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

AA&MDS International Foundation
Living with Aplastic Anemia, MDS, or PNH Patient and Family Conferences in 2014

Jaroslaw Maciejewski, MD PhD
Cleveland Clinic Taussig Cancer Institute
Dept. of Translational Hematology and Oncology Research
Cleveland, Ohio USA

APLASTIC ANEMIA

Paul Ehrlich
- Identification of bone marrow as site of blood cell production
- Concept of the "hematopoietic stem cell"
- Development of bone marrow transplantation

First clinical description of aplastic anemia

COMPONENTS OF BLOOD PRODUCTION

Crop
- Seeds
- Soil
- Mature blood cells
- Stem cells
- Stroma
CAUSES OF APLASTIC ANEMIA

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

CLASSIFICATION OF APLASTIC ANEMIA

Acquired Aplastic Anemia
- Idiopathic aplastic anemia
- Secondary aplastic anemia

Inherited Aplastic Anemia
- Fanconi anemia
- Dyskeratosis congenita
- Schwachman-Diamond syndrome
- Ataxia-telangiectasia
- Agranulocytic thrombocytopenia
- Familial aplastic anemia
- Platelet abnormality (megakaryocytopathy)
- Nonhematologic syndromes (Down, Dubowitz, Seckel)

Secondary aplastic anemia
- Irradiation
- Drugs and chemicals
  - Regular effects
  - Cytotoxic agents
  - Benzene
  - Miscellaneous reactions
  - Chloramphenicol
  - Antileukemic agents
  - Gold
  - Other drugs/chemicals
- Viruses
  - EBV (infectious mononucleosis)
  - Hepatitis virus (non-A, non-B, non-C, non-G hepatitis)
- Immune diseases
  - Eosinophilic fascitis
  - Hypogammaglobulinemia
  - Thymoma
  - Graft-versus-host disease
- Pregnancy

WHAT TRIGGERS IMMUNE AA?

- Viral antigen
- Cross-reactive antigen
- Product of a mutated gene
- Chemical

Adapted from Maciejewski & Young in Hoffman's Textbook of Hematology 2008
TUMOR SURVEILLANCE TRIGGERS

- Aplasia
- Stem cells
- Bystander/cross-reactive killing
- Lymphocytes
- Expansion
- Recognition of aberrant antigen

MDS - CLINICAL OVERLAP/ASSOCIATIONS

- PNH
- AA
- MDS
- PRCA
- LGL

COMPONENTS OF THE PATHOPHYSIOLOGY OF IDIOPATHIC AA

- Stem and progenitor compartment
- Immune T cells
- IFN
- Fas
- TNF
- Perforin/granzyme

- Growth factors
- Mature blood cells
- Stroma
**TREATMENT TARGET**

- Stem and progenitor compartment
- Immune T cells
- Growth factors
- Stroma
- Mature blood cells

**DIAGNOSTIC ALGORITHM IN APLASTIC ANEMIA**

<table>
<thead>
<tr>
<th>PB counts</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM for diagnosis</td>
<td>Blasts, Dysplasia, Fibrosis, MDS, AML, IMF</td>
</tr>
<tr>
<td>FA</td>
<td>Karyotyping</td>
</tr>
<tr>
<td>Acquired AA</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Classification:**
- Hypocellular BM, Normal karyotype, 2 lineage cytopenias
- Acquired AA
- Inherited AA
- Some MDS
- Rare aleukemic AML
- Some ALL
- Some lymphomas

- Q fever, Legionnaires’ disease
- Mycobacteria, Tuberculosis
- Anorexia nervosa, starvation
- Hypothyroidism

**Severe Aplastic Anemia**
- ANC <500/μL
- Retic count <40 000/μL
- Ptl <20 000/μL

**Moderate chronic AA**
- At least 2 lineage cytopenia
- Not fulfilling the severity criteria

**THERAPY TYPES**

- Induction
- Maintenance
- Supportive measures
- Salvage therapies

**STEM CELL TRANSPLANT**
THERAPY: DISEASE TARGETS

Severe AA
- hATG/CsA
- BMT

Refractory/relapsed severe AA
- ATG,
- Campath
- Anabolic steroids

Moderate AA
- CsA
- Watchful waiting
- Treat as severe AA

IMMUNOSUPPRESSION IN SEVERE AA

Survival

By response

Rosenfeld et al., 2003

---

RESULTS OF IMMUNOSUPPRESSIVE THERAPIES IN MAJOR CLINICAL TRIALS

<table>
<thead>
<tr>
<th>Study</th>
<th>ATG</th>
<th>N</th>
<th>Median (y)</th>
<th>Response (%)</th>
<th>Relapse (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacigalupo et al., 2000</td>
<td>ALSI</td>
<td>100</td>
<td>16</td>
<td>77 (6 mos)</td>
<td>12 (3 yrs)</td>
<td>87 (5 yrs)</td>
</tr>
<tr>
<td>Kojima et al., 2000</td>
<td>ALSI</td>
<td>119</td>
<td>9</td>
<td>71 (6 mos)</td>
<td>37 (4 yrs)</td>
<td>83 (4 yrs)</td>
</tr>
<tr>
<td>Frickhofen et al., 2003</td>
<td>ATG</td>
<td>84</td>
<td>32</td>
<td>70 (6 mos)</td>
<td>38 (11 yrs)</td>
<td>58 (11 yrs)</td>
</tr>
<tr>
<td>Scheinberg et al., 2004</td>
<td>ATG</td>
<td>104</td>
<td>30</td>
<td>64 (6 mos)</td>
<td>37 (3 yrs)</td>
<td>80 (3 yrs)</td>
</tr>
<tr>
<td>Zheng et al., 2006</td>
<td>ATG</td>
<td>74</td>
<td>34</td>
<td>76 (6 mos)</td>
<td>27 (5 yrs)</td>
<td>81 (5 yrs)</td>
</tr>
<tr>
<td>Tichelli et al., 2007</td>
<td>ATG</td>
<td>192</td>
<td>46</td>
<td>70 (6 mos)</td>
<td>33 (6 yrs)</td>
<td>73 (6 yrs)</td>
</tr>
<tr>
<td>Attie et al., 2010</td>
<td>ATG</td>
<td>71</td>
<td>19</td>
<td>59 (3 mos)</td>
<td>36</td>
<td>79 (2 yrs)</td>
</tr>
<tr>
<td>Mabe et al., 2011</td>
<td>ATG</td>
<td>85</td>
<td>36</td>
<td>58 (2 yrs)</td>
<td>56</td>
<td>64 (2 yrs)</td>
</tr>
</tbody>
</table>
SUPPORTIVE THERAPY

- Japanese study of 101 patients with sAA
- Randomized study; median follow-up time of 52 mos
- hATG + CsA vs hATG + CsA + G-CSF
- Results:
  - No diff in infection or febrile episodes
  - No diff in survival or MDS/AML evolution
  - Increased risk of relapse in G-CSF arm

Promacta/Nplate

THERAPEUTIC CONSIDERATIONS

- Not sufficient IS
- Repeated cycles of therapy
- BMT
- Genetic causes
  - TERC/TERT
  - Perforin
  - PA
- Exhusted stem cell reserve
- Undetected clonal disease
- Insufficient immunosuppression
- Exhaustion of stem cell reserves
- Misdiagnosis
- Hereditary bone marrow failure

RESPONSE RATES TO rATG OR hATG IN PATIENTS AA

<table>
<thead>
<tr>
<th>Year</th>
<th>rATG (%)</th>
<th>hATG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>2010</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>2011</td>
<td>45%</td>
<td>49%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>rATG (%)</th>
<th>hATG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>52%</td>
<td>58%</td>
</tr>
<tr>
<td>2010</td>
<td>60%</td>
<td>68%</td>
</tr>
<tr>
<td>2011</td>
<td>34.5%</td>
<td>59.5%</td>
</tr>
</tbody>
</table>

- Insufficient immunosuppression
- Non-immune pathogenesis
PROMACTA IN REFRACTORY AA

N=26 (median f/u 13 month)

- 11 responders (44%)
  - 9 platelet responses
  - 2 hemoglobin responses
    - additional 4 at > 12 wks
  - 4 neutrophil responses
    - additional 3 at > 12 wks
- 25 evaluable patients
- 14 non-responders
  - 10 stable disease
  - 2 died of progression
  - 2 clonal evolution to MDS
  - 1 died
  - 1 HSCT

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>BMT TRM</td>
<td>IS</td>
</tr>
<tr>
<td>Age 20-40y</td>
<td>No response</td>
</tr>
<tr>
<td>IS failure</td>
<td>IS</td>
</tr>
<tr>
<td>Age&gt;40y</td>
<td>IS</td>
</tr>
<tr>
<td>No response</td>
<td>BMT</td>
</tr>
</tbody>
</table>

- Second course of IS vs. MUD BMT
- Children
  1. Second course of IS
  2. Salvage therapy
  3. Androgens GF
- Older Adults

- Third course of IS vs. MUD BMT
- Refractory patients without Sibling donor
- Alternative treatments with Campath

HOW IMMUNOSUPPRESSION IS ADMINISTERED FOR SAA

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

How long to wait for response?
What to do if CsA is to toxic?
How long to treat?
When to think about BMT?
IMMUNOSUPPRESSION VS. BMT

- BMT
- Immunosuppression

% overall survival

Months after therapy

RELAPSE AFTER ATG THERAPY

- High relapse rate: up 40% in 10 years
- Good prognosis of reinduction therapy with similar response rate
- Maintenance therapy may be required (CsA dependence)
- OS not impacted by relapse

PATHOGENESIS OF CLONAL EVOLUTION

Dysplastic cell  Recognition of dysplastic clone  Clonal T cell expansion  Collateral damage/Cross-recognition  Acquisition of malignant phenotype  Immune Pressure  Immune inhibition  Clonal Evolution  AML  MDS  AA

CLONAL MDS EVOLUTION IN AA

Preexisting abnormal clone
Immune effector mechanisms

Immune attack precedes clonal evolution

Maciejewski et al at Blood 2001

LATE CLONAL COMPLICATIONS OF AA
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Hemolytic PNH
Reticulocytosis
LDH elevation
Urine hemosiderin
Cytopenia

AA/PNH syndrome

PNH CLONES IN BONE IMMUNE MEDIATED BONE MARROW FAILURE

-33% of AA patients have PNH clones at presentation
-Most clones minor
-Evolution in 20% of patients

Maciejewski et al Blood, 2000, BJH 1999