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

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

Today's agenda

Aplastic Anemia – general overview
Non-transplant treatment options
Novel agents and active research

Bone marrow failure syndromes

- AID: MS, IBD, uveitis, DM type 1, etc.
**AGE AT DIAGNOSIS**
Aplastic Anemia Admissions to NIH Clinical Center

<table>
<thead>
<tr>
<th>Age cohort</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>20</td>
</tr>
<tr>
<td>5-9</td>
<td>30</td>
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<tr>
<td>10-14</td>
<td>40</td>
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<tr>
<td>15-19</td>
<td>50</td>
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<td>20-24</td>
<td>60</td>
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<tr>
<td>25-29</td>
<td>70</td>
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<tr>
<td>30-34</td>
<td>80</td>
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<tr>
<td>35-39</td>
<td>90</td>
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<tr>
<td>40-44</td>
<td>100</td>
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<tr>
<td>45-49</td>
<td>110</td>
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<tr>
<td>50-54</td>
<td>120</td>
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<tr>
<td>55-59</td>
<td>130</td>
</tr>
<tr>
<td>60-64</td>
<td>140</td>
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<tr>
<td>65-69</td>
<td>150</td>
</tr>
<tr>
<td>70-74</td>
<td>160</td>
</tr>
<tr>
<td>75-79</td>
<td>170</td>
</tr>
<tr>
<td>&gt;80</td>
<td>180</td>
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</table>

**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

% Surviving

- AA Study Group, non-transplanted (n = 63)
- Utah, total (n = 99)
- Utah, extrapolated severe

Causes of Aplastic Anemia

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 as well (Benzene, Chloramphenicol)

All identifiable causes explain very few cases of AA
Pathophysiology of Aplastic Anemia

- Immune attack
- Stem cells
- Hematopoietic progenitors

- 1960's → 10% survival in 1 year
- 2010 → 90% survival in 1 year
• Immunosuppressive therapy
• Bone marrow transplantation
• Supportive care
• Novel agents

Immunosuppressive therapy

• Anti-thymocyte globulin (ATG)
  • Horse
  • Rabbit
• Cyclosporine (CsA)
• Campath
• Others

Immunosuppressive therapy

• First line of treatment in adults
• Salvage for treatment-refractory patients
• Treatment for relapsed disease
PROGRESS IN IMMUNOSUPPRESSIVE THERAPIES FOR SEVERE APLASTIC ANEMIA

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<th>Response</th>
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<td>40-50%</td>
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<td>1980s</td>
<td>ATG plus CSA</td>
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RESPONSE OF SEVERE APLASTIC ANEMIA TO INTENSIVE IMMUNOSUPPRESSION

ATG AND CSA FOR SEVERE APLASTIC ANEMIA
OVERALL SURVIVAL

ATG AND CSA FOR SEVERE APLASTIC ANEMIA
RESPONSE AT 3 MONTHS AND SURVIVAL
**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</th>
<th>Relapse</th>
<th>Clonal Evolution</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>German</td>
<td>1986-1989</td>
<td>64</td>
<td>32</td>
<td>65%</td>
<td>13%</td>
<td>8%</td>
<td>58% at 11 yrs</td>
</tr>
<tr>
<td>NIH</td>
<td>1991-1994</td>
<td>122</td>
<td>35</td>
<td>61%</td>
<td>30%</td>
<td>11%</td>
<td>55% at 7 yrs</td>
</tr>
<tr>
<td>EGAMT</td>
<td>1991-1994</td>
<td>100</td>
<td>15</td>
<td>77%</td>
<td>12%</td>
<td>11%</td>
<td>67% at 5 yrs</td>
</tr>
<tr>
<td>Japan</td>
<td>1990-1997</td>
<td>118</td>
<td>9</td>
<td>68%</td>
<td>20%</td>
<td>6%</td>
<td>88% at 3 yrs</td>
</tr>
<tr>
<td>German/Austrian</td>
<td>1993-1997</td>
<td>114</td>
<td>9</td>
<td>77%</td>
<td>12%</td>
<td>6%</td>
<td>87% at 4 yrs</td>
</tr>
<tr>
<td>Japan</td>
<td>1990-1999</td>
<td>101</td>
<td>34</td>
<td>74%</td>
<td>40%</td>
<td>6%</td>
<td>88% at 4 yrs</td>
</tr>
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<td>NIH</td>
<td>1999-2003</td>
<td>104</td>
<td>30</td>
<td>62%</td>
<td>37%</td>
<td>9%</td>
<td>60% at 4 yrs</td>
</tr>
<tr>
<td>EGAMT</td>
<td>2002-2006</td>
<td>182</td>
<td>45</td>
<td>79%</td>
<td>26%</td>
<td>4%</td>
<td>76% at 6 yrs</td>
</tr>
<tr>
<td>NIH</td>
<td>2003-2006</td>
<td>77</td>
<td>35</td>
<td>57%</td>
<td>26%</td>
<td>10%</td>
<td>90% at 3 yrs</td>
</tr>
<tr>
<td>NIH</td>
<td>2005-2010</td>
<td>132</td>
<td>28</td>
<td>68%</td>
<td>26%</td>
<td>21%</td>
<td>80% at 3 yrs</td>
</tr>
</tbody>
</table>

**NEW DIRECTIONS IN 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

**Survival of refractory SAA following retreatment with rabbit ATG + CsA (salvage)**

![Graph showing percent survival over time with response rates](image-url)

1/3 Response Rate

Young NS, Calado RT, Scheinberg P. Blood 2006

Scheinberg P, Nunez O, Young NS. Br J Haematol 2006
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>
</tr>
</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>
</tr>
</tbody>
</table>

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>Reticulocytes</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
</tr>
<tr>
<td>Neutrophils</td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
</tr>
<tr>
<td>Platelets</td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Graph" /></td>
</tr>
</tbody>
</table>
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 24: 718-725
Hernández-Campo RM, Cytometry B Clin Cytom. 2006 70:71

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>
</tr>
</tbody>
</table>
ATG AND CSA FOR SEVERE APLASTIC ANEMIA

RELAPSE

RELAPSE AFTER ATG + CSA

Cyclosporine-dependence Post-1\textsuperscript{st}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>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on CsA</td>
<td>20/22</td>
<td>19/20</td>
<td>14/18</td>
<td>11/17</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-1\textsuperscript{st}relapse \rightarrow 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>
INITIAL BLOOD COUNTS PREDICT RESPONSE TO IMMUNOSUPPRESSION AND SURVIVAL


Response (6 mos)

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>&lt; 18</td>
<td>78 (25)</td>
<td>58</td>
<td>0.0199</td>
</tr>
<tr>
<td>18 to 60</td>
<td>187 (59)</td>
<td>109</td>
<td>0.0014</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>51 (16)</td>
<td>37</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Survival Probability in Children

Survival in refractory SAA
1990s

Improved Survival Over Time

Improved Survival Over Time
**Hematopoietic Growth Factors as Therapy for SAA**

Ganser A et al, Blood 1990; 76:1287: IL-3 pilots
Kojima S et al, Blood 2002;100:786: GM-CSF monosomy 7
Tichelli A et al, Blood 2011; 117:4434: GM-CSF shows no survival benefit

**Eltrombopag for Refractory Severe Aplastic Anemia**

- SAA with plts < 30K/µL
- Refractory to ATG/CSA

Eltrombopag 50 mg/daily
Dose escalation every 2 weeks to 150 mg daily

Hematologic response at 3 months

Responders followed monthly on drug

Hematologic Response Criteria
- Platelets: >20K/µL increase, or transfusion-independence
- RBCs: >1.5 g/dL increase in Hb, or transfusion-independence
- ANC: >100% increase if severe neutropenia, or >500/µL increase

NIH Protocol 09-000154: ClinicalTrials.gov identifier: NCT00922883
REFRACTORY SAA ELTROMBOPAG STUDY RESULTS

Censure date 11/1/2011

Median follow up 13 months (range 4-28 months)

26 patients enrolled

1 patient ineligible, not treated

11 responders (44%)
- 9 platelet responses
- 2 hemoglobin responses
- additional 4 at >16wks
- 4 neutrophil responses
- additional 3 at >16wks

25 evaluable patients

14 non-responders
- 10 stable disease
- 2 died of progression
- 2 clonal evolution to MDS
- 1 died
- 1 HSCT

26 patients enrolled

25 evaluable patients

1 patient ineligible, not treated

MEDIAN FOLLOW UP 13 MONTHS (RANGE 4-28 MONTHS)

MULTI-LINEAGE HEMATOLOGIC RESPONSES TO ELTROMBOPAG

Platelets

Hemoglobin

Neutrophils

Trilineage = 6
Bilineage = 7
Unilineage = 4
INSIGHTS INTO SAA PATHOPHYSIOLOGY FROM ELTROMBOPAG RESPONSIVENESS

**SUMMARY**

- Eltrombopag can promote tri-lineage hematopoiesis in SAA patients refractory to IST
  - 44% clinical response rate
  - Transfusion independence
  - Well-tolerated

- Eltrombopag stimulation may expand the HSC pool in humans

- Addition of Eltrombopag early in SAA may increase response rate, decrease time to response, prevent HSC depletion, and avoid clonal progression

**ELTROMBOPAG FOR MODERATE AA**

NHLBI 09-H-0154

clinicaltrials.gov NCT00922883

Eltrombopag, dose escalation to 150 mg QD by mouth

>18 years old; platelet count <30,000/uL

Assessment by blood counts and BM at 3 and 6 months

Horse ATG + CSA and ELTROMBOPAG for treatment-naive SAA

NHLBI 12-H-xxxx

Add eltrombopag to existing horse ATG + CSA platform will increase overall response and decrease relapses
TELOMERE STRUCTURE AND BIOLOGY

- Cap chromosome ends
- Tandem TTAGGG repeats
- Bound to array of proteins: telomerase complex
- Forms higher order chromatin T loop
- Shields 3' end to prevent recognition as a DNA “break” by non-homologous end joining machinery
- TTAGGG loss with proliferation: “end replication problem”

DYSKERAOTOSIS CONGENITA

- Leukoplakia
- Hyperpigmentation
- Nail dystrophy

Courtesy by B. Alter, NCI
TELOMERE LENGTH IN 7ERT MUTATION LEUCOCYTES

controls

patients

His 412 Tyr

Val 684 Met

Ala 202 Thr

Val 1090 Met

Cys 772 Tyr

age, years

telomere length, kb

SHORT TELOMERE LENGTH PREDICTS RELAPSE AND EVOLUTION IN SEVERE APLASTIC ANEMIA

N = 168 consecutive patients on NIH IST protocols
Mean age = 34 years (4-82 years)
no relationship to response to treatment (PR, CR)

RELAPSE RATE BY TELOMERE QUARTILES

N. et al. JAMA 2010
EVOLUTION RATE BY TELOMERE LENGTH

MONOSOMY 7 EVOLUTION BY TELOMERE LENGTH

SURVIVAL PROBABILITY BY TELOMERE LENGTH

SURVIVAL PROBABILITY BY TELOMERE & ARC

SHANK'S DISEASE™ IN A MENNONITE FAMILY
LATE PRESENTATION OF DYSKERATOSIS CONGENITA

37 y/o US Army officer in Afghanistan
tongue ulcer, diagnosed as squamous cell carcinoma
single round of chemotherapy and radiation resulted in unexpected extreme,
persistent pancytopenia. Later, pulmonary metastases
novel Val329Gly mutation in DKC1

Early onset of graying (20's) and low platelets
Thrombocytopenia, gray hair, very short telomere, TERT mutation

ANDROGEN THERAPY FOR APLASTIC ANEMIA

ANDROGEN THERAPY FOR APLASTIC ANEMIA
SEX HORMONES INCREASE TELOMERASE ACTIVITY IN CULTURED HUMAN LYMPHOCYTES

Androgens

Calado RT et al, Blood 2009

Danazol for telomeropathy

ClinicalTrials.gov identifier: NCT01441037

http://clinicaltrials.gov/ct2/show/NCT01441037?term=danazol+for+telomere&rank=1

15 patients enrolled in first 6 months.
First patient enrolled on 08/19/2011
First 6 months – no drug-related toxicities.
(Minimal elevation in LFTs in almost all patients and controllable headaches in 4 patients).