Severe Aplastic Anemia

Monica S. Thakar, MD
Pediatric BMT
Medical College of Wisconsin

Outline of Talk

1. Clinical description of aplastic anemia
2. Data collection forms

And a couple of quizzes in between...

What is aplastic anemia?

- More than just anemia
  - Involves low counts in 2 of 3 cell lines: red blood cells (RBC), white blood cells (WBC), platelets
- Should NOT involve dysplasia
  - Exception: RBC can sometimes be dysplastic
- Should have NORMAL cytogenetics
- If dysplasia (beyond RBCs) or abnormal cytogenetics seen, think myelodysplastic syndrome (MDS)

What is “severe” aplastic anemia?

- Marrow cellularity ≤25% AND
- Two of the following peripheral blood features:
  - Absolute neutrophil count (ANC) < 0.5 x 10⁹/L
  - Platelet count < 20 x 10⁹/L
  - Absolute reticulocyte count < 40 x 10⁹/L
- “Very” severe aplastic anemia
  - Same as above except ANC < 0.2 x 10⁹/L

Bottom Line: Severely Reduced Hematopoietic Stem Cell Precursors In Bone Marrow
Epidemiology

- Half of cases seen in first 3 decades of life
- Incidence:
  - 2 cases/million in Western countries
  - 2-3 fold higher in Asia
- Ethnic predisposition:
  - Asian
    - Genetics vs different environmental exposures?
- Sex predisposition: M:F is 1:1

Causes of Aplastic Anemia

- Number 1 Cause: Idiopathic (unknown)
- Ionizing radiation
- Drugs
  - Chloramphenicol
  - Phenylbutazone
  - Sulfonamides
  - Gold
  - Certain anti-inflammatories (felbamate, carbamazapine)
  - Quinine
- Genetic disorders
  - Fanconi Anemia
  - Dyskeratosis congenita
  - Diamond-Blackfan anemia
  - Shwachman-Diamond Syndrome
- Viruses
  - Non-A, B, C Hepatitis
  - Parvovirus
  - Epstein-Bar Virus
- Autoimmune
  - Eosinophilic fasciitis
  - Pregnancy

Work-up and Evaluation

- CBC
- Reticulocyte count
- Bone marrow aspirate
  - Morphology
  - Cytogenetics
- Bone marrow biopsy
- Rule-out other disorders
  - Fanconi Anemia: chromosomal fragility (DEB/MMC)
  - Dyskeratosis congenita: short telomeres
  - Diamond-Blackfan Anemia: gene mutations (RPS19)
  - Shwachman-Diamond Syndrome: gene mutation (SBDS)
  - Paroxysmal Nocturnal Hemoglobinuria: flow cytometry (CD55/59)

Pathophysiology: 3 Main Mechanisms Proposed

1. Immune-mediated
   - Hypothesis: Revved-up T cells destroy stem cells
   - Observation: Immunosuppression improves blood counts
2. Stem-cell “depletion” or “defect”
   - Hypothesis: Drugs or viruses directly destroy stem cells
   - Observation: Syngeneic transplants without prior conditioning can cure disease
3. Abnormal marrow microenvironment (less likely cause)
   - Hypothesis: The marrow niche cannot support stem cells
   - Observation: Long-term culture of stromal cells from aplastic anemia patients can sometimes be difficult

Clinical Presentation

- Low RBC
  - Pallor
  - Fatigue
  - Exercise intolerance/heart failure
- Low Platelets
  - Bleeding
  - Bruising
- Low WBC
  - Infections

Treatment of Aplastic Anemia

- Immunosuppression
  - Gold standard: Anti-thymocyte globulin (ATG) and cyclosporine (CSP)
  - 2/3 of patients will initially respond
    - Response is typically NOT complete
    - Concerns: 1) Frequently not a durable solution
  - G-CSF (+immunosuppression)
    - Controversial; conflicting reports of benefit
    - Concern: Reports of transformation to MDS/AML
- Transfusion support
  - Rapid results for life-threatening anemia or bleeding
    - Concerns: 1) Not a durable solution
    - 2) Risk of antibody development–multiple-donor transfusions
    - 3) Risk of iron overload
Role of Transplantation for Aplastic Anemia

• Objective: Replace non-functional marrow with functioning marrow

• Indications for transplantation:
  – Matched-sibling donor
  – Refractory to immunosuppressive therapy
  – Transfusion dependence
  – Iron overload
  – Life-threatening bleeding
  – Life-threatening infections

What can Aplastic Anemia be confused for?

• Myelodysplastic syndrome
• Recovering marrow from chemotherapy
• Early presentation of leukemia

How can these entities be distinguished?

• Look at the time-line
  – What is the temporal relationship to chemotherapy?
• Evaluate bone marrow aspirate
  – Is there dysplasia and/or abnormal cytogenetics?
  – Are there hematopoietic precursors?

Can aplastic anemia be a predisposing condition for developing AML or MDS?

• YES! But overall a rare phenomenon
• May be due to prior therapy
  – Immunosuppression
  – Hematopoietic cell transplantation
• Why is this important to know?
  – Will affect which CIBMTR forms to fill out

Quick Quiz

1. A patient with aplastic anemia undergoes a marrow transplant. After transplant, she is still anemic and thrombocytopenic.
   a) She is still recovering from her transplant – give her time
   b) Her transplant has failed and she still has aplastic anemia

Quick Quiz

2. After finishing his third round of chemotherapy, a patient with AML has developed prolonged neutropenia. He undergoes a marrow aspirate that shows decreased WBC and RBC precursors.
   a) He has now developed aplastic anemia
   b) He has now developed MDS
   c) He has now developed recurrent AML
   d) He is still recovering counts—give him time
Data collection: Critical Points

- Date of diagnosis
- Pre-transplant co-morbidities
- Prior therapy
- Lab work that confirms diagnosis

CIBMTR Forms to Fill Out for Aplastic Anemia

Aplastic Anemia-specific forms:
1. Form 2028 (APL): Aplastic Anemia Pre-HSCT Data
2. Form 2128 (APL): Aplastic Anemia Post-HSCT Data

Also need to fill out:
1. Form 2000 (All diseases): Recipient Baseline Data
2. Form 2100 (All diseases): 100 Days Post-HSCT Data

May need to fill out:
1. Form 2014/2114 (MDS): Myelodysplasia /Myeloproliferative Disorders Pre-HSCT Data/Post-HSCT Data
2. Form 2010/2110 (AML): Acute Myelogenous Leukemia Pre-HSCT Data/Post-HSCT Data

Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (1)

Date of marrow that diagnosed SAA (or date that MD states SAA developed if source document not available)

ATTACH THE REPORT if available! This will save a future data manager from sifting through old charts in the future!
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (2)

Sometimes the etiology is known (frequently it is not!) Fill in what is known.

Key word is DIAGNOSIS!

Pay attention to UNITS!

Important to know—
1) transfusion dependence
2) counts may be inaccurate if pt was transfused.
This is asking for number of DONOR EXPOSURES (NOT number of transfusions). This comes into play if a patient received directed-donor transfusions.

Just yes-no question when asking about platelet transfusions.

Units!
Make sure to record the BM biopsy CLOSEST to the start of the preparative regimen.

Clinically important means:
1) An organism was found and treated
2) An organism was suspected and treated
3) A fever of unknown source occurred, but the patient improved on drug therapy

Correct date of diagnosis
Attaching BM biopsy reports when available
Recording the correct “start of preparative regimen” lab values
   - These are usually not the same as the lab values at time of diagnosis
A fever by itself does not count as a “clinically important” infection

Areas of concern on Pre-HSCT forms

Correct date of diagnosis
Attaching BM biopsy reports when available
Recording the correct “start of preparative regimen” lab values
   - These are usually not the same as the lab values at time of diagnosis
A fever by itself does not count as a “clinically important” infection
Form 2128 (APL): Aplastic Anemia Post-HSCT Data (1)

Visit: [ ] 100 day [ ] 6 month [ ] 1 year [ ] 2 years [ ] > 2 years, specify: 

Form 2128 (APL): Aplastic Anemia Post-HSCT Data (1)

Additional forms you may need to fill out

1. Form 2014/2114 (MDS): Myelodysplasia / Myeloproliferative Disorders Pre-HSCT Data/Post-HSCT Data

1. Form 2010/2110 (AML): Acute Myelogenous Leukemia Pre-HSCT Data/Post-HSCT Data

Rationale for Future Research

- These forms may change over time based on research directions of CIBMTR
- Important to attach reports even when optional to aid in data gathering for future research questions

Quick Quiz

1. A patient develops aplastic anemia and is treated with immunosuppression only with good response. Two years into therapy, the patient develops secondary AML and goes to transplant as a result. How do you report this to the CIBMTR?
   a) Use the insert form for Aplastic Anemia only
   b) Use the insert form for AML only
   c) Use both Aplastic Anemia and AML insert forms
Quick Quiz
2. A patient develops severe aplastic anemia and is transplanted. Six months after transplant, the patient develops secondary MDS. How do you report this to the CIBMTR?
   a) Pre-transplant: Aplastic Anemia insert
      Post-transplant: Aplastic Anemia insert
   b) Pre-transplant: Aplastic Anemia insert
      Post-transplant: MDS insert

Quick Quiz
3. Let’s say that this last patient who developed secondary MDS now goes on to have a second transplant. How do you report this to the CIBMTR?
   a) Pre-transplant #2: Aplastic Anemia insert
      Post-transplant #2: MDS insert
   b) Pre-transplant #2: MDS insert
      Post-transplant #2: MDS insert

Thank you for your attention!
Questions?