Overview in Pediatric Hematopoietic Stem Cell Transplantation: Pearls and Obstacles

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Topics outline

- Principles of HSCT
- Indications of HSCT in Pediatrics
- Complications post HSCT
- Experience of Pediatric HSCT in Siriraj hospital
- Conclusion
- In 1959, Thomas et al: syngeneic BMT in refractory ALL after supralethal TBI → BM recovery in 2 weeks → relapse ALL in 4 months
- In 1968, Gatti et al: 1st successful allogeneic BMT in SCID without immunosuppression before BMT
- 1st successful HSCT in pediatric pt.: Autologous HSCT in Burkitt’s lymphoma (Suvatte et al in August, 1987: Faculty of Medicine, Siriraj hospital)

- 1st successful of matched sibling CBSCT: Rx of beta Thal/Hb E
  (Issaragrisil and Suvatte et al in June, 1993: Faculty of Medicine, Siriraj hospital)
Pediatric HSCT in Thailand

Data from Thailand Health Intervention and Technology Assessment Program, May 2011
Principles of HSCT

**Nonmalignant diseases**: replacement of abnormal hematopoietic system after myeloablative Rx with the normal HSC

**Malignant diseases**: allow higher and more effective doses of chemoRx to eradicate the malignant cells before rescue the BM function with normal HSC

: offer immunotherapy (GVT) that can eradicate chemoresistant malignant cells
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<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td><strong>BM</strong></td>
<td>- adequate HSC content</td>
<td>- collect in OR, under GA</td>
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<td></td>
<td>- low T cell content</td>
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<tr>
<td><strong>PB</strong></td>
<td>- adequate HSC</td>
<td>- use growth factor</td>
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<td></td>
<td>- rapid hematopoietic recovery</td>
<td>- high T cell content</td>
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<td>- only adequate wt. donor</td>
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<tr>
<td><strong>CB</strong></td>
<td>- naive HSC (immature)</td>
<td>- low SC content</td>
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<td>- very low T cell content</td>
<td>- one-time collection only</td>
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<td>- low transmission of viral infection</td>
<td>- delay hematopoietic recovery</td>
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Types of HSCT

1. Autologous HSCT

2. Allogenic HSCT
   2.1 Related allogenic HSCT
   2.2 Syngenic HSCT
   2.3 Unrelated allogenic HSCT
   2.4 Haploidentical HSCT from parent
Indications for HSCT in Pediatrics

Autologous HSCT

- Hematologic malignancies: Relapsed NHL/HL
- Solid tumors:
  - Neuroblastoma stage IV
  - High risk or recurrent solid tumors: medulloblastoma, rhabdomyosarcoma, Ewing’s sarcoma, primitive neuroectodermal tumor etc.
- Autoimmune diseases
Indications for HSCT in Pediatrics

Allogeneic HSCT: Malignancies

• ALL: 1st CR in high risk case (Ph+ve ALL, induction failure, Infant ALL with MLL rearrangement, etc.)
  2nd or subsequent CR
• AML: 1st CR in high risk case (preceding MDS, high risk cytogenetics)
  2nd or subsequent CR
• CML in chronic or early accelerated phase
• JMMoL
• MDS - RAEB or RAEB-t
• NHL/HL: High risk in 1st CR, 2nd or subsequent CR or PR, Refractory
Indications for HSCT in Pediatrics

Allogeneic HSCT: Non malignancies

• Hematologic disorders:
  - Hemoglobinopathies: severe thalassemia
  - Bone marrow failure: severe AA, FA, cong. pure red cell anemia etc.
  - Red cell enzymopathies: PK def. etc.

• Immunodeficiencies: SCID, WAS, CGD etc.

• Lysosomal storage diseases: Gaucher’s disease etc.

• Infantile osteopetrosis

• Familial hemophagocytic lymphohistiocytosis

• Myelofibrosis

Major obstacle: no HLA-matched related donor
Thai National SC donor registry and CB bank

- Started in May, 2002 at National blood center, Thai Red Cross Society

- December, 2013
  Thai national stem cell donor registry  152,780 cases
  (HLA typed and available for search  147,996 cases )

  Thai national cord blood bank  2,397 cords
  (HLA typed and available for search  2,258 cases )

Possibility to find matched URD ~ 1 : 1,500 - 3,000 donors

Courtesy of Ms.Pavinee et al; National blood center, Thai Red Cross Society
Aims 1. Eradication of the abnormal hematopoietic system: Busulfan, Total body irradiation
   2. Suppression of the immune system: Cyclophosphamide, Fludarabine

Postgrafting immunosuppression for GVHD prevention:

1. Corticosteroids: prednisolone, methylprednisolone

2. T-cell signaling blockade:
   CSA, FK506

3. Antiproliferatives: MTX, MMF
Engraftment

**Evidence** - DNA analysis (chimerism study)
- donor’s sex chromosome
- donor’s blood group

**In thal pt** - normalization of Hb, Hct, reticulocyte count
- donor’s Hb type

**In malignant pt** - no evidence of disease

**In immunodeficiency pt** - normal or near normal immune function
Complications post HSCT

- Pancytopenia: Neutropenia, Thrombocytopenia
- Regimen-related toxicities: Mucositis, VOD
- Graft-vs-host disease: Acute GVHD, Chronic GVHD
- Infections: Gram positive, Gram negative, Encapsulated bacteria
- Fungal: Candida, Aspergillus
- Viral: HSV, CMV and adenovirus, VZV
Long term complications post HSCT

• Endocrine dysfunction esp.
  hypogonadism $\rightarrow$ delayed growth & puberty

• Infertility

• Chronic GVHD

• Iron overload

• Pulmonary/renal/cardiac dysfunction
A cost-utility and budget impact analysis

• Related HSCT for severe thalassemic patients aged < 10 years was more cost-effective option than hypertransfusion with iron chelation in Thailand

Leelahavarong P, et al. A cost-utility and budget impact analysis of allogeneic HSCT for severe thalassemic patients in Thailand, BMC Health Services Research 2010 (Health Intervention and Technology Assessment Program (HITAP), Ministry of Public Health, Thailand)
Factors that influence outcome of HSCT

• Underlying diseases
• Type of HSCT
• Degree of HLA matched
• Sources and cell doses of viable HSC
• Conditioning regimen
• Pre-HSCT condition of the pt: organ dysfunction
• Supportive care post-HSCT
Summary of HSCT

Pearls:

- Increase chance of curative Rx for various hematologic diseases, oncologic diseases, immunodef. diseases, inborn error of metabolism, autoimmune diseases

- More cost utility effectiveness in children with severe thalassemia than hypertransfusion with iron chelation
Summary of HSCT

Obstacles

- Rx has considerable risk → chance to mortality
  Pretransplant counseling is importance.
- Limit infrastructure resources availability → minority of patients can receive the Rx
  - High cost Rx for developing country which has limitation of financial support
- No available of proper donor
Thank you for your attention