TREATMENT OF APLASTIC ANEMIA AND PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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Director of the Leukemia Program at the Ottawa Hospital
September 29th 2012
DISCLOSURES
**DISCLOSURES**

<table>
<thead>
<tr>
<th>Role</th>
<th>Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant for</td>
<td>Celgene, Novartis, Pfizer,</td>
</tr>
<tr>
<td>Speaker Bureau</td>
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<tr>
<td>Grant/Research support</td>
<td>Celgene, Roche, Novartis</td>
</tr>
<tr>
<td>Stockholder</td>
<td></td>
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<tr>
<td>Honoraria</td>
<td>Celgene, Pfizer, Merck,</td>
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<tr>
<td></td>
<td>Novartis</td>
</tr>
<tr>
<td>Employee</td>
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OBJECTIVES

- To understand the role of the immune system in
  - Aplastic Anemia
  - Paroxysmal nocturnal hemoglobinuria

- To understand the tools in the treatment of these disease

- To understand how these tools are used and affect these diseases
Normal Bone Marrow

Aplastic Bone Marrow

ASH Image Bank
Review Background Aplastic Anemia

- Inherited
  - Fanconi’s anemia
  - Dyskeratosis Congenita
  - Diamond-Blackfan Anemia
  - Schwachman-Diamond Syndrome
  - Congenital neutropenia

- Acquired
  - Infections
  - Toxins/chemicals
  - Medication
  - Immune
Basics of the Immune System

- All cells made in the bone marrow
- T-cells get “educated” in the thymus
- In aplastic anemia T-cells appear to be directed against early blood cells
  - Initiating event is not clear.

http://www.the-immune-system.org/images/immune-system.jpg
ACQUIRED APLASTIC ANEMIA

- After ruling out other etiologies
  - Usually immune
  - 2/1 000 000
  - Then decide on severity
    - Mild, severe, very severe
**Grading of AA**

- **Mild**
  - Hypocellular marrow

- **Severe**
  - Bone-marrow cellularity < 25% and
    - neutrophil count < 0.5x 10^9/L
    - platelet count < 20x10^9/L
    - and absolute reticulocyte count 60x10^9/L.

- **Very severe**
  - neutrophil count <0.2x10^9/L
MILD AA

- Monitor for symptoms
- May not need any therapy
- Transfuse
- Look for any exacerbating factors
  - Vitamins
  - Bleeding
  - Infections

- Specific therapy
  - Immune- suppression
SEVERE AND VERY SEVERE AA

- Always requires therapy
- Exacerbating factors
- Associated disorders
  - i.e. PNH, MDS,
- Specific therapy
  - Stem cell transplant
  - Immune suppression
STEM CELL TRANSPLANT FOR AA

- Replace the blood and immune cells with a donor’s
- Curative in large proportion from matched donor
- Limited to age <40
- Complicated by graft vs host disease 20-40%

Gupta V. Haematologica 2010;95(12);2
Immune-suppression: Antithymocyte globulin (ATG)

- Anti-immune system product
- Created in either horse or rabbits.
- Pieces of thymus from donors undergoing cardiac surgery
- Injected into rabbits
- Serum is collected and prepared for use

- Many targets identified
- Mostly T-cells

Mohty M Leukemia (2007) 21;1387
How ATG Impairs the Immune System

1. T-cell depletion
2. B-cell depletion
3. Interfere with interaction between immune cells
4. Interfere with function of immune cells
5. Induction of certain immune cells

Mohty M. Leukemia (2007) 21;1387
**IMMUNE-SUPPRESSION:**

**ANTITHYMOCYSTE GLOBULIN (ATG)**

Side effects

- **Infusion-related**
  - Fevers, rigors, rash, low blood pressure

- **Serum sickness**
  - 1-2 weeks after infusion
  - Fever, rash, sore joints and muscles, ...

- Decrease in blood counts temporarily
**IMMUNE-SUPPRESSION: CYCLOSPORIN**

- Blocks signals in T-lymphocytes
- Dampening or interfering with their immune response.

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**Probability of Response to therapy**

- CSA + ATG (n=54), 77%
- CSA (n=61), 53%
- $p=0.02$

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**Failure of treatment**

- CSA + ATG (80%)
- CSA (51%)
- 20-30% relapse

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**Survival**

- CSA + ATG (n=54), 93%
- CSA (n=61), 91%

Marsh J Blood (1999) 93(7);2191
Immune-suppression: Cyclosporin

Side effects

- High blood pressure
- Kidney failure
- Hair growth
- Muscle aches
- ...
BMT vs. IST

Median age

- A = Immunosuppression, n=912, 68% = 23 (1 – 94)
- B = BMT, n=1567, 73% = 19 (1 – 67)

Locasciulli A. Haematologica 2007 92:11
Other forms of immune suppression: Alemtuzumab

- **Naive**
  - N=16
  - Response rate = 18%
  - 18% died early
  - DSMB stopped early b/c toxicity

- **Relapsed**
  - N=25
  - Response rate = 56%

- **Refractory**
  - N=54
  - Response rate = 37 and 33%
  - Alemtuzumab
  - antibody
  - Blocks lymphocytes
  - 90 patients
  - Median age = 40
  - 10 day treatment

Scheinberg P. Blood (2012) 119(2);345
Paroxysmal Nocturnal Hemoglobinuria

- Frequency: 1-2/million
- Median age: 40
- Median survival 10-15 years
PNH - SOME HISTORY

- 1882 – first description by Dr. Paul Strubing
  - 29-year-old with fatigue, abdominal pain, and severe episodes of dark urine at night (nocturnal paroxysms of hemoglobinuria)

- 1925 term paroxysmal nocturnal hemoglobinuria introduced

- 1938 – Ham’s test developed
  - Dr. Thomas Hale Ham and Co. discovered that the red cells were more fragile in an acidic environment

- 1954 alternate pathway of complement activation described
PNH - SOME HISTORY

- 1967 – Dr. William Dameshek
  - proposed that PNH, aplastic anemia, and acute leukemia were related
  - bone marrow injury might be initiating event

- 1980s GPI anchors were missing
  - 2 GPI proteins CD55 and CD59 regulators of the complement system

- 2004 Dr. Hillmen and Co. published
  - Eculizumab demonstrated effective
PNH - Etiology

Red cells have many proteins on its surface. Many are linked through GPI anchor.

PNH - Etiology

- Mutated PIGA gene

- PIGA essential for synthesis of a membrane anchor of many proteins (GPI-anchor).
PNH - ETIOLOGY

- Classic pathway
- Mannose-binding lectin pathway
- Alternative pathway

CD55

C3 convertase

C5 convertase

C5 convertase

Eculizumab

C5b

C5a

C5b

C6

C7

C8

C9

Membrane attack complex

Intrusion fluids

Complement proteins

Cytoplasm

Phospholipid bilayer
CD 55 and CD59 central proteins affected.

Results in uncontrolled complement activation
CONSEQUENCES OF PNH

- Hemolysis
  - Breakdown of red cells

- Muscle spasms
  - Abdominal pain, esophageal pain, erectile dysfunction
  - Nitric oxide depletion

- Thrombosis
  - Blood clotting
  - Unusual locations
  - Leading cause of death

- Bone marrow failure
  - No or dysfunctional precursors in the bone marrow (AA or MDS)
  - Low blood counts leading to transfusion dependence
## Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate of intravascular hemolysis</th>
<th>Bone marrow</th>
<th>Flow cytometry analysis</th>
<th>Benefit from eculizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Florid (markedly abnormal LDH often with episodic macroscopic hemoglobinuria)</td>
<td>Hypocellular with areas of erythroid hyperplasia and normal or near-normal morphology</td>
<td>Large (50–100%) population of GPI-AP-deficient PMNs</td>
<td>Yes</td>
</tr>
<tr>
<td>PNH in the setting of another bone marrow failure syndrome</td>
<td>Mild (often with minimal abnormalities of biochemical markers of hemolysis)</td>
<td>Evidence of a concomitant bone marrow failure syndrome</td>
<td>Moderate (25–50%) population of GPI-AP-deficient PMNs</td>
<td>Typically no, but some patients in this subcategory have clinically significant hemolysis and may benefit</td>
</tr>
<tr>
<td>Subclinical</td>
<td>No clinical or biochemical evidence of intravascular hemolysis</td>
<td>Evidence of a concomitant bone marrow failure syndrome</td>
<td>Small (&lt;25%) population of GPI-AP-deficient PMNs</td>
<td>No</td>
</tr>
</tbody>
</table>

Parker C. Blood (2005) 106;3699
TREATMENT APPROACH

- Symptomatic treatment
- Specific treatment
SYMPTOMATIC TREATMENT

- low blood counts
  - Transfusions
  - Folic acid

- thrombosis
  - Anticoagulation

- hemolysis
  - Steroids
  - Androgens
  - Eculizumab
SPECIFIC THERAPIES

- Hemolysis
  - Eculizumab

- Bone marrow failure
  - Immune suppression
  - Stem cell transplant
Marrow Failure Immune Therapy

- Similar approach to AA
- Higher responders to immune therapy than those without PNH clone
Bone marrow transplant

N=211

Survival

Years since transplant

Peffault de Latour R. Haematologica (2012) Epub
OS for different indications

OS after thrombosis
OS for aplastic anemia

Survival

<table>
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<tr>
<th></th>
<th>O/N</th>
<th>HR (95% CI)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Non-transplanted</td>
<td>2/30</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Transplanted</td>
<td>10/30</td>
<td>4.0 (0.9 - 18.9)</td>
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</table>

# at risk

<table>
<thead>
<tr>
<th></th>
<th>Transplanted</th>
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<tbody>
<tr>
<td>30</td>
<td>no</td>
</tr>
<tr>
<td>30</td>
<td>yes</td>
</tr>
</tbody>
</table>
**Eculizumab**

- Antibody targeted to C5
- Reduces rate of hemolysis and transfusions

**Cautions**
- Headaches
- Neisseria infections
- Effective for hemolysis (classic PNH)
- Expensive
- Therapy is lifelong
Eculizumab

- Based on work over a decade prior
- 2006 TRIUMPH study
  - Randomized study
  - Reduced hemolysis
  - Reduced transfusion requirements
  - Improved fatigue
- 2008 SHEPHERD study
  - Evaluated long-term safety and efficacy
  - Not randomized
  - Less stringent entry criteria

Brodsky RA. (2008) Blood 11;1840
TRIUMPH – results - LD

![Graph](image-url)

- **Lactate Dehydrogenase Level (U/liter)**
- **Week**: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26
- **Screening period**: 0
- **Placebo**
- **Eculizumab**

*P < 0.001*
TRIUMPH – results – time to need for first transfusion.
TRIUMPH – results - FATIGUE

The graph shows the change from baseline in fatigue score over 26 weeks for two groups: Eculizumab and Placebo. The Eculizumab group shows an increase in fatigue score, while the Placebo group shows a decrease. The error bars indicate the variability in the data.
THROMBOSIS

- One of the major problems in PNH
  - 40% incidence

- Rate reduced significantly on eculizumab
  - 5.6 compared to 0.8 events/100 patient years
LONG-TERM SURVIVAL

Kelly RJ Blood (2011) 117;6786
CONCLUSIONS

- AA and PNH
  - Treated based on understanding the immunological basis of the disease
  - Attack different aspects of the immune system
  - Treatment are improving with time
  - More effective treatment are competing with stem cell transplants
TREATMENT BASED ON CLASSIFICATION

- Subclinical PNH
  - MDS or AA
  - PNH clone <1%
  - No specific PNH treatment
  - Appear to respond better to immunosuppressive therapy.
TREATMENT BASED ON CLASSIFICATION

- PNH in the setting of another BM failure syndrome
  - Again no specific PNH therapy
  - Treatment directed at underlying marrow failure syndrome (i.e. AA or MDS)
    - Allogeneic stem cell transplant
    - Immunosuppressive therapy.
TREATMENT BASED ON CLASSIFICATION

- Classic PNH
  - Large clone (>50%)
    - Hemolysis, elevated LD, hemoglobinuria
    - Lethargy, malaise
  - Treated with eculizumab
  - +/- anticoagulation
  - Treatment of any other causes for cytopenias (i.e. vitamins, bleeding, infections, other medications...)
  - +/- danazol
  - +/- steroids
  - +/- splenectomy
To do

- Understand alemtuzumab study
- History of AA treatment
- NEJM editorial
- Organize