Bone Marrow Transplantation for Thalassemia

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Beta thalassemia major

• Decrease beta globin production
• Excess of alpha globin chains damage to red blood cells in bone marrow
  – Severe anemia
  – Massive overwork of bone marrow – bony changes, fractures, osteoporosis
  – Iron overload from transfusion and gut absorption – damaging heart, liver, endocrine glands
• Transfusion transmitted diseases – hepatitis, immune deficiency
Therapy

- **Adequate transfusion** – optimal growth and development
- **Adequate iron chelation** – achieving iron balance
- **Optimal comprehensive care** – physical, psychosocial development

Thalassemia has been transformed from a lethal disease of childhood into a chronic condition of adulthood - with a dramatic increase in both life expectancy and quality.
Bone marrow transplantation

• Theoretically, ridding oneself of the abnormal marrow, replace with a new unaffected marrow- will achieve a cure!
Marrow transplantation for thalassemia

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Abstract

Despite modern therapeutic regimens, thalassemia major remains a severe disease with an uncertain ultimate prognosis. Alternative and more definitive forms of treatment are actively sought; bone marrow transplantation is one of these. As of May 1984, data were available on 51 thalassemic children who had undergone the procedure: 29 of them are free of thalassemia 2 to 30 months after transplantation; 13 have died; 9 are alive with thalassemia after autologous reconstitution. Future developments in the field of transplantation should make the procedure safer and also render it available to the vast population of multiply transfused and hemosiderotic thalassemic patients who will not benefit from the improvement of conventional therapy.
Bone marrow

• **Immune system** – differentiate “self” from “non-self”
• Recognize and destroy foreign tissue – rejection
• In order for a new marrow to grow, the old one has to be wiped out – annihilated
• Flip side – when the new marrow grows in the new body environment, it recognized the minor difference between its original host, and the new body that it resides in
• It will start attacking the new body causing major and serious tissue damage – graft vs. host disease
Bone marrow transplantation - complications

• **High dose chemotherapy** – very toxic medications
• New marrow may take 2-3 weeks to grow
• Complications:
  – **Chemotherapy effects** – nausea, vomiting, hair loss, skin and mucous membrane break down, liver damage, other organ damage, long term – endocrine glands – infertility
  – **Infections** – bacteria, fungi, viruses
  – **Pain**
  – **Poor nutrition**
  – **Transfusions** of platelet and red cells
Bone marrow transplantation - complications

• Engraftment in 2-3 weeks – *graft versus host disease* – skin rash, diarrhea, liver damage

• After the first three months – *chronic GVHD* – immune imbalance – autoimmune disorder
  – Dry eyes, mouth
  – Skin rashes
  – Damage to lungs, gut

• Mortality – 5-10%
Bone marrow transplantation - complications

• Best results in
  – Age: young <16 years
  – Adherent to iron chelation
  – No organ damage – liver, heart, endocrine glands

• Survival: >90%, Event free survival: >80%
<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Survival</th>
<th>Event-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>absence of hepatomegaly (enlargeed liver), regular iron chelation before transplant, absence of fibrosis in pretransplant liver biopsy result</td>
<td>96%</td>
<td>90%</td>
</tr>
<tr>
<td>II</td>
<td>hepatomegaly, a history of irregular iron chelation before transplant, histological evidence of liver fibrosis, or various combinations of the above</td>
<td>86%</td>
<td>82%</td>
</tr>
<tr>
<td>III</td>
<td>all of the following: large liver, poor compliance with chelation therapy, liver damage</td>
<td>76%</td>
<td>53%</td>
</tr>
<tr>
<td>Adult</td>
<td>Class II or III, irregular iron chelation, with a range of clinical symptoms and other diagnoses</td>
<td>65%</td>
<td>63%</td>
</tr>
</tbody>
</table>
Donor bone marrow cells repopulate recipient bone marrow
**Alternative stem cell sources**

- **Cord blood** –
  - lower graft vs. host disease, limited number of cells, delayed engraftment

- **Matched unrelated donor** –
  - Good results only if high resolution molecular match
  - Survival – 80%, Event free survival – 65%

- **Partially matched donors**
  - Investigational
Alternative transplant

• Mini-transplant (non-myeloablative)
  – Less toxic, higher rejection rate
  – Higher chance of graft vs. host disease
• This decision process is by definition **highly individualized** and **patient specific**, since it must consider age, clinical status, willingness, capability and compliance to adhere to the appropriate transfusion-chelation regimen, quality of life and resources. For pediatric patients, parents face an even more difficult decision.
Figure 4. Factors that must be considered for individual decision making about HSCT for thalassemia.
Gene therapy

• Use Lentivirus carrying the corrected beta-globin gene to infect stem cells
• Chemotherapy to patient to prepare marrow
• Infusion of engineered stem cells

Message

• Rapid medical advances
• Cure around the corner
• Organ damage – hard to reverse
  – Adherent to chelation therapy and medications
• Physically healthy
• Psychologically and socially healthy
Really cool!

THANK YOU!