Aplastic Anemia: Understanding Your Diagnosis and Treatment Options

AAMDS Foundation
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Case

15 year old previously healthy white adolescent female referred to Hematology Clinic for evaluation of thrombocytopenia

History:
CBC obtained at primary care physician’s office
9/2016: WBC 7.7; Hb 11; platelet count 33
12/2016: WBC 3.7; Hb 10.6; platelet count 25

Past Medical History: Born FT by uncomplicated C-section for breech position. No hospitalizations or recurrent infections. Normal development. Immunizations up to date.

Medications: Lisdexamfetamine, Nu-Iron

Family History: No known bleeding disorders, anemia, thrombocytopenia, childhood cancers.

Social History: No full siblings. Jehovah’s witness.

Case

Exam: Ht 171 cm (92%), Wt 51.1 kg (45%), Normal except for one small bruise on anterior left leg
No dysmorphic features, congenital lesions, radial ray or nail abnormalities

Labs:
4.3 > 9.6 < 18, MCV 112, ANC 1800, ARC 56k
HbF 9.4% (elevated)
B12 704 pg/mL, Folate > 22.3 ng/mL (normal)
Peripheral blood smear consistent with pancytopenia

Case

Further testing:
CMV, EBV, Hepatitis A/B/C, Parvovirus, HHV6 negative
Normal chromosome breakage studies
Normal telomere lengths
PNH screen with 10% neutrophil clones and 8% monocyte clones
Shwachmann-Diamond gene sequencing negative

Bone marrow aspirate/biopsy

Hypocellular marrow 5-30%, normal cytogenetics
**Diagnosis:** Acquired Idiopathic SAA

**Treatment:**
- Horse anti-thymocyte globulin (ATG) x 4 days
- Methylprednisolone/Prednisone x 10 days
- Cyclosporine A twice a day
- Eltrombopag (50 mg/day beginning day 4)

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**Possible Mechanisms**

1. Direct progenitor cell death due to marrow toxins
2. Underlying HSC abnormality
   - Post immunosuppression, low stem cell #s persist and macrocytosis may not return to normal
   - Late clonal abnormalities
3. Immunologic destruction of hematopoietic stem cells
   - Clinical response to immunosuppressive therapies
4. Abnormal stromal microenvironment inhibiting hematopoiesis

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**Epidemiology**

- **Incidence:** ~ 2 per million per year
- **Peaks at ages 15-25 years and > 60 years

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**Etiologies**

- Careful and thorough H&P
  - Bleeding, fatigue, serious infections
  - Steatorrhea, diarrhea
  - FH blood disorders, malignancies, hepatitis, congenital anomalies, etc.
  - Developmental history
  - Meds, environment exposures, infections

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**Diagnosis**

- **History**
  - Petechiae, bruises, pallor, oral sores
  - Lymphadenopathy, hepatosplenomegaly
  - Growth curves, short stature
  - Congenital anomalies esp. radial ray abnormalities
  - Hyper/hypopigmented areas, dystrophic nails

- **Physical Exam**
  - Basic labs: CBC with diff, retic, PBS +/- HbF

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**Aplastic Anemia: Definitions**

<table>
<thead>
<tr>
<th>ANC*</th>
<th>Platelets</th>
<th>ARC*</th>
<th>BM cellularity</th>
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<tbody>
<tr>
<td>&lt; 500/μL</td>
<td>&lt; 20,000/μL</td>
<td>&lt; 40,000/μL</td>
<td>&lt; 25% for age</td>
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2 out of 3 blood count criteria

- *ANC = absolute neutrophil count
- *ARC = absolute reticulocyte count

- Very Severe Aplastic Anemia (vSAA): ANC <200/μL
Treatment Algorithm

Antimicrobials as needed
Prompt evaluations for neutropenia and fever
+/- G-CSF & GM-CSF
Restrictive transfusion thresholds
Iron chelation as needed

Supportive Care

Matched Related Donor Transplants

Conditioning
- Cy-ATG
- Cy alone
Graft Source
- Prefer BM > PBSC or UCB
- Standard care for GVHD prophylaxis
- Potentially equivalent efficacy, Continue ≥ 6 months post HCT

Engraftment rate 96%, OS 91%
No difference in OS, graft failure, or GVHD
Improved OS for BM (85%) vs PBSC (73%) grafts

OS 95%, aGVHD 2.3%, cGVHD 6.8%
5% ≤ 14 yrs, 32% ≥ 15 yrs
Mismatched unrelated donor
- Retrospective data with reasonable outcomes
OS (2 yr) 78% for 8/8, 60% for 7/8

Thrombopoietin (TPO)

Most potent regulator of megakaryopoiesis and thrombopoiesis
Binds to receptor (MPL) on hematopoietic stem cells and megakaryocyte colony-forming units (CFU-MK)
Stimulates megakaryocytic maturation, increases megakaryocyte size and ploidy
rh-TPO in cancer patients on chemotherapy increases platelet count, but also causes antibodies that cross-react with endogenous TPO

Immunosuppressive Treatment

4 months
10 yrs
10 yrs

Most potent regulator of megakaryopoiesis and thrombopoiesis

• Response to IST typically starts at ~ 1-3 months
• ATG + CSA > OR (but not OS) compared to ATG
• Horse ATG > Rabbit ATG for OR and OS
• Slow CSA wean

Predictors of response to IST
- SAA > SAA
- Younger age
- Higher Retic and ALC
- Quicker treatment
Eltrombopag

- Binds to transmembrane domain of MPL
- Rapidly absorbed after oral administration
- Should not be taken within 4 hour of food rich in cations such as Ca++
- Metabolized in liver, \( T_{1/2} = 21-32 \) hours
- Clearance 33-52% lower in Asians; therefore starting dose approximately \( \frac{1}{2} \) in Asians (in some trials)

Eltrombopag and refractory aplastic anemia

- Phase 2 study in adults with aplastic anemia refractory to immunosuppression (IS)
- \( N = 25 \); median age = 44 years (18-77)
- Eltrombopag dose: 50 → 150 mg/d x 12 weeks
- 11/25 (44%) had response in at least one lineage at 12 weeks
- 9 no longer needed platelet transfusion; 3 no longer needed PRBC transfusion; 9 had increase in ANC
- Conclusion: eltrombopag was associated with multilineage response in some patients with refractory SAA
- Follow-up study: 40% response rate

Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

- Phase 1-2 study of immunosuppression + eltrombopag in previously untreated patients with severe aplastic anemia (SAA)
- Patients (\( N = 92 \)) consecutively enrolled in 3 cohorts; median age = 32 years (3-82)
- Primary outcome = CR at 6 months
- Secondary outcomes = OR, survival, relapse, clonal evolution
Results

- CR at 6 mo. = 32%, 26%, 58% in cohorts 1, 2, and 3
- OR at 6 mo. = 80%, 87%, 94%
- In historical controls, CR = 10% and OR = 66%
- Survival = 97% at median follow-up of 2 years
- Relapse and clonal evolution similar to historical experience
- Toxicity: severe rash leading to discontinuation of eltrombopag in 2 patients
- Conclusion: Addition of eltrombopag to immunosuppression is associated with markedly higher rate of hematologic response in patients with SAA

Treatment Algorithm

NAPAAC/Novartis: Study Objectives

- 1st: Characterize the pharmacokinetics of eltrombopag at steady state in refractory, relapsed or previously untreated patients with SAA
- Key 2nd: Safety and tolerability; efficacy (overall response rate)
- Other 2nd:
  - Platelet and RBC transfusion independence
  - Hematologic counts, BM cellularity
  - Clonal evolution to PNH
  - Acceptability and palatability

Summary

- Eltrombopag is a promising new agent for improving the response to upfront immunosuppressive treatment in SAA
- Eltrombopag is of benefit for some patients that have refractory or relapsed SAA
- However, the improving results from alternative hematopoietic stem cell transplants must also be considered in treatment decisions