Overview of Aplastic Anemia

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Overview of Aplastic Anemia

- Epidemiology
- Normal hematopoiesis
- Causes of bone marrow failure
- Presentation of aplastic anemia
- Evaluation
- Treatment

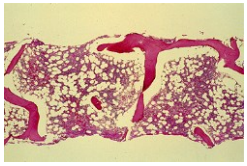
Epidemiology of aplastic anemia

- Incidence ~2 cases per million
- ~600 US cases annually
- 1:1 male:female incidence
- 50% cases in first 3 decades

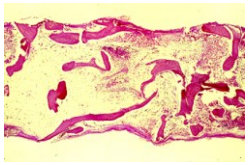
Normal hematopoiesis

- Bone marrow-derived hematopoietic stem cells are self-renewing and are responsible for production of normal blood cells (“hematopoiesis”):
  - White blood cells fight infection
  - Red blood cells carry oxygen to tissues
  - Platelets clot blood to prevent bleeding

Normal and aplastic bone marrow

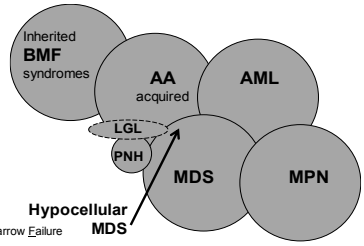


Normal bone marrow
30-70% cellularity



Aplastic anemia
<10% cellularity

Differential diagnosis of bone marrow failure



- Inherited Bone Marrow Failure
- Aplastic Anemia
- Acute Myeloid Leukemia
- Myelodysplastic Syndromes
- Myeloproliferative neoplasms
- Large Granular Lymphocytic leukemia
- Paroxysmal Nocturnal Hemoglobinuria

Inherited causes of bone marrow failure

- Fanconi anemia
- Dyskeratosis anemia
- Schwachman-Diamond anemia
- Amegakaryocytic thrombocytopenia
- Often associated with physical findings
- Typically (not always) diagnosed in childhood

Acquired causes of bone marrow failure

- Toxic insults
  - Chemotherapy, radiation, chemicals
- Idiosyncratic drug reactions
  - Antibiotics, anti-epileptics, non-steroidals
- Infections
  - Viral (HIV/EBV/HBV/CMV), sepsis
- Nutritional deficiencies
  - B12/folate/copper/iron
- Malignant
  - MDS/MPD/AML/LGL

Autoimmunity as a cause of acquired bone marrow failure

- Failure of the immune system (T cells) to discern normal HSC's as "self"
- May be precipitated by drugs, viruses, chemicals
- Association with autoimmune disorders
  - Lupus
  - Rheumatoid arthritis
  - Felty's syndrome
- "Idiopathic" aplastic anemia

Acquired pure red cell aplasia

- Profound anemia with otherwise normal blood counts
- Bone marrow shows absent red blood cell precursors with sparing of other lineages
- Many cases have serum inhibitory antibodies of erythropoeisis
- May be transient or chronic

Causes of pure red cell aplasia

- Autoimmune disorders
- Indolent hematologic malignancies (eg, LGL, CLL)
- Thymoma
- Drugs
- Viral infection (HIV/hepatitis/EBV/CMV)
- Parvovirus

Clinical presentation of aplastic anemia

- Fatigue
- Easy bruisability/bleeding
- Infection
- Pancytopenia (decreased blood cell numbers)
- Markedly hypoplastic ("empty") marrow
- 30-40% clonal hematopoiesis of uncertain significance ("CCUS")

Aplastic anemia clinical spectrum

- Moderate
  - 2/3 cytopenias, <30% marrow cellularity
- Severe
  - ANC <500, plts <20K, retics <40K
- Very severe
  - ANC <200
- Significant mortality without effective treatment

Evaluation of bone marrow failure

- Bone marrow biopsy, cytogenetics, PNH marker, ? MDS gene mutation screening
- Careful history:
  - Drugs, infections, family history…
- Physical exam:
  - Short stature, skin/nail changes, hypogonadism, developmental delay…
- PNH marker, genetic testing as appropriate for congenital syndromes

Treatment of aplastic anemia

- Supportive care
  - Transfusions (limit to minimize alloimmunization)
  - Prophylaxis/treatment of infection
  - Iron chelation?
- Immunosuppressive therapy (IST)
- Eltrombopag
- Allogeneic transplantation

Immunosuppressive therapy (IST) for aplastic anemia

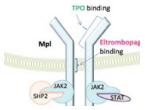
- Equine anti-thymocyte globulin (ATG) 40 mg/kg IV daily d1-4
- Cyclosporine (CSA) 5-6 mg/kg twice daily (titrated to target trough levels)
- Corticosteroids 1 mg/kg daily for 2 weeks with rapid taper
- Common toxicities:
  - Infusional fever, chills, hypoxia
  - Delayed “serum sickness”

Frickhofen et al. NEJM (1991) 324: 1297-1304

Majority of patients respond to IST

- ~65% overall response rate observed
- Majority incomplete
- Time to response often delayed
- Relapses not uncommon after tapering CSA
- Responses observed after retreatment

Eltrombopag following IST failure



Modified from Becker, P. *Hematologist*. March-April 2013, Volume 10, Issue 2

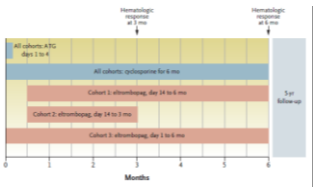
- Activates c-MPL by dimerizing receptor at transmembrane domain
- c-MPL expressed on hematopopietic stem/progenitor cells

- Phase 2 study of oral eltrombopag for patients with SAA refractory to standard IST
- 84% had 2 or more prior therapies
- 40% had hematologic response by 3-4 mo
- 5 of 43 had normalization of counts
- 8 of 43 had clonal evolution (acquisition of new cytogenetic abnormalities)

Olnes et al NEJM (2012) 367:11-19

Eltrombopag added to IST for previously untreated AA

- Phase 1-2 study of IST plus eltrombopag (150 mg) in 92 previously untreated patients with severe AA
- Three eltrombopag schedules analyzed individually and in composite
- Primary endpoint: complete hematological response at 6 months
- Secondary endpoints: ORR, survival, relapse, clonal evolution



N ENGL J MED 376;16 NEJM.ORG APRIL 20, 2017

Improved response rate compared with historical controls

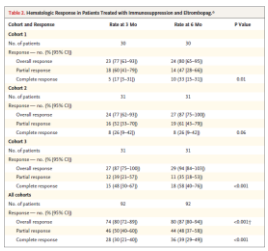


Table 2. Hematologic Response in Patients Treated with Immunosuppression and Eltrombopag.*

Cohort and Response	Rate at 3 Mo	Rate at 6 Mo	P Value
Cohort 1			
No. of patients	30	30	
Response — no. (% [95% CI])			
Overall response	23 (77 [62–93])	24 (80 [67–93])	
Partial response	18 (60 [43–79])	14 (47 [28–66])	
Complete response	5 (17 [3–31])	10 (33 [15–51])	0.01
Cohort 2			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	24 (77 [62–93])	27 (87 [75–100])	
Partial response	16 (52 [35–70])	19 (61 [45–78])	
Complete response	8 (26 [9–42])	8 (26 [9–42])	0.06
Cohort 3			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	27 (87 [75–100])	29 (94 [84–103])	
Partial response	12 (39 [21–57])	11 (35 [18–53])	
Complete response	15 (48 [29–67])	18 (58 [40–76])	<0.001
All cohorts			
No. of patients	92	92	
Response — no. (% [95% CI])			
Overall response	74 (80 [72–89])	80 (87 [80–94])	<0.001†
Partial response	46 (50 [40–60])	44 (48 [37–58])	
Complete response	28 (30 [21–40])	36 (39 [29–49])	<0.001

- Responses of the combined cohort superior to historical control:
  - ORR 80% vs 66%
  - CR 36% vs 10%
- 2 yr OS 97%
- 6 pts had no response; 12 patients received a transplant
- Relapse requiring resumption of CsA occurred in 32% after 6 months
- Clonal evolution occurred in 8% patients at 2 years
- Adverse events ≥ grade 3: rash (2%), ↑LFTs (18%)

Townsley et al NEJM 376: 16-

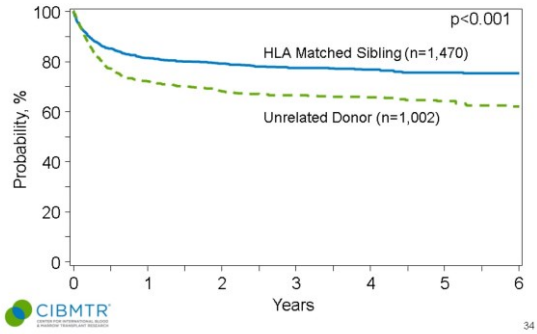
Donor transplant considerations

- Suitably matched donor availability
- Treatment-related toxicity
- Relapse risk (30-40% with IST)
- Late risk of clonal hematopoietic disorders (10-20% with IST)
- Improved upfront transplant outcome
- Increased transplant mortality with age

Factors impacting outcome after allogeneic transplant for AA

- Patient age
- Matched sibling donor
- Donor gender
- Bone marrow stem cell source
- Early transplant
- CSA/FK GVHD prophylaxis

Survival after Allogeneic HCT for Severe Aplastic Anemia, ≥18 Years, 2004-2014



34

Graft failure following allogeneic transplant for aplastic anemia

- Increased risk compared with other transplant indications (10-20%)
- Transfusion burden increases risk through alloimmunization
- Avoid transfusion of products from family members
- Leukoreduction of blood products

Strategies to reduce graft rejection

- Limit transfusions
- Early transplant
- Leukoreduced blood products
- Single donor platelets
- Increased immunoablative conditioning
  - Radiation, ATG, purine analogs

Alternative donor transplant for aplastic anemia

- 20-80% of transplant candidates lack a matched sibling or unrelated donor
- Inferior outcomes with mismatched unrelated donors
- Umbilical cord blood and haploidentical related donors provide alternative stem cell sources for transplant
- Ongoing BMT Clinical Trials Network (CTN) study of haplo vs cord donors

Summary

- Aplastic anemia is a serious but potentially treatable disorder
- Outcomes with both non-transplant and transplant approaches have improved
- Transplant candidates without suitably matched donors may benefit from alternative donor sources