Aplastic Anemia: Current Thinking

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Outline

➢ What is Aplastic Anemia?
  • Definition
  • Epidemiology
  • Things Not to be Confused With
  • Work-Up

➢ How do we treat Aplastic Anemia?
  • Supportive Care
  • Immunosuppressive Therapy
  • Current Role for Blood and Marrow Transplantation (BMT)

What is Aplastic Anemia?
Bone Marrow

Normal Cellularity = 100% - Age

<25% Cellular

Aplastic Anemia

Need 2 out of 3

Reticulocytes < 20

ANC < 500

Platelets < 20,000

Oxygen

Infection

Control, Bleeding

WB C

ANC

Hemoglobin (reticulocytes)

Normal

Cellularity = 100%
Definition

- Severe Aplastic Anemia – above definitions including ANC < 500
- Very Severe Aplastic Anemia – above definitions but with ANC < 200
- Mild to Moderate Aplastic Anemia – decreased marrow cellularity and/or decreased peripheral blood counts
  - does not meet definition for severe or very severe

Why does it happen?

- Inherited
- Hepatitis
- Drug induced
- Chemical induced
- Immune destruction
- Deficiency of hematopoietic stem cells

Epidemiology

- 2-3 cases per million population in the United States and Europe
- 600-900 new cases per year in the United States
- 2-3 times higher in parts of Asia
- Biomodal age distribution
  - Teens/young adults (10-25 years old)
  - Older adults (>60 years old)
- Equal male to female distribution
Things not to be confused with...

- Cancer – either blood cancer or spread of solid cancer
- Myelodysplastic Syndrome (MDS)
- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Inherited Bone Marrow Failure Syndrome (IBMFS)

Inherited Bone Marrow Failure Syndromes

- Fanconi Anemia (FA)
- Dyskeratosis Congenita (DC)
- Shwachman-Diamond Syndrome (SDS)
- Congenital Amegakaryocytic Thrombocytopenia (CAMT)
- Thrombocytopenia with Absent Radii (TAR)
- Diamond-Blackfan Anemia (DBA)
- Severe Chronic Neutropenia (Kostmann’s Syndrome)

When to suspect an inherited cause...

- Unusual physical exam
  - Growth issues, head shape, or neurologic findings
  - Skin, mouth, nail, hand, or other skeletal findings
- Unusual medical history
  - Heart, kidney, lung, liver, pancreas, or other findings
  - Unexpectedly severe response to chemotherapy or radiation
- Unusual family history
  - Others with bone marrow failure or cancers early in life
  - Unexplained lung, liver, or other problems
Recommended Work-Up

How do we treat Aplastic Anemia?

Supportive Care Treatments

Judicious Transfusion Support
Prevent/Treat Infections

Limited/No Role: growth factors, androgens, steroids, insufficient immunosuppression
Supportive Care Treatments

- Not curative
- Come with problems
  - Iron Overload from red blood cell transfusions – need for chelation
  - Antimicrobial resistance
  - Growth factors can increase risk of evolution to MDS or leukemia
- Can cause problems with later BMT
  - All immunization from multiple transfusions increses risk of graft failure

Immunosuppressive Therapy (ATG+CSA)

- Patients with Severe Disease
  - Cyclosporine Group (n = 34)
  - P = 0.07
- Control Group (n = 36)

- Patients received ATG

P = 0.006

Frickhofen et al
Scheinberg et al

Measuring Response

- Response
  - Complete
  - Partial
  - Stable disease
  - Non-response

-Patients receiving immunosuppressive therapy showed a decrease in transfusion requirements and a decrease in the need for additional medications.
Impact of Response

Can we predict response?

- Age
- Severity of Disease
- Biomarkers being studied (discussed in new directions talk)

What happens if no response?

Scheiberg et al

Rosenfeld et al

Samarasinghe et al
What happens if no response?

- Can proceed to BMT if good unrelated donor available
- Can try another round of immunosuppressive therapy
  - Generally switch from horse ATG to rabbit ATG
  - Trial other immunosuppressive regimens (discussed in new directions talk)

What happens if no response?

<table>
<thead>
<tr>
<th>(A)</th>
<th>(B)</th>
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<tbody>
<tr>
<td>Time (months)</td>
<td>Time (months)</td>
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<tr>
<td>Overall survival</td>
<td>Failure-free survival</td>
</tr>
<tr>
<td>Immunosuppressive Therapy</td>
<td>Matched Unrelated Donor Transplantation</td>
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Samarasinghe et al

Immunosuppressive Therapy Pitfalls

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<tbody>
<tr>
<td>Time frommatched transplantation</td>
<td>Days</td>
</tr>
<tr>
<td>Severity score (PA)</td>
<td>Severity score (PA)</td>
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Schreinemachers et al Socie et al
Current Role for BMT

- Standard of care for younger, newly diagnosed patients is matched related donor transplantation
- Reduced intensity regimens are used
- No role for use of total body irradiation

What do you mean by matched?

- Human Leukocyte Antigen (HLA)
  - A
  - B
  - C
  - DRB1
  - DQ
- 2 copies of each HLA from each parent
Survival after Allogeneic Transplants for Severe Aplastic Anemia, ≥ 20 Years, 2002-2012

Matched Related Donor Transplantation

Bacigalupo et al.
Current Role for BMT

- Standard of care for younger, newly diagnosed patients is matched related donor transplantation
  - reduced intensity regimens are used
  - no role for use of total body irradiation

- When no related donor available, standard of care for most is matched unrelated donor transplantation
  - failure of immunosuppressive therapy
  - evolution of disease

Impact of Immunosuppressive Therapy on Matched Related Donor Transplantation

- Matched related HSCT
- Transplantation

- Impact of Immunosuppressive Therapy on Matched Related Donor Transplantation

- Current Role for BMT

- Treatment Algorithm
Acknowledgements

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