

## Aplastic Anemia Update

Ron Paquette, MD  
UCLA  
Division of Hematology/Oncology

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## 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

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## What Causes AA?

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

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## 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

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## Classification

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

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## Treatment Options

- Stem cell transplantation
- Immunosuppressive therapy
- Blood cell growth factors

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## 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%

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## 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 give by 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%

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## 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

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### 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

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### 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%)

Deeg, et al. *Biol Blood Marrow Transplantation*. 2001;7:208.

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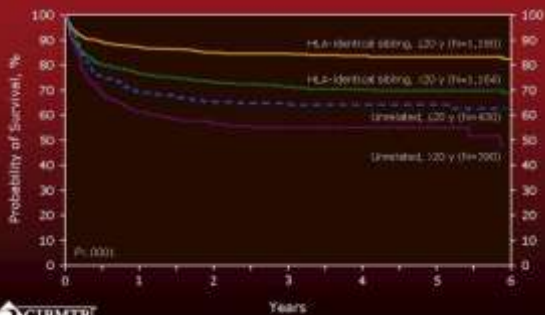
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**Probability of Survival After Allotransplants for Severe Aplastic Anemia, 1998–2006**  
By Donor Type and Age




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## 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

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## 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

Scheinberg P et al. *Br. J Haematol*, 2006;133:622.

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## 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)

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### Alemtuzumab Clinical Trials in Severe Aplastic Anemia

ATG vs Thymoglobulin vs Alemtuzumab for newly diagnosed patients

Thymoglobulin vs Alemtuzumab for patients who have not responded to ATG (refractory)

Alemtuzumab for patients who have had a relapse after ATG

All studies at the NIH  
More information at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

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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 NonHodgkin's lymphoma patients
- Rituximab is being given once weekly for 4 weeks (NIH)

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### 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

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## 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 ?

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## 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

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## 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)

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## 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

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## 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

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## 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

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## 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)

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## 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

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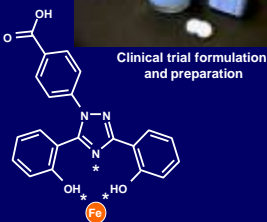
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## Deferasirox (Exjade): Oral Iron Chelator

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



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## 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

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## 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

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