Aplastic Anemia: Understanding Your Diagnosis and Treatments Options

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Disclosures

• Advisory Honoraria
  – Jazz Pharmaceuticals (defibrotide)
  – Alexion (eculizumab)

Learning Objectives

• Help you understand the diagnosis of aplastic anemia.
• Translate your understanding of aplastic anemia into options for treatment that are data based.
• Empower you to discuss with your physician treatment options.

Differential Diagnosis for Pancytopenia

• Acquired Severe Aplastic Anemia
• Inherited Marrow Failure Syndrome
  – Fanconi Anemia
  – Dyskeratosis Congenita
  – Schwachman-Diamond Syndrome
• MDS
• Leukemia
• Autoimmune Disease
• Nutritional Deficiencies

What is Aplastic Anemia

• Acquired Aplastic Anemia is a disease caused by too few hematopoietic progenitor cells leading to too few red blood cells, white blood cells, and platelets.
• Acquired Aplastic Anemia needs to be differentiated from inherited bone marrow failure syndromes.
CAMITTA CRITERIA for SEVERITY of APLASTIC ANEMIA

- SEVERE AA (SAA)
  PERIPHERAL BLOOD (2 of 3):
  - PMN < 500/ul
  - PLATELETS < 20,000/ul
  - RETICULOCYTES < 20,000/ul (< 1%)
  MARROW: hypocellular
- VERY SEVERE AA (VSAA): PMN < 200
- MILD AA: LESS AFFECTED THAN SAA

The Bone Marrow is Aplastic: Is it Acquired Aplastic Anemia?

- Important to discriminate between an inherited bone marrow failure syndrome and acquired aplastic anemia.
- Presentation is in adulthood as well as childhood.
- Proper treatment is based on the correct diagnosis.
- www.marrowfailure.cancer.gov

Inherited Bone Marrow Failure Syndromes

- Fanconi Anemia- 40% without physical stigmata so must do diagnostic/functional DEB test to look for chromosome breakage.
  - If DEB test abnormal, genetic testing to classify defect.
- Dyskeratosis Congenita- Classic telomere biology disease.
  - Nail dystrophy, leukoplakia, lung and liver disease significant.
  - Telomere length analysis is becoming a standard (?) test (stay tuned).
  - Genetic testing commercially available.

Inherited Bone Marrow Failure Syndromes

- Schwachman-Diamond Syndrome-SBDS gene defect. Exocrine pancreatic deficiency and neutropenia.
  - Isoamylase and Trypsinogen are easy screening tests.
  - Genetic Testing commercially available.
- Congenital Amegakaryocytic Thrombocytopenia-MPL gene defect. Profound thrombocytopenia even at birth.
  - Genetic testing commercially available.

Telomeres 101

- Telomeres are repeat sequences at the ends of chromosomes, which are protective chromosomal material.
- Molecular mechanisms have evolved to maintain telomere length and protective function.
- Mutations in the genes that maintain and protect telomeres cause human disease including marrow failure, liver fibrosis and lung fibrosis.
- Androgen’s can help certain patients with telomere disease.
- Dyskeratosis Congenita is the classic disease of telomere biology.
- Townsley, Bumitru and Young “Bone Marrow Failure and the telomeropathies”
  - DOI http://dx.doi.org/10.1182/blood-2014-05-526285

My patient has acquired SAA: What was the trigger?

- Inciting event leads to an immune mediated destruction of blood progenitor cells
- Trigger is usually not identified
- Check for CMV, EBV, HHV-6, Parvovirus, Hepatitis viruses
- History of jaundice
- Medication history
- Exposures
Pathophysiology of acquired aplastic anemia.

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Venn diagram of the clinical and pathophysiologic relationships among the bone marrow failure syndromes, leukemia, and autoimmune diseases.

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Pure Red Cell Aplasia=One Cell Line Down

CLASSIFICATION

Isolated reticulocytopenic anemias

Inherited

Congenital Anemias

BMF

Acquired

Secondary

Idiopathic

Autimmune

Viral

• CLL
• LGL
• MGUS
• CVID
• Good's syndrome
• Drug-induced
• ACD

• Transient aplastic crisis, B19
• Other viruses

The Bone Marrow Garden: Healthy Blood Stem Cells

Red Blood Cells

White Blood Cells
Healthy Platelets

Aplastic Anemia

Aplastic Anemia with T Cells

Aplastic Anemia with T Cells

Aplastic Anemia with T Cells

Aplastic Anemia—Fewer Stem Cells & Fewer Flowers
Aplastic Anemia—Fewer Flowers

Treating Bone Marrow Failure

Treating Aplastic Anemia

Immune Suppression Medications
Treatment Options for your bone marrow garden

- Bone Marrow Transplant
  - Immune suppresses and re-seeds the marrow with someone else's blood stem cells to restore the garden.
- Intensive Immune Suppression
  - Immune suppresses and use your own blood stem cells to restore the garden.
- Eltrombopag
  - Helps the seeds in the garden to grow better.

Case

- 15 year old male with newly diagnosed SAA.
- No prior transfusions.
- HLA Matched sibling is available.
- Work-up for Inherited Bone Marrow Failure Syndromes is negative.
Conventional Transplant

- HLA matched sibling transplants are an established curative approach to SAA.
- Other options include Intensive Immune Suppression (ATG or HighCY).
- Does the data continue to support Matched Sibling BMT as the first choice when available?

What is the data for an Adolescent with SAA

- Dufour et al 2014 “Outcome of AA in Adolescence: Report from the EBMT.
- N=537 patients aged 12-18 years in EBMT database (10 year period from 2000-2010).
  - MFD as first line
  - Front line IST not followed by BMT
  - Front line IST followed by BMT due to failed upfront IST.

- OVERALL SURVIVAL
- IST GROUP INCLUDES PEOPLE GOING TO BMT LATER
- EVENT-FREE SURVIVAL
- IST GROUP INCLUDES PEOPLE GOING TO BMT LATER
Conclusions

• In summary, this study demonstrates that AA in adolescents has a very good outcome.
• If an MFD is available, HSCT performed either in an adult or in a pediatric center using BM cells within two months of diagnosis is the first treatment choice.
• If an MFD is not available, for the moment, IST using the combination of ATG and CSA is still an acceptable second therapeutic choice.
  – This is largely because if IST fails, HSCT represents a very good rescue alternative both in terms of OS and EFS.
• Previous IST increases the risk of post-therapy tumors that must be monitored during long-term follow up.

Take Home Message

• Upfront matched sibling Bone Marrow Transplant is the treatment of choice for SAA in children and young adults due to excellent long term survival with few late effects.
  – c GVHD is the most impactful late effect
• Continued tinkering of the conditioning regimen and GVHD prevention strategies to minimize late effects especially c GVHD.
  – Campath, Fludarabine

Risk/Benefit

• Medical Decision Making is rooted in risk/benefit.
• Ideally, RCT help us make evidence based decisions.
• The art of medicine is making decisions when you don't have all the data you would like. [Bruce Camitta].
• Are we at a time to question the dogma of IST>MUD for children and young adults with SAA?

Immune Suppression Therapy

• Multiple approaches.
• NHLBI and EBMT set the benchmarks.
• Hopkins High CY approach
• NHLBI “gold standard” is ATG/CSA/Prednisone (Rosenfeld 1995, Young 2003, Scheinberg 2008)
• http://www.nhlbi.nih.gov/studies/nhlbi-trials/browse-category
  --Eltrombopag in addition to standard hATG/CSA for newly diagnosed patients with SAA. [HOT OFF THE PRESS..NEJM APRIL 20, 2017]

Case

• 10 year old girl with newly diagnosed acquired SAA
• 3 siblings, no HLA match
• Options:
  – Immune Suppression Therapy
  – Alternative donor HPC transplant
  – As outcomes change, should recommendations change?
What is the data re: IST and how does that affect decision making regarding BMT?

- Data from NIH
  - JAMA 2003
  - NEJM April 20, 2017

[Image: Late Events After Immunosuppressive Therapy]
RELAPSE: up to 46%
CLONAL EVOLUTION: MDS/MONOSOMY 7; 10-15%

[Image: Survival for Entire Cohort]
ALL PATIENTS: 60% survival
RESPONSE AT THREE MONTHS

[Image: Study Overview]
In a phase 2 clinical trial, eltrombopag plus standard immunosuppression resulted in a 6-month complete-response rate of 58% among patients receiving eltrombopag for 6 months.
Immunosuppression alone has induced complete responses in approximately 10% of patients historically.

[Image: Study Design and Treatment Plan According to Cohort]

[Image: Original Article]
Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia
Danielle M. Townsley, M.D., Phillip Scheinberg, M.D., Thomas Winkler, M.D., Ronan Desmond, M.D., Bogdan Dumitriu, M.D., Oiga Rios, R.N., Barbara Weinstock, B.S.N., Janet Valdez, P.A., Jennifer Lotter, P.A., Xingmin Feng, Ph.D., Marie Dessero, B.S., Harshraj Leuva, M.B., B.S., Margaret Bevans, Ph.D., Colin Wu, Ph.D., Andre Larochelle, M.D., Ph.D., Katherine R. Calvo, M.D., Cynthia E. Dunbar, M.D., and Neal S. Young, M.D.

N Engl J Med
Volume 376(16):1540-1550
April 20, 2017
Characteristics of the Patients at Baseline.

### 20% Pediatric Cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Incident (n=500)</th>
<th>Baseline (n=500)</th>
<th>Change (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>248 (49.6%)</td>
<td>246 (49.2%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Female</td>
<td>252 (50.4%)</td>
<td>254 (50.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>307 (61.4%)</td>
<td>309 (61.8%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Black</td>
<td>87 (17.4%)</td>
<td>85 (17.0%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>25 (5.0%)</td>
<td>26 (5.2%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>31 (6.2%)</td>
<td>30 (6.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe aplastic anemia</td>
<td>300 (60.0%)</td>
<td>298 (60.0%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Other</td>
<td>200 (40.0%)</td>
<td>202 (40.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hematologic Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Remission</td>
<td>100 (20.0%)</td>
<td>100 (20.0%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Partial Remission</td>
<td>150 (30.0%)</td>
<td>150 (30.0%)</td>
<td></td>
</tr>
<tr>
<td>No Response</td>
<td>150 (30.0%)</td>
<td>150 (30.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or Higher</td>
<td>50 (10.0%)</td>
<td>50 (10.0%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>10 (2.0%)</td>
<td>10 (2.0%)</td>
<td></td>
</tr>
</tbody>
</table>

### Adverse Events of Grade 3 or Higher or Serious Adverse Events Attributed to Eltrombopag.

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients (n=500)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucocutaneous rash</strong></td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td><strong>Phlebitis</strong></td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td><strong>Increased aminotransferase level</strong></td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td><strong>Increased aminotransferase level</strong></td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td><strong>Increased platelet aggregation</strong></td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

### Risk/Benefit? What is the data for Alternative Donor BMT in the current era?

- **Era’s (DM) in Unrelated donor BMT for SAA**
  - Pre Camitta era (pre 1988): 25% survival
    - (Greetings, Born to Run, Darkness, The River, Born in the USA)
  - Camitta era (1988-2000): 50-60% survival
    - (Tunnel of Love, Human Touch, Lucky-Town, Tom Joad)
  - Fludarabine Era (2000-present): >80% survival
    - (The Rising, Magic, Dream, Wrecking Ball, High Hopes)
  - Bacigalupo: reduction in CY and TBI dosing
  - Deeg: reduction in TBI dosing followed by reduction in CY dosing
  - Marsh: Use of Alemtuzumab and avoiding TBI in many cases.
Well Matched UNR donor BMT in the Current Era (2005)

- Significant improvements in outcomes in the last 10-15 years reproduced in North America, Europe, and Asia.
  - Deeg (BBMT 2001)
  - Bacigalupo (BMT 2005, Haematologica 2010)
  - Samarasinghe (BJH 2012)
  - Marsh (BMT 2014)
- Common themes include the use of Fludarabine and Cyclophosphamide in the conditioning regimen and bone marrow as the HPC source
- TBI dose eliminated or low (200 cGy=2Gy)

Excellent outcome of matched unrelated donor transplantation in paediatric aplastic anaemia following failure with immunosuppressive therapy: a United Kingdom multicentre retrospective experience

- Samarasinghe et al.
- BJH 2012
- N=44 for transplant with this package
  - Also evaluated those receiving IST first with rabbit ATG/CSA
  - All donors matched at A,B,C,DRB1,DQB1
- Fludarabine 150 mg/m2
- Cyclophosphamide
  - 11: CY 200; 33: CY120
- Alemtuzumab (Campath)
  - 14: 0.3 mg/kg/day x3
  - 30: 0.2 mg/kg/day x5

Samarasinghe et al. BJH 2012

MUD HSCT 2012

<table>
<thead>
<tr>
<th>Numbers</th>
<th>44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median year of diagnosis (range)</td>
<td>2006 (2000-2010)</td>
</tr>
<tr>
<td>Median age at HSCT (range), years</td>
<td>1 (3-8-15)</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>19 (43.2%)/25 (56.8%)</td>
</tr>
<tr>
<td>SAA/SSA</td>
<td>25/19 (56.8%/43.2%)</td>
</tr>
<tr>
<td>Prior IST (number of IST courses)</td>
<td>40 (90-0%) (1-1 IST, 8 x 2 IST, 1 x 3 IST)</td>
</tr>
<tr>
<td>No prior IST</td>
<td>4 (9.1%)</td>
</tr>
<tr>
<td>Median year of HSCT (range)</td>
<td>2007 (2004-2010)</td>
</tr>
<tr>
<td>Median interval between IST and HSCT (range), years</td>
<td>0 (5-0)</td>
</tr>
<tr>
<td>Stem cell source: bone marrow PBSC</td>
<td>26 (59.1%)/18 (40.9%)</td>
</tr>
<tr>
<td>CD34 (10^6/kg) (n = 35)</td>
<td>5.8 (1-17-5)</td>
</tr>
<tr>
<td>CD3 (10^5/kg) (n = 15)</td>
<td>30.5 (2-8-11)</td>
</tr>
<tr>
<td>Median Follow-up (years)</td>
<td>2.9 (1-6.3)</td>
</tr>
</tbody>
</table>

(A) Children with Idiopathic SAA who received Rabbit ATG/Cyclosporin as first-line therapy. The 5-year estimated failure-free survival (FFS) following immunosuppressive therapy was 13.3% (95% CI 4.0 to 27.8) and overall survival (OS) was 94.2% (95% CI 78.7 to 98.6). (n = 43).

(B) OS and FFS following matched unrelated donor-haematopoietic stem cell transplantation with the FCC (Fludarabine, cyclophosphamide, alemtuzumab) regimen. The estimated 5-year OS/FFS following HSCT was 95.01% (95% CI 81.38 to 98.74). (n = 44)
Outcomes from Marsh et al. 2011: Alemtuzumab/Fludarabine/Cytoxan based regimen


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Take Home Message

• Well matched unrelated donor bone marrow transplants have excellent survival with conditioning regimens that should limit late effects.
  – Mismatching and age are risk factors for rejection.
• Don’t be afraid to transplant in the current era.
• Continued refinement of the conditioning regimen to prevent rejection and GVHD prevention strategies to minimize late effects especially cGVHD.
  – Campath, Fludarabine (Marsh data)

What if one approached MUD like we do MSD Transplants for SAA?

• Ideally, a question for a RCT.
• However, this has taken off in Europe due to the data from Marsh and Bacigalupo.
• Case/Controlled Study provides provocative data.
• Dufour et al BJH 2015
  – Doi: 10.1111/bjh.13614

METHODS: Dufour et al. BJH 2015

• Upfront MUD/MMUD HSCT cohort
• Data from 29 consecutive children who all lacked a MSD but then who went on to receive an upfront unrelated donor HSCT was collected retrospectively from nine UK paediatric centres where HSCTs were performed between December 2005 and April 2014.
• High resolution tissue typing (four digit matching) was done at ten alleles (HLA-A, -B, -C, -DRB1, -DQ): 24-10/10; 5-9/10
• Matched historical controls
• The upfront MUD/MMUD cohort were then compared to historical controls from the EBMT SAA database who had undergone a first-line therapy with MSD HSCT or IST with horse ATG (lymphoglobulin) and ciclosporin or second-line therapy with MUD HSCT post-failed IST.
• Controls were extracted from the EBMT SAA Working Party database from the period spanning 1 January 2000 to 31 December 2009.

OVERALL SURVIVAL
MUD vs IST using eATG and CSA

EVENT-FREE SURVIVAL
upfront MSD VS
upfront MUD

OVERALL SURVIVAL
upfront MSD VS
upfront MUD
Conclusions

• IF no MSD available, a rapid unrelated donor search should be done.
• If there is a “high likelihood” of a MUD being available in 3-4 months of diagnosis, there should be a careful discussion between clinicians and families about the pro’s and con’s of upfront MUD HSCT.
• If low likelihood, proceed to IST.
• Make decision between 6-8 weeks from diagnosis to avoid impact of success of IST.
• Hopefully a RCT in US will look at this question.

Are all BMT outcomes for SAA as wonderful as the European Data?

• Role of race in BMT outcomes.
• Data points out that we may not be as good as we think we are (DAM opinion).
• “Effect of race on outcomes after allogeneic HPC transplant for SAA” by Eckrich et al.

Role of Race-Eckrich et al 2014
Am. J. Hematol. 89:125-129

• Registry review of US center transplants from 1990-2008
• Cases=84 African Americans – (median age 17)
• Controls=215 Caucasians – (median age 17)

The 5-year probability of overall survival, adjusted for interval from diagnosis to transplantation and performance score, was lower for African Americans 58% (95% CI 48-68) compared to Caucasians 73% (95% CI 67-79).

The adjusted probability of overall survival of patients after HLA-matched sibling donor transplantation by patient race (86% v 70%).  P value=0.02

The adjusted probability of overall survival of patients after unrelated donor transplantation by patient race (57% v 43).  P value 0.07
Alternative, Alternative Donor Transplant: Everyone has a donor!

- Haplo/Cord experience led by Rick Childs at NHLBI
- Haplo “Post Transplant Cyclophosphamide” Experience led by Dr. Amy DeZern at Hopkins
- Double Cord Blood Transplant Experience led by Regis Peffault deLatour.
- All show promising data.
- All should be done as part of a clinical trial IMHO.
  - Role of Eltrombopag instead of these options?

Is there anything besides BMT and Immune Suppression for refractory aplastic anemia?

- Eltrombopag Story.
- Eltrombopag is a thrombopoietin agonist.
- Dr. Cynthia Dunbar gets credit for thinking it may help with SAA.
- Initial study was for SAA patients without platelet recovery....

Original Article
Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

Matthew J. Olnes, M.D., Ph.D., Philip Scheinberg, M.D., Katherine R. Calvo, M.D., Ronan Desmond, M.D., Yong Tang, M.D., Ph.D., Bogdan Dumitriu, M.D., Ankur R. Parikh, M.D., Susan Soto, B.S.N., Angelique Biancotto, Ph.D., Yongmin Fang, M.D., Ph.D., Jay Lazor, M.D., Ph.D., Colin O. Wu, Ph.D., Neal S. Young, M.D., and Cynthia E. Dunbar, M.D.

N Engl J Med
Volume 367(1):11-19
July 5, 2012

Lineage Characteristics of Responses to Eltrombopag.

12 Wk — Primary End Point

Most Recent Follow-up

- Plueues
- Red cells
- Neutrophils
Bone Marrow Cellularity at Baseline and at 8 Months or Longer in Four Patients with Trilineage Responses to Eltrombopag.

- A phase 2 study showed a 44% response rate with eltrombopag, an oral thrombopoietin mimetic, among 25 patients with refractory aplastic anemia.

Conclusions
- Treatment with eltrombopag was associated with multilineage clinical responses in some patients with refractory severe aplastic anemia.

Questions in the Eltrombopag Era
- How will eltrombopag in combination with intensive immune suppression affect short term and long term outcomes? (Recent NHLBI study)
- Timing of alternative (alternative) donor transplants when eltrombopag is available?
- Concern for clonal hematopoiesis.

Eltrombopag FDA Approval
- In August 2014, eltrombopag was approved by the FDA for use in patients with SAA who have had an inadequate response to immune suppression therapy.
  - Personal communication: “...for those who do not have a good transplant option...”

Treatment Algorithm for SAA (Korthof et al for the EBMT. BMT 2013)
- A. Matched Sibling BMT
  - First Line Therapy
- B. Immune Suppression vs. Unrelated donor BMT
  - If no matched sibling, then IST is first line
- C. Unrelated Donor BMT
  - No response to IST or relapse after IST
- D. Haploidentical BMT
  - Rescue from primary graft failure
  - Urgent need due to neutrophil counts

Treatment Algorithm for SAA (Korthof et al for the EBMT. BMT 2013) with DAM opinions
- A. Matched Sibling BMT
  - First Line Therapy
- B/C. Immune Suppression and/or Unrelated donor BMT
  - If no matched sibling, ideally need a RCT.
  - In absence of open RCT, consider the crucial conversations in the informed consent process.
  - Set “lines in the sand” for all options and get the donors in the bullpen please.
- D. Alternative/Alternative donor BMT
  - Consider for relapse or refractory SAA
  - Urgent need due to neutrophil count
Learning Objectives

- Help you understand the diagnosis of aplastic anemia.
- Translate your understanding of aplastic anemia into options for treatment that are data based.
- Empower you to discuss with your physician treatment options.

THREAT OF IDIOPHATIC PRCA

Idiopathic PRCA:

Primary:
- Cytoxan po +/- Prednisone: minimum 3 months; monitor levels and retic
- Cytosine arabinoside: 6-8 weeks start with 25mg increase to 50mg monitor PIII and neutrophils, response may occur when drug d/c due to myelotoxicity

Salvage:
- ATG: Atgam 40 mg/kg/day x 4 days + seolometrol 1mg/Kg iv
- Campath: 10mg sc per week for 10 weeks
- Anadrol: 25 mg po ed
- Danazol: up to 200 mg po tid
- HSCT

Salvage in patients with MGUS:
- Velcade + dexamethasone

Salvage in patients with hypoglobulinemia:
- IVIG

THANK YOU!!!