Aplastic Anemia: Current Thinking on the Disease, Diagnosis, and Non-Transplant Treatment

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Objectives

• Review Current Thinking regarding differential diagnosis and physiology for a patient with bone marrow failure.
• Review Current Treatment Options.
• Discuss Current Treatment Algorithm
• Answer Questions as Best as Possible

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

When Should I think of Aplastic Anemia?

• Clues to the diagnosis:
  • Reasonably well appearing
  • More than one cell line affected
  • No significant lymphadenopathy or hepatosplenomegaly
When Should I think of Aplastic Anemia?

- Diagnostic Procedures:
  - CBC with manual differential/retic count
  - Bone Marrow Aspirate and Biopsy
  - Chromosomes/Flow Cytometry to look for malignancy and MDS
  - CD59 expression to look for evidence of paroxysmal nocturnal hemoglobinuria

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

- Important to discriminate between an inherited bone marrow failure syndrome and acquired aplastic anemia.
- 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.

- 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.

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.
Somatic mutations in lymphocytes might drive an aberrant immune response.

**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.
- Dyskeratosis Congenita is the classic disease of telomere biology.
- Townsley, Bumitru and Young “Bone Marrow Failure and the telomeropathies”
  - Prepublished 9/18/2014
  - DOI http://dx.doi.org/10.1182/blood-2014-05-526285

**Mechanisms of telomere attrition.**

- Patients with telomeropathies may be particularly responsive to male hormones.
- The mechanism of action of male hormones is likely direct modulation of TERT gene expression to increase telomerase, as inferred from tissue culture experiments and mouse models.
- Male hormones might help to slow the rate of telomere attrition, enhance cell regeneration, and improve not only hematopoiesis but also other organ dysfunction resulting from telomere attrition.
- In a prospective research trial at the National Institutes of Health that has enrolled >24 patients (clinicaltrials.gov identifier: #NCT0144137), danazol appears effective in improving blood counts and reversing telomere attrition.
Case 1

- 25 year old Caucasian female presents with a chief complaint of a heavy menstrual period.
- Current period is now at 4-5 days and she is changing a pad every 1-2 hours instead of a few times a day.
- In retrospect, has had “red dots” for a week or so.
- No fevers. Has had fatigue and has felt light headed for last day or two.

Immune Suppression Therapy

- Multiple approaches.
- NHLBI and EBMT set the benchmarks.
- NHLBI “gold standard” is ATG/CSA/Prednisone [Rosenfeld 1995, Young 2003, Scheinberg 2008]
  - Alemtuzumab for refractory or relapsed SAA
  - Fludarabine/CY for refractory SAA
  - Eltrombopag in Aplastic Anemia Patients
  - Randomized trial of Alemtuzumab versus r-ATG/CSA

What is the data re: IST and how does that affect decision making regarding BMT?

- Data from NIH
  - JAMA 2003

Survival for Entire Cohort


ATG experience in Kids from NIH (Scheinberg et al. J of Peds 2008; Vol 153 page 814)

- N=77 treated from 1989-2006
- The overall response rate in children at 6 months was 74% (57/77); 35% had a CR and 65% had a PR. All of the children achieved transfusion independence.
- The cumulative incidence of relapse at 10 years was 33%: the median time to relapse was 558 days
  - No difference in the incidence of relapse was seen between those with CR and those with PR.

Late Events After Immunosuppressive Therapy

- RELAPSE-up to 40%
- CLONAL EVOLUTION: MDS/MONOSOMY 7 10-15%
Take Home Message

• When a patient with acquired SAA does not have a matched sibling, the recommendation is to proceed with intensive immune suppression following Rosenfeld et al., 1995 with EQUINE ATG/Cyclosporine/prednisone.
• Other options include high dose Cyclophosphamide at Hopkins.
• Always consider a clinical trial.
• Clinical trials are starting to focus on not only the immune system but on the stem cell compartment as well (stay tuned).

What is eltrombopag and why might it help a patient with Aplastic Anemia?

• 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....
Conclusions

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

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..."

Follow Up Study

- Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug.
- Blood 2014 (March 20)
- Ronan Desmond1,
- Danielle M. Townsley1,
- Bogdan Dumitriu1,
- Matthew J. Olnes2,
- Phillip Schenberg3,
- Margaret Revanz4,
- Ankur R. Parikh1,
- Kinneret Broder1,
- Katherine R. Calvo5,
- Colin O. Wu6,
- Neal S. Young1, and
- Cynthia E. Dunbar1

Methods

- N=44 (25 were in NEJM study)
- We modified the protocol in August 2012 to include tapering of eltrombopag and discontinuation in patients with platelets >50 x 10^9/L, hemoglobin >10 g/dL, and neutrophils >1 x 10^9/L for more than 8 weeks, without transfusions.
- Five patients fulfilled these criteria, and eltrombopag was tapered and then discontinued after a median of 28.5 months (range, 9-37 months).
- All 5 patients have maintained stable counts with a median follow-up off drug of 13 months.
- Their bone marrows have remained normocellular.
Clonal Evolution

- 43 patients received eltrombopag
- Eight patients developed clonal cytogenetic abnormalities during eltrombopag administration.
- Seven had a normal karyotype confirmed within 3 months of starting drug, assessed by conventional cytogenetics.
- One patient (42) had insufficient metaphases on his sample prior to entering the study but a normal karyotype 9 months prior to entering the study.
- None had increased myeloblasts.
- Clonal evolution events occurred in 6 of 8 nonresponding patients, and the new cytogenetic changes were detected on the marrow performed on response assessment.
- Two responding patients evolved. One responder (53), whose counts had been gradually increasing while on the extension arm, was noted to have falling counts at 13 months, and the marrow showed mild dyserythropoiesis and 13q deletion.
- A second responder (32) had stable blood counts and on routine evaluation marrow at 10 months had also developed del 13q, but no dysplastic features were seen. Chromosome 7 abnormalities developed in 3 of 8 evolvers. Because many of these evolvers proceeded immediately to transplant, sequential cytogenetics were available on only 4, who showed no significant changes in clone size 1 to 9 months later.

My (DAM) Conclusions

- NHLBI group has taught us that eltrombopag has a role in patients with SAA.
- We are still learning what that role is.
- Patients who have responded to eltrombopag can come off the medication and have sustained response.
- Clonal Evolution is risk that needs to be factored into decision making in individual cases.

What’s the next logical question?

- Moving forward, can we integrate immune suppression and stem cell numbers?

Stem cells as limiting in the response to immunosuppressive therapy.

↑ probability of failure

↑ probability of recovery

stem cell number

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- Other options include high dose Cyclophosphamide at Hopkins.
- Always consider a clinical trial.

Treatment Algorithm for SAA

(Korthof et al for the EBMT. BMT 2013)

- A. Matched Sibling BMT
  - First Line Therapy
- B. Immune Suppression
  - 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
Take Home Message—Now in Question

• The previous take home message in general is rooted in the risk/benefit analysis utilizing older data of alternative donor transplants.
• What is the current data (post 2005) for alternative donor transplants for children and young adults with SAA?

Alternative Donor Transplant

• Historically, the major barriers to survival have been rejection and GVHD.

The Milwaukee Experience—Updated

1987-2003
N=41
Median age 10 y (1-24 y)
Median F/U is 10.5 years (2y-17y)
Deaths due to rejection, regimen related toxicity

Margolis et al. BJH 1996

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)
Landmark Paper!

- Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-vs-host disease after allogeneic stem cell transplantation for acquired aplastic anemia
- Blood 2011
- Judith C. Marsh
- Vikas Gupta
- Zhi Lim
- Alyosha R. Hoj
- Robin M. Ireland
- Janet Hayden
- Victoria Pote
- Mickei B. Koh
- M. Serajul Islam
- Nigel Russell
- david I. Marks
- Ghulam J. Mufti
- and
- Antonio Pagliuca

Methods

- Conditioning with Fludarabine, Alemtuzumab, low dose cyclophosphamide.
- NO TBI for matched donors (related or Unrelated)
- N=21 matched sibling donors
- N=29 UNR donor
- Median Age=35 (8-62) (12 over 50)

Overall survival (OS) curves for the study

Excellent outcome of matched unrelated donor transplantation in paediatric aplastic anemia 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

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)
Current State “Areas of Controversy”

- Timing, Timing, Timing
- Preceding therapy
  - No courses of IST - Can we just move to upfront MUD UNR donor BMT for certain age and ethnic groups based on published data?
  - Is a study required?
  - Fortunately, the question is being asked!

Background and Rationale

Classical treatment algorithm of SAA forsees IST (ATG and CsA) as first-line option, if a MFD is not available.

IST: very good survival rate but high rate of failures.

UD vs MFD HSCT CASE CONTROL STUDY
1 UD HSCT vs 3 MFD HSCT

Matches: gender
  source of cells
  age at transplant
  Interval Dx-HSCT

Events:
  deaths
  rejection

UD 96% MFD 91%
P=0.32

UD 90% MFD 87%
P=0.32

Interval: Dx- neutrophil recovery
UD MFD
0.39 yrs 0.31 yrs p= 0.93

Background and Rationale

Faulty hematopoiesis limits quality of life of children & adolescents.

HSCT from MUD as front-line treatment with no prior failed IST, never investigated so far in a comparative way.

We compared the outcome of a UK cohort with historical matched controls from EBMT data base.

UD vs IST front-line
1 UD HSCT vs 2 IST front-line (Horse ATG: Lymphoglobulin)

Matches: gender
  age at treatment

Events:
  death
  relapse
  no response
  need for transplant
  clonal evolution

UD 96% IST 94%
P=0.64

UD 92% IST 40%
P=0.0001

Response 3 months after h ATG 46% (~ 3/4 partial)
6 months after h ATG 61% (~ 2/3 partial)

Jeong et al, Haematologica 14
MUD vs MUD post-failed IST

1 MUD upfront vs 1 MUD post-failed IST
Matches: gender
   age at transplant
   source of cells

What do these findings say

- UD HSCT fares: similar to MFD with no significantly longer interval Dx-neut engraft
  better than IST front-line
  better than MUD post failed IST

Limitations

- Retrospective
- Different conditioning and serotherapy (Alemtuzumab vs ATG)
- Caucasian patients higher chances to find a donor

Take Home Message

- MUD HSCT is a good front-line option in children & adolescents with SAA
- Caveats:
  - Start donor search at diagnosis
  - Evaluate likelihood of MUD HSCT feasibility in 3-4 months since diagnosis
  - Careful discussion with family/patient of MUD vs IST
- Need for care in specialized AA haematology centres

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Treatment Algorithm for SAA 2014: The Hard Cases

- No response to IST or relapse after IST
- Well matched (10/10 or 12/12) UNR donor go to BMT with data based confidence.
  - Very important to have doctor/patient relationship because survival is not 100% across the board.
- No well matched donor are the hard cases now.
  - eltrombopag
  - Alternative, Alternative donor BMT
    - Post CY Haplo vs. Haplo+Cord vs. Double Cord
    - Other immune suppression such as Alemtuzumab
THANK YOU!

• Aplastic Anemia and MDS International Foundation/Staff
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