Overview

• What is aplastic anemia?
• Causes of aplastic anemia
  • Important lab tests
• Non-transplant treatment options
  • Supportive care options

Aplastic Anemia: Current Thinking on the Disease, Diagnosis and Non-Transplant Treatment

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Overview

Neutrophils

• Also called: granulocyte, “poly”, PMN, “seg”

• Function: Fights infection (bacteria and fungus) by engulfing/eating them

• ANC: Absolute Neutrophil Count
  – White blood cell count (WBC) X % neutrophils

Neutrophils

• “neutropenia”: ANC <1,500

• Generally do not start to see increased infection risk until ANC falls below 1,000

• Generally, the lower the ANC, the higher the potential risk of infection.
  • Mild: 500-1000
  • Moderate: 200-500
  • Severe: <200

Images courtesy of Dr. Min Xu, Dept of Pathology
Seattle Children’s Hospital, Seattle, WA
Platelets

- Function: Help the blood to clot

Platelets

- Thrombocytopenia: platelet count <150,000
- Bleeding risk generally starts to increase when platelet counts fall below 100,000.
  - Bleeding risk
    - 100,000-50,000: Mildly increased
    - 50,000-20,000: Moderately increased
    - <10,000-20,000: Significantly increased
- Need to assess bleeding risk within clinical context (eg: surgery, risk of trauma, location of bleed)

Red blood cells

- Function: Carry oxygen from the lungs to other organs/tissues
- “Hematocrit” and “Hemoglobin” provide a measure of the red blood cells. Normal levels vary with age and gender.
- “Reticulocytes” are young, newly produced red blood cells

Aplastic anemia

Primary marrow disease
- Acquired
  - autoimmune
  - idiopathic
  - post-hepatitis
- Inherited
  - Fanconi anemia
  - Dyskeratosis congenita
  - Shwachman-Diamond syndrome
  - Aegakaryocytic thrombocytopenia
  - Diamond-Blackfan anemia
  - GATA-2
- Secondary
  - infection
  - medications
  - toxins
  - other disease

Severe Aplastic Anemia (Camitta criteria)

- Two of the following:
  - ANC<500 (<200=“very severe”)
  - Platelets <20,000
  - Low reticulocyte count (corrected for hemoglobin)
- Marrow cellularity <25%
- Moderate aplastic anemia: variable definitions

Laboratory tests

- Complete blood count (CBC) with differential
- Bone marrow biopsy
  - Cellularity
- Bone marrow aspirate
  - Morphology
  - Culture
  - Cytogenetics
Cytogenetic clones

Cytogenetics

Monosomy 7

Fluorescent in-situ hybridization (FISH)

Normal (2 copies) Abnormal (one copy)

Paroxysmal nocturnal hemoglobinuria (PNH)

- Clinical features:
  - hemolytic anemia (red blood cell destruction -> anemia)
  - thrombosis (blood clots)
  - aplastic anemia

PNH (cont)

- GPI anchors other proteins to the cell surface
- PNH cells are deficient in all GPI-anchored cell surface proteins (eg: CD59 and CD55, which protect cells from complement)
PNH

- Small clone size typically asymptomatic
- Unclear whether presence of small PNH clone affects outcomes
- Treatment approach for AA with asymptomatic PNH clone is generally the same

Diagnostic Workup

- Why should we test for inherited bone marrow failure syndromes?
  - Poor response to ATG/Cyclosporine (CyA)
  - Standard transplant regimens may be highly toxic
    * Require reduced intensity conditioning regimen
  - Inform donor choice
  - Family counseling (eg: cord blood banking)

Diagnostic Workup

- Look for clues to inherited bone marrow failure syndrome:
  - Clinical history
  - Family history
    * Low blood counts, malignancies at a young age, excessive toxicity with chemo/radiation, physical disorders
  - Physical exam

Laboratory tests

- Paroxysmal nocturnal hemoglobinuria
- Fanconi anemia (children, young adults)
- AST, ALT, GGT, bilirubin (liver)
- BUN, creatinine, electrolytes (kidney)
- Tests for infections
- Tests for immune/rheumatologic disorders
- HLA testing of patient and siblings
- Telomere length testing?

Telomeres

Telomeres shorten with age

Telomere length and AA

- Very short telomeres are associated with an inherited bone marrow failure syndrome (dyskeratosis congenita)
- Shorter telomere length:
  - Decreased response to ATG/CyA
  - Increased risk of relapse
  - Increased risk of clonal progression (MDS)

Scheinberg et al. JAMA 2010; 304: 1358-1364

When to treat?

- Severe or very severe aplastic anemia
- Transfusion-dependent cytopenias
- Note: Limited data on whether it is advantageous to treat patients with moderate AA. Some are stable and some improve spontaneously. Generally work up and observe.

BMT vs ATG/CsA?

- Survival
- Short-term versus long-term complications
- BMT is curative

ATG: Anti-thymocyte globulin

Higher response rates to horse ATG over rabbit ATG.


ATG: toxicities

1. During infusion: Fevers, shaking chills, rash/hives, low blood pressure, difficulty breathing
2. 2-3 weeks post-infusion: serum sickness. Fever, rash, pain in muscles/joints, abdominal pain/diarrhea, neurological symptoms
3. Blood counts typically fall for the first few weeks (require intensive transfusion support)
4. Immunosuppression
Cyclosporine (CsA): toxicities
- High blood pressure
- Kidney toxicity
- Low magnesium
- Increased body hair/facial hair
- Swollen gums
- Neurologic toxicities (eg: seizure)
- Immunosuppression

Major life-threatening complications of ATG/CsA
- Infection
- Fungus
- Bacteria
- Bleeding (eg: stroke)

Goal of ATG/CsA
- Blood counts often fail to return to normal
- Goals:
  - transfusion-independence
  - low risk of severe, life-threatening infections
- (Responses typically seen after ≈3-6 months after initiation of treatment. Some improvement may continue even 1 year post-therapy.)

Complications after ATG/CsA
- Failure to respond (refractory disease): 25-30%
- Relapse after initial response: 30%
- Clonal evolution (10-15% at 10 years)
  - Prognosis varies with specific cytogenetic clones

Pediatric aplastic anemia: >70% response to ATG/CsA
(Adults: 60-70% response rate)

Pediatric aplastic anemia: survival after ATG/CsA
(Adults: 70-80%)
**Upfront treatment**

Other immunosuppressive agents failed to improve response, relapse or clonal evolution:

- Sirolimus (Scheinberg et al. Haematologica. 2009; 94: 348-354)


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**G-CSF**

No benefit for hematologic response or survival in randomized prospective trial

Association with clonal evolution in some retrospective studies

Consider in patients with active infection, persistent fever, or persistently low ANC

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**Cyclosporin taper**


More rapid taper if serious side effects with CsA

Counts may continue to improve over long term

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**Treatment of relapse**

- Often responds to re-starting or increasing dose of cyclosporin

- May require re-induction with ATG/CsA or consideration of bone marrow transplant
Refractory AA
Persistence of severe AA 6 months following initiation of ATG/CsA
Consider unrelated donor bone marrow transplant
If no suitable donor, consider:
   Second round of ATG/CyA (30-50% response)
   High dose cyclophosphamide (on study protocol)

Alemtuzumab (Campath)
- Antibody directed against CD52 which is found on the surface of lymphocytes
- Used in autoimmune diseases, lymphoid cancers, and transplants
- Prospective trial at NIH (Scheinberg et al., Blood 2012; 119: 345-354)
  Hematologic response at 6 months:
  Treatment-naïve: 16 patients
  Non-responders to ATG/CsA: 27 patients
  Relapse after ATG/CsA: 25 patients

Responses to Alemtuzumab

![Bar chart showing responses to Alemtuzumab](chart)

Eltrombopag (Promacta)
- Oral medication, stimulates the thrombopoietin receptor (c-MPL) which is on the surface of megakaryocytes (which make platelets) and blood stem cells
- Olnes et al. NEJM 2012; 367: 11-19
- Treated 25 patients refractory to ATG/CsA for 12 weeks
  - 11 (44%) had significant improvement in at least one blood cell type (many multilineage)
    - 9 became independent of platelet transfusions
    - 3 became independent of rbc transfusions
    - 9 had improved neutrophil counts (median increase 1350)

High dose cyclophosphamide
- Comparable response rates compared to ATG/CsA
- Lower relapse rates and lower rates of clonal evolution?
- High rates of fungal infection
- Prolonged neutropenia and very delayed responses requiring intensive supportive care
- Currently recommended on investigational protocols

Supportive Care
Supportive care: anemia

- Transfusion support (red cells)
  - Indications: Symptomatic anemia (fatigue, exercise intolerance, rapid heart rate and breathing, headache, light-headedness, poor growth)
  - Risks:
    - Allosensitization: patient develops antibodies against the transfused red cells or platelets such that transfused cells are rapidly destroyed
    - Iron overload secondary to red cell transfusions
    - Initiation of subcutaneous deferasirox infusions
    - Oral iron chelating medication (Exjade) is now available
    - Transfusion reaction
    - Infection

Clinical Complications of Iron Overload

- Liver disease with fibrosis and cirrhosis
- Cardiac failure, arrhythmias
- Hypopituitarism:
  - Central hypogonadism
  - Growth hormone deficiency
  - Central hypothyroidism
- Poor growth
- Diabetes mellitus
- Primary hypothyroidism
- Primary hypogonadism
- Hypoparathyroidism

Supportive care: thrombocytopenia

- Transfusion support (platelets)
  - Indications: Symptomatic (bleeding, increased bruising)
    - Prophylaxis: prior to surgical procedures history of recurrent or serious bleeding

Key points:

- For bleeding, evaluate other potential causes (eg: vitamin K deficiency, liver dysfunction)
- Anti-fibrinolytic agents may be helpful (eg: Amicar)

Follow-up post-treatment

- Monitor blood counts
- Post-therapy bone marrow exam
- ?Regular bone marrow exams thereafter?
- Check marrow if blood counts progressively fall without apparent cause

Iron Chelation Therapies