Pediatric Hematopoietic Stem Cell Transplantation

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Outline

• Overview
  – Indication
  – Stem cell source

• New revolution
  – Cord blood transplant

• Future
  – Preimplantation genetic diagnosis
  – Late complication
  – Regenerative Medicine: MSCs, Stem cell plasticity
Indication for HSCT

• **Neoplastic disorders**
  – Hematological malignancies
    • Lymphomas (Hodgkin and non-Hodgkin)
    • *Acute Lymphoblastic Leukemias*
    • Acute Myeloblastic Leukemia
    • Multiple myeloma
    • MDS
  – Solid tumors: **Neuroblastoma**

• **Non-neoplastic disorders**
  – Aplastic anemia
  – **Thalassemia major**
  – Immunodeficiency
  – Inborn errors of metabolism
Indications for Hematopoietic Stem Cell Transplantation in North America

- **Multiple Myeloma**
  - Allogeneic (Total N~8,150)
  - Autologous (Total N~11,500)

- **NHL**

- **AML**

- **Hodgkin Disease**

- **ALL**

- **MDS/MPD**

- **CML**

- **Aplastic Anemia**

- **Other Leuk**

- **Other Cancer**

- **Non-Malignant Disease**

Transplants
Sources of stem cells

• Bone marrow
• Peripheral blood
• Umbilical cord blood
• Other : Fetus liver
New Revolution

– Cord blood transplant
Allogeneic Stem Cell Sources by Recipient Age

1998-2007

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

Transplants, %

- 0
- 20
- 40
- 60
- 80
- 100

1998-2002
2003-2007
1998-2002
2003-2007

Age ≤20 yrs
Age >20 yrs
Cord Blood Transplantation

• Advantages
  – Waste product of normal deliveries
  – Readily available
  – lower incidence acute, chronic GVHD
  – less HLA matching required
  – Increased availability for minorities
  – Decreased transmission of viruses (e.g. CMV)

• Disadvantages
  – Limited cell dosage
  – Theoretical risk of genetic disease transmission
  – Efficacy in adults unknown
  – reduced GVT effect /no DLI
  – Late engraftment
  – More complication
• With a bank of 10,000 units, the probabilities of donor identification:

<table>
<thead>
<tr>
<th>Match</th>
<th>% identified</th>
</tr>
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<tbody>
<tr>
<td>6/6</td>
<td>2%</td>
</tr>
<tr>
<td>5/6</td>
<td>50%</td>
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<tr>
<td>4/6</td>
<td>94%</td>
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Improving outcomes with Cord Blood Transplants

• “New strategies are needed to improve hematopoietic recovery and reduce early transplant-related mortality after cord blood transplantation.”
  – Multiple-unit transplants
  – Co-infusion of MSC
  – Co-infusion of T depleted haploididentical PBSC
  – Injection of CB into the bone marrow
  – Expansion culture of CB
  – Growth factors for in vivo expansion and improved homing; niche manipulation
  – Safer preparative therapies
Who need Cord Blood?

• The chance of any child developing a disease that can be treated by a transplant
Previously Published Chances for Autologous Transplant Use

• **74 : 200,000 (< 20 yrs)**  

• **1 : 20,000 (< 20 yrs)**  
  G.J. Annas, 1999; NEJM 340: 1521-1524. (not substantiated)

• **1 : 10,000 – 1 : 200,000 (lifetime)**  
  R.M. Kline, April 2001; Sci Amer 4: 30-37. (not substantiated)
American Academy of Pediatrics

Estimates that the chance of a child needing their own stored cord blood range from 1:1000 to 1:200,000

Recommendations

• Cord blood donation should be discouraged when cord blood is to be directed for later personal or family use, as most conditions that might be helped by cord blood already exist in the infant’s cord blood
  – Cord blood banking for public use should be encouraged
  – Private storage of cord blood as “biological insurance” should be discouraged
Future Potential

– Preimplantation genetic diagnosis
– Late complication
– MSCs, Stem cell plasticity
Preimplantation genetic diagnosis

**PGD for Thalassemia**

(a) DNA is isolated from the removed cell

(b) 1 cell is withdrawn

(c) PCR is carried out on HBA1 or HBA2 genes using the isolated DNA as a template to produce many copies of the gene.

(d) The PCR-amplified DNA is then sequenced

- **normal DNA**: A T C T C A
- **mutant DNA**: A T C A C A

(e) The sequence is then compared to a database of known gene sequences to determine whether or not it will cause thalassemia

**Process Flow**

- **Egg donor is given fertility drugs**
- **Multiple eggs are produced**
- **Embryos analyzed for genetic defects**
- **Eggs are fertilized to produce embryos**
- **Only healthy embryos are injected into uterus**
- **Mother gives birth to genetically healthy baby**
FROM THE DIRECTOR OF ‘THE NOTEBOOK’
cameron diaz  abigail breslin
my sister’s keeper
Preimplantation genetic diagnosis + Cord Blood Transplantation

• 2 year old beta thalassemia major
• Preimplantation genetic diagnosis
  – One cell PCR technique
  – 2 genes analysis: beta globulin, HLA
  – 3 ovum retrieval & 2 embryo transfer
• Cord Blood Transplantation
  – Engraftment
  – Complicated with venous occlusive disease of liver
Late complication

- As survivors of pediatric hematopoietic stem cell transplantations (HSCTs) increase in number, it is increasingly important to evaluate their well-being.
- Late effects following HSCT are related to
  - underlying disease: relapse and rejection.
  - transplant process: delayed immune recovery
    chronic GvHD
  - preparative regimen: the endocrine system, eyes, lungs, bone and 2nd neoplasm.
Results

- Mortality: 31 patients (19.3%)
Late Complication

• Late reject : 2
• chronic GVHD : 51 (37.5%)
  – 21 mild and 30 extensive

• Pulmonary function
  – bronchiolitis obliterans : 4
  – restrictive ventilatory defect : 5

• Avascular necrosis : 1

• Renal function
  – Nephrotic syn : 1
  – Renal impairment : 3

• New neoplasms : 7
Late Complication

• Thyroid function
  – Follow-up 78 patients
  – Hypothyroidism : 3
  – Compensated hypothyroidism : 6
• Diabetes : 1

• Gonadal function
  – 65 patients follow-up, Age > 14
  – 25 M/40 F
  – 37 hypogonadism (3M/34F)
• Risk factors
  • Underlying disease : malignancy, thalassemia major
  • Gender*
  • Conditioning regimen : TBI, ATG*, myeloablative
Regenerative Medicine

• Stem cells as a tool to improve tissue renewal, repair and regeneration

• *In situ*: design new drugs targeting stem cells

• *Ex vivo*: expansion of stem cells in culture and transplantation
Regenerative Medicine
MSCs are a distinct population of stem cells in bone marrow.
Growing scientific evidence supports future potential

Regenerative Medicine: Focus on autologous use of stem cells

- Heart disease/angiogenesis
- Diabetes
- Stroke recovery
- Parkinson’s disease
- Brain/spinal cord injury
- Amyotrophic lateral sclerosis
- Muscular dystrophy
- Liver disease
• 計畫名稱：
• 中文：自體臍帶血幹細胞治療腦性麻痺患者
• 英文：Autologous cord blood transfusion in the treatment of cerebral palsy
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[Image of a group of people]
Thank You