Living with Aplastic Anemia

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The function of the bone marrow

<table>
<thead>
<tr>
<th>Bone Marrow Stem Cells Mature into Blood Cells</th>
<th>Mature Blood Cells and Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Function</td>
</tr>
<tr>
<td>-----</td>
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</tr>
<tr>
<td>Red Cells</td>
<td>Carry oxygen</td>
</tr>
<tr>
<td>Platelets</td>
<td>Prevent bleeding</td>
</tr>
<tr>
<td>White Cells</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Prevent bacterial infections</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
</tr>
<tr>
<td>Basophils</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms and signs of bone marrow failure

- Anemia
  - Fatigue, shortness of breath, racing heart
- Neutropenia
  - Fever, skin or nail infections, ulcers
- Thrombocytopenia
  - Bruises, nose bleeds, gum bleeding

A Case Study - I

- JW is a 52 year old previously healthy man who presents with fatigue, low-grade fevers, and a large bruise on his thigh
- Complete blood count demonstrates pancytopenia
  - Hgb 6.9 gm% (Normal 13.6 – 17.0)
  - Neutrophils 500 per cu mm (normal 3.6 – 10.5)
  - Platelets 22,000 per cu mm (normal 150 – 450)
- Referred for further evaluation

Bone marrow cellularity is an essential clue

- Pancytopenia
- Bone Marrow Cellularity
  - Hypercellular
  - Hypocellular
  - Acellular

Hypocellular bone marrow failure

- The Bone Marrow Biopsy
- The Possible Explanations
  - Normal Stem Cells
    - Inadequate supplies
    - Hostile environment
  - Damaged Stem Cells
    - Temporary
    - Permanent
  - A combination
A Case Study - II

- Vitamin B12 and folate levels normal
- Bone marrow biopsy 10% cellular without dysplasia in residual marrow tissue
- Cytogenetics: 46 XY [12 metaphases]
- Additional tests:
  - PNH
  - Chromosome breakage assay
  - Genomic sequencing
  - Flow cytometry

What is going on?

Immune system – marrow interactions

- A very rare disease (2 per million)
  - Compare to MDS (70 per million to 350 per million adults 60 – 69 years)
- Toxins or infections rarely identified
- A diagnosis of exclusion

Immune-Mediated Aplastic Anemia

Decision making process: SCT or IST?

Disease Features

- Newly diagnosed versus relapsed

Patient Features

- Age
- Sibling donor
- Health status

Preferences

- Salience of risks
- Short term goals
- Opportunity cost

Best Supportive Care - I

- Supportive care has contributed to a progressive improvement in survival in all patients
- Do not delay instituting optimal therapy waiting to see if there is a response to growth factors
- Limit transfusions in younger patients headed to SCT
- Regularly scheduled evaluations more accurate than waiting for symptoms

Best Supportive Care - II

- Neutropenia – risk of infection
  - Prophylaxis practice varies substantially
  - Avoid steroids: reduce risk of invasive fungal infections
- Anemia – fatigue, increased cardiac demand
  - Monitor response to red cell transfusions and identify meaningful trigger
- Thrombocytopenia
  - Trigger < 10,000 per microliter

What are the options?

- Anti-thymocyte globulin
  - Horse
  - Rabbit
- Cyclosporine A
- (Prednisone or other corticosteroids)
- Cyclophosphamide
- Alemtuzumab
- Danazol
- Hematopoietic growth factors
Living with Aplastic Anemia

IMMUNOSUPPRESSIVE THERAPY

Randomized trial of horse versus rabbit ATG

Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Horse</th>
<th>Rabbit</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Number</td>
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<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>58</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Age (mean, yrs)</td>
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<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>ANC (mean/cu mm)</td>
<td>408</td>
<td>356</td>
<td>NS</td>
</tr>
<tr>
<td>PMN clone &lt; 1%</td>
<td>35 (58%)</td>
<td>45 (68%)</td>
<td>NS</td>
</tr>
<tr>
<td>Response at 3 m</td>
<td>37 (62%)</td>
<td>20 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Response at 6 m</td>
<td>41 (68%)</td>
<td>22 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Clonal evolution</td>
<td>21%</td>
<td>14%</td>
<td>NS</td>
</tr>
<tr>
<td>Overall survival</td>
<td>96%</td>
<td>76%</td>
<td>NS</td>
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</table>

Survival Curves

Scheinberg P 2011 NEJM 365 430

Phase I/II trial of Eltrombopag and IST

Rationale for combined Rx

- Intensive immune suppressive therapy alleviates the T-cell mediated destruction of stem cells
- Hematopoietic growth factors encourage the stem cells to mature into peripheral blood cells

Rationale for TPO-mimetic

Phase I/II compared to prior experience

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<td>NS</td>
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<tr>
<td>PLT (mean/cu mm)</td>
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<td>18000</td>
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<td>80 (87%)</td>
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Phase I/II compared to prior experience

Townsley DM 2017 NEJM 376 1540

Life after IST

What are the events?

- Recurrence of immune-mediated aplastic anemia
- Emergence of “clonal disorder”
  - MDS
  - Acute Leukemia
- Other

What about people...

...who don’t benefit?

- Repeat IST
- Further evaluation for an alternative disorder
  - Emerging data on “late presentations” of constitutional mutations
- Allogeneic SCT
- Best supportive care

...who experience recurrent pancytopenia?

- Further evaluation for an alternative disorder
  - Emerging data on constitutional mutations and late presentations
- Tapered off of CSA?
- If AA – repeat IST, SCT?
- If MDS, Rx per standards

Neal S. Young Hematology 2013;2013:76-81

Townesly DM 2017 NEJM 376 1540
Recurrent cytopenias – late clonal disorder

Genomic sequencing and bone marrow failure
- Acquired mutations
  - Associated with MDS or AML
- Constitutional – present at birth
  - Current screen sequences 59 genes
- Late onset but constitutional – atypical features

Paroxysmal Nocturnal Hemoglobinuria
- Acquired mutations of the PIGA gene → increased sensitivity to complement-mediated lysis
- Clinical syndrome(s)
  - Unexplained hemolytic anemia
  - Unusual thrombosis
  - Bone marrow failure

PNH and bone marrow failure
- It is possible to detect PNH clones in up to 70% of patients with bone marrow failure (including AA or MDS)
- The clone is less than 1% in the majority
- Overtime the clone may...
  - Expand
  - Persist
  - Disappear
- The clinical significance remains undetermined
# Pure Red Cell Aplasia

## Clinical presentation and Rx
- **“Isolated Anemia”**
  - Absent or damaged erythroid precursors
- **Rx depends on cause:**
  - Thymoma – resection?
  - B19 – intravenous immunoglobulin
  - LGL – MTX?
  - Idiopathic – prednisone or cyclosporine

## Potential Causes
- **Constitutional**
  - Diamond-Blackfan Syndrome
- **Acquired**
  - In the setting of a chronic hemolytic anemia
  - Viral infection: parvovirus B19
  - Malnutrition
  - Thymoma
  - Idiopathic
  - Immune disorder: LGL