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Journal

Transfusion, 58(11)

ISSN

0041-1132

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Publication Date

2018-11-01

DOI

10.1111/trf.14871

Peer reviewed

HHS Public Access

Author manuscript

Transfusion. Author manuscript; available in PMC 2019 December 14.

Published in final edited form as:

Transfusion. 2018 November ; 58(11): 2483–2489. doi:10.1111/trf.14871.

How we evaluate red blood cell compatibility and transfusion support for patients with sickle cell disease undergoing hematopoietic progenitor cell transplantation

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Abstract

Multiple hematopoietic progenitor cell (HPC) transplantation options for patients with sickle cell disease (SCD) are currently under investigation. Patients with SCD have a high rate of alloimmunization to red blood cell antigens, often complicating transfusion support. Transfusion reactions, including acute and delayed hemolytic reactions, have been observed despite immunosuppressive regimens. Allogeneic donor transplants have been shown to carry a risk of prolonged reticulocytopenia and acute hemolysis with severe anemia in nonmyeloablative regimens. We discuss our experience providing transfusion support to patients with SCD undergoing HPC transplantation, propose an outline for a complete pretransplantation evaluation, and discuss donor/recipient compatibility issues and their implications.

Hematopoietic progenitor cell (HPC) transplantation can cure sickle cell disease (SCD),[1,2] but transfusion support of these patients presents unique challenges that are not frequently seen in patients undergoing HPC transplantation for other indications.[3] Patients with SCD have special transfusion needs due to high rates of red blood cell (RBC) alloimmunization.[4] Antigen-negative units are necessary for existing antibodies and recommended for prophylactic antigen matching,[4,5] which minimizes future alloimmunization and hemolytic transfusion reactions.[6,7] During HPC transplantation, in addition to being exposed to allogeneic RBC units for transfusion support, patients with SCD are also exposed to allograft-derived RBCs from the donor's hematopoietic stem cells.

Several studies have chronicled the transfusion strategy, incidence of new RBC antibodies, and morbidity from alloimmunization during HPC transplantation in this patient population.[3,8,9] These reports have documented challenges such as procuring blood that is negative for

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

high-prevalence RBC antigens and complications such as donor/recipient incompatibility leading to prolonged reticulocytopenia and transfusion dependence. Input from a transfusion medicine specialist during planning and management of HPC transplantation in patients with SCD is critical. At the National Institutes of Health (NIH) Clinical Center, a transfusion medicine consultation was performed on all patients with SCD who were candidates for transplantation. In this article, we review our consultative process and provide a template for consultation (Fig. 1), which was developed to ensure patient safety for this complex and increasingly common clinical scenario.

OUR EXPERIENCE

At the NIH Clinical Center, 93 patients with SCD have undergone HPC transplantation from matched related donors or haploidentical related donors since 2003. The National Heart, Lung, and Blood Institute (NHLBI) clinical research protocols we support[10,11] use nonmyeloablative regimens, which leave the patient in a state of mixed lymphocyte chimerism after transplant. Potential exists for recipient alloantibodies to persist after transplantation and bind to allograft-derived or transfused RBCs.[9] As a result, we pay particular attention to donor-recipient RBC compatibility during this process. It should be noted that mixed chimerism also has been reported in patients receiving myeloablative HPC transplantation.[12] The NIH Clinical Center has also performed five transplantations using autologous marrow with gene therapy.[13] In these cases, donor/recipient compatibility is moot; however, we perform an abbreviated consult as the issue of transfusion support remains critical.

Working in partnership with the clinical transplantation team throughout the process is essential. They schedule appointments for the potential donor and recipient in our department 2 to 4 months before transplantation, so we can obtain history and laboratory samples and have sufficient time to perform supplementary laboratory testing if necessary. We then complete the transfusion medicine consultation 1 to 3 months before HPC transplantation; it is a standard component of the pretransplantation evaluation and is included on checklists used by transplantation coordinators.

EVALUATION

Our evaluation requires thorough history-taking, laboratory testing, and interpretation (Tables 1 and 2). The goal is to determine 1) the eligibility of the donor and RBC compatibility; 2) the transfusion strategy, specifically the type of RBCs that will be provided; and 3) the feasibility of transfusion support and monitoring of donor- and residual recipient-derived erythropoiesis. At the time of our evaluation, donor/recipient human leukocyte antigen (HLA) compatibility has already been assessed by the clinical transplantation team; we confirm the results for all donor/recipient pairs as a quality measure. Determination of HLA compatibility is critical, but will not be discussed here.

DONOR ASSESSMENT, RECIPIENT TRANSFUSION HISTORY, AND RBC COMPATIBILITY

Donor suitability and eligibility

We obtain the donor's full medical history and assess for any contraindications to granulocyte–colony-stimulating factor (G-CSF) stimulation or apheresis peripheral blood stem cell (PBSC) collection. Allogeneic donors may have sickle cell trait; although the National Marrow Donor Program accepts sickle trait donors only for marrow donation, we have collected PBSCs from these donors without complications and do not consider this a contraindication.[14,15] Most donors are healthy, and any medical conditions are evaluated on a case-by-case basis with regard to safety of the donor and the acceptability of the product. Cardiac abnormalities such as coronary artery disease or heart failure are the most commonly encountered health problems that cause us to exclude a donor, as the published experience suggests that G-CSF stimulation of these individuals is unsafe.[16–18]

Next, we review required donor infectious disease testing and obtain the donor's social history to identify risk factors for communicable disease. Regulations allow facilities to choose the method by which they document screening for HPC donors, and we use the donor history questionnaire[19] (DHQ) as a resource for identifying and documenting potential donor-derived risks. Identified risks are included in our consultation report and discussed with the clinical transplantation team, who may choose to proceed with the collection. Additional testing and clinical intervention may be performed if warranted. The potential for transmission of infectious disease via HPC transplantation is documented.[20] In one case, *Plasmodium falciparum* was transmitted from an asymptomatic donor to the recipient via the HPC product.[21] As a result, we recommend polymerase chain reaction and enzyme-linked immunosorbent assay–based malaria testing for any donors who present a malaria risk based on the DHQ. Infected donors could be treated before HPC collection or, in urgent cases, the recipient could be presumptively treated after transplantation.

Recipient transfusion history

First, we obtain the patient's transfusion history directly from the individual and by contacting other treating institutions. All antibodies (including those that are no longer demonstrable) are recorded in our laboratory information system. We pay particular attention to any acute hemolytic, delayed hemolytic, or hyperhemolytic episodes noted by the patient or outside institutions. History of other transfusion reactions, such as allergic or febrile nonhemolytic reactions, is noted in our assessment.

RBC compatibility between donor and recipient

Evaluating donor/recipient RBC compatibility is the most extensive and specialized portion of our assessment. We test the recipient's ABO/Rh type, antibody screen, direct antiglobulin test (DAT), and RBC phenotype (at a minimum, D, C, E, c, e, K1, Fy^a, Fy^b, Jk^a, Jk^b, S, and s). If any alloantibodies are on record, we determine which are still demonstrable and assess for any new ones. Serologic methods of phenotyping may be used, but we recommend RBC genotyping techniques. Many patients with SCD are recently transfused, which renders

serologic typing unreliable.[22] Furthermore, RBC genotyping can detect certain clinically relevant antigenic variants not identified by serologic methods. Finally, confirming the presence of the Duffy *GATA* box mutation[23] may increase the number of units available for transfusion support of the recipient. For the donor, we perform the ABO/Rh typing, antibody screen, and RBC phenotype.

For all recipient alloantibodies (historic or current), we determine whether the donor expresses the corresponding antigen (and conversely for any donor alloantibodies, although these are rare). For donors, serologic phenotyping is often adequate. However, if the recipient is alloimmunized against a RBC antigen that lacks readily available antisera (such as Js^a), or we wish to probe the donor for antigenic variants present in the recipient, RBC genotyping is warranted. If several HLA-identical donors are eligible, such as siblings in a related transplantation setting, RBC genotyping may guide the final selection of the donor.[24]

If donor or recipient laboratory evaluation reveals unexpected results, such as serologic evidence of weak D, unidentified alloantibodies, presence of autoantibodies, or discrepant phenotyping, we continue our investigation. This may involve testing additional RBCs on the antibody identification panel or performing additional molecular testing such as *RHD* or *RHCE* genotyping.

Finally, we perform a crossmatch using the recipient plasma and donor RBCs. In one instance, our recipient had no history of alloantibodies and a negative antibody screen, but the crossmatch was positive. Further investigation revealed that the recipient had formed anti-V, and her donor expressed the low-prevalence V antigen.

When RBC incompatibility exists in a donor/recipient pair, we document in our consult note the specific incompatibilities, comment on the risk of hemolysis as reported in scientific literature, and coordinate with the cellular therapy laboratory for RBC and/or plasma depletion of the product. In some cases, we may recommend evaluation of alternate donors. For example, one of our patients was found to have an antibody to Go^a, a low-prevalence antigen that her potential HLA-matched sibling donor expressed. As case reports suggest the antibody is clinically significant,[25,26] we recommended other donors be evaluated. Unfortunately, no alternate donor was identified. The pair was, however, deemed suitable for HPC transplantation under a clinical trial with increased intensity immunosuppression for high-risk cases. Transplantation was successful, with no evidence of hemolysis. While we cannot be certain that hemolysis would have occurred in the absence of the more intense immunosuppression, our assessment identified a risk in the donor/recipient pair, which prompted our clinical colleagues to take additional precautions. In our experience with nonmyeloablative regimens, two of three patients with clinically significant RBC incompatibility before transplantation experienced long-term hemolysis and transfusion dependence.[9] Whether patients can undergo successful HPC transplantation *despite* donor-specific RBC antibodies is unclear—published cases suggest that it may be feasible,[9] in the setting of both Rh incompatibility during myeloablative transplantation[8] and ABO incompatibility during nonmyeloablative transplantation.[27] Our experience involves conditioning with alemtuzumab, which depletes recipient- and donor-derived lymphocytes

and may decrease the risk of alloimmunization. At this time, however, there is no regimen that is known to preclude the possibility of alloimmunization or hemolysis.

Autologous donors

Autologous donors presenting for gene therapy are collected by marrow aspiration, as G-CSF stimulation is contraindicated.[28] Recent reports describe the peripheral collection of a limited number of autologous donors using plerixafor as the mobilization agent; however, the safety of this method has not yet been established.[13,29,30] The DHQ is still administered to identify and address risk factors. While the transplant is autologous, obtaining the transfusion history and performing immunohematologic evaluation remain critical for the allogeneic transfusion strategy in the peritransplantation period.

TRANSFUSION STRATEGY

Type of RBCs to transfuse

We use hemoglobin (Hb)S-negative, leukoreduced, irradiated units. Accepted practice is to begin irradiating as soon as a patient is slated for transplant and continue indefinitely.[31] Due to the preponderance of patients undergoing HPC transplantation at our center, we irradiate all cellular blood components. Our experience is with ABO-identical or ABO minor–incompatible HPC transplantations. With regard to ABO blood groups, we select products according to standard medical practice,[31] including a stepwise transition from the recipient's to the donor's ABO type in ABO-mismatched HPC transplantation.[32]

We provide RBC units that are negative for any antigens against which the recipient or donor has clinically significant alloantibodies, whether current or historic. We then consider prophylactic antigen matching. For patients with SCD but without any RBC alloantibodies, we match the major Rh and Kell antigens (D, C, E, c, e, K1). For patients with RBC alloimmunization, we add prophylactic matching of the Duffy, Kidd, and S/s antigens (Fy^a, Fy^b, Jk^a, Jk^b, S, s). If the recipient or the donor is negative for any of these, we provide antigen-negative units. This strategy enables us to honor our standard prophylactic matching procedure for patients with SCD in a way that respects both the recipient's and the donor's hematopoietic system. In addition, it enables us to detect markers of erythropoiesis (described below), both allograft-derived and residual from the recipient, without interference from transfused units. If all antigens cannot be matched, priority is given to those antigens with the greatest potential clinical significance. Of note, if molecular testing reveals that the patient and donor harbor the Duffy *GATA* box mutation, we can provide Fy^b-positive RBC units.[33]

Other transfusion considerations

Additional concerns may also be addressed by transfusion medicine, such as manipulation of blood products to avoid recurrence of previously experienced transfusion reactions. Most frequently, we see HLA alloimmunization in the potential HPC recipient,[34] which may require recruitment of HLA-matched platelet (PLT) donors or PLT crossmatching during thrombocytopenia of engraftment. After transplantation, when notified by the clinical team

that the patient will be receiving care at an outside institution, we communicate product requirements to those transfusion services.

FEASIBILITY AND MONITORING

Feasibility of transfusion support

The number of units needed for adequate support varies in ways that are both predictable (the type of chemotherapy regimen, rate of engraftment, and risk of graft rejection) and unpredictable (bleeding or hemolysis events). The clinical transplantation team can often reliably estimate how many units the patient will require, and we also recommend tracking these patients' usage in your own institution. Our patients receive a mean of 20.4 RBC units after protocol enrollment (median, 15.0 units; range, 7.0–99.0 units), some transfused before transplantation, with a mean of 12.3 units after transplantation (median, 6.0 units; range, 0–87.0 units).[9]

There are three main reasons that transfusion support may not be feasible: alloimmunization against multiple antigens, single alloantibodies against high-prevalence antigens, or history of severe transfusion reactions.

In patients with multiple alloantibodies or a single alloantibody against a high-prevalence antigen (such as anti-U), obtaining an adequate number of RBC units to maintain the patient during the peritransplantation period may be difficult to impossible. Sometimes this problem can be overcome by advanced donor recruitment, coordination with various blood suppliers, or both. In other cases, we may consider removing some antigens from our prophylactic matching strategy and only provide units that are negative for antigens to which the patient is already immunized. While not ideal, this may allow us to procure a sufficient number of RBC units. Rarely, we recommend against transplantation. We always advise the clinical transplantation team of our limitations so they can weigh the risks and benefits of HPC transplantation. If they wish to proceed, we are updated on the timelines of the pretransplantation procedures and anticipated date of induction chemotherapy, *at least a month* in advance so that we can obtain a sufficient number of RBC units meeting the criteria determined in our transfusion strategy analysis.

Finally, severe transfusion reactions may preclude the ability to provide safe transfusion support. For example, one of our patients had a history of two episodes of posttransfusion hyperhemolysis (reaching a Hb nadir of 2.5 g/dL) despite receiving phenotypically matched RBC units. A thorough reference laboratory evaluation failed to elucidate the underlying cause. Because the pathologic mechanism triggering these reactions remained unknown, we had no strategy to reliably prevent them. Therefore, the transfusions that would be required during transplantation had the potential to induce fatal hyperhemolysis. We recommended against HPC transplantation for this patient, and after discussion, the clinical team agreed.

Markers of erythropoiesis

Any antigens that are expressed by the donor's RBCs but not the recipient's can serve as markers of allograft-derived erythropoiesis. Antigens expressed by the recipient's RBCs but not the donor's mark residual recipient erythropoiesis. In this way, we use RBC phenotyping

to provide qualitative information regarding RBC chimerism,[35] although notably, it does not provide quantitative results. Of course, transfused RBC units must be negative for these antigens to draw such conclusions, and we design a personalized transfusion regimen in our pretransplantation consultations (Fig. 1).

CONCLUSION

The strategy described above reflects our current efforts to ensure donor/recipient compatibility, provide the best available transfusion support, and minimize the risk of complications during HPC transplantation. RBC genotyping by a variety of molecular methods[36] is available at many transplantation centers and provides an ideal testing solution for frequently transfused patients. We often employ a combination of molecular and serologic methods in our laboratory. Lack of access to molecular methods may be a limitation, but does not preclude the potential benefit to patients with SCD of a thorough pretransplantation evaluation with serologic testing.

Patients with SCD have special transfusion needs and are at risk of immunohematologic complications during HPC transplantation. A transfusion medicine consultation is important for planning purposes and patient safety. Involvement by the transfusion medicine service before transplantation has the potential to predict and prevent morbidity by ensuring the blood bank is prepared to provide sufficient, highly personalized blood products. The considerations outlined above and the template in Fig. 1 are novel resources that will aid in this task as HPC transplantation for patients with SCD becomes more common.

ACKNOWLEDGMENTS

We acknowledge Rebecca P. Coward, MT(ASCP)SBB (Department of Transfusion Medicine, NIH Clinical Center) for assistance evaluating patients and developing the consultation report template. We acknowledge Drs Matthew M. Hsieh, Courtney D. Fitzhugh, and John F. Tisdale (NHLBI) for developing the clinical trials , , , , and ; caring for the patients during and after transplantation; and providing critical review of this manuscript. We acknowledge Dr Harvey G. Klein and Elizabeth J. Furlong (Department of Transfusion Medicine, NIH Clinical Center) for critical review of the manuscript.

This work was supported by the Intramural Research Program (project ID Z99 CL999999) of the NIH Clinical Center.

ABBREVIATIONS:

DHQ	donor history questionnaire
SCD	sickle cell disease

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History of Present Illness:
The patient Jane Patient is a 36 year-old female with homozygous sickle cell disease (SCD) complicated by frequent vaso-occlusive pain crises, pulmonary hypertension, and alloimmunization to multiple red cell antigens with a history of delayed hemolytic transfusion reaction, who is currently being evaluated for hematopoietic progenitor cell (HPC) transplantation from the matched-related donor Joe Patient, a healthy 47 year-old male with sickle cell trait.

	Name	Medical Record Number	Relationship	Sex
Recipient	Jane Patient	000-0000	N/A	Female
Donor	Joe Patient	111-1111	Brother	Male

Transfusion History:
Number of transfusions: Approximately 150 (on monthly red cell exchange since June 2017)
Last known transfusion: May 7, 2018 (Mercy Hospital)
History of autoantibodies: none
History of alloantibodies: anti-E, anti-Fya, anti-Jkb, anti-Jsa, anti-S
History of transfusion reactions: Delayed hemolytic transfusion reaction, May 2012 (University Hospital)

Laboratory data:
ABO-type: minor incompatible (Recipient: A; Donor: O)
HLA-type: 6/6 HLA match

	D	C	E	c	e	K1	Jsa	Jsb	Fya	Fyb	Jka	Jkb	S	s
Recipient	+	-	-	+	+	-	-	+	-	-	+	-	-	+
Donor	-	+	-	+	+	-	-	+	-	-	+	-	-	+

Recipient and donor RBC phenotype confirmed by molecular red cell genotyping*
GATA box mutation present

Recipient Antibody Screen: positive; anti-E, anti-Jsa (July 4, 2018)
Recipient DAT: negative (July 4, 2018)
Donor/Recipient crossmatch: compatible (July 4, 2018)

Assessment: 36 year-old female with homozygous SCD currently being evaluated for HPC transplantation from the HLA-matched, ABO minor incompatible, related donor, Joe Patient. This donor/recipient pair is acceptable from a transfusion medicine perspective.

Eligibility:

1. The prospective recipient has alloantibodies against the E, Fya, Jkb, Jsa, and S antigens. The prospective donor is negative for those antigens.
2. The prospective donor types C positive, whereas the prospective recipient is C negative. There is the potential for the recipient to develop an anti-C antibody.
3. The prospective recipient types D positive, whereas the prospective donor is D negative. There is the potential for the donor-derived immune system to develop an anti-D antibody.
4. The selected donor has a deferral for living in a malaria endemic region less than 3 years ago. The risks have been discussed with the clinical transplantation team, and PCR testing for *Plasmodium* will be performed on the HPC product.
5. Vascular assessment shows that the donor's peripheral veins are suitable for apheresis.

Transfusion Strategy:

1. If the team chooses to proceed with this donor/recipient pair, we recommend to transfuse group O, RhD-negative RBCs, phenotype-matched for all tested antigens (C, E, K1, Fya, Jkb, S negative). Crossmatch would be used to select Jsa-negative units.

Feasibility & Monitoring:

1. Obtaining blood that meets all required criteria is possible, but will require additional effort. Please notify us at least one month in advance of the patient's expected arrival, so we can collect the appropriate units to provide transfusion support.
2. The C antigen could be used as a marker of allograft-derived erythropoiesis.
3. The D antigen could be used as a marker of residual recipient RBCs.

*These results are not intended as the sole means for clinical diagnosis or patient management decisions. There are situations where the red cell genotype of a person may not reflect the red cell phenotype and not all performance characteristics have been determined. Nucleotide substitutions that inactivate gene expression or cause rare new variant alleles may not be identified in these assays.

Fig. 1.
Template for a transfusion medicine consultation in the pretransplantation setting for a patient with SCD.

TABLE 1.

Pertinent information during the initial consultation with the recipient and donor

Recipient
Date and location of transfusions within the past 3 months
Additional hospitals where the patient has been treated/transfused
Estimated number of RBC units transfused over the patient's lifetime
History of exchange transfusions
History of RBC alloantibodies
History of RBC autoantibodies
History of HLA antibodies
History of acute transfusion reactions
History of delayed hemolytic transfusion reactions
Does the patient typically receive premedication prior to transfusion?
Donor
Any ongoing medical conditions
Specifically, any cardiac abnormalities
List of current medications
Past medical and surgical history
Responses to the DHQ
Vascular assessment

TABLE 2.

Laboratory evaluation before HPC transplantation

	Recipient	Donor
Information from outside blood banks and transfusion services	RBC allo- or autoantibodies	
	Reported transfusion reactions	
	Date of last transfusion	
	ABO, Rh, and full RBC phenotype (if available) of any transfusions in the past 3 months	
	Transfusion strategy for this patient	
Initial testing	ABO type	ABO type
	RBC antibody screen	RBC antibody screen
	DAT	RBC phenotype by serologic methods
	RBC phenotype as predicted by RBC genotyping (if not available, by serologic methods)	
	Donor/recipient crossmatch	
Additional testing, as indicated	Identification of any antibodies currently demonstrating	Identification of any antibodies currently demonstrating
	Identification of any antibody detected in the donor/recipient crossmatch	RBC phenotype as predicted by RBC genotyping
	Elution to evaluate a positive DAT *RHD* or *RHCE* genotyping	*RHD* or *RHCE* genotyping