

A New Beginning: Stem Cell Transplant Challenges

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SickKids

THE HOSPITAL FOR
SICK CHILDREN

Objectives

1. Outline cellular therapy products and transfusion support for pediatric bone marrow / stem cell transplants
2. Describe the indications for the use of irradiated and CMV seronegative blood components



Stem cell source

- Bone marrow
- Peripheral blood stem cells
- Cord blood
- Sick Kids
 - About 100 transplants a year
 - Half autologous
 - Half allogeneic
 - 2 thirds are bone marrow (preferred for pediatric patients, less GVHD)
 - 1 third are peripheral blood stem cells and cords

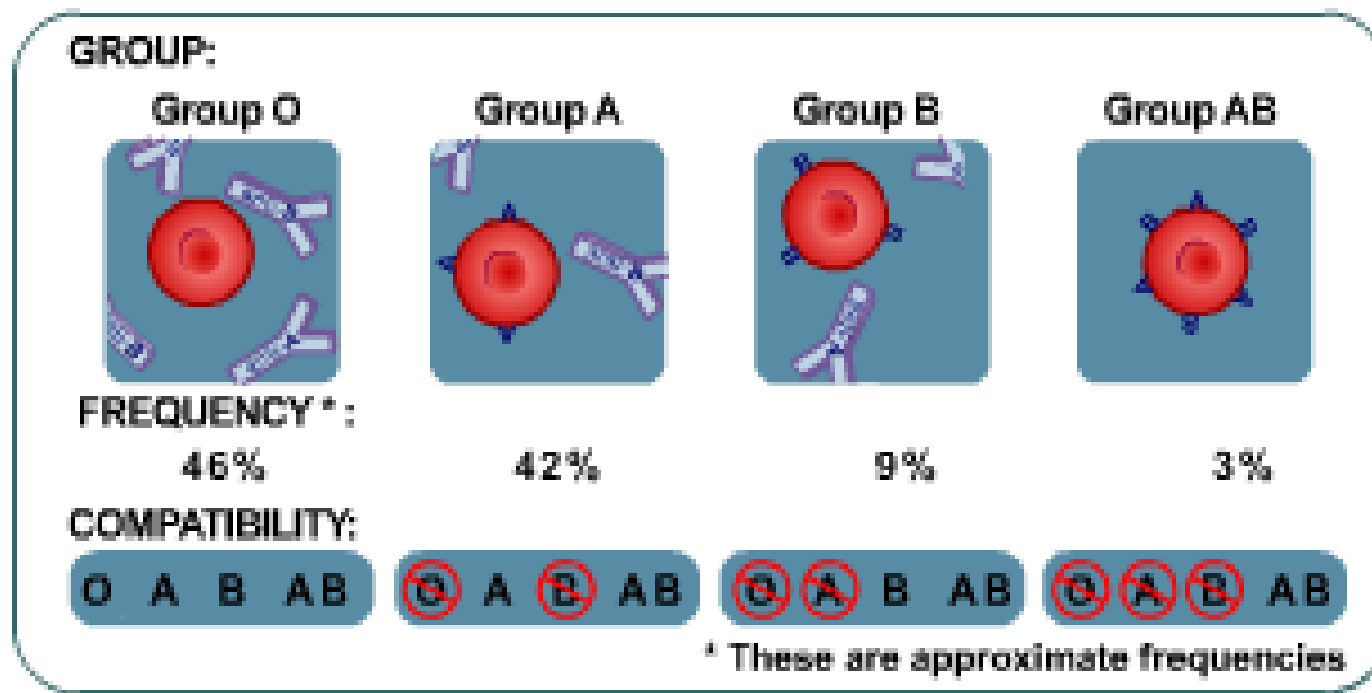


Infusing bone marrow is like transfusing whole blood

- BM donors are selected by HLA type, not blood group.
- 40-50% of transplants are ABO incompatible.
- 3 types of incompatibility
 1. Major mismatch: 20-25%
 2. Minor mismatch: 20-25%
 3. Both major and minor mismatch (bidirectional): 5%

Major ABO incompatibility

- Donor red cells incompatible with recipient's isoheamagglutinins (anti-A, anti-B)
 - Donor A, B, or AB, Patient O
 - Donor AB, Patient A or B



Major ABO incompatibility

- Potential adverse consequences
 - Immediate hemolysis
 - Delayed RBC engraftment
 - Pure red cell aplasia (residual recipient lymphocytes)
- Interventions
 - Plasmapheresis of recipient
 - Not routine in US or Canadian centres
 - Several centres in Europe still do routinely or based on recipient isoagglutinin titres
 - Red cell reduction
 - Manual method: Starch sedimentation
 - Newer automated devices

Major ABO incompatibility

Adult patients

- Maximum volume of major mismatched RBCs not clearly defined
 - Maximum allowable RBC volume differs between institutions (usually 10 to 40 mL)
 - Majority 20 to 30 mL or 0.2 to 0.4 mL/kg

Ref: How do I approach ABO-incompatible hematopoietic progenitor cell transplantation? J Daniel-Johnson, J Schwartz. Transfusion 2011;51:1143-9

ORIGINAL ARTICLE

Major ABO incompatible BMT in children: determining what residual volume of donor red cells can safely be infused following red cell depletion

K Patrick¹, W Lau², A Gassas¹, E McDougall², J Doyle³, M Ali¹, J Krueger¹, S Courtney¹, C Armstrong¹, RM Egeler¹ and T Schechter¹

Major ABO incompatible BM transplantation carries a risk of acute haemolysis. Red cell depletion reduces this risk but not all incompatible RBC (iRBCs) are removed and in children the residual volume can be significant relative to body weight. We sought to determine the volume of iRBCs that can be safely given to children. All patients receiving fresh BM from a donor with a major ABO blood group mismatch between January 2000 and July 2013 at the Hospital for Sick Children, Toronto, were included. Seventy-eight patients were identified. The median volume of iRBCs transfused was 1.6 mL/kg (range 0.1–10.6 mL/kg). Thirty-five patients had minor haemolytic events and five patients had clinically significant adverse events. Two patients, who received 3.66 and 3.9 mL iRBCs/kg, developed renal impairment and in one case hypoxia and hyperbilirubinaemia. One patient had mild hypotension that resolved with i.v. fluid. Two patients developed hypotension secondary to sepsis and unrelated to BM infusion. Although signs of haemolysis occur, with appropriate hydration and monitoring of renal function, clinically significant adverse events related to the infusion of ABO incompatible BM are rare, and, in this study, were only seen in patients receiving > 3 mL/kg of iRBCs per kg.

Bone Marrow Transplantation (2015) **50**, 536–539; doi:10.1038/bmt.2014.309; published online 26 January 2015

78 patients

Mean iRBCs 1.6 mL/kg (0.11 to 10.61 mL/kg)

30 patients (38%) minor hemolytic events

2 patients, 3.66 mL/kg, 3.9 mL/kg, significant events

Minor ABO incompatibility

- Donor isoheamagglutinins (anti-A, anti-B) against antigens on recipient red cells
 - Patient A, B, or AB, Donor O
 - Patient AB, Donor A or B
- Potential adverse consequences
 - Immediate hemolysis from passive antibodies
 - Delayed hemolysis due to the “passenger lymphocyte syndrome” (between days 5 and 15 posttransplant, from viable B lymphocytes in HPC product)
 - Most develop positive DAT, but only 10 to 15% DAT-positive recipients develop hemolysis, most are mild
- Plasma reduction: centrifugation

Transfusion Support for Major ABO incompatible BMT

Patient	Donor	RBCs	Plasma	Platelets
O	A	O	A	A, AB, B
O	B	O	B	B, AB, A
O	AB	O	AB	AB, A, B
A	AB	A	AB	AB, A, B
B	AB	B	AB	AB, B, A

Transfusion Support for Minor ABO incompatible BMT

Patient	Donor	RBCs	Plasma	Platelets
A	O	O	A	A, AB, B
B	O	O	B	B, AB, A
AB	O	O	AB	AB, A, B
AB	A	A	AB	AB, A, B
AB	B	B	AB	AB, B, A

Transfusion Support for Bidirectional ABO incompatible BMT

Patient	Donor	RBCs	Plasma	Platelets
A	B	O	AB	AB, B, A
B	A	O	AB	AB, A, B

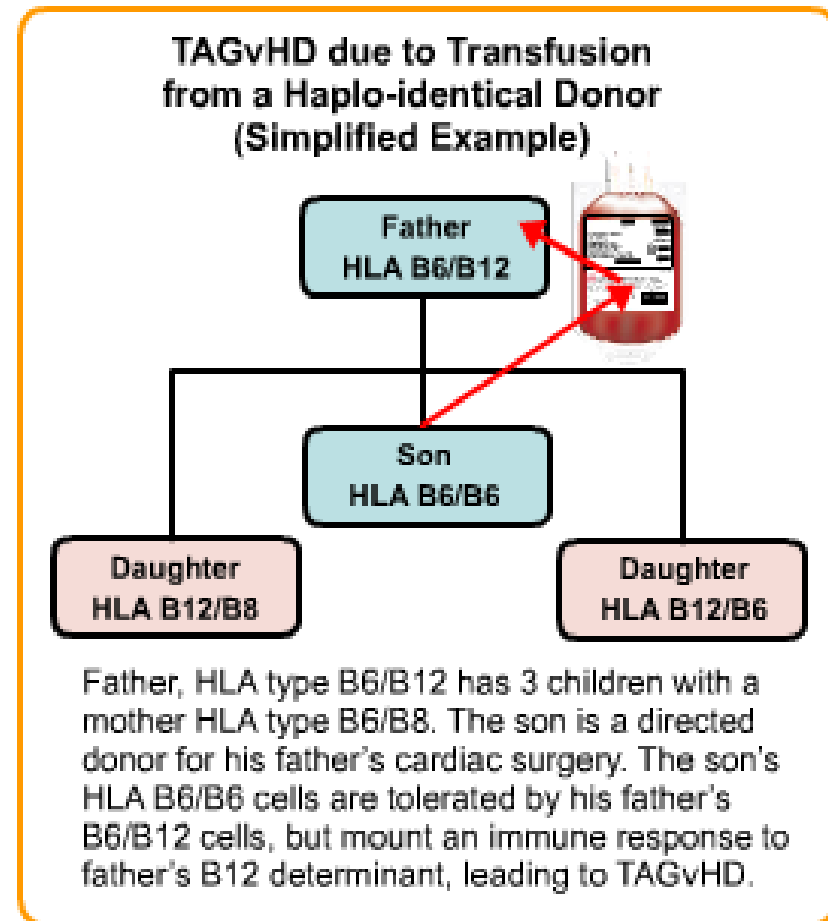
In all cases, Group O platelets may be given if titre of anti-A / anti-B low or plasma-reduced

BMT/Stem Cell Transplants

- Transfusion support for BMT patients: special consideration
 - Transfusion-associated Graft vs Host Disease Prevention
 - Cytomegalovirus (CMV) prevention

Transfusion Associated Graft vs Host Disease

- TA-GvHD occurs when transfused immunocompetent cells mount an immune response to recipient tissues
- Patients at risk:
 - Immuno-compromised individuals
 - Patients sharing HLA types
 - Family members
 - Fellow members of closed communities
- ❖ Directed donations: parent to child only
- ❖ Contraindicated for potential BMT patients



Irradiation to prevent TA-GVHD: Sick Kids policy

Infants under 6 months

Most at risk: premature, received IUTs, Exchange transfusion

Awaiting diagnosis of immune deficiency (especially in neonates with congenital heart disease)

Congenital T-cell immunodeficiencies, eg Di George, deletion 22q

All Hem/Onc patients with a malignant diagnosis on intense chemotherapy (including severe aplastic anemia)

All bone marrow transplant/stem cell transplant patients

Patients receiving or have received:

Purine analog (e.g. fludarabine, cladribine, pentostatin)

Alemtuzumab

Anti-thymocyte globulin

HLA matched platelets

All directed donations



Cytomegalovirus (CMV)

- CMV can be transmitted by transfusion
- Leukoreduced blood products are comparable to anti-CMV negative blood products in preventing transfusion-transmitted CMV infection

Agree

Disagree



CMV: the Sick Kids Journey (1)

1995: Anti-CMV negative blood to

Neonates

BMT pre and post

Hem/onc patients who are potential BMT recipients

Seronegative solid organ transplant recipients getting
seronegative donor organ

**A comparison of filtered leukocyte-reduced and
cytomegalovirus (CMV) seronegative blood
products for the prevention of transfusion-
associated CMV infection after marrow transplant**

Bowden, Blood, Nov 1995; 86: 3598 - 3603.



CMV: the Sick Kids Journey (2)

Prestorage leukoreduction in Canada

Feb 1998-platelets, Aug 1999-red cells

CMV Consensus Conference Jan 2000 Toronto:

CMV-seronegative pregnant women, intrauterine fetal transfusions, and CMV-seronegative allogeneic marrow transplant recipients.

2000-2005: meetings with neonatologists, infectious disease specialists

2005: stopped giving anti-CMV negative blood to neonates

However, Hem/Onc and BMT were resistant to change

Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. WG Nichols, Blood 2003;101;4195-4200 (Fred Hutchison Cancer Research Center, Seattle)



CMV: the Sick Kids Journey (3)

Chair of our Blood Transfusion Committee was also head of BMT at Sick Kids

“ Practice is hard to change.”

A large allogeneic stem cell transplant program in Germany: a decade of patients undergoing allogeneic transplant with leukoreduction as the sole strategy: no patient developed transfusion-transmitted CMV

Thiele T, Kruger W, Zimmermann K, et al. Transmission of cytomegalovirus (CMV) infection by leukoreduced blood products not tested for CMV antibodies: a single-center prospective study in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation. *Transfusion*. Dec 2011;51(12):2620-2626.

Many centers abandoned the use of anti-CMV negative blood products for transplant patients, eg. Germany, Netherlands, UK, Puget Sound Blood Center (Seattle), Harvard...



CMV: the Sick Kids Journey (4)

Sick Kids Policy since Aug 1, 2012:

anti-CMV neg blood to CMV IgG negative pre- allogeneic
BMT/SCT recipients who are CMV IgG negative 2-6
weeks pre-transplant

Rounds: Hem/Onc divisional rounds, Transplant rounds

Meetings

Memos, e-mails

Revised indications on order screens (electronic), order
sheets (paper)

Educational rounds, residents/fellows

❖ Nursing education



The Journey is not yet over

Constant reminders

Hold outs

Hematology/Oncology: some staff physicians

Immunology: concern about SCID (Severe Combined Immunodeficiency Disease) patients



Thank you





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Determine Blood Group of Products to Support ABO Incompatible Hematopoietic Progenitor Cell (HPC) Transplant
Blood Transfusion Laboratory

Patient's Group	Donor's Group	Red Cells	FFP	Cryo	Platelets	
					Preferred for Transfusion	Other Choices
O	A	O	A	Any Blood Group	A	*B, AB
						O concentrated SDP
O	B	O	B	Any Blood Group	B	*A, AB
						O concentrated SDP
O	AB	O	AB	Any Blood Group	AB	A, B
						O concentrated SDP
A	B	O	AB	Any Blood Group	AB	*B, A
						O concentrated SDP
A	AB	A	AB	Any Blood Group	AB	A, B
						O concentrated SDP
A	O	O	A	Any Blood Group	A	*B, AB
						O concentrated SDP
B	A	O	AB	Any Blood Group	AB	*A, B
						O concentrated SDP
B	AB	B	AB	Any Blood Group	AB	*A, B
						O concentrated SDP
B	O	O	B	Any Blood Group	B	*A, AB
						O concentrated SDP
AB	O	O	AB	Any Blood Group	AB	A, B
						O concentrated SDP
AB	A	A	AB	Any Blood Group	AB	*A, *B
						O concentrated SDP
AB	B	B	AB	Any Blood Group	AB	*B, *A
						O concentrated SDP