Aplastic Anemia: Current Thinking on Disease, Diagnosis and Non-Transplant Treatment

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National, Heart, Lung and Blood Institute
National Institutes of Health

Today’s agenda

Aplastic Anemia – general overview

Non-transplant treatment options

APPRAOXIMATE BLOOD CELL REQUIREMENTS

cell type | total number | life span (days) | daily production
--- | --- | --- | ---
neutrophils | $2 \times 10^{10}$ | 1 | $2 \times 10^{10}$
platelets | $1 \times 10^{12}$ | 5 | $2 \times 10^{11}$
erthrocytes | $3 \times 10^{13}$ | 120 | $2.5 \times 10^{11}$
AN HEMATOPOIETIC STEM CELL

NEUTROPHIL DIFFERENTIATION

Myeloblast  Promyelocyte  Myelocyte  Metamyelocyte  Band  Segmented neutrophil
Pathophysiology of Aplastic Anemia

Immune attack (T lymphocytes)

Hematopoietic Stem Cells

Hematopoietic Progenitors

Circulating blood cells

Most of the cases of Aplastic Anemia have no identifiable cause

Pregnancy, eosinophilic fasciitis, and seronegative hepatitis are associated with AA

Drugs and chemicals have been reported (Benzene, Chloramphenicol)

All identifiable triggers explain very few cases of AA

Bone Marrow Failure Syndromes

Aid: MS, IBD, uveitis, DM type 1, etc.
MAJOR PROSPECTIVE EPIDEMIOLOGIC STUDIES


BLEEDING MANIFESTATIONS OF THROMBOCYTOPENIA

AGE AT DIAGNOSIS

Aplastic Anemia Admissions to NIH Clinical Center

AGE cohort

Number

Male
Female
**NATURAL HISTORY** OF APLASTIC ANEMIA

Severity Criteria (two of three):
- platelets <20K/μL
- reticulocytes <1% (60K/μL)
- ANC <500/μL

Super-severe: ANC <200/μL

1. **1960’s** → 10% survival in 1 year
2. **2010** → 90% survival in 1 year

- Immunosuppressive therapy
- Bone marrow transplantation
- Supportive care
  - Iron Chelation
  - Blood Banking
  - Antifungals
Immunosuppressive therapy

- Anti-thymocyte globulin (ATG)
  - Horse
  - Rabbit
- Cyclosporine (CsA)

Therapy terminology

- Treatment Naïve
- Refractory
  - Salvage Therapy
- Relapsed
- Term “remission” not used

Anti-thymocyte Globulin (ATG) Production

- Immunization with human thymocytes
- Xenogeneic polyclonal antibodies
- Purification of sera
- Cytotoxicity assay
- IgG
- Thymus
- ATG
Lymphocyte depletion following horse and rabbit ATG

RESPONSE OF SEVERE APLASTIC ANEMIA TO INTENSIVE IMMUNOSUPPRESSION

PROGRESS IN IMMUNOSUPPRESSIVE THERAPIES FOR SEVERE APLASTIC ANEMIA

• Era    Drug       Response
• 1960s  corticosteroids ~10% (occasional)
• 1970s  ATGs       40-50%
• 1980s  ATG plus CSA 60-70%
**INTENSIVE IMMUNOSUPPRESSION FOR SAA COMPARISON OF RESULTS**

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>N</th>
<th>Median Age [years]</th>
<th>Response 60%</th>
<th>Relapses 12%</th>
<th>Clonal Evolution 6%</th>
<th>Survival 56% at 11 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>German</td>
<td>1986-1989</td>
<td>84</td>
<td>32</td>
<td>65%</td>
<td>19%</td>
<td>6%</td>
<td>58% at 11 yrs</td>
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<tr>
<td>NIH</td>
<td>1991-1998</td>
<td>122</td>
<td>35</td>
<td>67%</td>
<td>35%</td>
<td>11%</td>
<td>50% at 7 yrs</td>
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<tr>
<td>EGMBT</td>
<td>1991-1998</td>
<td>100</td>
<td>16</td>
<td>77%</td>
<td>12%</td>
<td>11%</td>
<td>81% at 5 yrs</td>
</tr>
<tr>
<td>Japan</td>
<td>1992-1997</td>
<td>119</td>
<td>9</td>
<td>68%</td>
<td>22%</td>
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<td>100</td>
<td>16</td>
<td>77%</td>
<td>12%</td>
<td>6%</td>
<td>87% at 4 yrs</td>
</tr>
<tr>
<td>Japan</td>
<td>1996-2000</td>
<td>101</td>
<td>54</td>
<td>75%</td>
<td>12%</td>
<td>6%</td>
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<td>NIH</td>
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<td>30</td>
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<td>21%</td>
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<td>80% at 4 yrs</td>
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<tr>
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<td>2002-2008</td>
<td>192</td>
<td>46</td>
<td>78%</td>
<td>13%</td>
<td>4%</td>
<td>78% at 6 yrs</td>
</tr>
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<td>NIH</td>
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<td>28</td>
<td>68%</td>
<td>18%</td>
<td>21%</td>
<td>96% at 3 yrs</td>
</tr>
</tbody>
</table>

Young NS, Calado RJ, Scheinberg P. Blood 2010

**ATG AND CSA FOR SEVERE APLASTIC ANEMIA OVERALL SURVIVAL**

60% response rate

**ATG AND CSA FOR SEVERE APLASTIC ANEMIA RESPONSE AT 3 MONTHS AND SURVIVAL**

Response at 3 mos: no response
Survival of refractory SAA following retreatment with rabbit ATG + CsA (salvage)

Scheinberg P, Nunez O, Young NS. Br J Haematol 2006

Alemtuzumab (Campath-1H)

- Anti-CD52 Antibody
- Murine hypervariable regions fused into human IgG1
- CD52 expressed:
  - B and T cells
  - NK cells, dendritic cells
  - Monocytes, macrophages
  - Plasma cells, Eos
- No CD52 expression on:
  - RBCs, platelets
  - Hematopoietic stem cells

Ravandi and O'Brien, Cancer Invest. 2007 26: 718-725
Hernández-Campo PM, Cytometry B Clin Cytom. 2006 70:1871

SECOND IMMUNOSUPPRESSION FOR REFRACTORY SAA

<table>
<thead>
<tr>
<th>Treatment arm (N=54)</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>rabbit ATG (N=27)</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>alemtuzumab (N=27)</td>
<td>10 (37%)</td>
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</table>
Campath in Refractory SAA (N=25)

Median + interquartile range

0 0.0 0.2 0.4 0.6 0.8 1.0
ANC per μL

0 1 2 3 4 6 8 10 12 14
Time in months

Hgb (g/dL)

0 500 1,000 1,500 2,000 2,500 3,000

ANC per μL

0 3 6 1 2 2 4 3 6

0 20,000 40,000 60,000 80,000 100,000

ARC per μL

0 3 6 1 2 2 4 3 6

0 1,000 10,000 100,000

Time in months

Plt per μL

0 3 6 12 24 36

0 500 1,000 1,500 2,000 2,500 3,000

ANC per μL

0 3 6 12 24 36

1,000 10,000 100,000

Time in months

Plt per μL

0 3 6 12 24 36

1,000 10,000 100,000

Time in months

INTENSIVE IMMUNOSUPPRESSION FOR SAA

COMPARISON OF RESULTS

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Young NS, Calado RT, Schenzenberg P. Blood 2006

ATG AND CSA FOR SEVERE APLASTIC ANEMIA

RELAPSE

Proportion relapsing

0 0.2 0.4 0.6 0.8 1.0

Days

0 1000 2000 3000 4000

0 1.0 0.8 0.6 0.4 0.2 0.0
RELAPSE AFTER ATG + CSA

Cyclosporine-dependence Post 1st relapse

<table>
<thead>
<tr>
<th>Years post-relapse</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>Patients on CsA</td>
<td>20/22</td>
<td>19/20</td>
<td>14/18</td>
<td>11/18</td>
<td>11/14</td>
<td>7/11</td>
<td>4/7</td>
</tr>
<tr>
<td>(86%)</td>
<td>(91%)</td>
<td>(78%)</td>
<td>(65%)</td>
<td>(79%)</td>
<td>(64%)</td>
<td>(57%)</td>
<td></td>
</tr>
</tbody>
</table>

Retreatment with rabbit ATG + CsA Post 1st relapse  → 2/3 response

Rosenfeld S, Follmann D, Nunez O, Young NS. JAMA 2003
Scheinberg P, Nunez O, Young NS. Br J Haematol 2006

CAMPATH IMMUNOSUPPRESSION FOR RELAPSED SAA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campath (N=25)</td>
<td>14 (56%)</td>
</tr>
</tbody>
</table>

CAMPATH in Relapse SAA (N=20)

Median + interquartile range

- Hgb (g/dL)
- Platelets per uL
- ARC per uL
- WBC per uL
EFFORTS TO IMPROVE TREATMENT FOR APLASTIC ANEMIA

- Add to horse ATG + CsA platform
  - G-CSF (Neupogen)
  - Mycophenolate mofetil
  - Sirolimus
  - Long course immunosuppression
- Augment initial lymphocytotoxicity
  - Horse ATG
  - Rabbit ATG
  - Campath

A Randomized Trial of H-ATG vs. R-ATG in SAA

Patients and Methods

- 120 consecutive patients (60 per arm)
- NIH Clinical Center
- 1:1 randomization
- Primary objective – response at 6 months

Scheinberg et al. NEJM 2011
A Randomized Trial of H-ATG vs. R-ATG in SAA
Hematologic Responses at 3 and 6 months

<table>
<thead>
<tr>
<th></th>
<th>Horse ATG</th>
<th>Rabbit ATG</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>3 months</td>
<td>37/60 (62%)</td>
<td>20/60 (33%)</td>
<td>0.003</td>
</tr>
<tr>
<td>6 months</td>
<td>41/60 (68%)</td>
<td>22/60 (37%)</td>
<td>&lt; 0.001</td>
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</tbody>
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A Randomized Trial of H-ATG vs. R-ATG in SAA
Blood Count Recovery in Responders

<table>
<thead>
<tr>
<th></th>
<th>Horse ATG</th>
<th>Rabbit ATG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute reticulocyte count</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
<tr>
<td>Platelets</td>
<td>[Graph]</td>
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INTENSIVE IMMUNOSUPPRESSION FOR SAA
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<th>Survival</th>
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<td>1986-1989</td>
<td>84</td>
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<td>87% at 8 yrs</td>
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<td>38</td>
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<td>28%</td>
<td>21%</td>
<td>86% at 3 yrs</td>
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</table>

Young NS, Calado RJ, Schrezenberg P. Blood 2006
ATG AND CSA FOR SEVERE APLASTIC ANEMIA

**EVOLUTION**

- Proportion evolving
- All evolution
- Evolution to monosomy 7

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>1000</th>
<th>2000</th>
<th>3000</th>
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<td>6</td>
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<td>mono 7</td>
<td>122</td>
<td>64</td>
<td>30</td>
<td>3</td>
</tr>
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**CYTOGENETIC EVOLUTION IN TREATED APLASTIC ANEMIA**

**incidence**

**prognosis**

-Cytogenetics

1. 46, XY
2. 45, XY, -7 [1]
3. 47, XY, +8 [1]
INITIAL BLOOD COUNTS PREDICT RESPONSE TO IMMUNOSUPPRESSION AND SURVIVAL

Probability of response according to age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of patients (%)</th>
<th>Response at 6 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td>95% CI</td>
</tr>
<tr>
<td>H-ATG</td>
<td>316 (100)</td>
<td>194</td>
<td>61.4</td>
</tr>
<tr>
<td>&lt; 18</td>
<td>78 (25)</td>
<td>58</td>
<td>74.4</td>
</tr>
<tr>
<td>18 to 60</td>
<td>187 (59)</td>
<td>109</td>
<td>58.3</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>51 (16)</td>
<td>27</td>
<td>52.9</td>
</tr>
</tbody>
</table>
Survival in refractory SAA
1990s

Improved Survival Over Time

All patients
N = 420
p < 0.001
Improved Survival Over Time

1989 - 1996
5-yr survival = 91%

1996 - 2002
5-yr survival = 92%

2002 - 2008
5-yr survival = 94%

Responders to IST
N = 246
p=0.54

Non-responders to IST
N = 174
p<0.001

Clin Infect Dis 15: 726, 2011

Laboratory of Neal Young
Genetics Group