APLASTIC ANEMIA

- Identification of bone marrow as site of blood cell production
- Concept of the “hematopoietic stem cell”
- Development of bone marrow transplantation

Paul Ehrlich

First clinical description of aplastic anemia

CAUSES OF APLASTIC ANEMIA

- Autoimmune attack
  - May be a common pathway
  - Likely most frequent cause of idiopathic aplastic anemia

Stem and progenitor cells

Viruses
Chemicals
Drugs
Radiation

Intrinsic susceptibility
Constitutional
Indirect effect
Immune system
Direct toxicity

Maciejewski & Young in Hoffman’s Textbook of Hematology 2008

COMPONENTS OF BLOOD PRODUCTION
COMPONENTS OF THE PATHOPHYSIOLOGY OF IDIOPATHIC AA

Stem and progenitor compartment

CTLs

IFN
Fas
TNF
Perforin/granzyme

Growth factors

Mature blood cells

Stroma

INCITING EVENTS IN AA

Viral antigen

Cross-reactive antigen

Product of a mutated gene

GPI-linked protein

AA/PNH

Adopted from Maciejewski & Young, NEJM 1995

RESULTS OF IMMUNOSUPPRESSIVE THERAPIES IN MAJOR CLINICAL TRIALS

<table>
<thead>
<tr>
<th>STUDY</th>
<th>AOS</th>
<th>N</th>
<th>AGE (MEDIAN)</th>
<th>RESPONSE (%)</th>
<th>RELAPSE (%)</th>
<th>SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacigalupo et al., 2000</td>
<td>hALG</td>
<td>100</td>
<td>16</td>
<td>77 (3 mos)</td>
<td>35 (3 yrs)</td>
<td>87 (5 yrs)</td>
</tr>
<tr>
<td>Kojima et al., 2000</td>
<td>hALG</td>
<td>119</td>
<td>9</td>
<td>71 (6 mos)</td>
<td>39 (4 yrs)</td>
<td>83 (4 yrs)</td>
</tr>
<tr>
<td>Frickhofen et al., 2003</td>
<td>hATG</td>
<td>84</td>
<td>33</td>
<td>78 (9 mos)</td>
<td>36 (7 yrs)</td>
<td>80 (7 yrs)</td>
</tr>
<tr>
<td>Scheinberg et al., 2003</td>
<td>hATG</td>
<td>73</td>
<td>35</td>
<td>87 (5 mos)</td>
<td>35 (3 yrs)</td>
<td>80 (3 yrs)</td>
</tr>
<tr>
<td>Teramura et al., 2007</td>
<td>hATG</td>
<td>101</td>
<td>34</td>
<td>76 (3 mos)</td>
<td>41 (3 yrs)</td>
<td>87 (3 yrs)</td>
</tr>
<tr>
<td>Tichelli et al., 2010</td>
<td>hATG</td>
<td>192</td>
<td>46</td>
<td>70 (12 mos)</td>
<td>36 (3 yrs)</td>
<td>76 (3 yrs)</td>
</tr>
<tr>
<td>Afable et al., 2011</td>
<td>hATG</td>
<td>71</td>
<td>19</td>
<td>88 (5 mos)</td>
<td>16 (2 yrs)</td>
<td>64 (4 yrs)</td>
</tr>
</tbody>
</table>

hALG: HLA-identical, ALLO: ALLO, AOS: ALLO stem cell, AGS: AUTOLOGOUSstem cell
**HOW IMMUNOSUPPRESSION IS ADMINISTERED FOR SAA**

- hATG with CsA wait for 3 months
- If no response repeated rATG/CsA
- Alternative treatments with Campath

**How long to wait for response?**

**What to do if CsA is toxic?**

**How long to treat?**

**When to think about BMT?**

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**HOW IMMUNOSUPPRESSION IS ADMINISTERED FOR LESS THAN SEVERE AA**

- No standard established if counts not severely depressed.
  - Wait and watch and treat if counts get worse
- CsA alone
- Campath
- Other immunosuppressive agents
- Androgenic steroids

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**THERAPEUTIC CONSIDERATIONS**

- Insufficient immunosuppression
- Exhaustion of stem cell reserves
- Misdiagnosis
- Hereditary bone marrow failure

- Non-immune pathogenesis

- Immune pathogenesis

- Repeated cycles of therapy
- BMT
- Alternative therapies
- BMT
RESULTS OF ALLOGENIC BONE MARROW TRANSPLANTATION

<table>
<thead>
<tr>
<th>N</th>
<th>Survival</th>
<th>Age</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>193</td>
<td>59% at 16 y for TAI/Cy</td>
<td>&lt;20y</td>
<td>France</td>
</tr>
<tr>
<td></td>
<td>95% at 4.4 y for ATG/Cy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>211</td>
<td>99% at 20 y without GvHD</td>
<td></td>
<td>FHCRC</td>
</tr>
<tr>
<td></td>
<td>69% at 20 y with GvHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>915</td>
<td>Actuarial survival 77% for patients &lt;16 y</td>
<td></td>
<td>EBMT</td>
</tr>
<tr>
<td></td>
<td>54% for patients 17-40 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>915</td>
<td>94% at 8 y with CsA/MTx</td>
<td>8</td>
<td>GITMO</td>
</tr>
<tr>
<td></td>
<td>78% at 7 y with CsA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1699</td>
<td>5 y survival 79% for patients &lt;20 y</td>
<td></td>
<td>IBMTR</td>
</tr>
<tr>
<td></td>
<td>68% for patients 20-40 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35% for patients &gt;40 y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IMMUNOSUPPRESSION VS. BMT

<table>
<thead>
<tr>
<th>Months after therapy</th>
<th>Overall survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
</tr>
</tbody>
</table>

TREATMENT ALGORITHM FOR sAA IN PATIENTS

<table>
<thead>
<tr>
<th>Sibling donor available</th>
<th>Refractory patients without Sibling donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&lt;20y</td>
<td>BMT</td>
</tr>
<tr>
<td>Age 20-40y</td>
<td>BMT</td>
</tr>
<tr>
<td>Age&gt;40y</td>
<td>BMT</td>
</tr>
<tr>
<td>IS failure</td>
<td>No response BMT</td>
</tr>
<tr>
<td>Children</td>
<td>Age</td>
</tr>
<tr>
<td>1. Second course of IS</td>
<td>1. Second course of IS vs. MUD BMT</td>
</tr>
<tr>
<td>2. Salvage therapy</td>
<td>3. MUD BMT</td>
</tr>
<tr>
<td>Androgens</td>
<td></td>
</tr>
<tr>
<td>GF</td>
<td></td>
</tr>
</tbody>
</table>
CURRENT ISSUES

• Rabbit ATG vs horse ATG
• Horse ATG vs. Campath
• Newer agents to replace CsA

NEW DRUGS

• Growth factors
  – Promacta (Elthrombopag)
  – Nplate (Thrombopoietin)
• New immunosuppressive agents
  – Arencia, Abatacept (soluble CTLA4)
  – Amevive, Alefacept (Soluble LFA-3)
  – Alemtuzumab (Campath)

ADULT STEM CELL RETRO-DIFFERENTIATION

• All cells in the body have a silenced potential to produce all tissues, this potential is encoded in the DNA which is identical in all cells.
• Multipotent stem cells have a potential to produce all tissues, similar to the ultimate stem cell: the fertilized egg.
• Through a process of differentiation, tissues and organs are formed and assume specific function and shape

Why it would not be possible to isolate cells and revert them in to a multipotent stem cell and direct their program to regenerate diseased tissues?
POTENTIAL OF THE ADULT STEM CELLS

- Skin cells
- Marker gene
- Transfer of 4 genes important for stem cells so that they are turned on
- Retrodifferentiation
- Transfer into 8-cell embryo
- Multipotent stem cell

Mouse with green organs

THERAPEUTIC POTENTIAL OF THE ADULT STEM CELLS

Allogeneic bone marrow transplant is limited by the availability of the donor, toxicity of GvHD and inability to replace diseased bone marrow stem cells.

- Retrodifferentiation
- Skin cells
- Therapy of leukemia aplastic anemia
- Expansion
- Differentiation into bone marrow stem cells
- Marrow stem cells
- Transplant to replace damaged stem cells