Bone Marrow Transplantation for Aplastic Anemia

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Outline

• Review of BMT process/protocols for adults and children with AA
• What is the best stem cell source for AA?
• Success rates in children and adults - Historical overview and current research findings.
• When should typing be undertaken?
• Decision making process – BMT or immunosuppressive therapy – how does one decide?
• Long-term and late effects to consider and concerns.
• Future directions
Survival in AA – Historical Context

- 70% mortality in first 5-6 mos

Historical Context

- Among the earliest indications for transplantation
- Provided indirect evidence that AA is usually immunologically mediated
  - Identical twin transplantation requires immunosuppression
- Initially only performed with marrow
- Until recently only performed with matched related donors
- Issues:
  - Graft rejection
  - Graft vs host disease
  - Immunological reconstitution

IST for Aplastic Anemia: Are We Hitting the Ceiling?

Passweg JR, Tichelli A. Haematologica 2009;94:310-312
Transplantation Conditioning

- **Immunosuppression**
  - Most AA is immunologically mediated
  - Must suppress both the autoimmune component and the ability of the recipient to reject the marrow
  - Intensity varies with:
    - Age
    - Transfusion history
    - Donor source
  - **Cytoxan-based**
    - ATG
    - Fludarabine
    - Low dose total body irradiation

Stem Cell Transplantation for Aplastic Anemia

- **Matched related donors**
  - DFS ≥85% using cyclophosphamide and ATG
  - Rejection rate 10%
- **Transplantation before transfusion is rarely feasible**

Doney, Ann Intern Med 1997;126:107

Flu/Cy/ATG versus Flu/Cy/ATG + 2Gy TBI

Conditioning Needs to be Intensified in Older Recipients of Unrelated Donor Transplantation

- Bone marrow stem cells can be collected from the pelvic bone by direct needle aspiration
- Stem cells can be collected from the blood by leukapheresis
- They can also be collected from the placenta after the baby is born

What is the Best Stem Cell Source?

- Bone Marrow
  - Traditional source
  - Speed of engraftment approximately 21 days
  - Collection requires operating room time
- Peripheral blood stem cells
  - Speed of engraftment 10-14 days
  - Requires donor to receive Neupogen
  - 6-12 hours on apheresis
  - Transfer of 10 fold more immune cells
Have Transplantation Outcomes Improved?

- Serologic vs molecular typing
- Improvement in supportive care

EBMT Analysis of Unrelated Donor BMT for SAA

Before 1998
After 1998

Overall Survival
Unrelated Donor BMT 2000-2007

- BM (N=173; 78%)
- PBSC (N=60; 60%)

HR 1.79; p=0.02
No effect of age

Should HLA Typing be done Early or After Failure of Immunosuppressive Therapy?

- Type early
  - Does not commit to BMT
  - If no donor is available, it allows search to proceed in the background
  - Cost of typing that may not be used

- Type if IST fails
  - May delay BMT
  - Saves money
Early Referral for HSCT makes a Difference

How Does Transplantation Compare with Immunosuppressive Therapy?

Complications

- Graft Rejection
- Acute GVHD
- Chronic GVHD
- Infections
CIBMTR Analysis 2010

Chronic GVHD

Long-term and Late Effects

- Chronic GVHD
  - Principal late complication
  - Worse with PBSC than marrow (48% vs 31%)
  - Not all severe; tends to resolve with time

Long-term and Late Effects

- Infertility
  - Much less an issue with AA than with malignancies
  - Compared with siblings of cancer patients

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<th>Table M1, Marked stress and fertility</th>
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<td>Case</td>
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<td>Chemotherapy</td>
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<td>Sex ratio</td>
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<td>Match to control</td>
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Long-term and Late Effects

- Other late effects

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<th>Table M2, Late medical outcome comparing SAA case with controls</th>
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Future Directions

• How can we best decide who should be transplanted vs who should receive IST?
  – Telomere length
  – Age
  – Reticulocyte count
  – Donor availability

• How can we reduce toxicity of BMT
  – Control of GVHD
  – Better antibiotics
  – Enhance immunologic recovery

Future Directions

• How can we provide donors for people with rare HLA types?
  – Cord blood transplantation
  – Mismatched transplantation

• How can we reduce toxicity of BMT
  – Control of GVHD
  – Better antibiotics
  – Enhance immunologic recovery

Questions?