Aplastic Anemia and Bone Marrow Failure Syndromes

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Disclosures

I have nothing to disclose.
Aplastic Anemia (AA)

Peripheral blood pancytopenia

Hypocellular Marrow for age (usually < 25%)

Severe AA requires ≥ 2 cytopenia
  a) Neutrophils < 500/µl
  b) Platelets < 20,000/ µl
  c) Retic count < 60,000/ µl

Very severe AA – neutrophils < 200/µl
Differential Diagnosis in Evaluation of Aplastic Anemia

1) Infection
   HIV, Hepatitis B/C, parvovirus B19, HHV6, CMV

2) Medication
   a) Antibiotics – Chloramphenicol, Bactrim, INH, Dapsone, Lamivudine
   b) Antineoplastics – Fludarabine, IFN
   c) Immunosuppressants – Tacrolimus, Cellcept, Azathioprine
   d) Antiepileptics – Dilantin, Valproic Acid

3) Hematologic Disorders
   a) Hypoplastic MDS
   b) Large Granular Lymphocytosis

4) Environmental Exposure - Pesticides

5) Nutritional Deficiencies

6) Inherited Bone Marrow Failure Syndrome
Inherited BM Failure Syndromes

Fanconi Anemia

Dyskeratosis Congenita

GATA\textsubscript{2} Disorders

Schwachman-Diamond Syndrome

Diamond Blackfan Anemia
Integration of Germ Line and Somatic Genetics Into Diagnostic Evaluation of Bone Marrow Failure

Clinical History
- CBC with Differential
- Bone Marrow Morphology Cellularity

Family History
- Assess Infections Medications Nutritional Other

Physical Anomalies

Chromosomal Breakage for FA
- Telomere Length for DC/TBD
- Trypsinogen, Pancreatic isoamylase

BMF Gene Sequencing:
- Single/Multiplexed
- Array-CGH for deletions, CNV

Constitutional BMF

Cytogenetics
- FISH del5q -7, del7q trisomy 8 del20q other
- SNP-array karyotyping
- Next-Gen Sequencing

Somatic Genetics
Work-up For Suspected Aplastic Anemia

Pancytopenia

BM biopsy

Histology: Exclude MDS – leukemia – metastatic cancer identify marrow hypo/aplasia

BM aspirate

Cytogenetics/FISH: identify chromosomal abnormalities
Cytology: confirm absence of marrow blasts

Peripheral blood

Neutrophil count: determine severity:
DEB test: exclude FA
Determine proportion of GPI-negative cells
Exclude antibody-mediated cytopenias
Determine telomere length

Acquired aplastic anemia

HLA typing: identify HLA-matched family donors

CHOSE TREATMENT

ATG + CSA (androgens/growth factors)

BM TRANSPLANTATION
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Condition</th>
<th>Description/Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCH</td>
<td>Aging related clonal hematopoiesis</td>
<td>Describes the presence of detectable, benign clonal hematopoiesis (defined by the presence of somatic mutations in the blood or bone marrow) whose incidence increases with age. No formal definition involving clonal abundance or types of mutations. No clinical significance is implied.</td>
</tr>
<tr>
<td>CHIP</td>
<td>Clonal hematopoiesis of indeterminate potential</td>
<td>Defined by somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at $\geq 2%$ variant allele frequency in individuals without a diagnosed hematologic disorder.</td>
</tr>
<tr>
<td>CHOP</td>
<td>Clonal hematopoiesis of oncogenic potential</td>
<td>Describes clonal hematopoiesis in a clinical context where it is associated with a significant likelihood of progressing to a frank malignancy.</td>
</tr>
<tr>
<td>IDUS</td>
<td>Idiopathic dysplasia of undetermined significance</td>
<td>Individuals with unexplained morphologic dysplasia of blood cells who are not cytopenic. Can occur with or without clonal hematopoiesis.</td>
</tr>
<tr>
<td>ICUS</td>
<td>Idiopathic cytopenia of undetermined significance</td>
<td>Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder. Can occur with or without clonal hematopoiesis although often used to refer to cytopenias without evidence of clonal hematopoiesis.</td>
</tr>
<tr>
<td>CCUS</td>
<td>Clonal cytopenia of undetermined significance</td>
<td>Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder, but who have somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at $\geq 2%$ variant allele frequency. Can be considered as the intersection between CHIP and ICUS.</td>
</tr>
</tbody>
</table>
Overlaps Between AA, PNH, and MDS
Variation of Risk Associated with Clonal Hematopoiesis
Recent Advances in Understanding Clonal Hematopoiesis in Aplastic Anemia
Mutation interpretation in cytopenic patients without extensive dysplasia, excess blasts, or an MDS-defining karyotype.

- Single mutation
- Low variant allele frequency (< 10%)
- Minimal or no cytopenia
- Mutation in common “CHIP” – associated genes (e.g. TET2, NDMT3A)

- Multiple mutations
- Higher variant allele frequency (> 20%)
- Cytopenia, especially if progressive
- Mutation in genes more commonly associated with MDS (e.g. U2AF1, TP53)

Favors CHIP

Favors MDS
Mutation Frequencies in AA, CHIP and MDS
Supportive Care

1) Limit Transfusion Exposure
   a) decrease risk of alloimmunization
   b) Irradiated blood products to decrease risk of GVHD
   c) Do not use family member who may be potential donor

2) Infection Prophylaxis
   a) Antifungal – posaconazole
   b) Pneumocystis (post ATG)
   c) Gram negative coverage (ANC ≤ 200)
   d) No vaccines for IST patients

3) Iron Chelation
SAA Therapy

Acquired aplastic anemia

> 40 years

- Horse ATG and cyclosporine

< 40 years and no matched sibling available

< 40 years and matched sibling available

Sibling HSCT

> 40 years with MRD

Consider HSCT if suitable

> 30 years with MUD (no MRD)

MUD HSCT after second-line non-transplant treatment

30 years or less with MUD (no MRD)

MUD HSCT within the first year of diagnosis

20 years or less with no MUD or MRD

Alternative HSCTs after second-line non-transplant treatment (MMUD, CB or Haplo)

Refractory at six months
Effect of Age on Outcome of IST for SAA

First-line IST for SAA (EBMT 2001-2010)

- Age 1-20 years; n = 870
  - Survival: 82%

- Age 21-40 years; n = 636
  - Survival: 69%

- Age >40 years; n = 226
  - Survival: 58%

Days from IST

Survival

0% 20% 40% 60% 80% 100%
Effect of Age on Survival Post Sibling Donor HCT

First-line HLA identical sibling BMT for SAA (EBMT 2001-2010)

- Age 1-20 years; n = 870
  - Survival: 86%
- Age 21-40 years; n = 636
  - Survival: 76%
- Age >40 years; n = 226
  - Survival: 55%

Days from transplant

Andrea Bacigalupo Blood 2017;129:1428-1436
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Targeting Immune Mediated Aplastic Anemia

Eltrombopag

[Diagram showing immune-mediated processes and the role of Eltrombopag in targeting immune-mediated aplastic anemia.]
## Immune Suppressive Therapy in SAA

### Initial Therapy CSA + ATG

<table>
<thead>
<tr>
<th>Horse ATG</th>
<th>Response</th>
<th>Relapse</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 pts</td>
<td>3 m</td>
<td>6 m</td>
<td>28</td>
</tr>
<tr>
<td>62%</td>
<td>68%</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rabbit ATG</th>
<th>Response</th>
<th>Relapse</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 pts</td>
<td>33%</td>
<td>37%</td>
<td>11</td>
</tr>
<tr>
<td>33%</td>
<td>37%</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

Relapse Rate at 3yrs: 28% horse, 11% rabbit

Overall Survival at 3yrs: 96% horse, 76% rabbit, $p=0.04$
SAA - Therapy for Primary Failure or Relapse Post IST

Alternate Immunosuppression
   a) Rabbit ATG
   b) Alemtuzumab – anti CD52 antibody

Eltrombopag

Allogeneic Transplant
   a) Matched Unrelated Donor (URD)
   b) Alternative Donor
      9/10 URD
      Haplo Identical Family Donor
      Cord Blood HCT
## Rabbit ATG for SAA Relapsed or Refractory to Horse ATG

### NIH Trial

<table>
<thead>
<tr>
<th></th>
<th>Refractory</th>
<th>Relapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts</strong></td>
<td>22 pts</td>
<td>21 pts</td>
</tr>
<tr>
<td><strong>Overall Response</strong></td>
<td>30%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Overall Survival 3y</strong></td>
<td>90% responders</td>
<td>65% non-responders</td>
</tr>
</tbody>
</table>

### Italian Intergroup

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Overall Response</strong></td>
<td>77% / CR 30%</td>
</tr>
<tr>
<td><strong>Overall Survival 3yr</strong></td>
<td>93%</td>
</tr>
</tbody>
</table>
## Alemtuzumab for SAA

<table>
<thead>
<tr>
<th></th>
<th>Overall Response (3m)</th>
<th>Relapse (3yr)</th>
<th>Clonal Evolution</th>
<th>OS 3yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Refractory (56pts)</strong></td>
<td>Rabbit ATG/CSA 19%/ 33%</td>
<td>19%</td>
<td>16%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>vs Alemtuzumab 19%/ 37%</td>
<td>9%</td>
<td>5%</td>
<td>83%</td>
</tr>
<tr>
<td><strong>Relapsed (25pts)</strong></td>
<td>Alemtuzumab 48%</td>
<td>23%</td>
<td>11%</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>56%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial Rx (16pts)</strong></td>
<td>Alemtuzumab 19%</td>
<td></td>
<td></td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>19%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Eltrombopag is a small molecule thrombopoietin receptor agonist which is thought to directly stimulate proliferation of residual stem cell progenitors.

Binds to c-mpl at membrane site different from TPO. May be able to escape inhibition produced by γ IFN.
Eltrombopag in Aplastic Anemia
Eltrombopag in IST Failure
Lineage Characteristics of Responses

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Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia

# Eltrombopag + IST as Initial Therapy For SAA

## NIH 90 Patients

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response 6m</td>
<td>80%</td>
<td>87%</td>
<td>94%</td>
</tr>
<tr>
<td>Complete Response 6m</td>
<td>33%</td>
<td>26%</td>
<td>58%</td>
</tr>
<tr>
<td>Median Time to Response</td>
<td>PMN ≥ 500</td>
<td>Platelets</td>
<td>Red Cells</td>
</tr>
<tr>
<td></td>
<td>48d</td>
<td>32d</td>
<td>39d</td>
</tr>
</tbody>
</table>
NIH Trial Eltrombopag + IST

Time to Relapse

No. at risk:
CSA discontinued 92 35 17 16 16
CSA continued    92 43 24 11  1

N Engl J Med 2017; 376:1540-1550
Long Term Outcomes of Eltrombopag + IST as Initial Therapy for SAA

<table>
<thead>
<tr>
<th></th>
<th>CSA Stopped 6m</th>
<th>CSA → 2yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>19/35 (54%)</td>
<td>6/43 (14%)</td>
</tr>
<tr>
<td></td>
<td>treatment failure (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>relapse (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>clonal evolution (3)</td>
<td></td>
</tr>
<tr>
<td>Salvage HCT</td>
<td>12/90 pt</td>
<td></td>
</tr>
</tbody>
</table>
Response to IST by Mutation Risk

A Response to Immunosuppressive Therapy

- CR
- PR
- NR

Frequency

- Unfavorable (N=33)
- Unmutated (N=173)
- Favorable (N=37)

P = 0.03

Response to IST by Mutation Risk

B Overall Survival

Overall Survival (%)

PIGA, BCOR or BCORL1
Unmutated
DNMT3A, ASXL1, TP53, RUNX1, CSMD1

P = 0.008

Months

No. at Risk

PIGA, BCOR or BCORL1 34 34 33 23 18 12 8 7
Unmutated 176 142 116 84 48 27 13 6
DNMT3A, ASXL1, TP53, RUNX1, CSMD1 30 24 17 12 11 8 6 4

Aplastic Anemia - Optimizing Outcome for HCT

Conditioning Regimen

- CTX + ATG
- Horse vs Rabbit ATG
- FLU/ CY - ATG for non MRD

Stem Cell Source

- Marrow vs PBSC
- Sib vs MUD
- Alternative donors

GVHD Prophylaxis

- CSA/ Tacrolimus/ MTX
- Tacrolimus/MMF
- Post transplant Cy
Effect of Age on Survival Post Sibling Donor HCT

First-line HLA identical sibling BMT for SAA (EBMT 2001-2010)

- Age 1-20 years; n = 870
  - Survival: 86%

- Age 21-40 years; n = 636
  - Survival: 76%

- Age >40 years; n = 226
  - Survival: 55%
Effect of Age on Survival Post URD BMT as Initial Treatment for SAA

Unrelated donor transplants for SAA (EBMT 2005-2009)

- Age 1-10 years; n = 101
  - Survival: 85%

- Age 11-30 years; n = 252
  - Survival: 77%

- Age 30-40 years; n = 56
  - Survival: 66%

- Age >40 years; n = 88
  - Survival: 49%

Days from transplant

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

- HLA Matched Sibling (n=1,094)
- Unrelated Donor (n=707)

p<0.001
Survival after Allogeneic HCT for Severe Aplastic Anemia, ≥ 18 Years, 2004-2014
<table>
<thead>
<tr>
<th>MRD</th>
<th>Hazard Ratio</th>
<th>URD</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATG Source</strong></td>
<td></td>
<td><strong>ATG Source</strong></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Horse</td>
<td>3.34</td>
<td>2.20</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 yrs</td>
<td>1.00</td>
<td>NCS</td>
<td></td>
</tr>
<tr>
<td>20-30 yrs</td>
<td>2.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 40</td>
<td>2.83</td>
<td>Degree HLA Match</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>8/8</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>1.81</td>
<td>7/8</td>
<td>1.91</td>
</tr>
</tbody>
</table>

Risk Factors for Acute GVHD in SAA CIBMTR (2008-2013)
<table>
<thead>
<tr>
<th>Matched Sib</th>
<th>URD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type ATG</strong></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>1.00</td>
</tr>
<tr>
<td>Horse</td>
<td>2.55</td>
</tr>
<tr>
<td><strong>Age at Transplant</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 yrs</td>
<td>1.00</td>
</tr>
<tr>
<td>20-39 yrs</td>
<td>4.38</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>3.49</td>
</tr>
<tr>
<td><strong>GVHD Prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>Tacro/ CSA + MTX</td>
<td>1</td>
</tr>
<tr>
<td>Tacro/CSA + MMF</td>
<td>not significant</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>2.46</td>
</tr>
</tbody>
</table>

**Risk Factors for Chronic GVHD in SAA CIBMTR (2008-2013)**

**Hazard Ratio**

- Rabbit: 1.00 (p<0.001)
- Horse: 2.55
- 20-39 yrs: 4.38 (p<0.001)
- > 40: 3.49
- Tacro/ CSA + MTX: 1
- Tacro/CSA + MMF: not significant
- Female: 1.00
- Male: 2.46

**URD**

- 1.00 (p=0.14)
- 1.36
- ≥ 20: 1.58

**Hazard Ratio**

- Gender: Not significant
## Haplo HCT as Primary Treatment in SAA

**Registry Data – China 2009 – 2016**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Haplo OS (%)</th>
<th>MRD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20yr</td>
<td>75%</td>
<td>86%</td>
</tr>
<tr>
<td>20-40yr</td>
<td>78%</td>
<td>76%</td>
</tr>
<tr>
<td>&gt; 40yr</td>
<td>37.5%</td>
<td>83%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GVHD Type</th>
<th>Haplo (%)</th>
<th>MRD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD</td>
<td>34%</td>
<td>25%</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>18.5%</td>
<td>28.8%</td>
</tr>
</tbody>
</table>
## Haplo HCT vs IST as Primary Therapy

### Pediatric Data – China 2009 – 2016

< 17 years

<table>
<thead>
<tr>
<th></th>
<th>IST</th>
<th>Haplo HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>73.4%</td>
<td>89.3%</td>
</tr>
<tr>
<td>10 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure Free Survival</td>
<td>52%</td>
<td>89%</td>
</tr>
</tbody>
</table>
Inherited Marrow Failure Syndromes

1) Fanconi Anemia

2) Dyskeratosis Congenita

3) Blackfan Diamond Anemia

4) Schwachman Diamond Syndrome
Monitoring of Patients with FA + DKC

**BM work-up and staging**

- No/mild cytopenias, no significant dysplasia, no karyotypic abnormality
- No/mild cytopenias, no significant dysplasia, sole chromosomal abnormality
  
  (+1q, -20q, -11q, -5q, or -Y)
- Severe BMF, or SIC, or significant dysplasia/MDS (but blast cells <10%), or poor risk chromosomal abnormality
  
  (+3q, -7q, RUNX1-abn, and/or complex)
- MDS >10% blast cells or AML

**Monitoring and treatment**

- Yearly BM monitoring
  
  Morphology and karyotype
- Close BM monitoring
  
  Morphology and karyotype; Possible FISH, CGH/SNP and molecular analyses
- HSCT, classical strategy
  
  RIC HSCT
- HSCT, sequential strategy
  
  FLAG chemotherapy followed by RIC HSCT

**Long-term follow up**

- Careful screening of solid malignancies, especially in patients with HSCT and chronic GVHD