Aplastic Anemia: Understanding your Disease and Treatment Options

Josh Sasine, MD, PhD
Hematopoietic Cell Transplant Program
Division of Hematology-Oncology
University of California, Los Angeles

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Overview of the Bone Marrow

Forming Blood Cells

- 10 billion red blood cells and 1 billion whites are produced per hour
- Cell numbers are maintained within narrow limits but can be greatly amplified on demand
- No other tissue has this output

Bone Marrow Niche
**Stem Cell Biology Crash Course**

- Fewer circulating mature cells
- Leukemia risk

**Bone Marrow Failure: Overlapping Diseases**

**Pure Red Cell Aplasia (PRCA)**

- Unable to produce sufficient red blood cells but marrow can make white blood cells and platelets

**Epidemiology of Aplastic Anemia (AA)**

- Rare: 2 cases per million people per year
- Higher incidence in Asia
- Male : Female ratio is equal
- Half occur before age 30

**Why Do Some People Get AA?**

- Damage to bone marrow cells: radiation, chemotherapy
- Exposure to chemicals → solvents, benzene
- Certain medications or antibiotics (chloramphenicol, carbamazepine, methimazole, etc.)
- Viral infections (hepatitis, EBV, CMV, HIV, parvovirus)
- Congenital mutations
- Pregnancy
- Paroxysmal Nocturnal Hemoglobinuria
- Immune alterations (lupus, eosinophilic fasciitis, thymoma)
- Idiopathic → unable to identify the cause

**Pure Red Cell Aplasia (PRCA)**

- Generally acquired but can be congenital
- Congenital: often Diamond-Blackfan anemia (DBA)
- Acquired:
  - 60% → no specific associated condition, antibodies against red blood cell precursors, EPO or its receptor
  - Autoimmune disorders (eg. lupus, thymoma)
  - Clonal disorder: LGL, MDS, plasma cell dyscrasia
  - Virus → eg Parvovirus B19
  - ABO-incompatible hematopoietic cell transplantation
  - Medications
DNA Damage

- DNA damage occurs naturally due to internal and external factors
- Internal: reactive oxygen species, normal metabolic byproducts
- External: radiation (include UV, though not in the bone marrow), x-rays, plant toxins, chemicals, viruses, etc.

Telomeres

- Telomeres are “caps” at the end of each chromosome which serve as a buffer against losing DNA when the cell divides and replicates the DNA
- Maintenance of telomeres is an active process

Inherited Conditions

- Fanconi Anemia
  - DNA repair problem, most common form of inherited AA
  - Pancytopenia, predisposition to malignancy, and physical abnormalities (eg, short stature, microcephaly, developmental delay, café-au-lait skin lesions)

- Dyskeratosis Congenita
  - Mutation in telomere machinery – short telomeres
  - Bone marrow failure, skin and nail findings, pulmonary fibrosis, cancer predisposition, mucosal leukoplakia

- Shwachman-Diamond syndrome
  - Usually presents in infancy with bone marrow failure, pancreas dysfunction, skeletal anomalies
  - AA can be seen but intermittent neutropenia (low white blood cells) is most common

- Congenital Amegakaryocytic Thrombocytopenia (CAMT)
  - Mutation in thrombopoietin (TPO) or its receptor
  - Low platelets which progress to pancytopenia

Fanconi Anemia

- DNA repair problem, most common form of inherited AA
- Pancytopenia, predisposition to malignancy, and physical abnormalities (eg, short stature, microcephaly, developmental delay, café-au-lait skin lesions)

Dyskeratosis Congenita

- Mutation in telomere machinery – short telomeres
- Bone marrow failure, skin and nail findings, pulmonary fibrosis, cancer predisposition, mucosal leukoplakia
Immunity and AA

• Autoimmune damage to bone marrow stem cells causes or contributes to most cases of AA, whether another underlying cause is identified or not

Diagnosis

AA = pancytopenia with loss of bone marrow cells and no abnormal infiltrate or fibrosis (scarring)

• CBC with reticulocyte count
• Liver tests
• Vitamins: B12 and folate
• Viruses: hepatitis, CMV, EBV, HIV, ParvoB19
• Autoimmune test
• Chromosome breakage tests
• Flow cytometry to look for PNH
• Bone marrow aspirate and biopsy
  • Cytogenetics and karyotype
  • Next-generation sequencing for mutations, acquired or inherited

AA Risk Stratification

Severe aplastic anemia

<table>
<thead>
<tr>
<th>Bone marrow cellularity</th>
<th>&lt;30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two of three peripheral blood criteria:</td>
<td></td>
</tr>
<tr>
<td>- absolute neutrophil count</td>
<td>500–200/mm³</td>
</tr>
<tr>
<td>- platelet count</td>
<td>&lt;20,000/mm³</td>
</tr>
<tr>
<td>- reticulocyte count</td>
<td>&lt;40,000/mm³</td>
</tr>
<tr>
<td>VERY SEVERE APLASTIC ANEMIA</td>
<td></td>
</tr>
<tr>
<td>- absolute neutrophil count</td>
<td>&lt;200/mm³</td>
</tr>
<tr>
<td>MODERATE APLASTIC ANEMIA</td>
<td></td>
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<tr>
<td>Patients with pancytopenia who do not fit the criteria of severe disease</td>
<td></td>
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</tbody>
</table>

Hematopoietic Cell Transplant

• Early identification of donor
• If age 20 – 50 with SAA and sibling donor → transplant (no IST)
  • Outcomes for matched unrelated donor are also very good
  • Haplo (half-matched) and cord blood donors are also options
• Bone marrow vs. peripheral blood
• Graft failure correlated with number of previous transfusions
• Monitoring for clonal evolution?

Historical Perspectives

<table>
<thead>
<tr>
<th>Era</th>
<th>Treatment</th>
<th>Response Rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960s</td>
<td>Corticosteroids</td>
<td>~10%</td>
<td>10 – 20%</td>
</tr>
<tr>
<td>1970s</td>
<td>ATG</td>
<td>40 – 50%</td>
<td>40 – 60%</td>
</tr>
<tr>
<td>1980s</td>
<td>ATG + cyclosporine</td>
<td>60 – 70%</td>
<td>60 – 70%</td>
</tr>
<tr>
<td>2000s</td>
<td>ATG + cyclosporine + eltrombopag</td>
<td>87%</td>
<td>80 – 90%</td>
</tr>
</tbody>
</table>

Outcomes for AA are Improving Over Time - Why?

• Better medicines to regenerate bone marrow
• Better supportive care
  • Antibiotics, safer blood transfusions, Chelation for iron overload, etc.
• Improvements in bone marrow transplantation with greater access
**Production of Anti-Thymocyte Globulin (ATG)**

- Immunization with human thymocytes
- Thymus
- ATG
- IgG
- Cytotoxicity assay
- Purification of sera
- Immune response

**Immunosuppressive Therapy (IST)**

- Horse ATG daily x 4 days vs rabbit ATG daily for 5 days (+ cyclosporine for both)
- Response at 6 months was better with horse ATG (68 vs 37%)
- Overall survival at 3 years was superior in the horse ATG group (96 vs 76%)

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**Patients Not Responding to IST**

- Non-responders to IST N=174
- 2002 – 2008
- 5-yr survival: 25%
- 1996 – 2002
- 5-yr survival: 17%
- 1989 – 1996
- 3-yr survival: 23%

- P < 0.001

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**Unsuccessful Attempts to Improve Treatment**

- **Add to or replace ATG with megadose corticosteroids**
  - No increase in response, high toxicity (Marmontl, Prog Clin Biol Res 1984)
- **Replace ATG with high dose cyclophosphamide**
  - Toxicity (Tisdale, Lancet 2001; Blood 2002)
- **Replace ATG with moderate dose cyclophosphamide**
  - Excessive toxicity from neutropenia (Scheinberg, Blood 2014)
- **Add mycophenolate mofetil to ATG/CsA**
  - No improvement in response/survival (Scheinberg, Br J Haematol 2006)
- **Add sirolimus to ATG/CsA**
  - No improvement in response/survival (Scheinberg, Haematologica 2009)
- **Add G-CSF to ATG/CsA**
  - No improvement in response/survival (Scheinberg, Haematologica 2008)
- **Prolonged CsA (2 years) to prevent relapse**
  - Delayed but ultimately equivalent rate (Scheinberg, Am J Hematol 2014)
- **Replace horse with rabbit ATG, or alemtuzumab, frontline**
  - No improvement in response/survival (Scheinberg, NEJM 2012)

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**All Patients Over Time: Survival**

- 2002 – 2008
  - 5-yr survival: 81%
- 1996 – 2002
  - 5-yr survival: 74%
- 1996 – 1996
  - 5-yr survival: 64%

- All patients
  - N=420
  - P < 0.001

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**Patients Responding to IST**

- 2002 – 2008
  - 5-yr survival: 49%
- 1996 – 2002
  - 5-yr survival: 67%
- 1996 – 1996
  - 5-yr survival: 51%

- Responders to IST
  - N=246
  - P = 0.54
**Can We Induce Hematopoietic Stem Cell Growth?**

- Hormones produced in the liver (like TPO) can maintain and promote bone marrow stem cells.
- Medicines can mimic the effect of TPO in the bone marrow.
- Local ‘hormones’ in the bone marrow can also make stem cells grow.

**What Do We Know About TPO and Hematopoietic Stem Cells?**

- TPO receptor (c-Mpl) is on HSCs and early progenitor cells.
- TPO expands HSCs in the lab.
- Deleting TPO or c-Mpl in mice reduces HSCs.
- Multi-lineage marrow failure occurs in some congenital amegakaryocytic thrombocytopenia.

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**Eltrombogab + IST**

- Overall response rate (no longer meeting criteria for severe AA): **87%**
  - 66% in historical control patients.
- Complete response (ANC >1000 + Hg >10 + plts ≥ 100): **39%**
  - (58% in high-dose cohort).
  - 10% in historical control patients.
- Survival: **97%** at 2 years.

**Clonal Evolution**

- Mutations are Non-Random
- A Subset of Mutations Correlate with Survival
  - P=0.008

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**Townsley et al. N Engl J Med 2017**

**Steensma et al. Blood. 2015**

**Yoshizato et al. NEJM. 2015**

**Steensma et al. Blood. 2015**

**Cazzola et al. Blood. 2013**

**Eltrombogab + IST**

**Clonal Evolution**
Monitoring → CHIP

- CHIP = clonal hematopoiesis of indeterminate potential
- Form of clonal evolution
- Common with age
- More common in AA
- Predisposition to leukemia and cardiovascular disease

![Graph showing frequency vs. age for CHIP](image_url)

- High cholesterol
- Hypertension

Important Lab Tests Over Time

- Ferritin
- Antibody levels
- Kidney function and magnesium if on cyclosporine
- Test for clonal evolution

What About Patients Who Don’t Benefit from IST?

- Return of AA occurs in 10 – 35% at 15 years
- No response to initial IST for 10 – 15%

Options:

- Repeat IST (horse or rabbit ATG is acceptable)
- Eltrombopag (+/- ATG +/− cyclosporine)
- Alemtuzumab (+/- cyclosporine)
- Transplant

- Must rule out clonal evolution such as MDS

- If not responsive to first IST: ongoing immune attack or persistent stem cell problem?

Research

Chemotherapy-free transplantation

- Bone
- Vessel
- Megac

Growth factors for HSCs

- HSC Regeneration
- PTN

Questions?