

ABO-incompatible Allogeneic Stem Cell Transplantation

Daniela Hermelin, MD **Transfusion Medicine Fellow** Saint Louis University School of Medicine Department of Pathology HAABB – Spring 2019 Conference April 10, 2019 0 0



Disclosures

None





Objectives

- ✓ History and Basic Theory
- ✓ Terminology
- ✓ Laboratory Processing
- ✓ Blood Bank Management



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

True or False?

In contrast to HSCT, ABOincompatible solid organ transplantation is a barrier.



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

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

A.) O recipient, A donorB.) O recipient, AB donorC.) A recipient, O donorD.) A recipient, AB donor

Human Major Histocompatibility Complex



https://www.researchgate.net/figure/Gene-map-of-the-human-leukocyte-antigen-HLA-region-The-HLA-region-spans-410-6_fig1_226487979

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



0

http://medweb4.unige.ch/immunologie/home/HSC/tran splantation_barriers/structures_recognized/major_histo compatibility_antigens/genetic.php

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



0

http://eastafricaschoolserver.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

	Group A	Group B	Group AB	Group O
Red blood cell type		B	AB	
Antibodies in Plasma	入 「人 Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens in Red Blood Cell	₽ A antigen	↑ B antigen	P A and B antigens	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

Characteristics of patients, their donors, and transplantation, 2007 to 2011

	Do	onor age, yea	rs
	18 to 32	33 to 50	>50
Number	2614	1794	282
Donor characteristics			
Donor-recipient HLA-match			
8/8 matched	2114 (81%)	1326 (74%)	181 (64%)
7/8 matched	500 (19%)	468 (26%)	101 (36%)
Donor-recipient ABO match			
Matched	874 (33%)	563 (31%)	79 (28%)
Minor mismatch	453 (17%)	374 (21%)	53 (19%)
Major mismatch	615 (24%)	442 (25%)	86 (30%)
Not reported	672 (26%)	415 (23%)	64 (23%)

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

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

Survival after ABO-incompatible HCT Transplantation

Study Authors	Year	Survival after ABO-Inco	Risk of Graft-versus-		
		Major	Minor	Bidirectional	
Kimura et al. [3]	2008	Decreased	Decreased	No difference	Increased with minor or major ABO mismatch
Helming et al. [13]	2007	No difference	No difference≞	No difference≞	No difference≞
Erker et al. [15]	2005	No difference	Decreased	Decreased	No difference
Kim JG et al. [12]	2005	No difference	No difference	No difference	No difference
Stussi et al. [14]	2002	Decreased	No difference	No difference	Increased with minor ABO mismatch
Benjamin et al. [18]	1999	Decreased	Decreased	No difference	No difference with minor or major mismatch
Bacigalupo et al. [19]	1988	-	-	-	Increased with minor ABO mismatch
Benisnger et al. [41]	1982	No difference	-	-	No difference with major ABO mismatch
Buckner et al. [17]	1978	-	No difference	-	No difference with minor ABO mismatch

Transplantation Time Periods



Phase 1

Phase 2

Phase 3

Pre-transplantation

Transplantation

Post engraftment

ABO-INCOMPATIBLE CLASSIFICATION

Table 1. ABO Matching of Donor and Recipienta				
	Recipient			
Donor	Α	В	AB	0
А	Compatible	Major/Minor	Minor	Major
В	Major/Minor	Compatible	Minor	Major
AB	Major	Major	Compatible	Major
0	Minor	Minor	Minor	Compatible
 Major and m not, complicat mismatch com 	ajor/minor mismatches may tions of ABO mismatch nee pplications can happen	better be avoided if other d to be dealt with in collab	HLA-matched (8/8) donor poration with the blood ban	options are available. If k. Major/Minor, both

MAJOR

DONOR: Type A, B, AB

RECIPIENT: Type O

Anti-A, Anti-B

Anti-donor antibodies

MINOR

DONOR: Type O, Anti-A, Anti-B Incompatible transfer of donor antibodies

RECIPIENT: Type A, B, AB

BIDRECTIONAL

DONOR: Type A or B Anti-A or Anti-B

RECIPIENT: Type A or B Anti-A or Anti-B



"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)

0

- 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



Red Cell Reduction

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
- Method 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 a 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

0

Plasma Reduction

- 1. Centrifugation of product in blood bags
- 2. Automated processing instrument (COBE 2991) or apheresis instrument
- 3. Crypopreservation 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 depletion2.Minor mismatch: plasma depletion3.Bidirectional: consider both product modifications in appropriate clinical context

From CELLULAR THERAPY to the BENCH



RED CELL SELECTION for HSCT Patients

Recipient Type	Donor Type	Transplant Incompatibility	Transfuse: Red Blood Cells	Plasma
А	0	Minor	0	A, AB
Α	В	Major	0	AB
Α	AB	Major	A, O	A, AB
В	0	Minor	0	B, AB
В	A	Major	0	AB
В	AB	Major	B, O	B, AB
0	А	Major	0	A, AB
0	В	Major	0	B, AB
0	AB	Major	0	AB
AB	0	Minor	0	AB
AB	А	Minor	A, O	AB
AB	В	Minor	В, О	AB

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.

SLUH Policy Tech: RED CELL SELECTION for HSCT Patients

- 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

SLUH BMT PATIENT – BLOOD BANK MAINTENANCE

- 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

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

True or False?

In contrast to HCT, ABOincompatible solid organ transplantation is a barrier. TRUE



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

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

A.) O recipient, A donorB.) O recipient, AB donorC.) A recipient, O donorD.) A recipient, AB donor

Table 1. ABO Matching of Donor and Recipienta				
	Recipient			
Donor	Α	В	AB	0
А	Compatible	Major/Minor	Minor	Major
в	Major/Minor	Compatible	Minor	Major
AB	Major	Major	Compatible	Major
0	Minor	Minor	Minor	Compatible



"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"

Thanks for listening!



References

- 1. Rowley SD, Donato ML, Bhattacharyya P. Red blood cell-incompatible allogeneic hematopoietic progenitor cell transplantation. *Bone Marrow Transplant.* 2011;46(9):1167-1185.
- 2. Booth GS, Gehrie EA, Bolan CD, Savani BN. Clinical guide to ABO-incompatible allogeneic stem cell transplantation. *Biology of Blood and Marrow Transplantation*. 2013;19(8):1152-1158.
- 3. Wingard JR, American Association of Blood Banks. *Hematopoietic stem cell transplantation : a handbook for clinicians.* Bethesda, Md.: American Association of Blood Banks; 2009.
- 4. Kollman C, Spellman SR, Zhang M-J, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. *Blood.* 2016;127(2):260-267.



.

0

•

Thanks for listening.