New Advances in Pediatric Aplastic Anemia

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Outline

• What is Aplastic Anemia?
• Treatment
• Advances
Children are **NOT** Little Adults
Aplastic Anemia

• First described in 1888, Paul Ehrlich
  – Autopsy of pregnant woman
  – Fatal illness with bleeding, fever, anemia

• Aplastic Anemia coined in 1904
Aplastic Anemia

- Empty bone marrow
  - Low white blood cells
  - Low red blood cells
  - Low platelets
Bone Marrow Biopsies
White Blood Cells Protect!

...from infection
Low White Blood Cells
Red Blood Cells carry oxygen, which gives you energy.
Low Red Blood Cells
Platelets prevent bleeding
Low Platelets
Severe Aplastic Anemia

• Two of the following:
  – Neutrophils < 500/L  (1500-5000)
  – Platelet count < 20 x 10⁹/L  (180-440)
  – Abs. Reticulocyte count < 40 x 10⁹/L  (20-80)
• Bone Marrow biopsy < 25% cellularity
Age Distribution
How do you get aplastic anemia?

• Inherited
• Acquired
Acquired

- Pregnancy
- Infections
- Benzene
- Ionizing radiation
- Drugs
- Idiopathic
Pathophysiology

- Lymphocytes attack own stem cells in bone marrow
- With less stem cells, less red blood cells, white blood cells, and platelets are produced
Stem Cell

- red blood cells
- platelets
- granulocytes
- macrophages
- eosinophils, basophils, mast cells
- B lymphocyte
- T lymphocyte
- plasma cell
Each type of white blood cell has a unique function to help protect your body.
T-lymphocyte

Infected Cell
Supportive Care

- Blood transfusions
- Platelet transfusions
- Soft toothbrushes
- Stool softeners
- Avoidance of aspirin/ibuprofen, etc
- Avoidance of trauma
- Investigation of fever
Treatment

- Immunosuppressive therapy (IST)
- Hematopoietic stem cell transplantation (HSCT)
Immunosuppressive Therapy

- If no matched related donor
- Response rate 55-77%
- ~70% disease free @ 10 years

Scheinberg et al J Peds 2008
Immunosuppressive Therapy

• Antithymocyte Globulin (ATG)
• Cyclosporine
Cyclosporine

Inhibits T-lymphocytes
IST Risks

- Myelodysplasia
- Relapse
Is there a way to Predict Response to IST?

• Telomeres
DNA is Organized into a Double Helix
TELOMERES

Embryonic Stem Cells

Adult Stem Cells

Chromosome

Telomere long

Telomere short

Telomerase active

Telomerase inactive or absent

Telomere is a repeating DNA sequence

EXTENDING THE LENGTH OF A TELOMERE

Before

Short end of DNA

Telomerase

RNA template

New DNA

DNA polymerase

After
Bone Marrow Transplantation

• 70-97% failure free survival

  Kojima et al *Br J Haem* 2000

• Less risk for MDS or leukemia
BMT limitations

• Only 53-65 % chance of finding match for African, Hispanic, Asian patients
  Maiers M et al Human Immunol 2006

• Graft versus host disease
  – 20-25% risk
BMT Late Effects

- Infertility
- Reduced height
- Abnormal thyroid function
- Secondary malignancies
Recent Improvements in treatment

• Improved graft versus host medications
• Alternative donor sources
  – Matched unrelated adult donors
  – Cord Blood
Alternate Donors

- Increased graft rejection
- Increased graft versus host disease
- CB may contain too few cells
Alternate Donor Advances

- Conditioning
- Better GVHD meds
- Improvements in HLA typing
- Double cords?
“Typical” Case

• MD, a 7 year old boy
• Presented in Oct. 2007 with:
  – Easy bruising, fatigue
MD’s CBC

- WBC - $2.5 \times 10^9/L$
- HGB - 6 g/L
- Platelet - $6 \times 10^9/L$
- Neutrophils - $0.3 \times 10^9/L$

- Bone Marrow Showed…
MD Cont’d

- MD had no matched sibling
- Started IST
- 6 months later - 2\textsuperscript{nd} IST
- 3 months later, still no response
MD Cont’d

• MD telomeres- short
• Underwent 10/10 MUD
• Now, 4 months later…
MD is doing well with normal counts!
Conclusion

• Aplastic anemia is when the bone marrow fails to make cells
• Treatment may be with IST or BMT
• Advances are constantly being made
Any Questions?