Not So Benign Hematology

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Disclosures

• Dr. Brodsky serves as a Scientific Advisory Board member to:
  – Alexion Pharmaceuticals
  – Achillion Pharmaceutical
  – Apellis Pharmaceuticals

• Grant funding: Alexion
Organization

- **Bone Marrow Failure**
  - Aplastic anemia
    - Is the era of IST coming to an end?
  - New complement inhibitors for PNH?

- **Thrombotic Microangiopathies**
  - aHUS
    - Modified Ham to distinguish aHUS from TTP
    - Do aHUS patients need lifelong therapy with eculizumab
Severe Aplastic Anemia

Definitive management

• Allogeneic bone marrow transplantation
• Immunosuppressive therapy
Acquired SAA is an Acute and Chronic Disease

Take Home:
Autoimmune attack on stem cells
Predisposes to clonal escape/malignancy
Severe Aplastic Anemia

• First line therapy
  – BMT
    • Matched sibling donor
    • Matched unrelated donor
  – IST (ATG/CSA)

• Refractory Disease (poor response/prognosis)
  – Eltrombopag
  – Alternative donor BMT
  – Androgens
  – Other IST
ATG/CSA: Late complications

Risk of relapse > 40% in responders
Risk of clonal evolution

30% failure-free survival
Refractory SAA
2yr mortality approaches 50% 

• Repeat IST
  – low response rate

• Eltrombopag

• BMT
  – usually from a MUD or alternative donor
Eltrombopag for Refractory SAA
Desmond et al, Blood 2014

• 43 patients with refractory SAA
  – 1st endpoint: response at 3mos. in at least 1 lineage
  – Response criteria (e.g., doubling of ANC, decrease in PRBCs)

• Results:
  – 17/43 (40%) at 3 mos
  – 9/43 (21%) met standard response criteria at 6 mos
  – 7/43 (16%) trilineage response

• Relapse: 3/17 (18%) responders within a year

• MDS: 8/43 (16%) within 1 year
Responses to eltrombopag by lineage.

43 patients
Just 17 remained on drug

Table 2. Characteristics of patients who evolved while on eltrombopag

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age (y)</th>
<th>Response</th>
<th>Baseline</th>
<th>At evolution</th>
<th>Time on eltrombopag (mo)</th>
<th>Dysplasia</th>
<th>Outcome</th>
<th>Time posttransplant (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>60</td>
<td>NR</td>
<td>46XY[20]</td>
<td>−7[20]</td>
<td>3</td>
<td>N</td>
<td>Died of progressive cytopoenias</td>
<td>N/A</td>
</tr>
<tr>
<td>19</td>
<td>20</td>
<td>NR</td>
<td>46XY[20]</td>
<td>−7[5][t(1;16)[3]/46XY[12]</td>
<td>3</td>
<td>N</td>
<td>Transplanted successfully</td>
<td>18</td>
</tr>
<tr>
<td>32</td>
<td>66</td>
<td>R</td>
<td>46XY[20]</td>
<td>46XYdel13q[2]/46XY[18]</td>
<td>9</td>
<td>N</td>
<td>Under observation</td>
<td>N/A</td>
</tr>
<tr>
<td>42</td>
<td>17</td>
<td>NR</td>
<td>No</td>
<td>+1,der(1;7)[4]/46XY[16]</td>
<td>3</td>
<td>N</td>
<td>Transplanted successfully</td>
<td>4</td>
</tr>
</tbody>
</table>

N/A, not applicable; NR, nonresponder; R, responder.
Reduced intensity haploidentical BMT with post-transplant Cyclophosphamide (CY)

- Mitigates GVHD

- Allows for greater use of alternative donors (haplo BMT)
  - No difference for engraftment or GVHD btw matched sibs and HLA-haplo identical donors

- Average person in US has >4 HLA haplo-identical donors
HLA Haplo-identical BMT for Refractory SAA
DeZern et al, Johns Hopkins

Marrow Infusion

GVHD Prophylaxis: Tacrolimus, MMF, & Post-HSCT Cy

Fludarabine 30 mg/m² IV daily
Cyclophosphamide 14.5 mg/kg IV daily
Cyclophosphamide 50 mg/kg IV daily
Thymoglobulin 0.5 mg/kg (day-9) & 2 mg/kg (day -8,-7)
Johns Hopkins Alternative Donor BMT for Acquired SAA

- **17 patients with refractory SAA** (median f/u 22 (range, 3-66) months
  - Median age: 27 range (11-69) yrs
  - 14 haplo, 1 MUD (9/10), 2 MUD (10/10)
  - 11 with documented clonal hematopoiesis (10 PNH clone, 2 karotypic)

- **Rapid engraftment:**
  - Median: ANC 19 days; Reds 25 days; plts 27 days
  - Day 60 chimerism 100% in all pts
  - No primary or secondary graft failure

- **Excellent Disease-Free Survival**
  - All 17 alive with KPS 100
  - Acute GVHD grade II-IV: 1/17 (5.8%)
  - Extensive Chronic GVHD: 0/17
  - Secondary clonal disease resolved in all cases

Eltrombopag
Just 7 of 43 Pts with Trilineage Response

DeZern et al, Biol Blood Marrow Transplant 2016, Epub ahead of print
Optimized Cord Blood and Haplo-identical Aplastic Anemia Transplantation (CHAMP)

Co-chairs:
- Amy DeZern, MD, MHS
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- Michael A. Pulsipher, MD

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- Joseph Antin, MD
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- Alyssa Ramirez
- Brent Logan, PhD
- Julie Talano, MD
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BMT-CTN 1502
Paroxysmal Nocturnal Hemoglobinuria

Biology

• Acquired Clonal Hematopoietic Stem Cell Disease

• *PIGA* mutation
  – *X*(p22.1)

• *PIGA* gene product necessary for 1\textsuperscript{st} step in the biosynthesis of GPI anchors

• PNH cells have deficiency or absence of all GPI anchored proteins
PNH
Pathogenesis of hemolytic anemia

- **CD59**
  - Membrane inhibitor of reactive lysis
  - Prevents incorporation of C9 into C5b-8; thus, MAC does not form

- **CD55**
  - Decay accelerating factor
  - Block C3 convertase

- Protect cells from complement-mediated destruction
Effects of Terminal Complement on RBCs and Clinical Consequences in PNH

Intact RBC

Complement Activation

Free hemoglobin in the blood from destroyed PNH RBC

Free hemoglobin is a nitric oxide scavenger

esophageal spasm, abdominal pain, male ED

Fatigue

Thrombosis ?

Renal Failure

Anemia/Transfusions
Lectin Pathway
- MBL, MASP, C4 + C2

Classical Pathway
- C1q, C1r, C1s
- C4 + C2
- C3 convertases: C4b2a, C3bBb
- C3b
- C5 convertases: C4b2a3b, C3bBb3b
- C5a
- Membrane attack complex (MAC)

Alternate Pathway
- C3
- Factor B + D

CD55

CD59
- C6, C7, C8, C9
- Eculizumab
- Membrane attack complex (MAC)
Lessons from Eculizumab Trials

- Safe
  - Mild side-effects
  - Increased risk for Neisserial infections (~0.5% per year)

- Effective
  - Decreases intravascular hemolysis
  - Decreases (>90%) or eliminates (70%) need for PRBC
  - Improves quality of life
  - Reduces the risk for thrombosis by >90%

Brodsky et al, Blood 2008, 111: 1840-47
Lessons from Eculizumab Trials – cont.

• **Drawbacks**
  – Lifelong therapy intravenous therapy
  – Cost (> 400K a year)
  – Some patients have a lot of extravascular hemolysis

• **Not as effective in patients with AA/PNH**
  – Does not treat bone marrow failure

• **Indications (classical PNH)**
  – Large PNH populations (>10% type III red cells, > 50% PNH granulocytes)
  – LDH > 2 x upper limit of normal
  – Retics > 3%
  – Severe symptoms (Thrombosis, Pain, dyspnea, transfusions etc)

Brodsky et al, Blood 2008, 111: 1840-47
Novel Strategies to Treat PNH

Eculizumab
ALXN1210
ALNCC5
Conversin

APL-2
RA101495
Atypical hemolytic uremic syndrome (aHUS)

- **Clinical Presentation**: MAHA, renal failure, and thrombocytopenia

- **Pathophysiology**: excessive activation of alternative complement pathway (APC)

- **Treatment**: Eculizumab -- Monoclonal Ab that blocks terminal complement activation (FDA approved 2011)

- **Diagnosis**: Clinical – must exclude TTP and typical HUS (shiga toxin)
  - Often leads to reluctance to initiate expensive therapy
Atypical Hemolytic Uremic Syndrome: excessive activation of the APC

1. Genetic loss of natural APC inhibitors
   - C3
   - C5
   - MAC

2. Uncontrolled complement activation
   - Systemic endothelial damage

3. Inflammation
4. Surgery
5. Pregnancy
6. Autoimmunity
Atypical hemolytic uremic syndrome (aHUS)

Suspected TMA
- ADAMTS13%
- shiga-toxin

Plasma exchange (x4-5)

Poor response and ADAMTS13%>10%

Consider aHUS diagnosis

Initiate eculizumab treatment

Adapted from Cataland SR, Wu HM. Blood Reviews. 2014
Modified Ham test in aHUS

Modified Ham Can Distinguish aHUS from TTP

Mutations in aHUS

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>42%</td>
</tr>
<tr>
<td>CFH</td>
<td>25%</td>
</tr>
<tr>
<td>CFH/CD46</td>
<td>8%</td>
</tr>
<tr>
<td>DGKE</td>
<td>8%</td>
</tr>
<tr>
<td>CFH/THBD</td>
<td>8%</td>
</tr>
</tbody>
</table>

aHUS on eculizumab
Eculizumab can be Discontinued in Some aHUS Patients

Approx cost 25K/dose (650K/yr)
Savings > $13 million

Decision points:
- Mutations
- Trigger
- Compliance

Labs
- Cbc, retic, LDH, comp, PBS
- 2 weeks post last dose
- Weekly x 4
- Biweekly x 2
- Monthly x 4
Take Home

• **SAA: IST vs BMT**
  – Exciting clinical trials of IST and BMT
  – BMT advancing faster; solves problem of relapse and clonality

• **PNH:**
  – Novel complement inhibitors under development
  – Precision medicine

• **aHUS:**
  – Modified Ham test distinguishes aHUS from TTP
  – Not all patients need lifelong eculizumab