Objectives

- To give a general overview of the diagnosis and pathogenesis of aplastic anemia (AA)
- To give a brief historical overview of AA
- To present the updates on efficacy of pharmacologic therapies for AA
- To present the common side effects encountered with specific pharmacologic therapies used in AA

Overview

Epidemiology of AA

- 0.4 per 100,000 individuals per year
- 2-3 fold higher in Asia

Decision to treat

Based on Disease Severity

Moderate AA

1) ANC < 0.5 x 10^9/L
2) BM cellularity < 30%
3) No other causes of anemia

Severe AA

1) ANC < 0.1 x 10^9/L
2) BM cellularity < 20%
3) Other causes of anemia

Very Severe AA

1) ANC < 0.1 x 10^9/L
2) BM cellularity < 10%
3) Other causes of anemia

Natural Disease History by Disease Severity without treatment

IAA and vAA

Inherited AA

Acquired AA

Causes of Aplastic Anemia

- Idiopathic Aplastic Anemia
- Secondary Aplastic Anemia
- Infection
- Radiation
- Chemotherapy
- Idiopathic Myelofibrosis
- Other Myeloid Dysplastic Disorders
- Drug-Induced Aplastic Anemia
- Idiopathic TTP

Inherited Aplastic Anemia

- Fanconi anemia
- Dyskeratosis congenita
- Severe combined immunodeficiency syndrome
- Reticular dysgenesis
- Amegakaryocytic thrombocytopenia
- Familial aplastic anemia
- Pelz-Baumgartner syndrome
- Nonhematologic syndromes (Down, DUBowitz, Seckel)
Overview

How to treat AA?

Severe AA or Very Severe AA

Age <40 years old
With Matched Sibling Donor
Age >40 years old
No Matched Sibling Donor

Bone Marrow Transplant
Immunosuppression

Historical Perspective

1888
Paul Ehrlich described the first case of Aplastic Anemia

1899
Anti-thymocyte globulin (ATG) first described by Metchnikoff

Non-Transplant Pharmacologic Options

Non-Transplant Pharmacologic Treatments (AAT)

Anti-Thymocyte Globulin / Anti-Lymphocyte Globulin

- Polyclonal purified IgG fraction of sera from animals like rabbit, horses or fetal calf that are immunized with human thymocytes or T cell lines
- Mainstay in the treatment of severe AA or very severe AA
- Combined with cyclosporine or tacrolimus for the treatment of AA
- Results in 70-80% overall response rate in the frontline setting
- Can be used in the salvage setting
- Available as rabbit or horse

ATG + Cyclosporine

Mechanism of Action

A TCR
B CD28
C T cells
D CD28
E T cells
F Treatment Options
G Cytokine Release
H Effector Mechanism
I Stem cells
J Cellular Damage
K Bone Marrow Treatment
L Immunosuppression
M T cells
N Effector T cells
O Antigenic Peptide
P MHC I
Q MHC II
R B cells
S Immunosuppression
T Antigen Presenting Cells
U Monocytes
V T cells
W B cells
X T cells
Y Stem cells
Z Vascular Endothelial Cell
AA Endothelial Cells
BB Aplastic Anemia
CC Bone Marrow
DD Aplasia
Non-Transplant Pharmacologic Treatments (sAA)

How can we improve these results?

Strategies Employed
1) Use a different ATG
2) Add Additional Agents
3) Use a completely different Agent/Pathway

How can we improve these results?

Try a Different ATG

Non-Transplant Pharmacologic Treatments (sAA)

Rabbit Anti-Thymocyte Globulin (ATG) – Relapsed/ Refractory setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of AA</th>
<th>Median Age (y)</th>
<th>Other Treatment Schema</th>
<th>Dose</th>
<th>Response Rate</th>
<th>Survival % (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frickhofen N et al. Blood. 2003</td>
<td>ATG Alone</td>
<td>50-70</td>
<td>GM-CSF (20 µg/kg/d)</td>
<td>2.5 mg/kg D1-5 D</td>
<td>65% relapsed</td>
<td>100% of patients remained free of relapse at 3 yrs.</td>
</tr>
<tr>
<td>Di Bona E. et al. BJH. 1999</td>
<td>ATG + CsA</td>
<td>21 (2-67)</td>
<td>CsA 5 mg/kg PO D1-180</td>
<td>3.5 mg/kg D1-5 D</td>
<td>73% refractory</td>
<td>93% (30 mos)</td>
</tr>
</tbody>
</table>

Which ATG is better? Horse ATG or Rabbit ATG?

Non-Transplant Pharmacologic Treatments (sAA)

Horse ATG vs Rabbit Anti-Thymocyte Globulin

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Median Age (y)</th>
<th>Treatment Schema</th>
<th>Dose</th>
<th>Response Rate</th>
<th>Survival % (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atta EH et al. Ann Hematol. 2010</td>
<td>Frontline Retrospective</td>
<td>34 (2-71)</td>
<td>EATG</td>
<td>12 mg/kg/day x 5 D</td>
<td>58%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Arm 1=hATG
Arm2=hATG + CsA
Arm3=hATG+rhuGM-CSF/rhu-EPO
Arm4=rATG+rhuGM-CSF/rhu-EPO

All patients received stanozolol/ testosterone propionate

Arm1=12 mg/kg/day x 5 D
Arm2=CsA 5 mg/kg/D x 6 mos and maintenance 2.5 mg/kg/D x 6 mos

Arm †
Arm4 5 mg/kg/D IV D1-5 D

ORR
Arm1=58%
Arm2=79%
Arm3=73%
Arm4=53%

5 yr act survival
Arm1=58%
Arm2=81%
Arm3=80%
Arm4=66%

† rhuGM-CSF- 5 µg/kg/D SC started on Day31 was administered 3 days a week for the first month, 2 days/ week for the 2nd month, 1 day/ week during the 3rd month

rhuEPO 100 units/kg/D IV x 3 days/ week x 1st month, 2 days/ week x 2nd month, 1 day/ week x 3rd month

Horse ATG vs Rabbit Anti-Thymocyte Globulin

A. Comparison of Treatment Responses between 4 treatment arms

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>IST regimen</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>HR (%)</th>
<th>The overall response rate (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>33</td>
<td>EATG</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td>37.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Group 2</td>
<td>47</td>
<td>EATG+CsA</td>
<td>20</td>
<td>8</td>
<td>10</td>
<td>57.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Group 3</td>
<td>20</td>
<td>EATG+rhuGM-CSF/rhu-EPO</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>26.5</td>
<td>0.048</td>
</tr>
<tr>
<td>Group 4</td>
<td>32</td>
<td>ATG + rhuGM-CSF/rhu-EPO</td>
<td>10</td>
<td>7</td>
<td>15</td>
<td>53.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Non-Transplant Pharmacologic Treatments (sAA)

**Horse ATG vs Rabbit Anti-Thymocyte Globulin**

B. Overall Survival by Kaplan Meier Estimate of 4 treatment arms

- **12 months actuarial survival**
  - Arm 1 = 70%
  - Arm 2 = 91% (*p* = 0.01 vs 1)
  - Arm 3 = 83% (*p* = 0.2 vs 1)
  - Arm 4 = 78% (*p* = 0.4 vs 1)

- **60 months actuarial survival**
  - Arm 1 = 58%
  - Arm 2 = 81% (*p* < 0.001 vs 1)
  - Arm 3 = 80% (*p* = 0.002 vs 1)
  - Arm 4 = 66% (*p* = 0.505 vs 1)


Afable M et al. Haematologica. 2011

Scheinberg et al. NEJM. 2011

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**Non-Transplant Pharmacologic Treatments (sAA)**

A. Comparison of Treatment Responses, Early Mortality and Relapse Rate

<table>
<thead>
<tr>
<th>Type of ATG</th>
<th>H</th>
<th>Early Mortality (%)</th>
<th>Response (%) at 3 months</th>
<th>Response (%) at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>hATG</td>
<td>67</td>
<td>6</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>rATG</td>
<td>20</td>
<td>2</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

*p* value: 1.005 (ORR: hATG vs rATG)

Afable M et al. Haematologica. 2011

B. Predictive Biomarkers at 6 months

**Factor** | Odds Ratio (95% Conf. Interval) | P
---|---|---
PHH clone (no vs yes) | 9.25 (1.38 - 61.45) | 0.026

Afable M et al. Haematologica. 2011

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**Non-Transplant Pharmacologic Treatments (sAA)**

A. Comparison of Treatment Responses at 3 mos and 6 mos

<table>
<thead>
<tr>
<th>Response</th>
<th>Horse ATG (95% CI)</th>
<th>Rabbit ATG (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 3 m</td>
<td>37 (26 - 49)</td>
<td>41 (32 - 50)</td>
<td>0.002</td>
</tr>
<tr>
<td>At 6 m</td>
<td>41 (32 - 50)</td>
<td>56 (48 - 64)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Scheinberg P et al. NEJM 2011

**Non-Transplant Pharmacologic Treatments (sAA)**

A. Prognostic Grouping for Survival

<table>
<thead>
<tr>
<th><strong>Factor</strong></th>
<th><strong>Hazard Ratio (95% Conf. Interval)</strong></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;70 vs 70-79 vs &gt;80)</td>
<td>0.48 (1.51 - 7.90)</td>
<td>0.603</td>
</tr>
<tr>
<td>NCI (&lt;5 vs &gt;5 vs &gt;5 vs 100)</td>
<td>2.39 (1.18 - 4.57)</td>
<td>0.02</td>
</tr>
<tr>
<td>ALC (&lt;3 vs &gt;3 vs &gt;3 vs 100)</td>
<td>2.82 (1.10 - 7.19)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

The groups are not independent (see Table 4 and Figure 1). While the overall survival rate was not significantly different between the groups in this study, the number of deaths was significantly different between the groups in this study.
Common Side Effects associated with Cyclosporine therapy
1) High Blood Pressure
2) Kidney Problems (Renal insufficiency)
3) Thickening of the gums (gingival hyperplasia)
4) Peripheral neuropathy
5) Infections

Non-Transplant Pharmacologic Treatments (sAA)

Add New Agents

Mycophenolate Mofetil
- Blocks proliferation of activated T cells by inhibition of inosine monophosphate Dehydrogenase (IMD)
- Has been used as a kidney sparing immunosuppressant as an adjunct to CsA in renal and other solid organ transplantation
- May reduce tolerance to allografts
- Dose tested in phase II single arm trial in the NIH is 600 mg/m² PO once daily starting on Day 1 for 18 months. This was given in conjunction with iATG + CsA.

Scheinberg P. et al. JAMA 2005

Mycophenolate Mofetil

Add New Agent

SIROLIMUS
- Inhibits the mammalian target of rapamycin (m-TOR) pathway
- May work through a non-calcium dependent calcineurin inhibitor
- Dose tested in phase III randomized trial in the NIH is 2 mg PO once daily starting on Day 1 for 6 months.
- Associated with hyperglycemia and hypercholesterolemia

Virus
Unknown Antigens
Activated TCR
Effector Mechanisms

Non-Transplant Pharmacologic Treatments (sAA)

Try New Non-ATG based Treatments

Non-Transplant Pharmacologic Treatments

Alectuzumab (Campath) – Frontline setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Descr</th>
<th>Median Age (y)</th>
<th>Additional Treatment</th>
<th>Dose</th>
<th>Response Rate (%)</th>
<th>Survival % (meds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraham I. et al. 2010</td>
<td>RIT-ATG AM</td>
<td>60</td>
<td>14 days for rITG</td>
<td>13</td>
<td>60%</td>
<td>82%</td>
</tr>
<tr>
<td>Chevret S. et al. 2010</td>
<td>RIT-ATG AM</td>
<td>57</td>
<td>14 days for rATG</td>
<td>13</td>
<td>60%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Alectuzumab
- Selectively kills CD-52 bearing cells via ADCC and complement mediated lysis
- CD-52 is a GPI linked molecule expressed in T, B, and monocytes
- Drug can be given subcutaneously
- CMV reactivation is a concern during therapy

Alectuzumab

How can we improve these results?

82% at 2yrs
Commonly used alkylating agent for chemotherapy and immunosuppression.

- used for AA in 10 patients in Johns Hopkins 45 mg/kg/D x 4 days (3 of these received concomitant CSA)
- High mortality and morbidity rate particularly with invasive fungal infection was seen in a randomized trial performed by the NIH leading to premature closure of the study
- The most frequently used conditioning regimen before BMT for AA.

**Cyclophosphamide**

- **Mechanism of Action**
  - Alters growth and division of immature hematopoietic cells
  - Induces apoptosis through DNA alkylating effect
  - Inhibits cell cycle progression

- **Treatment Options**
  - Non-Transplant Pharmacologic Expanded Effector
  - Cell Cycle Contact
  - Effector Mechanism
  - Apoptosis

- **Survival**
  - ORR = 84%

**Relapsed/Refractory AA**

**Rabbit Anti-Thymocyte Globulin (rATG) – Relapsed/Refractory setting**

**Cyclophosphamide (Cytoxan) Alone – Salvage setting**
**Eltrombopag**

- Thrombopoietin agonist that stimulates platelet production
- A drug currently FDA approved for the treatment of Chronic ITP and hepatitis C associated thrombocytopenia
- Mechanism of Action of Thrombopoietin agonists (AMG-531 and Emtrombopag)

**Thrombopoietin Agonist (Mechanism of Action)**


**Eltrombopag (Platelet Response)**

Olnes M. et al. *NEJM.* 2012

**Eltrombopag (Hemoglobin Response)**

Olnes M. et al. *NEJM.* 2012

**Eltrombopag (Neutrophil Response)**

Olnes M. et al. *NEJM.* 2012

**Eltrombopag (Side Effect Profile)**

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>N (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>URTI</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Fever with (+) cultures</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Shingles</td>
<td>1 (4)</td>
</tr>
<tr>
<td>C.diff coliA</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>N (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Weakness</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Myositis</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

**Side Effects N= (% of patients)**

URTI 3 (12)
Fever with (+) cultures 3 (12)
Fever w/o positive culture 3 (12)
Musculoskeletal pain 2 (8)
Orthostatic Hypotension 2 (8)
Shingles 1 (4)
C.diff coliA 1 (4)
Abdominal pain 1 (4)
Nausea and vomiting 1 (4)
Viral hepatitis 1 (4)
Liver enzymes 1 (4)
Gingival bleeding 1 (4)
Depression 1 (4)
Weakness 1 (4)
Myositis 1 (4)
**Special Considerations**

- Cyclosporine Taper
- Addition of Growth factors
- Moderate Aplastic Anemia

**Growth Factors**

- Japanese study of 101 patients with uAA
- Randomized study: median follow-up time of 52 mos
- tATG + CsA vs tATG + CsA + 8 CSF
- Results:
  - No diff in infection or hybrid chimerism
  - No diff in survival or MDS/AML evolution
  - Increased risk of relapse in G-CSF arm

**Supportive**

**Cyclosporine Taper (slowly taper CsA)**

Cumulative incidence of relapse

<table>
<thead>
<tr>
<th>CsA Discontinuation</th>
<th>Cumulative probability of CsA Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>5%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**Daclizumab**

- Humanized monoclonal antibody
- Recognizes 55 kDa α-chain of heterodimeric IL-2 receptor
- Has been used in acute rejection in kidney transplantation
- Good toxicity profile.

**Moderate Aplastic Anemia**

**Daclizumab**

- Generalized erythematous pruritic rash

**Supportive**

**Moderate Aplastic Anemia**

**Daclizumab**

- ORR 6/16
- Survival % (mos)

**Daclizumab (Zenapax)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Median Follow-up time (y)</th>
<th>Additional Treatment</th>
<th>Dosage</th>
<th>Response Rate</th>
<th>Survival % (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman JA et al. Am J Hematol. 2002</td>
<td>2.5 years</td>
<td>None</td>
<td>1 mg/kg x 4 wk, 6 mo</td>
<td>98% (21 mo)</td>
<td></td>
</tr>
</tbody>
</table>

**Supportive**

**Moderate Aplastic Anemia**

**Daclizumab**

- Skin rash, esophagitis, pruritus, rash and also some cases of death.
Conclusion

- ATG remain the standard approach for the management of severe AA although newer agents like Alemtuzumab are showing great promise.

- Horse ATG in combination with cyclosporine is superior to rabbit ATG in combination with CsA in the management of newly diagnosed severe AA.

- Re-treatment with ATG can successfully salvage patients with Aplastic Anemia who previously failed a prior course of ATG.

- Cyclophosphamide show promise as a therapeutic agent but has not gained popularity because of the bad reputation (high mortality rate) it received in the past. It is associated with prolonged cytopenia. Improvement in supportive care management of AA including anti-fungals may allow for improvement in its safety profile.

- Eltrombopag is a thrombopoietin agonist that can lead to improvements in hemoglobin, platelet counts, and neutrophil counts in AA patients who have previously failed immunosuppressive agents.

Thank You