ABO-incompatible Allogeneic Stem Cell Transplantation

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Disclosures

None
Objectives

- History and Basic Theory
- Terminology
- Laboratory Processing
- Blood Bank Management
QUESTION #1

Which of the following has the least impact on clinical survival outcomes for allogeneic stem cell transplants?

A. HLA match
B. Graft source
C. ABO-compatibility
D. Risk of infection
E. Donor age and gender
QUESTION #2

True or False?

In contrast to HSCT, ABO-incompatible solid organ transplantation is a barrier.
QUESTION #3

What is the RBC threshold volume for administering incompatible RBCs in an HPC collection?

A.) 0.1-0.2 mL/ kg
B.) 0.2-0.3 mL/ kg
C.) 0.3-0.4 mL/ kg
D.) 0.4-0.5 mL/ kg
E.) >0.5 mL/ kg
QUESTION #4

Which of the following are considered a minor ABO-mismatch?

A.) O recipient, A donor
B.) O recipient, AB donor
C.) A recipient, O donor
D.) A recipient, AB donor
Human Major Histocompatibility Complex

- 3 regions of chromosome 6p21
- Critical to engraftment
- Prediction of clinical outcomes
- Balancing potential harm from GVHD and GVL


ABO Carbohydrate glycosyltransferases

- Located on chromosome 9q34
- Inherited independently of HLA
- ABO group Ags sugars expressed: RBC surface, WBCs, vascular and organ endothelium and plasma


http://eastafriaschoolserver.org/Wikipedia/wp/a/ABO_blood_group_system.htm
Landsteiner’s Law

➤ Dr. Karl Landsteiner
➤ Discovered the ABO Blood Group System in 1901
➤ 1927 he discovered new blood groups: M, N, and P
➤ Received the Nobel Prize
  Dec. 11, 1930
### Landsteiner’s Law

<table>
<thead>
<tr>
<th>Red blood cell type</th>
<th>Group A</th>
<th>Group B</th>
<th>Group AB</th>
<th>Group O</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="A antigen" /></td>
<td><img src="image" alt="B antigen" /></td>
<td><img src="image" alt="AB antigens" /></td>
<td><img src="image" alt="None" /></td>
<td><img src="image" alt="O antigen" /></td>
</tr>
<tr>
<td>Antibodies in Plasma</td>
<td>Anti-B</td>
<td>Anti-A</td>
<td>None</td>
<td>Anti-A and Anti-B</td>
</tr>
</tbody>
</table>

- **Group A**: Contains A antigen.
- **Group B**: Contains B antigen.
- **Group AB**: Contains both A and B antigens.
- **Group O**: None.
ABO Incompatibility

- 25-50% of transplants are ABO incompatible
- Both ABO-identical and ABO-incompatible HSCT require extensive transfusion support
- ABO-mismatch results in complications caused by the interactions between the ABO antigens and isohemagglutinins in the plasma
- Clinical outcomes - degree of HLA match, graft source, risk of infection and donor age and gender

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Donor age, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18 to 32</td>
</tr>
<tr>
<td>Number</td>
<td>2614</td>
</tr>
<tr>
<td>Donor characteristics</td>
<td></td>
</tr>
<tr>
<td>Donor-recipient HLA-match</td>
<td></td>
</tr>
<tr>
<td>8/8 matched</td>
<td>2114 (81%)</td>
</tr>
<tr>
<td>7/8 matched</td>
<td>500 (19%)</td>
</tr>
<tr>
<td>Donor-recipient ABO match</td>
<td></td>
</tr>
<tr>
<td>Matched</td>
<td>874 (33%)</td>
</tr>
<tr>
<td>Minor mismatch</td>
<td>453 (17%)</td>
</tr>
<tr>
<td>Major mismatch</td>
<td>615 (24%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>672 (26%)</td>
</tr>
</tbody>
</table>

**ABO Incompatibility**

- 25-50% of transplants are ABO incompatible
- Both ABO-identical and ABO-incompatible HSCT require extensive transfusion support
- Survival after transplant is modest
- Can result in complications caused by the interactions between the ABO antigens and isohemagglutinins in the plasma

---

**Table 3**

Donor characteristics associated with mortality and GVHD for

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality*</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Donor age, years</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≤32</td>
<td>1.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>33 to 50</td>
<td>1.13 (1.05-1.20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;50</td>
<td>1.29 (1.14-1.46)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Donor-recipient HLA-match</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>8/8 HLA-match</td>
<td>1.00</td>
<td>.001</td>
</tr>
<tr>
<td>7/8 HLA-match</td>
<td>1.24 (1.15-1.34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6/8 HLA-match</td>
<td>1.62 (1.47-1.79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>5/8 or lower HLA-match</td>
<td>1.89 (1.67-2.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood group ABO match</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ABO matched</td>
<td>1.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ABO minor mismatch</td>
<td>1.10 (1.01-1.18)</td>
<td>.002</td>
</tr>
<tr>
<td>ABO major mismatch</td>
<td>1.13 (1.05-1.21)</td>
<td>.001</td>
</tr>
</tbody>
</table>

# Survival after ABO-incompatible HCT Transplantation

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Year</th>
<th>Survival after ABO-Incompatible HCT Transplantation</th>
<th>Risk of Graft-versus-Host Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Major: Decreased, Minor: Decreased, Bidirectional: No difference</td>
<td>Increased with minor or major ABO mismatch</td>
</tr>
<tr>
<td>Helming et al. [13]</td>
<td>2007</td>
<td>No difference, No difference, No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Erker et al. [15]</td>
<td>2005</td>
<td>No difference, Decreased, Decreased</td>
<td>No difference</td>
</tr>
<tr>
<td>Kim JG et al. [12]</td>
<td>2005</td>
<td>No difference, No difference, No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Stussi et al. [14]</td>
<td>2002</td>
<td>Decreased, No difference, No difference</td>
<td>Increased with minor ABO mismatch</td>
</tr>
<tr>
<td>Benjamin et al. [18]</td>
<td>1999</td>
<td>Decreased, Decreased, No difference</td>
<td>No difference with minor or major mismatch</td>
</tr>
<tr>
<td>Bacigalupo et al. [19]</td>
<td>1988</td>
<td>–, –, –</td>
<td>Increased with minor ABO mismatch</td>
</tr>
<tr>
<td>Benisnger et al. [41]</td>
<td>1982</td>
<td>No difference, –, –</td>
<td>No difference with major ABO mismatch</td>
</tr>
<tr>
<td>Buckner et al. [17]</td>
<td>1978</td>
<td>–, No difference, –</td>
<td>No difference with minor ABO mismatch</td>
</tr>
</tbody>
</table>
Transplantation Time Periods

Phase 1: Pre-transplantation
Phase 2: Transplantation
Phase 3: Post engraftment
# ABO-Incompatible Classification

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
<th>Bidirectional</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DONOR:</strong> Type A, B, AB</td>
<td><strong>DONOR:</strong> Type O, Anti-A, Anti-B</td>
<td><strong>DONOR:</strong> Type A or B Anti-A or Anti-B</td>
</tr>
<tr>
<td><strong>RECIPIENT:</strong> Type O Anti-A, Anti-B</td>
<td><strong>INCOMPATIBLE TRANSFER OF DONOR ANTIBODIES</strong></td>
<td><strong>RECIPIENT:</strong> Type A or B Anti-A or Anti-B</td>
</tr>
<tr>
<td><strong>ANTI-DONOR ANTIBODIES</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. ABO Matching of Donor and Recipient**

<table>
<thead>
<tr>
<th>Donor</th>
<th>A</th>
<th>B</th>
<th>AB</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Compatible</td>
<td>Major/Minor</td>
<td>Minor</td>
<td>Major</td>
</tr>
<tr>
<td>B</td>
<td>Major/Minor</td>
<td>Compatible</td>
<td>Minor</td>
<td>Major</td>
</tr>
<tr>
<td>AB</td>
<td>Major</td>
<td>Major</td>
<td>Compatible</td>
<td>Major</td>
</tr>
<tr>
<td>O</td>
<td>Minor</td>
<td>Minor</td>
<td>Minor</td>
<td>Compatible</td>
</tr>
</tbody>
</table>

*Major and major/minor mismatches may better be avoided if other HLA-matched (8/8) donor options are available. If not, complications of ABO mismatch need to be dealt with in collaboration with the blood bank. Major/Minor, both mismatch complications can happen.

“Minor is from A to O, plasma reduction is the way to go”
“Major is from O to A, RBC reduction will save the day”
Major ABO-Incompatibility

Clinical Manifestations

• Hemolysis
• Delayed RBC engraftment
• Pure red cell aplasia

Preventative Measures

• RBC depletion (reduction in overall CD34 content)
• Reduce titer of incompatible recipient isohemagglutinins (PEX)
• Donor-type secretor plasma
• Slow infusion of donor-type RBCS to deplete recipient isohemagglutinins before HCT
Major Recipient/Donor ABO incompatibility

- < 0.2-0.4mL/kg or 20 - 30 ml donor RBC is considered safe
- RBC reduction (eg. by sedimentation) may lose 20 – 30% of MNC & CD34

<table>
<thead>
<tr>
<th>Recipient ABO Type</th>
<th>Donor ABO Type</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>A, B, or AB</td>
<td>Infuse without modification. Monitor for acute hemolytic reaction</td>
</tr>
<tr>
<td>A</td>
<td>B or AB</td>
<td>If critical HPC dose, slow infusion in two doses, ≥6 hours apart, otherwise RBC deplete</td>
</tr>
<tr>
<td>B</td>
<td>A or AB</td>
<td>RBC depletion of component</td>
</tr>
<tr>
<td>AB</td>
<td>N/A</td>
<td>Double buffycoat or Prepacyte procedure</td>
</tr>
</tbody>
</table>

Recipient anti-donor isohemagglutinin titer

- ≥ 1:32
- ≤ 1:16

- Infuse without modification
- RBC depletion of PBSC component
- Double buffycoat or Prepacyte procedure for BM

HPC, CORD BLOOD – RBC replete

- Large Volume Wash
- Major ABO Incompatibility

- Infuse without modification

CTL MD to consult with Transplant Attending MD
Thresholds for Administration of Incompatible Red Cells

- Institutions-defined limits, total volume of red cells (20-30 mL) or a volume red cell per recipient weight (0.2 to 0.3 mL/per kg).

- Significant loss of red cells during the freeze/thaw process when DMSO is used

- Volumes of red cells up to 0.5 mL/kg are generally tolerate in patients with normal renal function
Red Cell Reduction

Methods

- Red cell reduction techniques rely on the density differences between red cells and mononuclear
- Methods are manual or automated with or without rouleaux-enhancing agents such as HES
Red Cell Reduction

1. **Manual Centrifugation**
   - Transferring the product to the blood bag and centrifuging that bag with the drain port down
   - Does not separate mononuclear cells from granulocytes

2. **Density Separation using HES**
   - HES causes rouleaux formation, increasing their density and allows them to differentially sediment from nucleated cells
   - Adjusting Hct to optimize rouleux
   - Large blood bag filled with HES/product, with drain port toward the bottom
   - Red cells sediment while leukocytes remain higher in the plasma
   - Red cells are slowly drained from bottom of bag

3. **Density Separating Using a Density Gradient**
   - Relies on density differences between red cells and nucleated cells
   - Red cell containing product is diluted and layered over a density gradient solution such as ficoll-hypaque
   - Following centrifugation, the mononuclear cells remain in a layer above the density gradient, with the mature granulocytes and red cells at the bottom of the cell suspension

4. **Automated Apheresis Instruments**
Minor ABO-Incompatibility

Clinical Manifestations

• Massive hemolysis of recipient RBCs

• Immediate – donor isohemagglutinins in the graft

• Delayed (5-15 days after transplant) Passenger lymphocyte syndrome (PLS): Ab-producing immune cells contained in donor graft

Preventative Measures

• Plasma reduction in stem cell infusion

• Recipient RBC exchange prior to transplant

• Rituximab to reduce PLS
Plasma Reduction

1. *Centrifugation of product in blood bags*
2. *Automated processing instrument (COBE 2991) or apheresis instrument*
3. *Cryopreservation begins with plasma reduction step*
Suggested Approach to ABO-Incompatible HPC Transplantation

Evaluation – Transplant Coordinator
Phase I, Pre-transplantation conditioning

Donor and recipient laboratory analysis

Evaluate ABO/Rh status, presence or absence of antibodies
1. Two independent peripheral blood samples for ABO/Rh typing and antibody screen
   a. Determination of clinical significance or insignificance of all non-ABO minor RBC antibodies (i.e., anti-K versus anti-N)
   b. Determination of ABO-incompatibility type: major, minor, bidirectional, or none

2. Communication with clinical teams regarding transfusion support and risk for hemolysis
Suggested Approach to ABO-Incompatible HPC Transplantation

**HCST Collection and Manipulation of Product – Cellular Therapy Lab**

Confirmation of ABO-incompatibility and stem cell dose.

- If product contains transplant dose (or approximate dose), HPC product manipulation may not be warranted given anticipated CD34 loss with product modification.

1. Major mismatch: RBC depletion
2. Minor mismatch: plasma depletion
3. Bidirectional: consider both product modifications in appropriate clinical context
From CELLULAR THERAPY to the BENCH
## RED CELL SELECTION for HSCT Patients

<table>
<thead>
<tr>
<th>Recipient Type</th>
<th>Donor Type</th>
<th>Transplant Incompatibility</th>
<th>Transfuse: Red Blood Cells</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>O</td>
<td>Minor</td>
<td>O</td>
<td>A, AB</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
<td>Major</td>
<td>O</td>
<td>AB</td>
</tr>
<tr>
<td>A</td>
<td>AB</td>
<td>Major</td>
<td>A, O</td>
<td>A, AB</td>
</tr>
<tr>
<td>B</td>
<td>O</td>
<td>Minor</td>
<td>O</td>
<td>B, AB</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>Major</td>
<td>O</td>
<td>AB</td>
</tr>
<tr>
<td>B</td>
<td>AB</td>
<td>Major</td>
<td>B, O</td>
<td>B, AB</td>
</tr>
<tr>
<td>O</td>
<td>A</td>
<td>Major</td>
<td>O</td>
<td>A, AB</td>
</tr>
<tr>
<td>O</td>
<td>B</td>
<td>Major</td>
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<td>AB</td>
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<tr>
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<td>O</td>
<td>Minor</td>
<td>O</td>
<td>AB</td>
</tr>
<tr>
<td>AB</td>
<td>A</td>
<td>Minor</td>
<td>A, O</td>
<td>AB</td>
</tr>
<tr>
<td>AB</td>
<td>B</td>
<td>Minor</td>
<td>B, O</td>
<td>AB</td>
</tr>
</tbody>
</table>
STEP 1: Determine Blood Unit Selection for ABO-Mismatch

If the ABO types of the patient and donor are different, the following chart will guide transfusions starting at Day 0 until the change of patient blood type.
STEP 2: Monitor Forward and Reverse

Patient blood type may be changed when the ABO (forward and reverse) and Rh is of the HPC donor type on TWO consecutive samples with Medical Director approval.
The change in blood type will be defined as the loss of patient isohemagglutinins against the donor’s RBCs.

With the loss of isohemagglutinins, the transfusion policy will be that of the donor blood type.

*Note: Any changes require approval from the Transfusion Services Medical Director.
STEP 3: BMT Patient Record Maintenance

Update patient CMV and Irradiated status
Weekly updates from BMT department on patients scheduled for collections

- Pre allo/auto transplant list
- Post allo/auto transplant list
Future Research Interests

• Tracking RBC engraftment
• Generating better software systems for BMT patients
• Integrating surveillance with PLT refractoriness
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TRUE
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B.) 0.2-0.3 mL/ kg
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Thanks for listening!
References


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