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

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Objectives

• To review a brief history/epidemiology of aplastic anemia
• To review what makes the diagnosis of Aplastic Anemia
• To discuss non-transplant treatment options for newly diagnosed AA
• To discuss non-transplant treatment options for relapsed or refractory AA

Textbook Definition of Aplastic anemia (AA)

• deficiency of all types of blood cells caused by failure of bone marrow development.
• Diagnosis of exclusion
• Most cases are autoimmune and acquired

HISTORY & EPIDEMIOLOGY

From where we come...

History

• 1888 Earliest case description of AA by Dr. Ehrlich
• 1899 Anti-lymphocyte serum (immunosuppression) describe by Dr. Metchnikoff
• 1904 Aplastic Anemia coined by Dr. Chauffard
• 1972 First successful bone marrow transplant for AA
• Later 1970s immunosuppressive regimens progressed

Epidemiology

• Precise estimates of number of patients with AA are confounded by imprecision in diagnosis
  – In Europe, Israel, USA ~2-4 cases per 1 million people
  – Higher in Asia ~5-8 cases per 1 million people
• Two age groups for presentation
  – Ages 15-25 years
  – Age >60 years
• Acquired and inherited cases
  – Most acquired are idiopathic
  – Drug or toxins cause are minority
CAUSES & PATHOGENESIS

Drug/Toxin Causes

- Carbamazepine
- Phenytoin
- Hydantoins
- Sulfonamides
- Chloramphenicol
- Phenytoin
- Indomethacin
- Methimazole
- Propylthiouracil
- Gold
- Arsenicals
- Benzene

What causes acquired AA? (Pathophysiology)

- T cell immune attack at the CD34 progenitor cell

APLASTIC ANEMIA: Pathophysiology

- High quality HSC
- Low quality HSC
- Progenitors

Aplastic Anemia is Bone Marrow Failure

- The bone marrow is the spongy stem cell tissue that produces the blood:
  - Red cells
  - White cells (neutrophils)
  - Platelets
- When all three cell lines are low → Pancytopenia

From where we come...to how we get there...

DIAGNOSIS
Bone marrow failure: Overlapping diseases

- Aplastic anemia (acquired)
- Paroxysmal nocturnal hemoglobinuria
- Inherited syndromes
- Hypoplastic MDS
- Myelodysplastic syndrome
- Large granular lymphocyte leukemia
- Pure Red Cell Aplasia
- Myeloproliferative disorders
- (AML)

Aplastic Anemia: Differential Dx

- Congenital disorders
  - Fanconi: all patients < 40yo (DEB,MMC)
  - Others: careful history
- PNH - flow cytometry, LDH
- Hypoplastic MDS – morphology, cytogenetics, CD34 count

Patient History
- Duration of cytopenias (Are pediatric records available?)
- Medications (prescribed and over-the-counter supplements)
- Immunization records
- Exposures
- Transfusions

Family History
- Constitutional abnormalities
- Malignancies

Physical examination
- Height (in context of mean parental height)
- Limb abnormalities
- Skin and nail abnormalities (café au lait spots, nail dystrophy, pale patches)

Laboratory
- Peripheral blood
  - Beta-HCG (Consider even if intercourse is not explicitly stated)
  - Complete blood count with differential
  - Reticulocyte counts
  - Chemistries
  - Transaminases and bilirubin; Hepatitis serologies
  - FLAER assay for PNH
  - Chromosome breakage tests, Telomere length, Mutational analysis
- Bone marrow
  - Aspirate and biopsy
  - Flow cytometry (including quantitative CD34)
  - Cytogenetics

Classification of AA: Camitta Criteria

<table>
<thead>
<tr>
<th>Peripheral Blood Cytopenias</th>
<th>Non-severe (Moderate) aplastic anemia (not meeting criteria for severe disease)</th>
<th>Severe aplastic anemia (any 2 of 3)</th>
<th>Very-severe aplastic anemia (meets criteria for severe disease and absolute neutrophils &lt; 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow cellularity</td>
<td>&lt; 25%</td>
<td>&lt; 25%</td>
<td>&lt; 25%</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>&lt; 500 / µl</td>
<td>&lt; 200 / µl</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt; 20,000 / µl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>&lt; 1.0% corrected or &lt; 60,000 / µl</td>
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Decision to treat

- Based on disease severity
  - Severe and Very Severe AA require prompt therapy
  - Moderate AA does not necessarily

- Natural History of Untreated Disease

Types of AA

SAA, vSAA

Moderate AA

Years

0 1 2 3 4 5 6 7 8 9 10
Non-severe (Moderate) Aplastic Anemia

- 36 yo Asian male with pancytopenia and fatigue
  - Counts last normal 6 years ago
  - ANC 85000 (no infections)
  - Hemoglobin 8.9-10.3 (no transfusions)
  - Platelets 51 (no spontaneous bleeding, maybe increased bruising)
  - Bone marrow biopsy 25% cellular, normal cytogenetics, no dysplasia
  →will monitor as all counts safe (monitoring for 5 years and NO change)
  - 1/3 will improve
  - 1/3 will stay moderate (Counts abnormal but may not need treatment)
  - 1/3 will progress to severe aplastic anemia
  - Can consider low dose immunosuppression (like cyclosporine alone)

Severe Aplastic Anemia

- 18 yo male 5’4” presented with non-traumatic retinal hemorrhages and petechiae in palate
  - Therapy started within 1 week of making diagnosis
- WBC 2200 ANC 330
- Hb 3.6 Plts 10
- Peripheral smear : no blasts
- Retic (corrected) 0.7%
- Biopsy: hypocellular <5%
- Karyotype normal

Inherited versus Acquired

**Acquired Aplastic Anemia**
- Loss of hematopoietic stem cells via immune attack or toxin exposure
- Treated with immunosuppressive therapy or bone marrow transplant
- Can evolve to MDS/AML

**Inherited Aplastic Anemia**
- Genetic disorder
- May only be single lineage cytopenias
- Associated with other syndromic features or phenotypic abnormalities
- Less likely to respond to immunosuppressive therapy
- Can evolve to MDS/AML

Rule out a Congenital Syndrome

- May be seen at time of progression to AML/ clonal evolution
- Consider in patients age <30-40 with pancytopenia
  - May have therapeutic implications
- History and physical
  - Family with cytopenias, premature graying, pulmonary fibrosis
  - Short stature, physical abnormalities
- Differential of Aplastic Anemia
  - Fanconi anemia, Dyskeratosis congenita, Diamond-Blackfan anemia; Scwachman-Diamond; congenital Amegakaryocytic thrombocytopenia, Thrombocytopenia with absent radii

**VERY Severe Aplastic Anemia**

- 58 yo female presented with shortness of breath, pale, easy bruising
  - Therapy started within 1 week of making diagnosis
- WBC 1200 ANC 180
- Hb 7.6 Plts 18
- Peripheral smear : no blasts
- Retic (corrected) 0.3%
- Biopsy: hypocellular <5%
- Karyotype normal

**MDS** | **Aplastic Anemia**
--- | ---
Cellularity | Increased or normal* | Decreased
CD34 count | Normal or increased | Decreased (< 0.1%)
Dyserythropoiesis | Common | Common
Ringed sideroblasts | Common | Never
Myelodysplasia or blasts | Common | Never
Dysplastic megakaryocytes | Common | Never
PNH population | Rare | Common
Abnormal karyotype | Common | Rare
Useful tests

**Karyotype**
- Karyotype abnormal
  - 19% AA
  - 54% hMDS

**CD34%**
- Normal or increased percentage of CD34+ cells more likely to be hMDS
- Low marrow CD34+ cells more likely AA


Useful tests: PNH Clones

- Populations of GPI-AP deficient cells (usually 0.1 to 15%) can be found in most patients with acquired AA at diagnosis


Why it matters to us...

**Time to Response with PNH clone present is shorter**

**Overall Survival is Shorter if hMDS compared to AA**

Telomeres

- Telomeres: regions of repetitive nucleotides at the ends of chromosomes that are there to protect the chromosomes from damage and breakdown.
- Telomere length testing very helpful in inherited AA DKC (very short)
- Reports suggest that telomeres are shorter (not very short) in up to one-third of patients with acquired SAA
- At NIH, telomere lengths measured in the white blood cells of 183 patients treated with IST
- Shorter telomeres not found to predict who would have improved blood counts at 6 months after IST
- Shorter lengths may be associated with late effects such as relapse or clonal evolution to MDS

Scheinberg et al. JAMA, 304 (2010), 1358-64.

Ideal therapy for SAA

- Available to all patients
  - Not limited by age and donor status
- Low toxicity
  - Rapid hematopoietic reconstitution
  - Low risk for graft failure/GVHD/infections
- Reduces or eliminates risk of secondary clonal disease
  - MDS/Leukemia
  - PNH

TREATMENT

Now we have the diagnosis, on to…

7/12/2016
Treatment in AA affected by

1. AGE
2. Availability of matched sibling donor

Young patients (<40 years Old)

Severe Aplastic Anemia

- With HLA matched sibling
- Without HLA matched sibling

Hematopoietic Cell Transplant
Immunosuppressive Therapy

Response
Relapse

Clinical follow up
Alternative donor transplantation versus repeat immunosuppression
Assessment of late effects

Older patients (>40 years Old) or No Suitable Donor

Severe Aplastic Anemia

Immunosuppressive Therapy

Response
Relapse

Clinical follow up
Alternative donor transplantation versus repeat immunosuppression
Assessment of late effects

Allogeneic BMT for SAA

- Type of graft and age are the 2 most important prognostic factors for survival

Data from CIBMTR

Immunosuppressive therapy (IST)

- STANDARD OF CARE:
  - Anti-thymocyte globulin (ATG) (anti lymphocyte globulin ALG)
  - Polyclonal buffed serum from horse or rabbit that has been immunized with human T cells
    - HORSE > RABBIT in USA
  - Often ATG is usually combined with pill immunosuppressants as well- usually CYCLOSPORINE (CsA)
- Metrics to evaluate treatment: response, relapse, survival, clonal evolution (getting MDS, AML, PNH)

NON-TRANSPLANT TREATMENT OF AA
PREPARATION and use of ATG

Efforts to Improve Response

- Change type of ATG
  - Horse vs Rabbit

- Add more IST
  - Other pills or IV chemos

2003 Report of Response rates

<table>
<thead>
<tr>
<th>ATG alone</th>
<th>ATG + CsA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>41%</td>
<td>70%</td>
</tr>
<tr>
<td>Relapse Rate</td>
<td>45%</td>
<td>30%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>54%</td>
<td>58%</td>
</tr>
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Kinetics of Response to Therapy

Clonal Evolution
The actuarial probability of malignant diseases was 18% at 11.3 years. It was 8% for MDS or leukemia. The interval from treatment of AA to the diagnosis of MDS or leukemia was 6.6 to 9.5 years.

IST

- Antithymocyte globin (ATG) + Cyclosporine (CsA)
  → 60-70% response rate!!
  - Horse (71% response rate) versus Rabbit (43% response rate)
  - 2005-2010 hematologic response at 6 mos (blood counts) 120 patients (60 in each group)

<table>
<thead>
<tr>
<th>ATG</th>
<th>ATG + CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>85% (62)</td>
<td>80% (60)</td>
</tr>
<tr>
<td>65% (41)</td>
<td>75% (50)</td>
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Side Effects OF ATG
usually temporary

- Decrease in blood counts further
  - Increased need for transfusions
  - Increased risk of bleeding
  - Increased risk of infection

- Liver toxicity
  - Rise in transaminases (AST/ ALT)

- Kidney Toxicity
  - Rise in creatinine
Serum sickness

- Reaction to the horse (or rabbit) proteins
  - Immune complex hypersensitivity reaction
- Flu-ish feeling when getting ATG
- High fevers, flushing, myalgias
- Usually within 4-10 days of ATG
- To reduce the incidence of this, methylprednisolone 1mg/kg should be administered with the ATG and then steroids continue and are tapered over the subsequent month

Side Effects of CsA

- Usually decrease when drug decreased/ stopped
- GI toxicity (nausea, diarrhea)
- High blood pressure
- Kidney toxicity
- Headaches
- Tremor (can limit driving rarely)
- Infections
- Thickening of gums in mouth
- Increased hirsutism
- Peripheral neuropathy

Addition of MORE IST

- CellCept (mycophenolate mofetil = MMF)
  - hATG + CsA + MMF in 104 pt study
    - Response rate 64% at 6 months
    - Relapse 37% at 4 years
    - Overall survival at 4 years 80%
    - Clonal Evolution 9% at 4 years
- Sirolimus
  - hATG + CsA + Sirolimus in 35 pts study (randomized to hATG + CsA)
    - Response rate (partials only) 51% at 6 months
    - Not as good as hATG + CsA = 62%
- BOTH additional added limited improvements in response over hATG + CsA and slightly more toxicity

Alemtuzumab

- Anti CD52 antibody
  - Immunosuppresses by selectively killing cells that have this cell surface marker

High dose cyclophosphamide

- Another form of IST
  - High dose = 50mg/kg daily for 4 days (similar to conditioning regimen for BMT)
  - 66 patients studied at Hopkins
    - 44 treatment naïve (Response: 31/44 = 71%)
    - 23 refractory to standard ATG/CSA
  - Median follow-up 63 months
  - Median time to response: 5 (IQR, 2-10) months
  - Study at NIH stopped due to toxicity from HiCY
    - Even moderate doses (30 mg/kg) of CY may be too toxic

High Dose Cy for SAA

- Overall survival
- Failure-free survival

- Table 2. Table summarizing the response, DO, relapse, and clonal evolution in refractory. All patients treated w/ alemtuzumab-based IST

- n = 44
- n = 23

- Scheinberg et al, ASH Abstract 2012 #1259
- Aarabian Bell-Hammond 2006
- Aarabian Bell-Hammond 2008
- Blood 2010
- Blood 2010

**Response to Immunosuppression**

- PNH clone presence predicts:
  - Response to immunosuppressive therapy (IST)
  - Favorable prognosis in patients with aplastic anemia
- HLA DR15 predicts response to IST in hMDS
  - 8.5 x more likely to respond to IST in NIH study
- Shorter telomere lengths by PCR methods have been suggested to show same response rate but more clonal evolution or increased incidence of relapse

**Supportive Care**

- Central Venous Catheter
  - Considered for all patients with AA, given the frequency of phlebotomy, transfusions, and administration of therapeutic medications (PICC, Hickman, Mediport)
- Blood transfusions
  - Irradiated -- prevent transfusion associated GVHD
  - Leukofiltered -- reduce viral infections and prevent alloimmunization
- Growth factors
  - May provide clinical benefit but do not induce disease remissions
- Infections
  - Granulocyte transfusions -- controversial
  - Antibiotics = important

**Relapsed or refractory?**

- NON Transplant options
  - Repeat ATG -- try rabbit if previously given horse -- response rates reported ~60% after 2nd dosing
  - ELTROMBOPAG
- Transplant really must be considered
  - Sibling transplant
  - Alternative donor transplant -- related or unrelated
- Clinical trials
  - Majority at present focus on transplant or combination with eltrombopag

**Eltrombopag**

- Thrombopoietic agonist that stimulates platelet production
  - Pill taken orally
  - Increases platelet production by increasing megakaryocytic differentiation and proliferation
- Previously FDA approved for low platelets in chronic ITP and Hepatitis C

**Eltrombopag**

**FDA approval 8/2014**

- Phase II study of IST refractory SAA pts
- 11/25 patients (44%) had a hematologic response in at least one lineage at 12 weeks
- 9 became plt independent
- 6 with Hb increase (only 3 TI)
- 9 increase ANC
- Minimally toxic
- Unclear durability; ? Cytogenetic abnormalities
Increased hematopoiesis
longer term follow up on total 43 patients

- No change in QoL metrics
- Toxicity profile favorable
- 8 pts developed clonal cytogenetic abnormalities during etrombopag therapy

Algorithm for initial management of SAA. In patients who are not candidates for a matched related HSCT, immunosuppression with horse ATG plus cyclosporine should be the initial

Summary for Aplastic Anemia

- Get correct diagnosis and move efficiently to treatment
- SAA can be treated with immunosuppressive therapy or transplant
  - BMT preferred for young patients with matched sibling donor
  - Horse ATG in combination with CsA preferred upfront therapy (over rabbit ATG)
    - Monitor for secondary PNH, MDS, leukemia post IST
- Options for refractory or relapse SAA
  - Etrombopag
  - Clinical trial
  - Unrelated and mismatched BMT for SAA in setting of clinical trial at specialized center

THANK YOU!