TRANSFUSION SUPPORT FOR HEMOTOPOIETIC STEM CELL TRANSPLANT (HSCT) PATIENTS

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Introduction

- HSCT increasingly performed with better clinical outcomes, and expanding indications.
- Indications include:
  - hematological malignancies
  - solid tumors
  - aplastic anemia, marrow failure
  - metabolic disorders
  - autoimmune diseases
  - immunodeficiencies.
Introduction

Types of HSCT

- By donor:
  - Autologous
  - Allogeneic
    - Related vs. unrelated
    - Matched vs mismatched

- By source of hematopoietic stem cells:
  - Bone marrow
  - Peripheral blood stem cells
  - Cord blood
Transfusion Practices Overview

- Transfusion considerations in this unique patient population:
  - Alloimmunization
  - Issues related to ABO incompatibility
  - Post transplant:
    - Cytopenias: long term support
    - Immune suppression: risks of transfusion transmitted CMV infection, and TA-GVHD

- Transfusion practices in this population primarily based on anecdotal reports of toxicities, institutional experiences, and common-sense understanding of the pathophysiology involved. (*i.e. very little evidence derived from well designed randomized controlled trials*)
Once patient has been identified as a transplant recipient, consider the need for “special blood products”

- Product modifiers:
  - CMV seronegative products
  - Leukoreduced products
  - Irradiated products

- Directed donor program
CMV seronegative

- Collected from CMV-seronegative donors
- Indicated for immunocompromised patients who are CMV negative or with unknown CMV status, including HSCT transplant
- CMV seropositivity rate in the donor pool: 50-80%
- Seronegative donors may be in the acute infection window -> serology negative but high levels of viremia
Leukoreduced

- WBC in the RBC/platelet unit removed by filtration
- Why get leukoreduced product?
  - “CMV safe” (CMV lives in WBCs)
  - Reduces non-hemolytic febrile transfusion reactions
  - Reduces alloimmunization (anti-HLA)
- Consider LR when
  - CMV negative products desired
  - Patient had 2 febrile reactions
  - Patient will need long term transfusion support/transplant candidate
LR Product vs. CMV Seronegative

- CMV virus mostly reside within WBCs, therefore LR provides alternative, CMV-safe blood products.
- Considered to be equivalent to CMV seronegative products by AABB
- Some studies show slight advantage of CMV negative product over LR products
CMV Seronegative vs. Leukoreduction: A Survey

- Practices choosing CMV seronegative or LR blood products for HSCT patients variable across the country
  - ~60% consider LR equivalent to CMV seronegative
  - Some institutions use the belt and suspender (LR AND CMV seronegative) approach for high risk patients, including HSCT patients
The CMV Seropositive Recipient

Severe co-infection/superinfection with a second strain of CMV transmitted by transfusion is a theoretical possibility.
No direct evidence of such case occurring.
Co-infections of CMV usually clinically mild due to cross-reactive antibodies.
Greatest risk is reactivation of CMV in these patients.
Unnecessary to provide CMV seronegative or LR products, additional benefit would be marginal.
Reduction of Alloimmunization

- RCT trial showed that leukoreduction reduces alloimmunization rate in AML recipients of platelet transfusions.
- Risks are the same with leukoreduced platelet concentrates or apheresis platelet products, i.e. not affected by donor exposure.
- Still 10-15% of patients would be alloimmunized even with LR blood products.
Irradiation

- Blood products can be irradiated to prevent transfusion-associated graft vs host disease (TA-GVHD) in at-risk individuals.
- Dose: 25Gy at the center of the unit, at least 15Gy everywhere else (AABB Standards)
In a immune-competent host, donor lymphocytes are seen as foreign -> donor lymphocytes neutralized / inactivated by the host’s immune system.

However, if the donor lymphocytes somehow escape the host immune surveillance, they will attack the host.

Result is TA-GVHD
TA-GVHD: Clinical Aspects

- Uncommon, but high mortality -> 90%
- Presents 4-30 days after transfusion
- Hallmark: bone marrow aplasia with pancytopenia
- Also rash, bloody diarrhea, fever
- Treatment option: transplant
Prevention of TA-GVHD

- NOT proven effective (All reduce viable WBC count):
  - leukofiltration
  - Washing
  - freezing and thawing,
- Proven to be effective: **irradiation**
- Irradiation: induces DNA crosslinks, prevents (dividing) lymphocyte proliferation
- When to provide irradiated products:
  - Throughout the entire pre, peri and post HSCT course
  - Possibly for the life of the patient at most centers - no diagnostic test to confirm the reconstitution of the immune system
Direct Donation

- Units collected from family and friends (directed donors), specifically designated for the patient
- Paul Gann Act in California: Physicians required to offer the options of directed or autologous donations to patients
- Used after autologous unit, but before units from the general inventory
- Crossed into general inventory 5-10 days before expiration for RBCs, 1-2 days for platelets
- Irradiated to prevent GVHD
TA-GVHD can occur in an immune-competent person...

Recipient will not see donor WBCs as foreign, but donor WBCs will see recipient cells as foreign and mount an attack.
Direct Donations (DD) - Advantages

- Psychosocial benefits for the patient, family and friends
- Boost to the inventory
- Potential recruitment tool for future donors
DD-Disadvantages

- Increased cost to blood center and logistic issues
- Not proven to be safer: Directed donors are under pressure -> may impact donor reliability
- Alloimmunization pre-transplant:
  - Alloimmunization to major and minor HLA molecules may occur, impacting graft survival
  - Some center avoid transfusion with blood products from blood relatives/directed donors pretransplant
  - Some argue that fear is unfounded, especially with the new generation of LR filters and pre-transplant conditioning regimen.
Patients with Aplastic Anemia

- Presents with pancytopenia -> become transfused frequently
- High incidence of alloimmunization
- Data showed that multitransfusion in this group -> increased graft failure due to alloimmunization
- Prudent to avoid transfusions as much as possible before transplant
- Minimize donor exposure: potential strategies
  - Use directed donors to limit donor exposure
  - Apheresis platelets instead of pooled platelet concentrates
Peri-Transplant
Graft/Donor Selection: Overview

- Screening: similar to blood donor screening, exceptions can be made with some ineligibilities, including infectious disease risks.

- Further Considerations:
  - HLA matching (most important)
  - ABO/Rh typing: disparity does not preclude transplant; mismatch usually not associated with graft failure – although some data showing delayed RBC/plt engraftment
  - Donor health, size etc
Major ABO incompatibility

- **Recipient** has naturally ABO antibodies against donor:
  - O recipient getting A or B graft
- Recipient’s anti-A/B can hemolyze RBCs in the graft, resulting in acute hemolytic transfusion reaction.

Therefore, must minimize RBC content in graft
Major ABO incompatibility

- Bone marrow: can have 500cc of RBCs or more.
  - Remove RBCs by density gradient separation
  - PB-HPSC collected by apheresis
  - Usually <20ml of RBC, not a problem
    - Hct kept below 2% in the product collect line to minimize RBC contamination

*In Addition: Plasma exchange for recipients with high anti-A/B titers*
Minor ABO Incompatibility

- **Donor** has naturally ABO antibodies against recipient RBCs: A or B recipient getting O graft.
- **Risk of acute hemolysis:**
  - Bone marrow: can have 500cc or more plasma -> Must be plasma depleted
  - PB-HPSC collected by apheresis: Already plasma depleted, not a problem
Minor ABO Incompatibility

- Risk of delayed hemolysis as donor lymphocytes engraft and start producing anti-A or B, which can hemolyze recipient’s residual RBCs
- May monitor post transplant with H/H, DAT, hemolytic laboratory parameters – no standard protocol available
- Optional: RBC Exchange transfusion /”hypertransfuse” recipient pretransplant with type O RBCs
Major and Minor ABO Incompatibility

- A to B or B to A
- Need to be concerned about issues associated with both major and minor ABO incompatible HSCT
  - Bone marrow: deplete both RBC and plasma
  - Recipient may be candidate for plasma exchange or RBC exchange
- Monitor for both acute and delayed hemolysis, and pure RBC aplasia
Product blood type selection for ABO incompatible HSCT recipients

- Recipient’s own RBCs and antibodies in plasma can stay in circulation for weeks to months
- Graft may contain some anti-A/B or RBCs from donor. Amount should increase with engraftment
- As soon as the donor-recipient pair confirmed:
  
  RBCs given must be compatible with both recipient and donor’s plasma.
  Plasma/platelet given must not contain ABO antibodies against either the recipient’s or donor’s RBCs
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Post-Transplantation
How long to continue providing special blood products?

- No consensus – no established guidelines
- CMV Safe Products:
  - Prudent to continue until withdrawal of immunesuppression
- Leukoreduced:
  - Risk of alloimmunize low post HSCT
  - May continue for CMV protection or to reduce FNHTR
- Irradiated:
  - No good test to confirm complete reconstitution of immune system
  - Continue for the life of the patient?
Complications Post Transplant

- Delayed Engraftment
- Immune hemolysis
- Pure RBC aplasia
- Platelet Refractoriness
Immune Hemolysis

- **Acute vs. Delayed**
  - Acute: due to existing (ABO) antibodies. Unusual with RBC/plasma depletion of graft, plasma/RBC exchanged of the recipient
  - Delayed: Occurs as donor lymphocytes start producing antibodies and cause hemolysis

- **Alloimmune vs. Autoimmune**
  - Alloimmune
    - Due to ABO incompatibility
    - Passenger lymphocyte syndrome
  - Autoimmune
Passenger Lymphocyte Syndrome

- Lymphocyte from graft produces antibodies directed against host cells.
- E.g. Anti-Kell from donor lymphocytes directed against host’s Kell+ RBCs -> hemolysis
- Risk of passenger lymphocyte syndrome is higher if
  - (Theoretically) PB- HSCT
  - Lack of anti-proliferative immunosuppression (such as MTX)
- Timeline
  - Onset 1-2 week post transplant
  - Lasts about 1-2 weeks, stops as incompatible recipient cells are eliminated and replaced by transfused RBCs
- Severe hemolysis may occur – bystander hemolysis?
Detection of hemolysis

- Not always straightforward
- VOD (GVHD of the liver), TTP etc may have elevated bilirubin, LDH, lower hct, obscuring underlying hemolysis
- DAT should be positive
- Request an eluate, need to also specifically look for anti-A, B antibodies (eluate routinely only ran with type O reagent cells)
Management

- Transfuse O RBCs or antigen negative RBCs
- RBC exchange a possibility – but has not been shown to be effective at UCLA in the past
Autoimmune Hemolytic Anemia

- Develops in post-transplant patients, (3-5% of adults, 6% of children); incidence much higher than what is seen in the general population
- Arises due to incomplete reconstitution and dysregulation of the immune system post transplant
- May have warm, cold, or mixed AIHA
- Serological findings similar to conventional AIHAs
AIHA in HSCT Recipients

- May have somewhat worse prognosis
- O’Brien et al: Mortality >50%, due to infection secondary to immunosuppression and hemolysis
- Treatment: same as conventional AIHA as allowed by patient’s condition, but often often refractory to first line therapy (steroids)
- Newer agents such as rituximab, mycophenolate mofetil, Campath-1 etc and splenectomy maybe considered.
Pure RBC Aplasia

- Results form major ABO mismatched HSCT
- Recipient’s lymphocytes/antibodies attacks donor’s RBC and precursors during engraftment - > Suppresses erythropoiesis
- Recipient ABO antibodies may be detectable up to 605 days!
- Patient may be RBC-transfusion dependent for more than a year

Management:
- Rule out parvo B19
- Plasma exchange (not very effective)
- Reduce immunesuppression, to allow some degree of GVHD
Platelet Refractoriness

- Failure to achieve expected increment twice in a row
- Refractoriness may develop, likely multifactorial in this patient population
  - Nonimmune: fever, sepsis, splenomegaly, bleeding, DIC etc
  - Immune: due to alloimmunization to HLA antigens
- Distinguish non-immune vs. immune by doing a 10-60 min post transfusion platelet count
Platelet Refractoriness - Management

- Non-immune: More frequent transfusions, correct underlying cause

- Immune:
  - Prevention: provide LR products, limiting donor exposure (?)
  - Product selection
    - Consider HLA matched platelets
    - HLA-antigen negative platelets
    - Crossmatch negative platelets

- Monitor response to specially selected products with a 10-60min post transfusion platelet count

- Other hemostatic agents: Amicar, rFVII etc
Which of the following statement about irradiation is true?

- A. Irradiation does not change shelf life of the RBC product
- B. Irradiation is the most effective method to reduce HLA alloimmunization
- C. The dose to the center of the unit should be 20Gy
- D. Products from blood relatives should be irradiated, only if recipient is immunocompromised
- E. None of the above
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- C. The dose to the center of the unit should be 20cGy
- D. Products from blood relatives should be irradiated, only if recipient is immunocompromised
- E. None of the above
Which of the following is true about an A positive patient receiving an HSCT from O donor?

- A. There is no risk of delayed hemolysis due to the incompatibility
- B. This is a case of major ABO incompatibility
- C. Patient can receive O RBCs and A RBCs
- D. Patient can receive type AB or A plasma
- E. None of the above
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- E. None of the above
Which statement about blood product modification for HSCT patients is true?

- A. Leukoreduction is the most effective way to prevent TA-GVHD
- B. As soon as engraftment occurs, the patient no longer needs irradiated products
- C. Leukoreduced products have slightly lower risk of CMV transmission than CMV seronegative products
- D. Leukoreduction of cellular products transfused is required pre-transplant
- E. CMV safe products should be provided regardless of recipient’s CMV status
Which statement about blood product modification for HSCT patients is true?

- A. Leukoreduction can effectively prevent TA-GVHD
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