The Latest in Aplastic Anemia: Managing Your Disease and New Research

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Aplastic Anemia: Historical Prospective

- **1888**: aplastic anemia case first described by Paul Ehrlich in a case of a young pregnant female patient who died shortly after contracting an illness resulting in anemia, bleeding and infections
- **1904**: disease is given a name of aplastic anemia
Aplastic anemia: epidemiology

Rare disease
Incidence: 1-2/million in Europe, 0.6 cases per million in US
More common in Asia
Acquired or inherited bone marrow failure syndrome
Biphasic age distribution: 15-24 years and > 65 years of age
May evolve into other hematological disorders such as PNH, MDS or acute leukemia
Differential diagnosis of pancytopenia and a hypocellular bone marrow

- Hypocellular MDS/AML
- Hypocellular ALL - 1–2% of cases of childhood ALL
- Hairy cell leukemia
- Lymphomas
- Myelofibrosis
- TB infections
- Anorexia nervosa
# APLASTIC ANEMIA: SEVERITY

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Severe</td>
<td>BM cellularity &lt; 25% (or &lt; 50% if &lt; 30% of BM is hematopoietic cells)</td>
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<td>AND ≥ 2 of the following:</td>
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<tr>
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<td>• Peripheral blood neutrophil count &lt; $0.5 \times 10^9$/L</td>
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<td></td>
<td>• Peripheral blood platelet count &lt; $20 \times 10^9$/L</td>
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<tr>
<td></td>
<td>• Peripheral blood reticulocyte count &lt; $20 \times 10^9$/L</td>
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<tr>
<td>Very severe</td>
<td>As above, but peripheral blood neutrophil count must be &lt; $0.2 \times 10^9$/L</td>
</tr>
<tr>
<td>Nonsevere</td>
<td>Hypocellular BM with peripheral blood values not meeting criteria for severe aplastic anemia</td>
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AA: underlying cause

- Immune mediated destruction of stem cells
Definition

- the bone marrow produces too few of all three types of blood cells: red cells, white cells, and platelets (pancytopenia)
Bone marrow biopsy: Aplastic Anemia

Figure 1. Bone marrow biopsy specimens from A) a healthy patient and B) a patient with aplastic anemia.
DEFINITION

• Pancytopenia (low red cells, platelets, white cells) + hypocellular bone marrow
Types of Aplastic Anemia

- **Constitutional** (Fanconi anemia, dyskeratosis congenital)
- **Acquired**
  - Idiopathic
  - Secondary: radiation, drugs + toxins, viruses (EBV, HIV, Parvovirus, Hepatitis), autoimmune, PNH, pregnancy
- **Iatrogenic** (caused by treatment such as intensive chemo)
DRUGS THAT CAN CAUSE APLASTIC ANEMIA

- Linezolid, Chloramphenicol
- Indomethacin, naproxen, sulfasalazine, diclofenac
- Phenytoin, carbamazepine
- Chloroquine
- Thiazide diuretics, allopurinol
Clinical Presentation

- Fatigue
- Shortness of breath on exertion
- Easy bruising and bleeding (for example, nose bleed, gum bleeding, heavy menses, eye hemorrhages, blood in the stool, etcetera.)
- Petechiae (most commonly in the mouth or on the legs)
- Pallor
- Headache
- Fever due to infection
- Mouth sores due to low white cell count
Aplastic Anemia: treatment overview

- Supportive care: transfusions, antibiotics, growth factor support
- Immunosuppression – ATG + cyclosporine
- Stem cell/bone marrow transplant
Treatment Algorithm
Aplastic anemia: Supportive Care

- Blood products should be irradiated to prevent transfusion-associated graft-versus-host disease (GVHD) in patients who could proceed to transplantation.
- Blood products should also be filtered to reduce the incidence of viral infections.
- Transfusions from family members should be avoided, to decrease sensitization to potential bone marrow donors.
Immunosuppression (IST): ATG

- Safe but watch out for side effects
- Infusion reaction: fevers, chills, severe rigors, low blood pressure, anaphylaxis
- Usually in the beginning of the treatment
- Pre medications are important: Tylenol, Benadryl, steroids
- Response is not immediate, can take few months
Types of ATG: Horse vs Rabbit

Horse ATG

Rabbit ATG
### Hematologic Response

#### Table 2. Hematologic Response at 3 and 6 Months to Horse ATG and Rabbit ATG.

<table>
<thead>
<tr>
<th>Response</th>
<th>Horse ATG (N=60)</th>
<th>95% CI</th>
<th>Rabbit ATG (N=60)</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 3 mo</td>
<td>37 (62)</td>
<td>49–74</td>
<td>20 (33)</td>
<td>21–46</td>
<td>0.002</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>41 (68)</td>
<td>56–80</td>
<td>22 (37)</td>
<td>24–49</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Kaplan–Meier Curves of Overall Survival

A Data Censored for Stem-Cell Transplantation

Survival (%)

P=0.04

Days

No. at Risk
Horse ATG  60  39  23  10
Rabbit ATG  60  34  12  1
Horse vs Rabbit ATG

- Randomized prospective trial with 120 patients
- Response at 6 months (68% vs 37%), and overall survival at 3 years (96% versus 76%) was largely in favor of horse ATG
- 4 death in the horse and 14 death in the rabbit ATG group
IST: Bottom Line

- Horse ATG + Cyclosporine is a preferred first line of immunosuppression
- Rabbit ATG still has a role in a relapsed/refractory setting

Thank you
ATG/Cyclosporine: IS IT THAT GOOD?

- Although 66% responses are seen promptly after therapy, only 60% of such population shall be in true remission.
- Remaining patients eventually either relapse or blood counts are dependent on cyclosporine administration.
- Other attempts to increase response rates by intensifying immunosuppression have failed.
- There is also an incidence of secondary clonal diseases. At 5 years, 10 to 15% of patients will develop MDS or PNH.
A dose of 5 mg/kg orally per day for 6-12 months is considered as standard followed by tapering.

Tapering should be very slow (less than 10% of the dose/month) for at least 1 year, to minimize the risk of relapse.

The risk of relapse is in the order of 30% and is not easily predictable.
IST: High dose Cyclophosphamide

- Given at a dose of 50mg/kg/day for 4 days
- The response rates after high-dose CY are 70% and there appears to be slightly lower risk for relapse and secondary clonal diseases, but this has not been proven in a randomized controlled trial.
- High CY is less effective for patient with refractory SAA, but about 25% of patients still respond with durable hematopoietic remissions.
Problems with IST

- Delayed blood count recovery – 2-6 months
- Relapse - (25-40% at 5 years)
- Primary refractory to immunosuppression – 10-20%
- Clonal evolution to PNH – 25% have clone at diagnosis
- Clonal evolution into MDS/AML – 20-25% at 10 years
- NOT curative
APLASTIC ANEMIA: WHAT'S NEW?

• Eltrombopag – thrombopoietin receptor agonist
• 2014 – approved for SAA after an insufficient response to initial IST
• Single agent – 40-50% recovered blood counts at times involving more than one cell line
• Achievement of transfusion independence
• Increase in marrow cellularity and stem cells suggested recovery to a more functioning marrow
THE EBMT RACE STUDY
Study flow-chart

Initial treatment

3 month evaluation: primary endpoint

6 month evaluation: stop eltrombopag
Possible cross-over (standard arm only)

12 month evaluation:
Relapse: possible eltrombopag re-starting (investigational arm only)

24 month evaluation: end of the study
What else can we do to improve?
| Cohort 1 (n=30) | EPAG d14 – 6 mos | OR | 23 (77) | 24 (80) |  
|                |                 | PR | 18 (60) | 14 (47) |  
|                |                 | CR | 5  (17) | 10  (33) |  
| Cohort 2 (n=31) | EPAG d14 – 3mos | OR | 24 (77) | 27 (87) |  
|                |                 | PR | 16 (52) | 19 (61) |  
|                |                 | CR | 8  (26) | 8   (26) |  
| Cohort 3 (n=27) | EPAG d14 – 6mos | OR | 19 (90) | 12 (92) |  
|                |                 | PR | 9  (43) | 5   (39) |  
|                |                 | CR | 10 (48) | 7   (54) |  

*Evaluable as of 10/29/2015
Overall response (OR) = blood counts no longer meeting criteria for SAA
Partial response (PR) = blood counts not meeting criteria for SAA or CR
Complete response (CR) = ANC ≥1,000/μL, hemoglobin ≥10 gm/dL, and platelets ≥100,000/μL.
Eltrombopag

Promacta

• synthetic thrombopoietin-receptor agonist

• Faster recovery, better response rate with eltrombopag added to standard immunosuppression
Eltrombopag: refractory setting

- At least 24 weeks of EPAG administration in refractory SAA patients may be required to determine responsiveness to drug.
- Twenty of 40 (50%) responded at 24 weeks, 5/20 (25%) would have been deemed non-responders at 12 weeks, the endpoint of the prior study.
New Research Summary

- Eltrombopag associated with horse ATG plus cyclosporine in first line
- Increase in overall (at about 90%) and complete response rate (at about 40%)
- Leading to transfusion independence and excellent survival
- Best results observed when all drugs started simultaneously
- Incidence of clonal cytogenetic abnormalities to date compared favorably with IST alone
Indications for Hematopoietic Stem Cell Transplantation in North America 2005

- Allogeneic (Total N=7,880)
- Autologous (Total N=10,840)

Transplants

- Multiple Myeloma
- NHL
- AML
- Hodgkin Disease
- ALL
- MDS/MPD
- CML
- Aplastic Anemia
- Other Leuk
- Other Cancer
- Non-Malignant Disease
Severe Aplastic Anemia Overall Survival

Adult Patient Transplantation by Year of Transplant
Unrelated Transplants Facilitated by NMDP/Be The Match

(1987–2016)

Survival (%)

Survival rates for different years of transplant:
- 1987–2003 (n=185)
- 2004–2008 (n=263)
- 2009–2012 (n=220)
- 2013–2016 (n=321)

Log-rank p-value < 0.001

Source: CIBMTR®, the research program of NMDP/Be The Match
Allogeneic BMT

• Allogeneic hematopoietic stem cell transplantation (HSCT) from a matched sibling donor remains the treatment of choice for children and young adults (age less than 30 years)

• Bone marrow source of stem cells is thought to be best in aplastic anemia
Survival after Allogeneic HCT for Severe Aplastic Anemia, ≥18 Years, 2005-2015

- HLA Matched Sibling (n=1,427)
- Unrelated Donor (n=1,024)

p < 0.0001

Probability, %

Years

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Aplastic Anemia: Treatment Summary

Treatment for adults with acquired severe aplastic anaemia.

- **Age of patient**
  - ≤ 40yr
    - HLA identical sibling
      - Yes
        - ATG (horse)+CSA
      - No
        - ATG (horse)+CSA + G-CSF only as part of clinical study
    - No
      - HLA id sib BMT
        - Maintain on CSA while FBC rising, then very slow taper, often over one/more years
- > 40yr
  - ATG (horse)+CSA
    - Response at 4 months
      - Yes
        - 2nd ATG (rabbit/horse) + CSA
      - No
        - MUD available
          - Yes
            - Adequate performance status
              - Yes
                - MUD BMT
              - No
                - Supportive therapy
          - No
            - Options

- 1. 3rd ATG if previous response to ATG
- 2. CRP using novel IST
- 3. BMT using CRP with UCB
CONTACT INFORMATION

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Thank you!

- Questions?