A Review of Umbilical Cord Blood Transplantation

Philippine Association of Medical Technologists
Northern California Chapter
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Objectives

Upon completion of this presentation, participants will be able to:

- Describe how cord blood transplant (CBT) works
- Define at least five conditions treated by CBT
- Discuss what the future is likely to hold for CBT
Disclosure

I am an owner of stock in StemCyte, a for-profit cord blood bank headquartered in Southern California.
Focus: Hematopoietic Stem Cell Transplant
(with some brief discussion of other applications)
Umbilical Cord Blood Transplant

Outline

• Case Study
• History
• Background + Science
• Clinical Applications
• Miscellaneous Important Issues
• The Future
• Summary
Umbilical Cord Blood Transplantation

Case Study
Case Study

• 5 year-old male with Fanconi’s anemia

• **About Fanconi’s anemia**
  o Inherited (homozygous) disorder leading to impaired DNA repair
  o All patients have reduced numbers of RBCs, WBCs, and platelets
  o Many also are affected by (non-exhaustive list):
    ▪ Abnormal heart, lungs, G.I. tract
    ▪ Skin changes
    ▪ Deafness due to abnormal ears
    ▪ Eye or eyelid problems
    ▪ Misshapen kidneys
    ▪ Problems with arms and hands
    ▪ Short height and small head
    ▪ Small testicles and genital changes
    ▪ Greatly increased risk of developing a variety of malignancies
Case Study

From:
http://dxline.info/diseases/fanconis-anemia#prettyPhoto
(accessed 05-08-15)
Case Study

• Cord blood was collected at birth from sibling shown by prenatal testing not to have Fanconi’s anemia
• Patient received pre-transplant conditioning similar to that used for traditional (bone marrow) transplantation
• Frozen cells were transported from Indiana to Paris
• Engraftment began on day 22
• No significant complications (including graft-versus-host disease)
• **Patient remains healthy 27 years later**
Umbilical Cord Blood Transplantation
Umbilical Cord Blood Transplantation

Milestones

- **Mid/late-1980s**: Optimized collection and storage
- **1988**: First HLA-identical sibling cord blood transplant
  - 5-year-old boy with Fanconi’s anemia
- **1990**: First HLA-mismatched transplant in child
  - 30-month-old boy with ALL in 2nd clinical remission
- **Early-1990s**: Development of cord blood banks
- **1993**: First unrelated transplant in child
  - 3-year-old with T cell ALL

Umbilical Cord Blood Transplantation

Milestones

• **1995**: First transplant in adult leukemic patient
• **2005**: First large series of double cord transplants reported
  o Pioneered by University of Minnesota
  o Now represents a standard of care for many adults
• **As of now ...**
  o > 25,000 cord blood transplants performed
  o NMDP estimates > 95% patients can find at least 1 potential 4/6-matched CB unit
  o Non-hematopoietic stem cells from cord blood being used for regenerative medicine

Umbilical Cord Blood Transplants

Source: National Marrow Donor Program/Be The Match FY 2014
Role of Cord Blood in Transplants by Patient Race

- **Black/African American**
  - Cord Blood: 38%
  - Bone Marrow or Peripheral Blood: 62%

- **American Indian/Alaska Native**
  - Cord Blood: 24%
  - Bone Marrow or Peripheral Blood: 76%

- **Native Hawaiian/Other Pacific Islander**
  - Cord Blood: 71%
  - Bone Marrow or Peripheral Blood: 29%

- **Asian**
  - Cord Blood: 24%
  - Bone Marrow or Peripheral Blood: 76%

- **White**
  - Cord Blood: 12%
  - Bone Marrow or Peripheral Blood: 88%

Source: National Marrow Donor Program/Be The Match FY 2014
Umbilical Cord Blood Transplantation
Pulling Back from the “Trees” to the “Forest”

General Overview of Hematopoietic Stem Cell Transplantation
Definitions

- **Autologous**: Self-directed donation with subsequent reinfusion
- **Allogeneic**: Donation for the transplant of another
Typical Schema for Autologous Bone Marrow Transplant

Collection
Stem cells are collected from the patient's bone marrow or blood

Processing
Blood or bone marrow is processed in the lab to purify and concentrate the stem cells.

Cryopreservation
Blood or bone marrow is frozen to preserve it

Reinfusion
Thawed stem cells are reinfused into the patient

Chemotherapy
High dose chemotherapy and/or radiation therapy is given to the patient

BoneMarrowMX
Autologous Transplant Process

BloodSource
Yes, you do save lives. | www.bloodsource.org | not-for-profit since 1948
Typical Schema for Allogeneic Bone Marrow Transplant

- **Donor**
  - Collection: Stem cells are collected from the patient’s bone marrow or blood
- **Processing**
  - Blood or bone marrow is processed in the lab to purify and concentrate the stem cells.
- **Cryopreservation**
  - Blood or bone marrow is frozen to preserve it.
- **Patient**
  - Reinfusion: Thawed stem cells are reinfused into the patient.
  - Chemotherapy: High dose chemotherapy and/or radiation therapy is given to the patient.
Cytotoxicity: Pertaining to destruction of cells; many chemotherapeutic drugs are cytotoxic, typically leading to death of the most rapidly dividing cells.

Engraftment: Establishment of a self-renewing population of hematopoietic cells in the marrow following transplant.

Hematopoietic Growth Factors: These most commonly are called colony stimulating factors, and are comprised of glycoprotein hormones that regulate division and differentiation of hematopoietic cells.

- **G-CSF**: Induces both (1) final stages of neutropoiesis and (2) entrance of early, pluripotent stem cells into active cell cycle.
- **GM-CSF**: Assists in (1) directing multipotent stem cells into becoming committed lineages and (2) entrance of early, pluripotent stem cells into active cell cycle.
**Hematopoietic Stem Cells:** The relatively undifferentiated cells from which all hematopoietic cells originate

- **Pluripotent Stem Cell:** This is the common precursor that gives rise to all other types of blood cells
- **Multipotent Stem Cells:** These include the colony-forming unit-granulocyte-erythrocyte-macrophage-megakaryocyte (CFU-GEMM) and the CFU-lymphocyte. They’ve not yet committed to a single lineage
- **Committed Stem Cells:** These cells (e.g., the BFU-E, the CFU-GM, etc.) have committed themselves to differentiating along the erythroid, megakaryocyte, granulocyte/macrophage, eosinophilic, basophilic, B-cell, or T-cell pathways, respectively
Definitions
(Cont.)

Hematopoietic Stem Cells

Normal haematopoiesis and the concept of stem cell transplantation
Expert Reviews in Molecular Medicine ©2004 Cambridge University Press
Definitions (Cont.)

- **Mobilization**: Process of stimulating the donor (with hematopoietic growth factors and – sometimes – low-dose chemotherapy) to increase concentration of circulating stem cells

- **Myeloablation**: Irreversible ablation of all mature and immature hematopoietic cells

- **Myelosuppression**: Suppression (not ablation) of cell development within the marrow
Definitions (Cont.)

With myeloablation . . .

This

Becomes

This
Basic Theory Behind Hematopoietic Stem Cell Transplantation (HSCT)

• **Killing the Cancer**: Cytotoxic drugs (with or without total body irradiation and immune-directed agents) are generally used to kill the malignancy

• **Double-Edged Sword**: These treatments also lead either to myeloablation or to profound myelosuppression—either of which can be fatal.

• HSCT allows for a work-around by reconstituting the damaged marrow cells

• **[Alternate Mechanisms]**: HSCT also sometimes serves as a means for “transferring” normal genes into a patient with abnormal marrow cells (e.g., as when used to treat severe sickle cell disease) … plus … it also has other possible utilities (to be discussed)
HSCT: The Worldwide Scope

- > 50,000 HSC transplants occur annually worldwide, allowing for the treatment of patients with life-threatening malignant and nonmalignant diseases

Types of HSCT

- Bone marrow transplant (BMT)
- Peripheral blood stem cell transplant (PBSCT)
- Umbilical cord blood transplant (UCBT)
Bone Marrow Transplant – Collection
Marrow Transplantation

Collection

- Aspiration from iliac crests using large bore needles
- 3-5 mL aspirated per puncture to a total of 15-20 mL/kg of donor’s body weight
- Mixed in bag with citrate and/or heparin and then filtered through series of screens to remove spicules and aggregates
- Most marrow harvests today are transplanted fresh, via the NMDP’s unrelated HSCT program
Marrow Transplantation

Collection

- The total nucleated cell count (TNC) is used to guide the endpoint of the harvest.
- For un-manipulated related transplants, a TNC of $2.0 \times 10^8$/kg (which corresponds to an MNC of $1.0 \times 10^8$/kg or a CD34+ count of $2.0 \times 10^6$/kg) is generally considered acceptable.

$$\text{TNC} \times 10^8$/kg \times \frac{\text{Volume (mL)} \times \text{TNC} \times 10^9/L}{\text{Body weight (kg)} \times 100}$$
Peripheral Blood Stem Cell Collection
PBSC – Mobilization

**Theory**

- In steady state, blood contains 10-100-fold fewer HSCs than marrow (per unit volume).
- **Chemotherapy-Induced Mobilization**: In the mid-1970’s, C. Richman, et al. showed that post-chemo patients had 25-100x increases in CFU-GM and 10-20x increases in BFU-E levels.
- **Hematopoietic Growth Factor-Induced Mobilization**: By the mid-1980’s, G-CSF and GM-CSF were shown to increase stem cell levels by 50-100-fold.
- **Combination Mobilization**: When used together, the two frequently have synergistic effects.
PBSC – Mobilization

The Composition of Mobilized Cells

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pctg. Of MNCs that are CD34+</th>
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</thead>
<tbody>
<tr>
<td>Steady State</td>
<td>0.1%</td>
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<tr>
<td>Post-Chemo</td>
<td>0.7-5.0%</td>
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<tr>
<td>Post-Chemo + CSF</td>
<td>10-20%</td>
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</table>

PBSC – Mobilization

Example of a Typical Mobilization Schema

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<th>5</th>
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<th>7</th>
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</tr>
</tbody>
</table>

Legend: C = Cyclophosphamide; P = Prednisone; G = G-CSF; L = Leukapheresis
PBSC – Collection

**Theory:** Collections are performed via apheresis methods, which utilize centrifugal force to separate a patient’s blood into its various constituents.
Umbilical Cord Blood Transplantation

Collection/Use

• Historically used in allogeneic setting, only
• (Autologous approach becoming more common)
• May be collected in a:
  o “Directed” manner (e.g., from siblings) or in a
  o “Non-directed” manner (e.g., from mothers who volunteer to give the product for others unknown to them)
• Degree of HLA mismatch may be greater with UCBT than with other two methods of HSCT
Umbilical Cord Blood Transplantation

Further discussions about collection, storage, research, and related issues to be covered by Drs. Pontow and Walker.
One-year Survival by Year of Transplant, Donor and Age, Worldwide

Acute Leukemia, CML or MDS early disease status.
## Selected Outcome Comparisons Between the 3 Methods of HSCT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BMT</th>
<th>PBSCT</th>
<th>UCBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to engraftment</td>
<td>Mid</td>
<td>Fastest</td>
<td>Slowest</td>
</tr>
<tr>
<td>Risk of acute GVHD</td>
<td>Similar to PBSCT</td>
<td>Similar to BMT</td>
<td>Lowest</td>
</tr>
<tr>
<td>Risk of chronic GVHD</td>
<td>&lt; PBSCT but &gt; UCBT</td>
<td>Highest</td>
<td>Lowest</td>
</tr>
<tr>
<td>CD34+ Cell Dose</td>
<td>Generally enough</td>
<td>Best</td>
<td>Limited</td>
</tr>
<tr>
<td>2nd Donation</td>
<td>Generally available</td>
<td>Generally available</td>
<td>Original donor generally unavailable</td>
</tr>
<tr>
<td>Time to ID &amp; collect cells from unrelated donor</td>
<td>Approx. 6-7 weeks</td>
<td>Approx. 6-7 weeks</td>
<td>&lt; 2 weeks</td>
</tr>
</tbody>
</table>
Umbilical Cord Blood Transplantation

Dose limitations can be a challenge, necessitating the need for novel approaches to transplantation [Data from University of Minnesota website, Feb., 2005]
Historically Delayed Engraftment

Laughlin et al. NEJM. 2004; 351:2265
Contributors to Delayed Engraftment

- Degree of HLA-match
- Cell dose:
  - 10-fold lower cell dose with CBT\(^1\)
    - BM or PBSC transplant: \(2 \times 10^6\) CD34+ cells/kg
    - Cord blood transplant: \(1.37 \times 10^5\) CD34+ cells/kg for single cord
- Conditioning regimen\(^2,^3\)

HOW TO IMPROVE DELAYED ENGRAFTMENT AFTER CBT?

Double Cord Blood Transplantation
23 patients, median age 24 (13-53)

2 cord blood units given:
- 10 (43%) patients received 4/6-matched units
- 11 (48%) patients received at least one 5/6-match
- 2 (9%) patients received at least one 6/6-match

Infused cell doses:
- Median cryopreserved TNC/kg = 4.8 x 10^7/kg
- Median infused TNC/kg = 3.5 x 10^7/kg
- Median infused CD34+/kg = 4.9 x 10^5/kg
All 21 evaluable patients achieved sustained neutrophil engraftment

- Median of 23 days (range 15-41)
- Complete donor chimerism
  - 76% with single donor dominance by day 21
  - 100% by day 100
- No secondary graft failure

71% achieved platelet engraftment (> 50,000) by day 180
Demonstrated feasibility and safety of double CB unit transplantation as a means to improve engraftment
Umbilical Cord Blood Transplantation

Clinical Applications
Clinical Applications

**Hematopoietic**

- **Malignant Diseases and Marrow Failure States**
  - Leukemias
  - Aplastic anemias
- **Non-malignant Diseases**
  - Hemoglobinopathies (e.g., sickle cell and thalassemia)
  - Metabolic storage diseases (e.g., Hurler’s syndrome)
  - Other (e.g., Fanconi anemia, SCID)
Clinical Applications

Other

- **Regenerative Medicine**
  - Ischemic heart diseases (e.g., myocardial infarct)
  - Neurologic diseases (cerebral palsy, stroke)
- **Other**
  - Cellular vehicle for gene therapy
Allogeneic Stem Cell Sources by Recipient Age

- Bone Marrow (BM)
- Peripheral Blood (PB)
- Cord Blood (CB)

Transplants, %

- 2002-2006
- 2007-2011

Age ≤ 20 years

Age > 20 years

www.bloodsource.org
Likelihood of finding matched unrelated adult donor

Range 66-97%: Available suitable match, by race/ethnic group, Be The Match Registry®

Transplants by Cell Source
Adult Recipients (18 years and older)

Source: National Marrow Donor Program/Be The Match FY 2014
Transplants for Minority Patients by Cell Source

Source: National Marrow Donor Program/Be The Match FY 2014
Unrelated Cord Blood Transplants by Age Registered with the CIBMTR
Umbilical Cord Blood Transplantation

Miscellaneous Important Issues
Selection of Cord Blood Units

- Traditionally based on HLA-match, dose, unit quality
  - HLA-A and –B typing at antigen level, high resolution typing for HLA-DRB1 alleles
  - Minimum 4/6-matched, each \( \geq 1.5 \times 10^7 \) TNC/kg
    - 6/6-match: minimum single unit dose required \( \geq 3 \times 10^7 \) /kg
    - 5/6-match: \( \geq 4 \times 10^7 \) /kg
    - 4/6-match: \( \geq 6 \times 10^7 \) /kg
- Ongoing studies on benefit of further high resolution typing, effect of HLA-C matching
Other Factors

  - More significant for 6/6-matched CBT
    - Transplant-related mortality 9% with C-match vs. 26% with C-mismatch
  - Also for 5/6-matched CBT
    - Transplant-related mortality 32% with C-match vs. 44% for C-mismatch
Umbilical Cord Blood Transplantation

The Future
(A Few) Questions for the Future

• Will double cord blood transplants become the standard for adult patients?
• Or will single BC transplants … supported by haploidentical transplants … win out?
• Will haploidentical transplants replace cord blood transplants in some cases?
• What role will manipulation of cord blood stem cells continue to play?
Umbilical Cord Blood Transplantation
Umbilical Cord Blood Transplant

What We Covered

• Case Study
• History
• Background + Science
• Clinical Applications
• Miscellaneous Important Issues
• The Future
• Summary
With gratitude to, and respect for, all of my friends and colleagues at PAMET
Thank You ... 

Q & A + Other Discussion

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