gavva C, Barroso J, Gernsheimer T, Metcalf RA, Warner P, Pagano MB. Response to random apheresis PLTs versus HLA-selected PLTs versus pooled PLTs in HLA-sensitized patients. Transfusion 2019;59(7):2276–81.
[61] Estcourt LJ, Stanworth SJ, Murphy MF. Different PLT count thresholds to guide use of prophylactic PLT transfusions for patients with hematological disorders after myelosuppressive chemotherapy or stem cell transplantation. JAMA Oncol 2016;2(8):1091–2.
[62] Cid J, Guijarro F, Carbasse G, Lozano M. 24-h continuous infusion of PLTs for patients with PLT transfusion refractoriness. Brit J Haematol 2018;181(3):386–9.
[63] Karlstrom C, Linjama T, Edgren G, Lauronen J, Wikman A, Hoglund P. HLA-selected PLTs for PLT refractory patients with HLA antibodies: a single-center experience. Transfusion 2019;59(3):945–52.