Bloodless Medicine in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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BACKGROUND: Allogeneic hematopoietic stem cell transplantation (alloHSCT) poses challenges for patients who decline blood products because of religious beliefs or other reasons. Despite potential curative prospects, many institutions refrain from offering alloHSCT to patients who decline blood products because of safety concerns associated with cytopenias.

OBJECTIVES: This review focuses on one institution's experience of conducting alloHSCT without blood components, emphasizing preparation and supportive care.

METHODS: The approach of conducting alloHSCT without blood components, which involves ABO-compatible donor matching, nonmyeloablative regimens, and pretransplantation optimization of red blood cell production, is discussed.

FINDINGS: The clinical team can minimize transfusion needs by using erythropoiesis-stimulating agents, thrombopoietin agonists, and peri- and post-transplantation management strategies. These recommendations can ensure patient safety and successful outcomes with bloodless medicine.

KEYWORDS
bloodless medicine; transfusion; allogeneic hematopoietic stem cell transplantation

DIGITAL OBJECT IDENTIFIER
10.1188/24.CJON.463-468

BECAUSE OF MYELOSUPPRESSION DURING THE PRE-ENGRAFTMENT PHASE, the use of allogeneic hematopoietic stem cell transplantation (alloHSCT) presents challenges. Most transplantation centers refrain from offering alloHSCT to patients who decline blood products because of potential safety concerns and the risk of bleeding-related mortality (Beck et al., 2020). The cornerstone of care for patients declining blood products lies in detailed documentation and preparation. This review focuses on one institution's experience of conducting an alloHSCT using a nonmyeloablative regimen without blood components.

Although autologous hematopoietic stem cell transplantation has proven to be feasible in patients with multiple myeloma and other plasma cell dyscrasias who reject blood products, its applicability in those with myelodysplastic syndrome (MDS) or acute myeloid leukemia is limited (Michel et al., 2023; Zhao et al., 2019). Despite alloHSCT's potential curative prospects for high-risk MDS or acute myeloid leukemia, numerous institutions refrain from practicing bloodless medicine with alloHSCT because of the inherent risks. However, advancement in reduced intensity regimens and enhanced supportive care render alloHSCT a viable option for select patients (Beck et al., 2020).

Background

In patients who decline blood product components for religious reasons, such as Jehovah's Witness (JW) patients, bloodless medicine is not an absolute contraindication to alloHSCT. However, because of the risk of multilineage cytopenias, it is imperative to discuss the potential risks associated with alloHSCT with practicing JW patients. Restricting the administration of alloHSCT for JW patients to institutions specializing in bloodless medicine allows for an interprofessional approach to ensure patient safety, risk mitigation, proper counseling prior to transplantation, and equitable access to specialized care.

The term *bloodless medicine* refers to medical practices and procedures that are performed without the use of whole blood or major blood components, such as red blood cells, plasma, or platelets (Beck et al., 2020; Coltoff et al., 2019). Bloodless medicine is a specialty, ensuring patients receive appropriate medical care while respecting their beliefs and preferences regarding blood transfusions (Coltoff et al., 2019; Domaradzki et al.,

2024). JW patients abstain from autologous or allogeneic blood products, such as red blood cells or platelets, although some JW patients may accept blood-derived products, such as albumin or stem cells. Many JW patients are amenable to minor blood fractions and products like erythropoiesis-stimulating agents (ESAs) or granulocyte–colony-stimulating factor. Therefore, it is crucial for applicable patients to enroll in institutional bloodless medicine programs to safeguard individual preferences and communicate the personal treatment plan for each patient.

Pretransplantation Preparation and Evaluation

ABO-compatible donor matching is a mandatory prerequisite for alloHSCT. Employing a nonmyeloablative regimen (e.g., fludarabine, low-dose total body irradiation regimen) aims to diminish marrow aplasia duration, with peripheral blood stem cell sources preferred over bone marrow to expedite engraftment (Anasetti et al., 2012).

At a large academic medical center in the northeastern United States, guidelines were devised for bloodless alloHSCT, integrating ESAs, thrombopoietin receptor agonists (TPO-RAs), and standard procedures to mitigate thrombocytopenia and anemia risks. After a patient is deemed to be eligible for transplantation and an appropriate ABO-compatible donor is identified, planning ensues. Pretransplantation red blood cell production optimization can prevent profound anemia post-alloHSCT, entailing a comprehensive evaluation for nutritional anemias, including iron, B_{12}, and folate deficiencies. Clinicians prescribe parenteral cyanocobalamin for B_{12} deficiencies and oral folic acid if there is evidence of folate deficiency. The transplantation team obtains iron studies, including ferritin, transferrin saturation, and total iron-binding capacity; patients with iron deficiency receive IV iron, with retesting to ensure goal levels are achieved. This institution prefers IV iron to oral formulations because oral iron usually does not provide enough iron to correct iron-deficient erythropoiesis (Beck et al., 2020; Coltoff et al., 2019; DeLoughery, 2020).

To minimize transfusion needs, a priming method targeting a hemoglobin level greater than 12 gm/dl precedes admission for alloHSCT, with ESAs initiated four to eight weeks pretransplantation to achieve a hemoglobin level greater than or equal to 11 gm/dl (see Table 1). Managing anemia involves telemetry initiation for patients with a hemoglobin level less than 6 gm/dl, alongside ESA administration post-alloHSCT until hemoglobin levels are greater than 10 gm/dl (Beck et al., 2020; Coltoff et al., 2019; Resar & Frank, 2014). Admission triggers folic acid, vitamin B_{12}, and/or vitamin K supplementation, whereas patients of childbearing potential continue hormone contraceptives to halt menses. Thrombocytopenia management entails prophylaxis against bleeding, using TPO-RAs such as romiplostim and aminocaproic acid upon platelet count decrease to maintain a platelet count greater than 50×10^3/mcl. Refractory bleeding may necessitate aminocaproic acid, desmopressin, or tranexamic acid administration, with alternative agents such as conjugated estrogen or medroxyprogesterone for breakthrough vaginal bleeding (Beck et al., 2020; Coltoff et al., 2019).

> **"The primary goal in managing patients who decline blood products is to minimize blood loss."**

To mitigate blood loss during menstrual periods, patients of childbearing potential are initiated on oral contraceptives or gonadotropin-releasing hormone agonist agents like leuprolide at least four weeks before transplantation. Medications that impede platelet function, such as aspirin or celecoxib, are discontinued four weeks prior to alloHSCT in an effort to decrease bleeding risk (Coltoff et al., 2019). For patients requiring anticoagulants, this bloodless medicine program employs bridging agents such as low-molecular-weight or standard heparin. Close monitoring of international normalized ratio levels is crucial pretransplantation and on admission for patients requiring anticoagulants. A platelet count exceeding 10×10^3/mcl or greater before transplantation admission supports the expected decline in platelet count after chemotherapy.

Peri- and Post-Transplantation Management

The primary goal in managing patients who decline blood products is to minimize blood loss. Methods aimed at blood conservation for patients receiving bloodless medicine include the minimization of laboratory testing by decreasing and consolidating blood studies to reduce blood draws (DeLoughery, 2020). Another blood-saving technique is to use low-volume microcontainers for phlebotomy such as pediatric collection tubes. Clinicians can collect blood samples via venipuncture, reserving central venous catheter use for medication administration only. Figure 1 presents additional recommendations for reducing the need for transfusions for JW patients undergoing alloHSCT.

Management of Anemia

Telemetry is initiated in patients with a hemoglobin level less than 6 gm/dl to monitor for arrhythmias. In addition to the priming method prior to transplantation, beginning on day +6, ESAs are started and continued until hemoglobin levels are greater than 10 gm/dl. On admission, patients are started on folic acid,

IMPLICATIONS FOR PRACTICE

- Use an interprofessional approach to manage patients undergoing allogeneic hematopoietic stem cell transplantation who prefer not to receive blood products.
- Minimize blood loss and bleeding in patients with cytopenias who are not receiving transfusion support.
- Obtain education and guidelines for managing patients and their preferences regarding blood products and transfusions from bloodless medicine programs.

vitamin B_{12}, and/or vitamin K to replenish the body stores to support erythropoiesis. Patients of childbearing potential are continued on hormone contraceptive agents to facilitate the cessation of menses. All patients receive gastrointestinal ulcer prophylaxis using proton pump inhibitors to reduce the risk of gastrointestinal-related blood loss until blood counts recover post-transplantation. Stool softeners are offered daily to avoid hemorrhoidal bleeding associated with straining on defecation (Beck et al., 2020; Coltoff et al., 2019; Frank et al., 2019, 2022).

Management of Thrombocytopenia

A prophylactic approach to prevent bleeding is a standard practice in patients undergoing transplantation in bloodless medicine programs (Coltoff et al., 2019). This includes the use of TPO-RAs, such as romiplostim 4 mcg per week starting on day +6, until the platelet count is greater than 50×10^3/mcl. Patients also receive 500–1,000 mg oral aminocaproic acid two to three times per day once the platelet count is less than 10×10^3/mcl (Coltoff et al., 2019). Caution is exercised in patients with renal dysfunction because of the potential risk of seizures.

In the event of refractory bleeding, the transplantation team uses 1–4 g of aminocaproic acid every four to six hours, 0.3 mcg/kg IV desmopressin twice daily, and/or 500 mg tranexamic acid via nebulizer three times daily or soaked onto pledgets three times daily. Alternative agents, such as conjugated estrogen or medroxyprogesterone, may be employed for breakthrough vaginal bleeding (Beck et al., 2020; Coltoff et al., 2019).

Interprofessional Care

An interprofessional approach in the context of bloodless medicine ensures that patient preferences regarding the refusal of blood products are respected and integrated into the overall care plan. This approach involves collaboration among hematologists, surgeons, anesthesiologists, nurses, ethicists, and other healthcare professionals to develop comprehensive treatment strategies that align with the patient's beliefs and medical needs. In practical terms, this means establishing clear protocols and guidelines within healthcare institutions to manage patients who decline blood products. For safety and quality, medical records can include specific flags or alerts that notify clinicians of patients' preferences and necessary accommodations. These alerts can serve as reminders to tailor medical interventions and treatments accordingly, such as using blood substitutes or alternative methods to manage anemia and bleeding risks (Beck et al., 2020; Frank et al., 2022).

This interprofessional approach requires specialized education and training programs. Nurses have a crucial role in implementing these protocols on a day-to-day basis, ensuring that they are familiar with the specific needs and challenges of patients receiving bloodless medicine. They need to be knowledgeable about alternative therapies for anemia management, strategies to minimize blood loss during procedures, and protocols for monitoring and managing postoperative complications without blood transfusions. Institutional support, with ongoing education and training programs designed to keep nurses updated on the latest advancements and best practices in bloodless medicine, can ensure that nurses are equipped to provide safe, effective, and compassionate care while respecting patients' religious or personal beliefs regarding blood transfusions.

TABLE 1.
ERYTHROPOIESIS-STIMULATING AGENTS

AGENT	INITIAL DOSE AND FREQUENCY	SPECIAL CONSIDERATIONS
Darbepoetin	2.25 mcg/kg subcutaneously weekly	■ Albumin free ■ Discontinue therapy when hemoglobin levels are greater than 11 g/dl.
Epoetin alfa	150 units/kg subcutaneously 3 times per week or 40,000 units subcutaneously weekly	■ Contains albumin ■ Discontinue therapy when hemoglobin levels are greater than or equal to 11 g/dl.
Epoetin alfa-epbx	150 units/kg subcutaneously 3 times per week or 40,000 units subcutaneously weekly	■ Albumin free ■ Availability may be limited. ■ Discontinue therapy when hemoglobin levels are greater than or equal to 11 g/dl.

Note. Based on information from Bohlius et al., 2019; Zhao et al., 2019.

FIGURE 1.
RECOMMENDATIONS FOR REDUCING THE NEED FOR TRANSFUSIONS FOR JEHOVAH'S WITNESS PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

- Replete vitamin K, vitamin B_{12}, and folate.
- Cease menses for patients using oral contraceptives.
- Avoid anticoagulation, aspirin, or nonsteroidal anti-inflammatory drugs.
- Minimize phlebotomy and use pediatric collection tubes.
- Avoid invasive procedures unless absolutely necessary.
- Administer gastrointestinal prophylaxis with proton pump inhibitors and stool softeners.
- Reduce the risk of epistaxis in dry hospital environments using saline nasal spray.
- Treat fever aggressively with acetaminophen.
- Avoid myelosuppressive medications (e.g., linezolid).
- Optimize pretransplantation hemoglobin using ESAs and IV iron until hemoglobin is greater than 12 g/dl.
- Increase vitamin C in the diet with over-the-counter supplements to absorb iron more effectively.
- Use peripheral blood stem cell sources over bone marrow to hasten engraftment.
- Use a nonmyeloablative conditioning regimen.
- Start a granulocyte–colony-stimulating factor on day +9 or sooner.
- Implement an ESA on day +6 and thrombopoietin receptor agonists starting on day +6, continuing until the platelet count is greater than 50 x 10^3/mcl.
- Begin an antifibrinolytic agent (e.g., aminocaproic acid) once the platelet count is less than 10 x 10^3/mcl.
- Use a nasal vasoconstrictor, such as oxymetazoline or phenylephrine, for epistaxis. (Limit use to 48 hours to prevent rebound.) Consider nasal tranexamic acid for excessive epistaxis.
- Maximize systemic antifibrinolytic therapy for refractory bleeding.
- Use topical aminocaproic acid for mucosal bleeding.
- Consider nebulized tranexamic acid for pulmonary hemorrhage.

ESA—erythropoiesis-stimulating agent
Note. Based on information from Coltoff et al., 2019; Resar & Frank, 2014.

Case Study

S.K., a 55-year-old male JW, was referred for a hematology evaluation following routine laboratory work that revealed thrombocytopenia. A bone marrow biopsy conducted in June 2022 revealed 30%–40% cellularity with megakaryocytic dysplasia, including nuclear separation and monolobated forms. In addition, there were 10%–15% cluster of differentiation (CD) 34+ myeloblasts, 12% blasts on aspirate smear, multilineage dysplasia, and ringed sideroblasts. Cytogenetics were diploid, with next-generation sequencing detecting genomic alterations in *SRSF2*, *ASXL1*, *IDH2*, and *RUNX1*. The final diagnosis was MDS, with excess blasts 2. Laboratory evaluation revealed an absolute neutrophil count of 0.17 × 10^3/mcl, a hemoglobin level of 9.7 g/dl, and a platelet count of 41 × 10^3/mcl. S.K. initiated therapy with 100 mg enasidenib daily and received two erythropoietin injections.

S.K. opted to pursue alloHSCT as the sole curative option for high-risk MDS. Despite initial challenges in finding a suitable transplantation center because of his refusal of blood products, a consultation at the study institution led to acceptance based on specific criteria and established protocols to minimize blood loss. An unrelated ABO-compatible and human leukocyte antigen–matched male donor was identified, with the donor and recipient testing positive for cytomegalovirus antibodies. S.K. enrolled in the institutional bloodless medicine program to delineate acceptable blood products preferences. Pretransplantation evaluation confirmed complete remission and peripheral blood count recovery.

In January 2023, S.K. underwent unrelated alloHSCT using a nonmyeloablative conditioning regimen consisting of 30 mg/m^2 fludarabine per day on days –4 to –2 and 200 cGy total body irradiation on day –1. He received a peripheral blood stem cell infusion of 5.16 × 10^6 CD34+ cells/kg, 13.72 × 10^7 CD3+ cells/kg and a total nucleated cell count of 5.38 × 10^8/kg. Graft-versus-host disease prophylaxis included cyclosporine, sirolimus, and mycophenolate mofetil. Antimicrobial prophylaxis included valacyclovir, posaconazole, trimethoprim–sulfamethoxazole, and letermovir.

Post-transplantation, standard bloodless medicine practices were implemented to minimize S.K.'s blood loss. Peripheral blood tests were collected in pediatric tubes, and romiplostim was administered for a platelet count of less than 50 × 10^3/mcl. There was a standing order for aminocaproic acid for a sustained platelet count of less than 10 × 10^3/mcl, which was not required because platelets promptly increased to greater than 10 × 10^3/mcl by day +12. Maintaining a hemoglobin level of greater than 10 g/dl negated the need for erythropoietin injections. S.K. received oral vitamin B_{12} 100 mcg daily from day –5 to day +8. He received filgrastim 480 mcg from day +9 to day +13.

S.K. remained afebrile throughout the peritransplantation period on prophylactic antimicrobials. He achieved prompt hematologic recovery with filgrastim support, reaching an absolute neutrophil count greater than 500 cells/mcl on day +9. On day +9, he developed a skin rash that was treated with corticosteroids. On meeting discharge criteria and improvement in the rash, S.K. was discharged home on day +15 with a steroid taper.

Mycophenolate mofetil was discontinued according to institutional standard on day +40.

The rash recurred on day +41, necessitating an escalation of corticosteroids to 2 mg/kg per day. After an inadequate response, S.K. was treated with a calcineurin inhibitor and other salvage agents.

Following resolution of the skin rash, steroids were discontinued on day +246, and S.K. continued with a calcineurin inhibitor taper. On day +303, he presented with papulosquamous skin lesions, oral hyperkeratosis, and dry eyes. Systemic corticosteroids were restarted at a dosage of 0.25/mg/kg per day, with the addition of topical oral corticosteroid rinses. After clinical improvement, a corticosteroid taper was initiated. At present, S.K. has mild chronic graft-versus-host disease based on National Institutes of Health criteria (Jagasia et al., 2015), as evidenced by ocular sicca syndrome not affecting activities of daily living and requiring moisturizing eye drops less than three times daily. In addition, S.K. has mild hyperkeratosis of the oral mucosa, not limiting oral intake.

Infectious complications, including Epstein–Barr virus viremia and sinusitis, were managed with rituximab and oral antibiotics, respectively. Mixed chimerism was observed in the peripheral blood at day +28, 70% CD3+ donor chimerism, 90% donor CD15. Bone marrow at six months showed 86% CD34 donor chimerism. Repeat peripheral blood chimerism at eight months post-transplantation increased to 90% on the CD3+ fraction. Bone marrow biopsies performed at three and six months post-transplantation showed continued remission with normal morphology, no blasts, and trilineage hematopoiesis. Next-generation sequencing testing in the bone marrow at six months was without alterations. Hematopoietic parameters remained stable, with hemoglobin ranging from 11.1 to 13 g/dl and platelet counts fluctuating but ultimately stabilizing at 162 × 10^3/mcl 13 months post-transplantation.

Implications for Nursing and Conclusion

alloHSCT in JW patients who decline blood products poses unique challenges, but with stringent criteria and adherence to bloodless medicine program guidelines, successful outcomes are achievable. By employing these criteria and guidelines, patients who decline blood products have equitable access to curative therapies such as hematopoietic stem cell transplantation for life-threatening hematologic conditions. An interprofessional approach ensures patient preferences are respected, and the use of flags in medical records can alert clinicians to individualized care requirements. Staff education and institutional programs specific to managing patients who decline blood products can ensure safe and effective care in this patient population. Although reports have been published on the use of autologous hematopoietic stem cell transplantation in JW patients, additional research on the use of alloHSCT, including best practices and outcomes, is needed. Additional data are needed regarding the optimal use and timing of ESAs, TPO-RAs, and antifibrinolytic agents. Improvements in conditioning regimens, supportive care, and the establishment of programs to support care of JW patients can allow for increased access to alloHSCT.

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Journal club programs can help to increase your ability to evaluate the literature and translate those research findings to clinical practice, education, administration, and research. Use the following questions to start the discussion at your next journal club meeting.

- What did this article reveal to you about bloodless medicine in patients undergoing allogeneic hematopoietic stem cell transplantation?
- Does your organization have a bloodless medicine program or bloodless medicine protocols to enhance care equity?
- What next steps can you take to incorporate this evidence or questions as a result of this article into practice?

If you implement practice changes as a result of this journal club article, visit https://bit.ly/3XDlyWh to share those with the *Clinical Journal of Oncology Nursing* editor and ONS members (must be logged into ONS account to access). Visit http://bit.ly/1vUqbVj for details on creating and participating in a journal club. Photocopying of this article for discussion purposes is permitted.

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The authors take full responsibility for this content and did not receive honoraria or disclose any relevant financial relationships. The article has been reviewed by independent peer reviewers to ensure that it is objective and free from bias.

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