Leukemia to Leukodystrophy: Curative Role of Umbilical Cord Blood Transplantation

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Hematopoietic Stem Cell Transplantation

- Bone Marrow
- Peripheral Blood Stem Cell
- Umbilical Cord Blood
Hematopoietic Stem Cell Transplantation

Fundamental Concepts

Elimination of Hematopoietic elements in bone marrow and other organs (Myeloablation) then
Marrow Reconstitution

Hematopoietic Stem Cell Transplant versus
Solid Organ Transplant
• Mendelian Inheritance - 25% chance of matching
• Overall chance in the sibship = 1 - (0.75)^n  n = number of siblings
• USA – 25-30% chance of finding a matched sibling
• Higher chances in inbred and consanguineous marriage
Hematopoietic Stem Cell Transplant

- Allogeneic
- Autologous
- Syngeneic
- Xenogeneic

- PBSCT
- Cord Blood Transplant
- BMT

- T-Cell depleted

- Matched
- Mismatched
- Haplo donor

- Myeloablative
- Non-Myeloablative

- Related Donor
- Unrelated Donor
Unrelated Donor Transplants by NMDP (Be-The-Match Registry)

Total Numbers

Patients < 18 years old
UCB-T for Malignant Diseases

- **Acute Leukemia**
  - Acute Lymphoblastic Leukemia (ALL)
  - Acute Myelogenous Leukemia (AML)
  - Secondary AML
  - Acute Undifferentiated Leukemia and Biphenotypic Leukemia

- **Chronic Leukemia**
  - Chronic Myelogenous Leukemia (CML)
  - Juvenile CML (JCML) or CMML
  - Juvenile Myelomonocytic Leukemia

- **Myelodysplastic Syndromes (MDS)**
  - Including Secondary or Monosomy 7

- **Lymphoma**
  - Non-Hodgkin’s Lymphoma: Lymphoblastic, Burkitt’s, Mantle Cell
  - Hodgkin’s Disease (HD)

- **Solid Tumors**
  - PNET, Neuroblastoma, Ewing’s Sarcoma
U-CBT: Nonmalignant Diseases

• Immunodeficiency Syndromes
  – Severe Combined Immunodeficiency Syndrome (SCID)
    • X-Linked, ADA Def., PNP Def., Nezelof Syndrome, Zap-70 Def., Idiopathic
  – Combined Immunodeficiency (CID)
  – X-Linked Lymphoproliferative Syndrome
  – Wiskott-Aldrich Syndrome (WAS)
  – Cartilage-Hair Hypoplasia
  – Reticular Dysgenesis
  – Omenn Syndrome

• Familial Erythrophagocytic Lymphohistiocytosis (FEL)

• Osteopetrosis

• Bone Marrow Failure Disorders
  – Fanconi Anemia
  – Blackfan-Diamond Syndrome
  – Dyskeratosis Congenita
  – Paroxysmal Nocturnal Hemoglobinuria (PNH)
  – Acquired Severe Aplastic Anemia
U-CBT: Nonmalignant Diseases

• White Blood Cell Disorders
  – Leukocyte Adhesion Deficiency (LFA-1 Deficiency, CD11/18)
  – Chronic Granulomatous Disease (CGD)
  – Chediak Higashi Syndrome
  – Kostmann’s Syndrome (Congenital Neutropenia)

• Hemoglobinopathies
  – Sickle Cell Anemia
  – Thalassemia Major

• Platelet Disorders
  – Amegakaryocytic Thrombocytopenia (AMT); TAR Syndrome

• Inborn Errors of Metabolism
  – Mucopolysaccharidoses (Hurler, Hunter, San Filippo)
  – Neiman-Pick, Sandhoff, Fucosidosis, Batten Disease
  – Leukodystrophies (Adrenoleukodystrophy, Krabbe or Globoid Leukodystrophy, Metachromatic Leukodystrophy)
# Pediatric Unrelated Cord Blood Transplants at Duke

**August 1993 - December 2012**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>ALL</td>
<td>191</td>
</tr>
<tr>
<td>AML</td>
<td>147</td>
</tr>
<tr>
<td>Inherited Metabolic Disorder</td>
<td>235</td>
</tr>
<tr>
<td>Immune Deficiency</td>
<td>70</td>
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<tr>
<td>Bone Marrow Failure</td>
<td>43</td>
</tr>
<tr>
<td>MDS</td>
<td>44</td>
</tr>
<tr>
<td>CML</td>
<td>21</td>
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<tr>
<td>Lymphoma</td>
<td>26</td>
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<tr>
<td>Hemoglobinopathy</td>
<td>14</td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td>9</td>
</tr>
<tr>
<td>Others</td>
<td>18</td>
</tr>
</tbody>
</table>

**Total Unrelated Cord Blood Transplants** 873

| Total Number of Transplants          | ~2000              |
BMT → Hematopoietic Stem Cell Transplant

First Successful BM Transplants - 1968
First URD Transplant – 1973
First Cord Blood Transplant – 1988
First Unrelated Cord Blood Transplant - 1993
"The significant problems we face cannot be solved at the same level of thinking we were at when we created them."

- Albert Einstein

As relevant in 1980..
Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling

E Gluckman, HA Broxmeyer, AD Auerbach, HS Friedman, GW Douglas, A Devergie, H Esperou, D Thierry, G Socie, P Lehn, and et al.

Bone Marrow Transplant Unit, Hopital Saint-Louis, Paris, France.

Transplant 1988
Published 1989

May 2008
Umbilical cord blood contains sufficient numbers of stem and progenitor cells to rescue marrow after myeloablative therapy.
Transplant Details

- Organ function studies: similar to other transplant
- Airway optimization: MPS
- Enzyme level and other diagnostic work
- G-tube: Younger children; Leukodystrophy
- Neuroradiology Testing: MRI
- Neuro-cognitive Testing: UNC-CH
- Neurophysiology Testing: EEG, BAER, VER
- Cell dose: >3x10^7 cells/kg
- CB UNIT Enzyme: 2-5 units screened; unit with highest level selected
- Conditioning: Busulfan (targeted 1st dose PK - Css 600-900ng/ml; q 6 hrs x 16 doses); Cyclophosphamide – 50 mg/kg x 4; eATG 30 x 3
- GvHD Prophylaxis: CYA/Steroids; CYA/Cellcept (n=28)
- Supportive Care: Anti-fungal, -viral, -PCP prophylaxis, IVIG, G-CSF, TPN, Transfusions, VOD prophylaxis with LD heparin, PCA
3 year old (14.1 kg) with relapse T-cell ALL
- No family or adult BM donor
- 4/6 Cord blood unit from NYBC; TNC – 4.6x10^7/Kg
- Engrafted Day +31 (ANC >500)
- Severe Pulmonary Hemorrhage and died Day +61

1 yr old infant leukemia Sept 93
- 4/6 CBU; TNC 4.86x10^7/kg
- Long term survivor
The first prospective, multicenter study of UCBT with standard protocol and supportive care.

ENGRAFTMENT
- Median time to ANC 500 - 27 days (range 11-90)
- Graft failure 23 (12%)
- Median time to Platelet 50K - 174 days (range 21-353)

GVHD
- Grade III/IV aGVHD - 19%; cGVHD - 20% (70% limited).

Incidence of relapse was 25% (77% of patients were high risk)

Overall survival: Early engraftment, patient CMV negative serology and male gender being favorable risk factors.

Ethnic minority had same outcomes as Caucasians

Kurtzberg, Prasad.., Blood 2008
COBLT:
Pediatric Hematologic Malignancy
191 subjects transplanted between 1999-2003
Leukemia Free Survival: URD BMT vs. UCBT

Eapen et Lancet 2007
HLA Identical sibling UCB vs. BM
Rocha et al NEJM 2000

- Slower and lower engraftment
- Lower Acute & Chronic GVHD
- Similar Mortality

- Younger (5 yr vs 8 years)
- Weighed less (17 kg vs 26 kg)
- Less MTX (28% vs 65%)
Single vs. Double Cord Blood Transplant

- **UCB 1**
  - HLA ≤ 2 ag mm
  - TNC > 2.5 x 10^7/kg

- **UCB 2**
  - HLA ≤ 3 ag mm

- **TBI**
  - TBI twice daily
  - Flu 25 mg/m2 daily
  - TBI 165 cGy twice daily
  - Cy 60 mg/kg daily

- **Cy**
  - Cy twice daily

- **REST**
  - Rest period

- **G-CSF**

Days from Transplant

CSA

MMF
14 Domestic Cord Blood Banks
250,000 CBU in USA
600,000 worldwide

Growth of Cord Blood Units on the Be The Match Registry® 2010
Cord Blood Collection and Banking

Not the Duke way
Inherited Metabolic Disorders: Lysosomal and Peroxisomal Diseases

- **Mucopolysaccharidoses:** defective metabolism of glycosaminoglycans
  - MPS I (Hurler) | MPS II (Hunter) | MPS III | MPS IV | MPS VI | MPS VII

- **Glycoproteinoses:** Defective degradation of glycoproteins
  - Aspartylglucosaminuria | Fucosidosis, type I - II | Mannosidosis | Sialidosis

- **Sphingolipidosis:** Defective degradation of sphingolipid
  - Acid sphingomyelinase deficiency | Fabry disease | Farber disease | Gaucher disease | GM1 gangliosidosis | Tay-Sachs disease | Sandhoff disease | Krabbé disease | metachromatic leukodystrophy

- Defective degradation or transport of cholesterol or other complex lipids
  - Neuronal ceroid lipofuscinosis

- Multiple deficiencies of lysosomal enzymes
  - Galactosialidosis | Mucolipidosis

- Transport and trafficking defects
  - Cystinosis | Mucolipidosis IV | Infantile Sialic acid storage dis (ISSD) | Salla disease

- **Glycogen Storage Diseases:** Defective degradation of glycogen
  - Pompe disease

- **Peroxisomal Storage Disorder**
  - Adrenoleukodystrophy
Enzyme could be transported from normal cells to deficient cells
Elizabeth Neufeld Group
1968 Science; 1976 PNAS

How does UCBT correct IMD?

- Donor engraftment
- Donor leukocytes produce enzyme which circulates in the body with blood
- Cells migrate to brain, cross blood brain barrier, replace enzyme in brain. Microglia in the brain derived from the donor cells
- Enzyme helps defective cells by “Cross-correction”
- “Cellular Enzyme Therapy”
- Non-hematopoietic cell engraftment
ALDH Cells from Human Cord Blood in MPS VII/SCID NOD Mice

Jane Nolta’s Group
Need for Donor for transplant

**Inheritance of HLA**

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>C</td>
<td>A</td>
<td>D</td>
</tr>
<tr>
<td>A</td>
<td>D</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>B</td>
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<td>C</td>
</tr>
<tr>
<td>A</td>
<td>C</td>
<td>B</td>
<td>D</td>
</tr>
</tbody>
</table>

**Chance of matching:** 1 in 4

**Chances that a brother or sister will be a suitable bone marrow donor:** $\frac{1}{4} \times \frac{1}{4} = \frac{1}{16}$

**Inheritance of MLD**

- **Unaffected "Carrier" Father**
- **Unaffected "Carrier" Mother**

**Chance of having an unaffected and non-carrier sibling:** 1 in 4
Unrelated UCBD-T for IMD: Demographics
DUMC Aug 1995 – April 2007

TOTAL PATIENTS – 159
Age – Median (range) 1.5 yrs (0.05 – 26.25)

Prasad et al Blood 2008
Overall Survival by Performance Status

- 80-100 at 1 Year: 84.5% (95% CI 77.0%-92.0%)
- <80 at 1 Year: 54.5% (95% CI 42.5%-66.5%)

Prasad et al. Blood 2008
Krabbe Disease

- Deficiency of Galactocerebrosidase (GALC)
- Accumulation of lipids in the CNS leading to demyelization.
- Incidence - 1/100,000 to 200,000
- Age of onset -
  - Early infantile – Death by 1-2 years of age
  - Late infantile
  - Childhood
- Autosomal recessive; Scandinavian descent
- Irritability, hypertonia, spasticity,
- Peripheral neuropathy, pain, seizures,
- Optic atrophy, visual loss
- Mental deterioration, vegetative state
- GALC level: blood, fibroblasts, prenatal sampling
- MRI/CT brain - attenuation of white matter
- Elevated CSF protein
- Decreased nerve conduction
Adrenoleukodystrophy (ALD)

- Movie “Lorenzo’s Oil”
- Deficiency of peroxisomal membrane transport protein leads to accumulation of very long chain fatty acids and progressive CNS white matter and the adrenal cortex damage.
- Incidence: 1/100,000; X-linked recessive;
- Childhood type: 4-8 yrs (as early as 2 yrs); Adolescent type - 10-21 years of age
- Neurological: hyperactivity, ataxia, poor handwriting, subtle changes in affect, behavior, and attention span, seizures
- Visual: field cuts, strabismus, visual acuity
- Endocrine: adrenal insufficiency and crisis
- Death follows within a short period of time
- Transplant outcome - Beam et al BBMT 2007
UCBT Summary Data

- COBLT:
  Vermeris et al 2010
- BMT CTN: Protocol 0501 – Single vs. Double UCBT

Almost 30,000 umbilical cord blood transplants of which >25,000 from unrelated donors have been performed worldwide
Thanks.
Please Wake up and ask Questions......
<table>
<thead>
<tr>
<th>Adrenoleukodystrophy</th>
<th>Hurler</th>
<th>Thalassemia</th>
<th>Metachromatic leukodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krabbe Disease</td>
<td>Acute Myeloid Leukemia</td>
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<td></td>
</tr>
</tbody>
</table>
Register and you can save a life........Really....

Bhairavi, two-time PBSC donor, pictured above with her husband.

If you register a South Asian Child will not die...
## Transplant for Chronic Granulomatous Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at HCT (months)</th>
<th>Conditioning Regimen</th>
<th>Donor Source</th>
<th>HLA Match (of 6)</th>
<th>GvH Prophylaxis</th>
<th>Follow Up (years)</th>
<th>aGvHD Grade</th>
<th>aGVHD Location</th>
<th>cGVHD</th>
<th>Donor Chimerism</th>
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<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>Bu/Cy</td>
<td>Sibling BM</td>
<td>6</td>
<td>Csa/Mtx</td>
<td>12</td>
<td>0</td>
<td>None</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>Bu/Cy</td>
<td>Sibling BM</td>
<td>6</td>
<td>Csa/Mtx</td>
<td>12.5</td>
<td>0</td>
<td>None</td>
<td>98%</td>
<td></td>
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<tr>
<td>3</td>
<td>140</td>
<td>Flu/Bu/Cy/ATG</td>
<td>Sibling BM</td>
<td>6</td>
<td>Csa/Mtx</td>
<td>1</td>
<td>2</td>
<td>Gut</td>
<td>Limited skin</td>
<td>94%</td>
</tr>
<tr>
<td>4</td>
<td>122</td>
<td>Bu/Cy</td>
<td>Sibling BM</td>
<td>6</td>
<td>Csa/Mtx</td>
<td>5.5</td>
<td>0</td>
<td>None</td>
<td>&gt;98%</td>
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<tr>
<td>5a*</td>
<td>73</td>
<td>Bu/Cy/ATG</td>
<td>Unrelated Cord</td>
<td>5</td>
<td>Csa/Steroid</td>
<td>4.75</td>
<td>3</td>
<td>Skin</td>
<td>gut &amp; skin</td>
<td>&gt;98%*</td>
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<tr>
<td>5b</td>
<td>TBI(200cGy)/Flu/Cy</td>
<td>Unrelated Cord</td>
<td>Unrelated Cord</td>
<td>5</td>
<td>Csa/Steroid</td>
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<tr>
<td>6</td>
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<td>Csa/MMF</td>
<td>4</td>
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<td>&gt;98%*</td>
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<tr>
<td>7b</td>
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<td>Unrelated Cord</td>
<td>Unrelated Cord</td>
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<td>Csa/MMF</td>
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<td>&gt;98%</td>
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<td>2</td>
<td>Skin</td>
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