

TITLE: Transfusion Support in Hematopoietic Stem Cell Transplant

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Slide 1: Title Slide

Hello, my name is Erin Meyer. I am the medical director of apheresis and associate medical director of Transfusion Services at Nationwide Children's Hospital in Columbus Ohio. Welcome to this Pearl of Laboratory Medicine on "Transfusion Support in Hematopoietic Stem Cell Transplant or HSCT."

Slide 2: Transfusion Support for Hematopoietic Stem Cell Transplant (HSCT)

The objectives of my talk are a brief overview of the different types of HSCT followed by a review of the sources of HSCT available and transfusion thresholds for patients receiving the different types of HSCT. Finally, I will discuss ABO-incompatible HSCT with a focus on the complications of and transfusion support for each possible ABO-incompatible combination.

Hematopoietic stem cells came to light after the dropping of the atomic bombs in 1945. People who survived the initial explosions later died of bone marrow failure from radiation. A series of sentinel experiments by Till and McCulloch in the 1960s then showed that transfer of bone marrow cells from donor mice into lethally irradiated recipient mice resulted in the formation of colonies of myeloid, erythroid, and megakaryocytic cells in the recipient's spleen approximately 7-14 days later.

Stem cells have two very unique properties: the ability to self-renew and the ability to regenerate. The field of stem cell biology has only grown and HSCTs are able to be transplanted now to recipients to help a variety of diseases. It can be used to eliminate a bone marrow infiltrative process like leukemia or correct a congenital immunodeficiency or hemoglobin disorder. Also it can allow patients with cancer to receive higher doses of chemotherapy that the bone marrow can tolerate, with subsequent rescue with a bone marrow transplant. The length of transfusion support and type of transfusion support is dependent on the patient's underlying condition, types of previous treatment, dose of the stem cell transplant, and conditioning regimen.

Slide 3: Two Types of Hematopoietic Stem Cell Transplant (HSCT)

Patients can receive stem cells from themselves, which is called an autologous transplant, or from another person, which is called and allogeneic transplant. Allogeneic HSCT has a potent graft-versus-tumor effect and thus results in low rates of relapse. But this is a trade off because it also has a high risk of graft-versus-host-disease. Autologous stem cell transplants do not have a risk for graft-versus-host-disease but also has no graft versus tumor. And there is a risk of the stem cell product possibly being contaminated with tumor cells. Disease type, patient factors, and the presence of a related donor influence the type of HSCT used.

Slide 4: Overview of HSCT Sources

There are three major sources of HSCT used clinically today: bone marrow derived, peripheral blood derived, collected by an apheresis machine, and umbilical cord blood derived. The bone marrow transplant physician will help select the most appropriate source based on the patient's clinical status and HLA-type. Traditionally the source of hematopoietic stem cells in autologous and allogeneic transplantations was bone marrow. This remains one of the most commonly used sources for pediatric allogeneic transplants. It is derived by multiple aspirations of the posterior iliac crest of the hip. Bone marrow derived HSCT have a low number of T cells thus less of a risk of GVHD and they engraft at a moderate pace. The use of peripheral blood as a source of these cells has replaced bone marrow for most autologous transplantations and a significant proportion of allogeneic transplantations especially in adults. Donors are stimulated with a hematopoietic growth factor such as GCSF and the stem cells are collected on an apheresis machine from peripheral whole blood. Peripheral blood HSCT have a large number of T cells and thus the highest risk of GVHD of any of the stem cell sources. But they are also the fastest to engraft. Umbilical cord blood is collected at birth directly from the umbilical cord then banked. It has the lowest rate of engraftment of all the stem cell sources and is gaining in use in both pediatric and adult stem cell transplants.

Slide 5: Allogeneic Transplants: Types of Conditioning Regimens

The conditioning regimen prior to an allogeneic HSCT is important as it provides the necessary innate immunosuppression so that the graft is not rejected as well as helps to irradiate the disease process. Traditionally myeloablative regimens have been used but due to the high level of chemotherapy and/or total body irradiation required, it is fraught with toxicity and they are often not well tolerated for older patients. These regimens have good innate tumor control but can have delayed engraftment and require longer transfusion support. Nonmyeloablative regimens or reduced intensity regimens are also used to try to induce a state of mixed chimerism between the donor and recipient to help induce graft-versus-tumor-effect. These regimens minimize toxicity to the patient and can be used for older individuals.

Slide 6: Engraftment Definitions

Patients who have received an HSCT will require extensive red cell and platelet transfusion support until their stem cell transplant engrafts. These patients generally do not require plasma and/or cryoprecipitate transfusions as the HSCT process typically does not affect the liver where coagulation factors are made. Red cell engraftment can be hard to evaluate but is generally defined as the presence of at least 1% reticulocytes in the peripheral blood and the absence of RBC transfusions for 30 days. Platelet engraftment is defined as a platelet count of at least 20,000/uL for three consecutive days without any platelet transfusions. Neutrophil engraftment is the presence of an absolute neutrophil count of greater than 500(/uL) for three consecutive days.

Slide 7: Peri/Post-Transplant Transfusion Thresholds

For the majority of patients in the peritransplant and posttransplant phase, a hemoglobin level below 7 g/dL would warrant a red cell transfusion. There is evidence that patients immediately after surgery, or after cardiopulmonary bypass, or with a preexisting cardiovascular disease should be transfused below levels of 8 g/dL. There are no set hemoglobin transfusion levels for a patient who is actively bleeding. The hemoglobin should not be the sole determinant for transfusion, the patient's entire clinical picture must be taken into consideration. Autologous HSCT maintain adequate erythropoietin levels throughout the post-transplant course and require less intensive RBC support as compared to allogeneic. Factors affecting the duration of RBC support include the dose of erythroid progenitors in the

stem cell graft, if the graft is ABO incompatible, the type of myelosuppressive drugs used, and the presence of graft-versus-host-disease.

Slide 8: Peri/Post-Transplant Transfusion Thresholds

Platelet transfusion thresholds vary depending on clinical situations. Generally in a stable, nonfebrile patient, a platelet count of 5,000-10,000/ μL is a reasonable platelet transfusion threshold. A patient on heparin should be maintained at a level greater than 20,000/ μL and a patient with significant bleeding should be maintained at a level of 50,000/ μL . There are several factors that affect the duration of platelet support after HSCT. Patients who received a graft from an unrelated donor generally require a longer course as does the presence of acute graft-versus-host-disease, veno-occlusive disease (VOD), or CMV infection. Other factors affecting platelets transfusion support are the number of stem cells infused, the use of bone marrow as the stem cell source, and use of methotrexate for graft-versus-host-disease prophylaxis.

Slide 9: Granulocyte Transfusions

Neutropenia causes significant morbidity and mortality in HSCT patients. Granulocytes may be used in specific instances to assist these patients. They may be indicated for patients with an absolute neutrophil count $< 500/\mu\text{L}$ with either a bacterial infection unresponsive to antimicrobial therapy or an invasive fungal and/or yeast infection. The minimum dose of granulocytes of 1×10^{10} per infusion is necessary to determine any clinical benefit.

Slide 10: The RING study: A Randomized Controlled Trial of G-CSF-Stimulated Granulocytes in Granulocytopenic Patients

The clinical utility of granulocyte transfusions in neutropenic patients has been unclear. Therefore the ring study, R I N G, or randomized controlled trial of G-CSF-stimulated granulocytes in granulocytopenic patients, attempted to examine the efficacy of high-dose granulocyte transfusion therapy. The study was carried out in 14 sites as part of the NHLBI Transfusion Medicine/Hemostasis Clinical Trials Network. Subjects eligible for the study were those with neutropenia defined as an ANC < 500 and with proven, probable or presumed bacterial or fungal infection. Subjects were randomized to receive either: standard antimicrobial therapy; or standard antimicrobial therapy plus daily granulocyte transfusions from normal donors stimulated with G-CSF at a dose of 450 μg and dexamethasone at a dose of 8mg. The primary endpoint was a composite one: it included survival plus a microbial response, both evaluated 42 days after randomization. The study showed no benefit of granulocyte transfusion therapy in these patients BUT the power of the study was greatly reduced due to low patient accrual.

Slide 11: ABO-Incompatible HSCT

Although the HLA system plays a critical role in identification of compatible related and unrelated donors for HSCT, the red cell antigens, including ABO, are not part of the HLA system. Unlike selection of donors in solid organ transplantation, ABO compatibility is not considered critical in selection of potential HSCT donors because stem cells do not express ABO antigens. The relationship between ABO types of the donor and recipient can fall into one of four categories: compatible, major incompatibility, minor incompatibility, and bidirectional incompatibility.

Since HLA and ABO antigens are encoded on different chromosomes, some degree of ABO incompatibility occurs in 20-50% of allogeneic HSCTs. There is no conclusive evidence that ABO incompatibility significantly impacts overall survival, the incidence of acute or chronic graft-versus-host disease (GVHD), or relapse rate after allogeneic HSCT.

Slide 12: Types of ABO - Incompatible HSCT

A compatible transplant is one in which the donor and the recipient have the same ABO type. A major incompatibility occurs when the recipient has ABO antibodies or isohemagglutinins against red cell antigen(s) present on donor RBCs for example when the donor is group A and the recipient is group O. Minor incompatibilities are defined as the presence of donor ABO antibodies or isohemagglutinins against antigen(s) present on the recipient's red blood cells. For example the donor is group O and the recipient is group A. Finally a bidirectional incompatibility is the existence of both major and minor incompatibilities. For example when a group B donor donates stem cells to a group A recipient.

It should be noted that these terms are more frequently used in the context of the ABO system, but they are, and should be, used to describe the presence of other red cell antibodies such as anti-Kell or anti-D in the plasma of the donor and/or the recipient. Generally, however, ABO incompatibilities are the primary concern in clinical practice.

Slide 13: Potential ABO Combinations Potentially Existing Between Donors and Recipients for HSCT

This table lists all the potential ABO combinations that could exist between a stem cell donor and recipient. Overall ABO incompatibilities are present in approximately 20-50% of donor/recipient pairs. They can cause both delayed and late complications and transfusion support is a major cornerstone of treatment.

Slide 14: ABO Compatibility in HSCT

There are several immediate and delayed complications to each type of ABO-incompatible HSCT combination. The main complications of major ABO incompatible HSCT are RBC hemolysis at the time of graft infusion, delayed donor red blood cell engraftment, and pure red cell aplasia. Red cell depletion of the major incompatible HSC graft should be considered to prevent acute hemolysis at time of graft infusion. Red blood cells comprise approximately 25-35% of marrow product volume, which is over 1000 mL typically, for adult recipients and thus incompatible red blood cells during bone marrow infusion pose a significant risk for acute hemolysis. Another strategy for major incompatible HSCT is to reduce the recipient's isohemagglutinin titers transiently around the time of infusion by plasma exchange via apheresis though there is no consensus with regard to best practice of this strategy.

In minor ABO incompatible HSCT, the passive transfer of donor isohemagglutinins in the HSC graft may result in acute hemolysis during stem cell infusion. However a delayed form of hemolysis can also occur due to the persistence of donor lymphocytes generating antibodies and is called passenger lymphocyte syndrome. Strategies to mitigate the infusion of a large volume of incompatible isohemagglutinins include plasma reduction of the stem cell graft.

Bidirectional ABO incompatibility contains both major and minor ABO incompatibility. The clinical manifestations of bidirectional ABO incompatibility include the potential for immediate and delayed hemolysis similar to that caused by major and minor incompatibility. Clinical approaches to lessen the complications of bidirectional incompatibility include a combination of practices for both major and minor incompatibility.

Please bear in mind that the HSC product manipulation strategies do incur the risk of HSC loss and delay in HSC infusion, and do not protect against delayed RBC engraftment, pure red cell aplasia, or passenger lymphocyte syndrome.

Slide 15: Transfusion Support in HSCT

Transfusion support is required after transplantation before red blood cell engraftment which may take up to 6 weeks or longer. Transfusion support is especially critical in ABO-incompatible HSCTs and is outlined here. The principle behind appropriate selection of components is to provide, during the

transplant phase and until recipient antibodies are no longer detectable, components that are compatible with the ABO groups of both the donor and recipient in order to minimize potential hemolysis. There are no set national standards for transfusion support during ABO incompatible HSCTs: each institution must define its own policies to maximize safety specific to the patient populations and transplant protocols.

This table is organized into the following three clinical phases: 1. Pretransplant phase, which is from diagnosis until prior to initiation of the conditioning regimen; Phase 2. The transplant phase: from conditioning, or preparative, regimen until recipient isohemagglutinins are no longer detectable and recipient red blood cells are no longer circulating; and finally phase 3. The Post-engraftment phase: defined as after the front and back type of the recipient have converted to the donor's ABO group.

Patients who have received a major ABO incompatible HSCT should receive red cell transfusions of the recipient type and platelets and plasma of the donor type during the transplant phase until the recipient has converted to the donor's ABO type. This is the exact reverse for recipients receiving a minor ABO incompatible transplant: red blood cell transfusions until the recipient converts to donor type should be donor type, while platelets and plasma should be recipient's ABO group. Bidirectional incompatibility patients need to have Group O red blood cells and Group AB plasma and platelet products until they convert to the donor ABO type. Management of platelet transfusions in ABO-mismatched HSCT patients can be challenging, since group AB and group B platelets are hard to find.

Slide 16: Conclusions

The ABO blood group system is not a barrier to successful allogeneic HSCT transplantation. However, the institution performing ABO-incompatible HSCTs must have a clear understanding of the potential adverse events, and have systematic policies in place for transparent communication between the transplant program, HPC processing laboratory, and blood bank to help mitigate such events throughout the donor selection and transplant process. The transfusion service is a critical partner in providing compatible blood products throughout the entire course and helping to assist the transplant team should adverse complications arise.

Slide 17: References

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Slide 18: Disclosures: The presenter has nothing to disclose.

Slide 19: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on “**Transfusion Support in Hematopoietic Stem Cell Transplant.**”