Aplastic Anemia Update

Ron Paquette, MD
UCLA
Division of Hematology/Oncology

Aplastic Anemia - What is it?

- Disease affecting blood forming stem cells in the bone marrow
- Moderate to severely reduced blood counts involving at least 2 cell types (red cells, white cells, platelets)
- Decreased bone marrow cells without dysplasia, increased blasts, or chromosome abnormalities

What Causes AA?

- Rarely, inherited bone marrow disease (Fanconi’s anemia)
- Medications (all rarely)
  - Anti-inflammatory drugs (Indocin, Motrin)
  - Sulfur drugs (antibiotics, diabetes drugs, diuretics)
  - Anti-seizure drugs (Dilantin, Tegretol)
  - Rheumotropic drugs (gold, allopurinol)
- Direct injury to the bone marrow
  - Chemotherapy
  - Benzene and petroleum products
  - Radiation
- Hepatitis (not viral)
What Causes AA?

Immune destruction of bone marrow stem cells

- More common in people with certain type of immune cell protein (HLA-DR2)
- Increased killer lymphocyte populations (cytotoxic T lymphocytes) in the bone marrow
- Lymphocytes produce proteins that suppress bone marrow cell growth (interferon-gamma)
- Patients respond to immunosuppression

Classification

- Severe AA: any two criteria
  - absolute neutrophil count <500/µL
  - absolute reticulocyte count <20,000/µL
  - platelet count <20,000/µL
- Very severe AA: neutrophil count <200/µL
- Moderate AA: any two criteria
  - absolute neutrophil count <1200/µL
  - hemoglobin <8 g/dL with reticulocyte count <60,000/µL
  - platelet count <60,000/µL

Treatment Options

- Stem cell transplantation
- Immunosuppressive therapy
- Blood cell growth factors
Bone Marrow Transplantation

- Indicated for severe or very severe AA
- Initial treatment of choice for "younger patients"
- Survival 65%–80% at 10 years
- Risks
  - graft failure: 10%–15%
  - acute graft vs host disease: 20% grade 3/4
  - fatal infection or organ failure: ≤10%
  - chronic graft vs host disease: 20%–40%
  - late solid tumors: 10%

Immunosuppressive Therapy with Antithymocyte Globulin

- Antithymocyte globulin (ATG) is serum collected from horses after immunizing them with human T lymphocytes
- ATG 40 mg/kg/d x 4 doses is given IV, once daily
- Cyclosporine 5-12 mg/kg/d by mouth for >6 months
- Response: 60%–65%
- Survival 55%–60% at 7-11 years
- Risks
  - fatal infection/bleeding: 10%
  - AML or MDS: 10%–15% at 10 years
  - PNH: 10%
  - relapse: 35%–45%

White Blood Cell Growth Factors

- Granulocyte colony stimulating factor (Neupogen or Neulasta) and granulocyte-monocyte colony stimulating factor (Leukine) increase production of white blood cells by the bone marrow
- They can increase the neutrophil counts of some AA patients, but the likelihood of response is inversely proportional to the baseline neutrophil count
- They do not improve the response rates or survival of patients receiving immunosuppressive therapy
- They should not be used as the only treatment for patients
- They may benefit patients with active/recurrent infection
- Neupogen may increase the risk of MDS or AML when given over a prolonged period of time
What to Do if ATG Doesn’t Work

- Unrelated donor bone marrow transplantation
- Umbilical cord blood transplantation
- Second course of horse ATG
- Rabbit antithymocyte globulin (Thymoglobulin)
- Prolonged cyclosporine alone
- Experimental trials

Unrelated Donor Bone Marrow Transplantation

- Indication: severe AA that did not respond to immunosuppressive therapy
- Median age: 14 years (range 1–46 years)
- Conditioning: TBI/ATG/Cytoxan
- Survival: 57% at 2 years
- Prognostic variables (% surviving 2 years):
  - age ≤20 yrs (67%) vs >20 yrs (43%)
  - disease duration <1 yr (73%), 1–3 yrs (53%), >3 yrs (39%)

**Unrelated Donor Umbilical Cord Blood Transplantation**

- Umbilical cord blood (UCB) remaining after a baby is delivered contains enough stem cells to engraft children and small adults
- The stem cells are tested and stored until needed
- Unrelated UCB has been used successfully to transplant aplastic anemia patients
- Conditioning of the patient is similar as for unrelated adult
- **Advantages of UCB**
  - Lesser degree of tissue type matching with recipient than with adult stem cells
  - Ready availability, no delay for donor workup
- **Disadvantages**
  - Limited to small recipients
  - Higher rate of engraftment failure than using adult stem cells

**Salvage Therapy with Rabbit Thymoglobulin**

- Thymoglobulin is serum collected from rabbits after immunizing them with human T lymphocytes
- 22 AA patients who did not respond to ATG were treated
- Thymoglobulin 3.5 mg/kg/d x 5 doses is given by IV, once daily
- Cyclosporine 10 mg/kg/d by mouth in divided doses x 6 months
- Response: 30%
- Risks were similar to ATG


**Alemtuzumab in Aplastic Anemia**

- Monoclonal antibody that binds CD52, a protein present on T and B lymphocytes
- FDA approved to treat chronic lymphocytic leukemia
- 10 pts with severe AA treated
- Alemtuzumab given daily by SQ injection for 5 days
- Additional medications given:
  - Cyclosporine 1 mg/kg/d
  - Bactrim (antibiotic)
  - Valgancyclovir (antiviral)
- Responses: 4 complete, 2 partial
- Relapses occurred in half of the responders
- Side effects: viral infections

Risitano et al Blood 2008;112(11):381 (abstract1042)
### Alemtuzumab Clinical Trials in Severe Aplastic Anemia

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### Clinical Trials for Moderate Aplastic Anemia

- **Daclizumab (Zenepax)** is a monoclonal antibody that binds to a protein on T lymphocytes (interleukin-2 receptor) and blocks their activation.
- FDA approved for kidney transplant patients.
- Daclizumab is being given by IV every 2 weeks for 8 weeks (NIH).
- **Rituximab (Rituxan)** is a monoclonal antibody that binds to a protein on B lymphocytes (CD20) and kills them.
- FDA approved for Non-Hodgkin’s lymphoma patients.
- Rituximab is being given once weekly for 4 weeks (NIH).

### Late Complications of Immunosuppressive Therapy

- Many aplastic anemia patients treated with immunosuppression can go on to live normal lives.
- Some patients have late or delayed problems related to the aplastic anemia or its treatment.
- Knowledge of these potential problems can help to prevent or minimize their impact on health and quality of life.
Incomplete Response

- Approximately half of patients receiving ATG/CsA ultimately achieve a complete response.
- The remaining patients must continue to live with blood counts that are lower than normal.
- This should not cause chronic anxiety; the survival of patients experiencing a partial response is not different from that of patients who have a complete response.
- What is the minimal acceptable level of blood counts?
  - Platelet count >20,000/mcL without bleeding
  - Neutrophil count >500/mcL without recurrent infections
  - Hemoglobin ?

Falling Counts!

- What is causing it?
  - Relapse: 35-45% risk at 10 years
  - MDS or AML: 10-15% at 10 years
  - PNH: 10% risk at 10 years
- How much of a drop is important?
  - Traditionally 50% decrease from best response is used to define relapse, but I would take notice sooner
- What to do?
  - Bone marrow biopsy, flow cytometry for CD55/59

Risk Factors for Late Hematologic Complications

- Relapse of AA
- Cyclosporine withdrawal
- Pregnancy (19% risk)
- MDS/AML
  - Older age
  - Lack of response to immunosuppression
  - Use of G-CSF (especially monosomy 7)
Salvage for Relapsed Aplastic Anemia

- Second course of ATG/cyclosporine
  - consider for more severe disease
  - response: 50%–70%
- Restart cyclosporine alone if it was discontinued, or increase the dose
  - reasonable for early or partial relapse
- Stem cell transplantation
  - appropriate for severe disease
  - consider if pediatric patient, suboptimal initial response to ATG, or intolerance of immunosuppression

Kidney Insufficiency Due to Cyclosporine

- Prolonged cyclosporine administration is frequently required to optimize response, maintain response (25% of pts are CsA dependent), and prevent relapse
- Chronic cyclosporine causes progressive deterioration of kidney function in most patients
- Kidney insufficiency frequently necessitates CsA dose reduction that can increase relapse risk
- Therefore, the minimum effective dose of CsA should be used
- However, there are minimal data regarding the optimal therapeutic dose or blood level of CsA for aplastic anemia
- Doses from 2 to 5 mg/kg/day appear to be active
- Careful attention to blood pressure control may help to minimize kidney toxicity

Avascular Necrosis

- AVN is caused by high dose steroids used to prevent and treat serum sickness from ATG
- Incidence is approximately 20%
- Most commonly affects hips (head of femur), but can also affect shoulders or knees
- Progressive joint pains occur months or years after ATG
- Plain X-rays can detect advanced AVN
- MRI is most sensitive test
- Joint replacement is only effective treatment, but is reserved for advanced disease
Iron Overload

- Transfusions (>20–30 units) are associated with iron overload
- Iron overload can eventually (over years) cause cirrhosis, heart failure, diabetes or other hormone deficiencies
- Survival in low risk MDS patients is adversely affected by a high burden of iron; this is likely to be true for aplastic anemia as well
- Iron chelation therapy is usually initiated after the ferritin is over 1000 mg/dL
- Treatment continues until the ferritin is less than 1000 mg/dL
- Two drugs are available:
  - Deferoxamine (Desferal)
  - Deferasirox (Exjade)

Deferoxamine (Desferal)

- High affinity iron chelator
- Causes iron to be excreted in the urine
- Dosing
  - SQ dosing: 1-2 g over 8-24 hours
  - IV dosing: 50 mg/kg/d by continuous IV infusion
  - IM dosing: 0.5-1g qd
- Side effects
  - Abdominal discomfort
  - Decreased visual acuity, loss of color vision, cataracts
  - Hearing loss, ringing in ears
  - Increased susceptibility to fungal infections

Deferasirox (Exjade): Oral Iron Chelator

- Oral, dispersible tablet
- Taken once daily
- Highly specific for iron
- Iron excreted mainly in feces
  - < 10% in urine
Side Effects of Exjade

- Most common adverse experiences
  - GI: nausea (10%), vomiting (9%), abdominal pain (14%), diarrhea (12%)
  - Skin rash (8%)
  - Renal: creatinine more than 33% above baseline and above ULN (2.4%), proteinuria (19%); rare acute renal failure, some cases fatal.
  - Hematologic: neutropenia and thrombocytopenia have been rarely reported, mostly in patients with prior blood disorders
  - Vision problems or hearing loss in <1%.

- Safety monitoring
  - Serum creatinine monthly
  - Urinalysis for proteinuria monthly
  - LFTs monthly
  - Auditory and ocular testing at baseline and every 12 months

Conclusions

- Aplastic anemia patients can be treated successfully with several options
- Careful selection of initial and salvage therapies is important – risks and benefits of available options should be fully discussed
- Awareness of potential complications of treatment will often help to minimize toxicities
- Consulting a physician familiar with aplastic anemia can be beneficial
- Patient education is important in achieving a favorable outcome of aplastic anemia therapy