Aplastic Anemia: Understanding Your Diagnosis and Treatments Options

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Disclosures

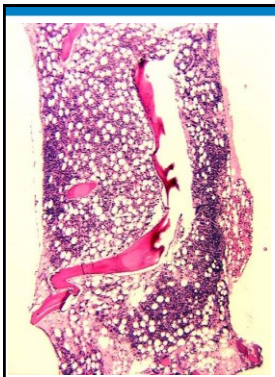
- Advisory Honoraria
  - Jazz Pharmaceuticals (defibrotide)
  - Alexion (eculizumab)

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.

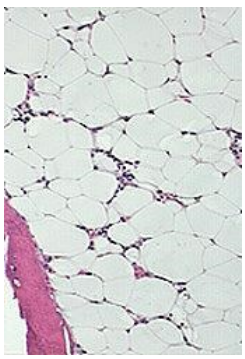
Differential Diagnosis for Pancytopenia

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



HEALTHY BONE MARROW

APLASTIC BONE MARROW



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.

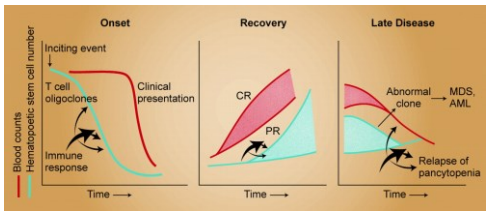
Telomeres 101

- 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
  - Young et al. Blood, 15 October 2006, Vol. 108, No. 8, pp. 2509-2519
- Trigger is usually not identified
- Check for CMV, EBV, HHV-6, Parvovirus, Hepatitis viruses
- History of jaundice
- Medication history
- Exposures

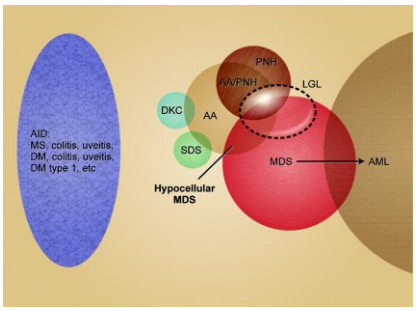
Pathophysiology of acquired aplastic anemia.



Neal S. Young et al. Blood 2006;108:2509-2519

blood

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



Neal S. Young et al. Blood 2006;108:2509-2519

blood

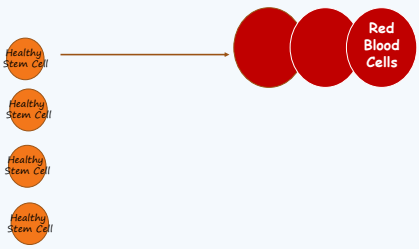
Pure Red Cell Aplasia=One Cell Line Down
CLASSIFICATION

- **Isolated reticulocytopenic anemias**
  - Inherited
    - Congenital Anemias
    - BMF
  - Acquired
    - Secondary
      - CLL
      - LGL
      - MGUS
      - CVID
      - Good's syndrome
      - Drug-induced
      - ACD
    - Idiopathic
      - Thymoma
    - Autoimmune
      - Epo antibodies
    - Viral
      - Transient aplastic crisis, B19
      - Other viruses

The Bone Marrow Garden: Healthy Blood Stem Cells

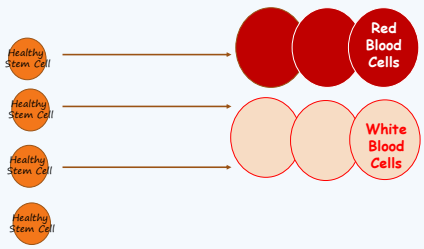
SEEDS FLOWERS

Red Blood Cells

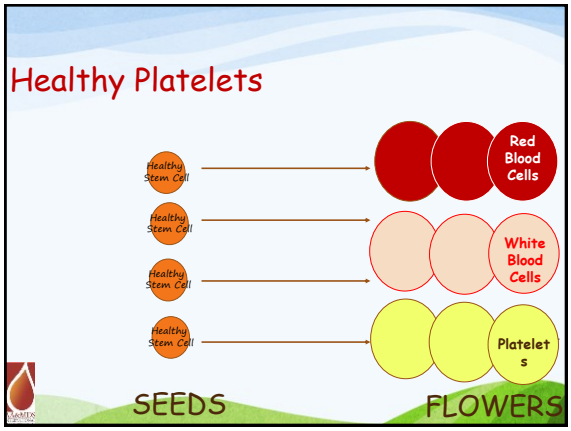


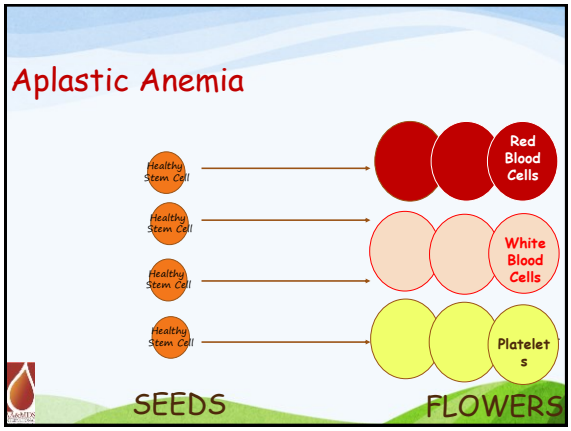
SEEDS FLOWERS

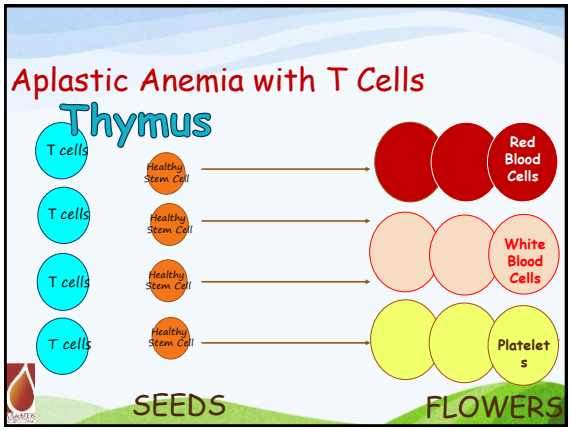
White Blood Cells

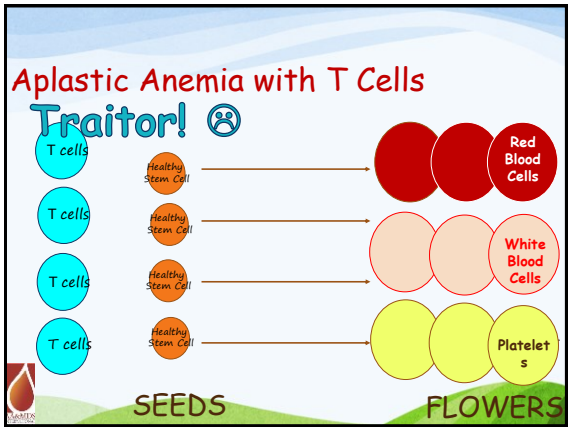


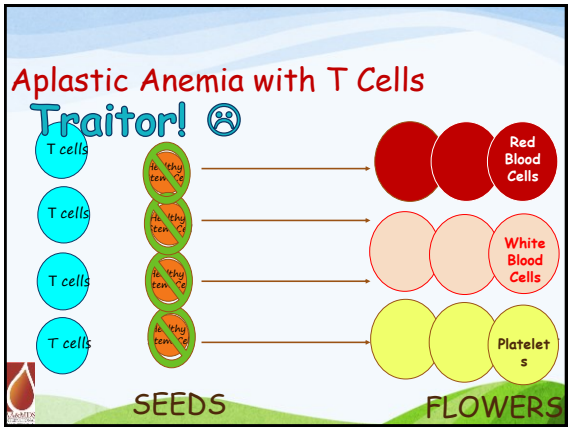
SEEDS FLOWERS

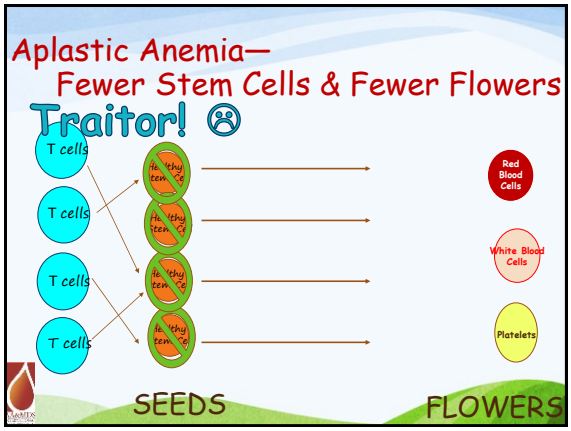

Healthy Platelets
Healthy Stem Cell
Healthy Stem Cell
Healthy Stem Cell
Healthy Stem Cell
Red Blood Cells
White Blood Cells
Platelets
SEEDS
FLOWERS

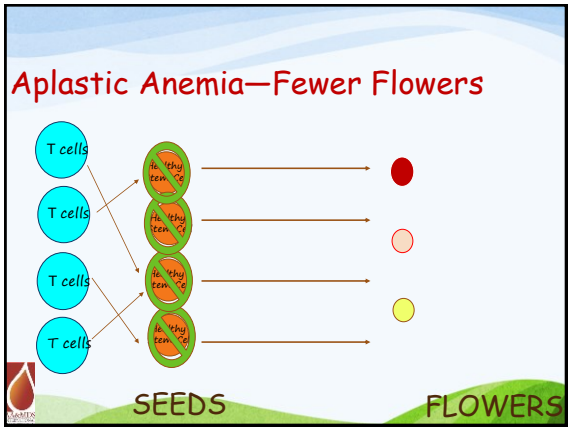

Aplastic Anemia
Healthy Stem Cell
Healthy Stem Cell
Healthy Stem Cell
Healthy Stem Cell
Red Blood Cells
White Blood Cells
Platelets
SEEDS
FLOWERS

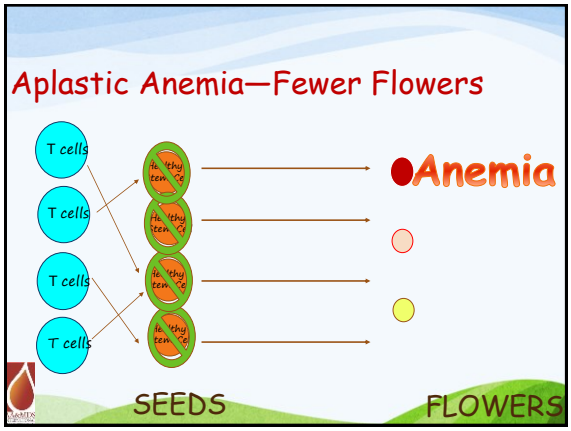

Aplastic Anemia with T Cells
Thymus
T cells
T cells
T cells
T cells
Healthy Stem Cell
Healthy Stem Cell
Healthy Stem Cell
Healthy Stem Cell
Red Blood Cells
White Blood Cells
Platelets
SEEDS
FLOWERS

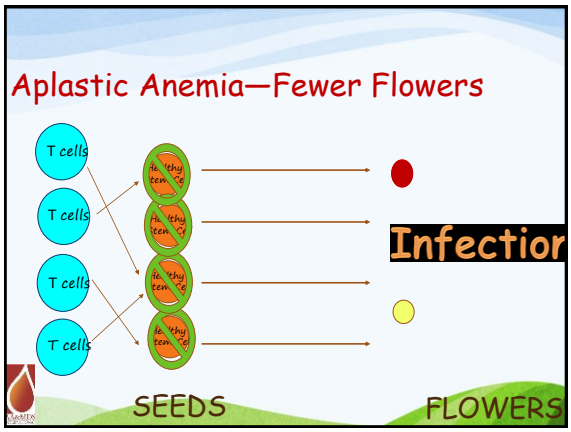

Aplastic Anemia with T Cells
Traitor! ☹
T cells
T cells
T cells
T cells
Healthy Stem Cell
Healthy Stem Cell
Healthy Stem Cell
Healthy Stem Cell
Red Blood Cells
White Blood Cells
Platelets
SEEDS
FLOWERS

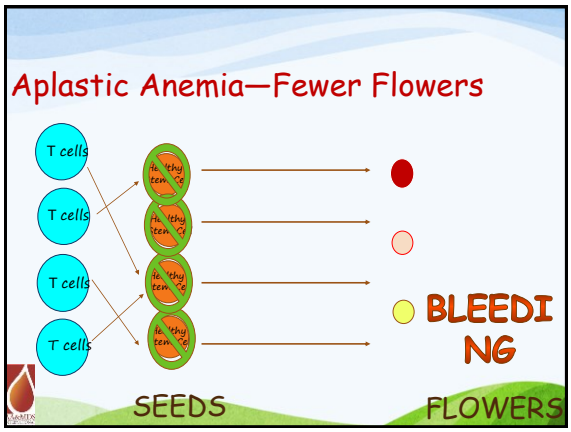

Aplastic Anemia with T Cells
Traitor! ☹
T cells
T cells
T cells
T cells
Red Blood Cells
White Blood Cells
Platelets
SEEDS
FLOWERS


Aplastic Anemia—
Fewer Stem Cells & Fewer Flowers
Traitor! ☹
T cells
T cells
T cells
T cells
Red Blood Cells
White Blood Cells
Platelets
SEEDS
FLOWERS

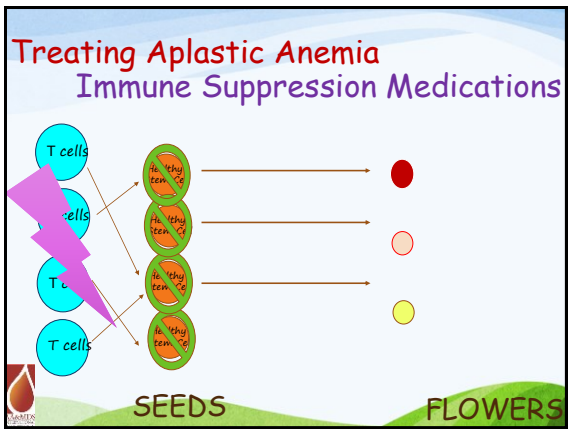

Aplastic Anemia—Fewer Flowers
T cells
T cells
T cells
T cells
SEEDS
FLOWERS

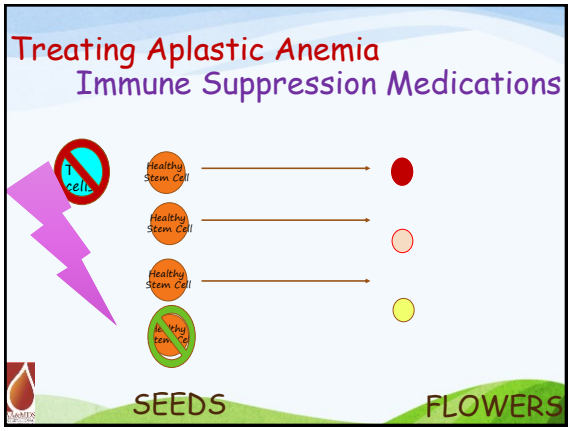

Aplastic Anemia—Fewer Flowers
T cells
T cells
T cells
T cells
Anemia
SEEDS
FLOWERS

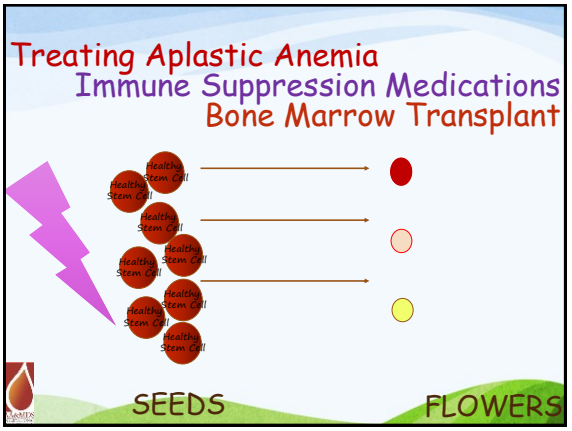

Aplastic Anemia—Fewer Flowers
T cells
T cells
T cells
T cells
Infection
SEEDS
FLOWERS

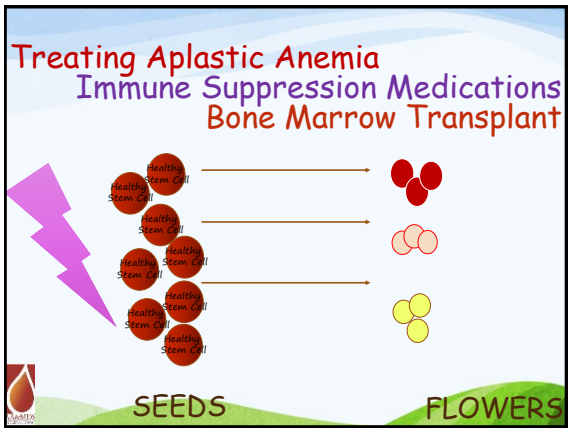

Aplastic Anemia—Fewer Flowers
T cells
T cells
T cells
T cells
BLEEDING
SEEDS
FLOWERS


Treating Bone Marrow Failure


Treating Aplastic Anemia
Immune Suppression Medications
T cells
T cells
SEEDS
FLOWERS







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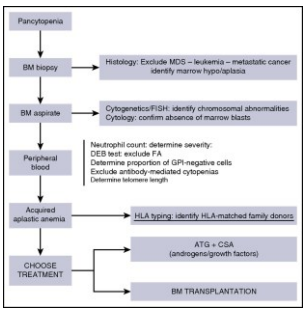
Treatment Options for your bone marrow garden

- 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.

Diagnostic procedures in patients with pancytopenia.



Andrea Bacigalupo Blood 2017;129:1428-1436

blood

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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 form 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.

A

Front-line IST (defined as IST)	143 pts
Pre 2007	118 pts (82%)
Post 2007	25 pts (18%)
No further treatment after IST (defined as IST alone in Methods)	64 pts (45%)

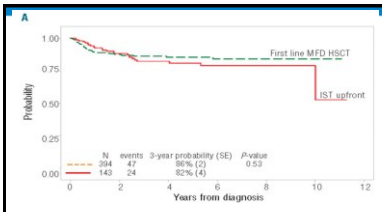
B

Transplantod population	HSCT after failed IST	Front-line MFD HSCT
473 pts	79 pts	394 pts
Donor		
MUD	64%	
MFD	23%	100%
MMF or MMUD	13%	
Conditioning		
Cy +Flu	41%	17%*
Cy alone	20%	72%*
Cy +Flu+others	18%	2.5%*
Cy+others	14%	6%*
Flu ± others	7%	2.5%*
ATG no/yes	49%/51%	42%/58%
GVHD PROPH		
CsA+Mtx	56%	73%
CsA	16%	18%
CsA +MMF	21%	5%
Others	15%	4%

MUD: matched unrelated donor; MFD: matched family donor; MMFD: mismatched family donor; MMUD: mismatched unrelated donor. *percentages are calculated from 321 of 394 patients of whom data were available.Cy: cyclophosphamide; Flu: fludarabine; ATG: globulin; CsA: cyclosporine A; MTX: methotrexate; MMF: mycophenolatemofetil. •percentages are calculated from 318 of 394 patients for whom data were available for MFD, 69% of grade 2/4 from 66 of 79 patients for whom data were available for HSCT.

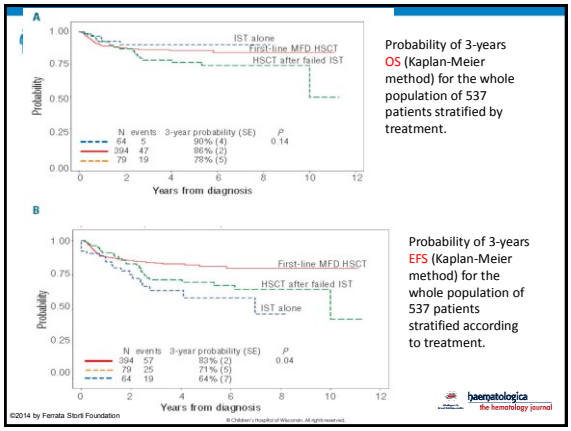
Pre 2007 eATG
Post 2007 rATG

Characteristics of 537 adolescents diagnosed with AA included in the study.



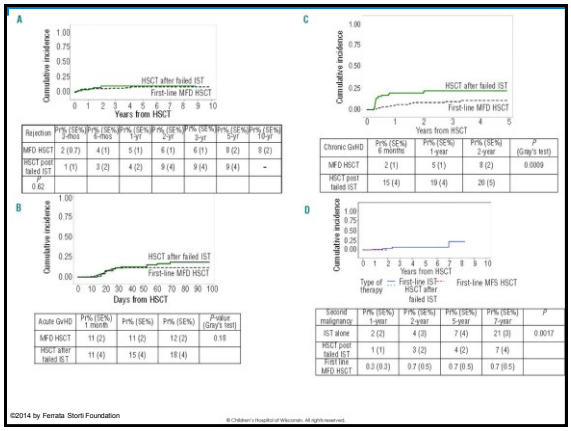
- OVERALL SURVIVAL
- IST GROUP INCLUDES PEOPLE GOING TO BMT LATER
- EVENT-FREE SURVIVAL
- IST GROUP INCLUDES PEOPLE GOING TO BMT LATER

Carlo Dufour et al. Haematologica 2014;99:1574-1581



Probability of 3-years OS (Kaplan-Meier method) for the whole population of 537 patients stratified by treatment.

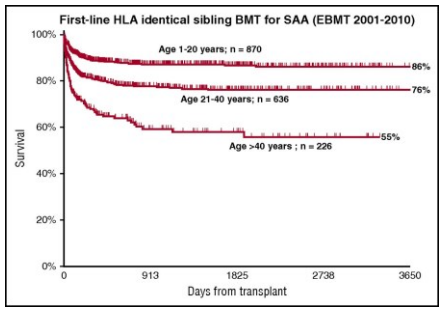
Probability of 3-years EFS (Kaplan-Meier method) for the whole population of 537 patients stratified according to treatment.



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.

A strong age effect in patients with aplastic anemia, after transplantation from an HLA identical sibling.



Andrea Bacigalupo Blood 2017;129:1428-1436

blood

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

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?

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

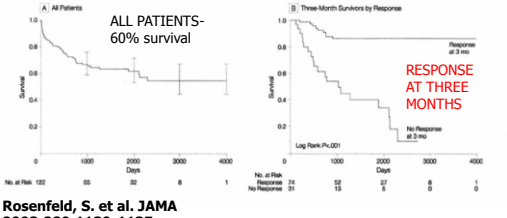
- Multiple approaches.
- NHLBI and EBMT set the benchmarks.
- Hopkins High CY approach
- NHLBI "gold standard" is ATG/CSA/Prednisone (Rosenfeld 1995, Young 2003, Scheinberg 2008)
- http://www.nhlbi.nih.gov/studies/nhlbi-trials/browse-category

  --Eltrombopag in addition to standard hATG/CSA for newly diagnosed patients with SAA (HOT OFF THE PRESS..NEJM APRIL 20, 2017)

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

- Data from NIH
  - JAMA 2003
  - Journal of Pediatrics 2008
  - NEJM April 20, 2017

Survival for Entire Cohort

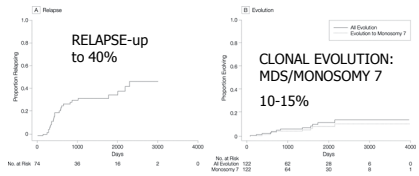


ALL PATIENTS-
60% survival

RESPONSE AT THREE MONTHS

Rosenfeld, S. et al. JAMA 2003;289:1130-1135.

Late Events After Immunosuppressive Therapy



RELAPSE-up to 40%

CLONAL EVOLUTION: MDS/MONOSOMY 7

10-15%

JAMA

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., Olga Rios, R.N., Barbara Weinstein, B.S.N., Janet Valdez, P.A., Jennifer Lotter, P.A., Xingmin Feng, Ph.D., Marie Desierto, 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

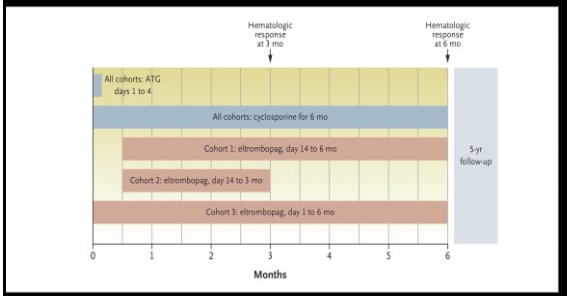
The NEW ENGLAND JOURNAL of MEDICINE

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.

The NEW ENGLAND JOURNAL of MEDICINE

Study Design and Treatment Plan According to Cohort.



Townsley DM et al. N Engl J Med 2017;376:1540-1550

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort 1 (N = 30)	Cohort 2 (N = 31)	Cohort 3 (N = 31)	All Patients (N = 92)
Age — yr				
Median	39	28	29	32
Range	12–72	3–68	11–82	3–82
Age distribution — no. (%)				
<18 yr	5 (17)	6 (19)	8 (26)	19 (21)
18–64 yr	20 (67)	23 (74)	18 (58)	61 (66)
≥65 yr	5 (17)	2 (6)	5 (16)	12 (13)
Sex — no. (%)				
Male	16 (53)	17 (55)	17 (55)	50 (54)
Female	14 (47)	14 (45)	14 (45)	42 (46)
GPI-deficient neutrophils†				
Range — %	<1–99	<1–99	<1–79	<1–99
Distribution — no./total no. (%)				
<1%	20/28 (71)	18/30 (60)	15/26 (58)	53/84 (63)
≥1%	8/28 (29)	12/30 (40)	11/26 (42)	31/84 (37)
Neutrophil count — per cubic millimeter				
Median	275	330	300	310
Range	0–1380	0–900	0–1810	0–1810
Reticulocyte count — per cubic millimeter				
Median	22,550	14,600	24,300	19,950
Range	2400–51,600	1600–52,900	2000–60,400	1600–60,400
Platelet count — per cubic millimeter				
Median	9500	8000	8000	9000
Range	2000–37,000	1000–14,000	0–27,000	0–37,000
Thrombopoietin — pg/ml				
Median	3133	3255	3111	3163
Range	1945–4443	1806–4955	2003–4793	1806–4955

* The baseline characteristics of the enrolled patients are shown according to cohort and in the total population of patients. All patients received horse antithymocyte globulin on days 1 to 4 and cyclosporine from day 1 to 6 months. All the patients received eltrombopag at an age-dependent dose, with cohort 1 receiving eltrombopag from day 14 to 6 months, cohort 2 from day 14 to 3 months, and cohort 3 from day 1 to 6 months. Patient 11 in cohort 1 was excluded from the analysis owing to ineligibility (Fig. S1A in the Supplementary Appendix). Patient 17 in cohort 1 had fluctuating blood counts at the 6-month time point owing to a viral infection and was categorized as having a complete response.
† Glycosylphosphatidylinositol (GPI)–deficient neutrophils could not be measured in eight patients owing to severe neutropenia.

Characteristics of the Patients at Baseline.

20% Pediatric Cohort

50

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Table 2. Hematologic Response in Patients Treated with Immunosuppression and Eltrombopag.*

Cohort and Response	Rate at 3 Mo	Rate at 6 Mo	P Value
Cohort 1			
No. of patients	30	30	
Response — no. (% [95% CI])			
Overall response	23 (77 [61–93])	24 (80 [65–95])	
Partial response	18 (60 [41–79])	14 (47 [28–66])	
Complete response	5 (17 [3–31])	10 (33 [15–51])	0.01
Cohort 2			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	24 (77 [62–93])	27 (87 [75–100])	
Partial response	16 (52 [33–70])	19 (61 [43–79])	
Complete response	8 (26 [9–42])	8 (26 [9–42])	0.06
Cohort 3			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	27 (87 [75–100])	29 (94 [84–103])	
Partial response	12 (39 [21–57])	11 (35 [18–53])	
Complete response	15 (48 [30–67])	18 (58 [40–76])	<0.001
All cohorts			
No. of patients	92	92	
Response — no. (% [95% CI])			
Overall response	74 (80 [72–89])	80 (87 [80–94])	<0.001†
Partial response	46 (50 [40–60])	44 (48 [37–58])	
Complete response	28 (30 [21–40])	36 (39 [29–49])	<0.001

* Complete response was defined as an absolute neutrophil count of at least 1000 per cubic millimeter, a hemoglobin level of at least 10 g per deciliter, and a platelet count of at least 100,000 per cubic millimeter. Partial response was defined as blood counts no longer meeting the criteria for severe aplastic anemia but not meeting the criteria for complete response. The results for overall response correspond to the proportions of patients with a partial or complete response. Three patients in cohort 1 withdrew from the study before 6 months, as did two patients in cohort 2 and one in cohort 3 (Fig. S1A, S1B, and S1C in the Supplementary Appendix). The P value is for testing the null hypothesis that the rate of complete response at 6 months would be 30% or greater. The 95% confidence intervals were computed on the basis of normal approximation.
† The overall response rate in all cohorts was an exploratory end point. The P value is for testing the comparison of the overall response rate to the overall response rate in a historical cohort (67 of 102 patients [66%]).

Hematologic Response in Patients Treated with Immunosuppression and Eltrombopag.

ALL COHORTS
80% OR AT 3 MONTHS
87% OR AT 6 MONTHS

30% CR AT 3 MONTHS
39% CR AT 6 MONTHS

0-1550

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

Event	Patients (N = 92)
	no. (%)
Skin	
Maculopapular rash†	2 (2)
Pruritus	1 (1)
Abdominal pain	2 (2)
Liver test abnormality	17 (18)
Increased alanine aminotransferase level	9 (10)
Increased aspartate aminotransferase level	3 (3)
Blood bilirubin increased	12 (13)

* All the adverse events of grade 3 or higher that were attributed by the investigators to eltrombopag are shown. The data-cutoff date was May 25, 2016. Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4. Patient 87 required a temporary dose reduction of cyclosporine and eltrombopag owing to conjugated bilirubinemia associated with pruritus. Eltrombopag was discontinued temporarily as mandated by the protocol in seven patients owing to a transient elevation in the liver-enzyme levels during the administration of antithymocyte globulin or during serum sickness that occurred during the first 2 weeks.
† Severe adverse events were observed in Patient 54 (in cohort 2) and Patient 86 (in cohort 3), who had maculopapular rashes of grade 3 and 2, respectively, that were associated with fever and oral pain and that resulted in hospitalization, discontinuation of eltrombopag, and treatment with glucocorticoids.

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

-1550

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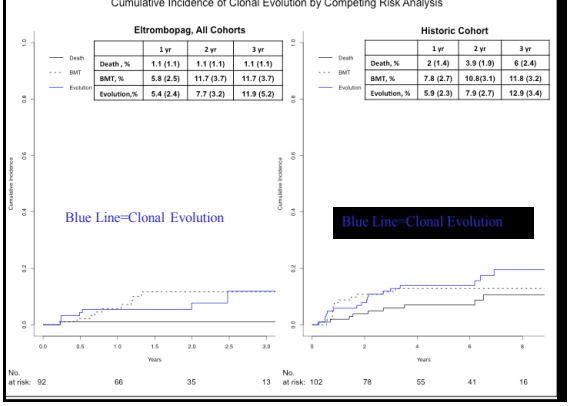
Cumulative Incidence of Clonal Evolution by Competing Risk Analysis

Eltrombopag, All Cohorts

	1 yr	2 yr	3 yr
Death , %	1.1 (1.1)	1.1 (1.1)	1.1 (1.1)
BMT, %	5.8 (2.5)	11.7 (3.7)	11.7 (3.7)
Evolution,%	5.4 (2.4)	7.7 (3.2)	11.9 (5.2)

Historic Cohort

	1 yr	2 yr	3 yr
Death, %	2 (1.4)	3.9 (1.9)	6 (2.4)
BMT, %	7.8 (2.7)	10.8(3.1)	11.8 (3.2)
Evolution, %	5.9 (2.3)	7.9 (2.7)	12.9 (3.4)



Blue Line=Clonal Evolution

Conclusions

- The addition of eltrombopag to immunosuppressive therapy was associated with markedly higher rates of hematologic response among patients with severe aplastic anemia than in a historical cohort.

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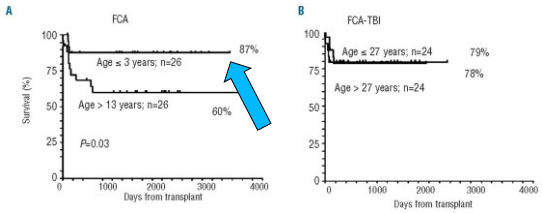
Risk/Benefit? What is the data for Alternative Donor BMT in the current era?

- 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)

(A) Effect of age in patients receiving FCA (left panel), stratified by the median age of 13 years.



Bacigalupo A et al. Haematologica 2010;95:976-982

haematologica the hematology journal

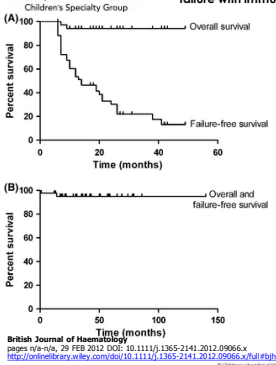
Excellent outcome of matched unrelated donor transplantation in paediatric aplastic anaemia following failure with immunosuppressive therapy: a United Kingdom multicentre retrospective experience

- 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
Numbers	44
Median year of diagnosis (range)	2006 (2000-2010)
Median age at HSCT (range), years	8·1 (3·8-19)
Gender (Male:Female)	19 (43·2%):25 (56·8%)
SAA/vSAA	25/19 (56·8%/ 43·2%)
Prior IST (number of IST courses)	40 (90·9%) (31 x 1 IST, 8 x 2 IST, 1 x 3 IST)
No prior IST	4 (9·1%)
Median year of HSCT (range)	2007 (2004-2010)
Median interval between IST and HSCT (range), years	0·75 (0·4-2)
Stem cell source: bone marrow/ PBSC	26 (59·1%)/18 (40·9%)
CD34 (x10^6/kg) (n = 35)	5·8 (1·1-17·5)
CD3 (x10^7/kg) (n = 35)	30·5 (2·8-101)
Median Follow-up (years)	2·9 (1·6·3)

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



(A)Children with Idiopathic SAA who received Rabbit ATG/Ciclosporin 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).

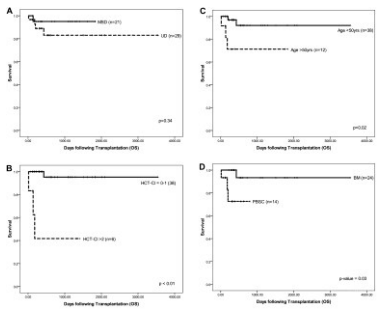
(B)OS and FFS following matched unrelated donor-haematopoietic stem cell transplantation with the FCC (fludarabine, cyclophosphamide, alemtuzumab) regimen. The estimated 5-year OS/FFS following HSCT was 95·01% (95% CI 81·38 to 98·74). (n = 44)

British Journal of Haematology
pages n/a-n/a, 29 FEB 2012 DOI: 10.1111/j.1365-2141.2012.09066.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09066.x/full#bjh9066-fig-0001

Samarasinghe et al. BJH 2012

	MUD HSCT
5-year cumulative incidence of acute GVHD	38·45% (95%CI 19·49-19·74)
5-year cumulative incidence of chronic GVHD	11·55% (95%CI 6·92-16·43)
5-year cumulative incidence of graft failure	0%
Median donor chimerism at last follow-up (n = 42)	100% (88-100%)
5-year cumulative incidence of clonal evolution	0%

Outcomes from Marsh et al. 2011: Alemtuzumab/Fludarabine/Cytoxan based regimen



Judith C. Marsh et al. Blood 2011;118:2351-2357

blood

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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)

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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

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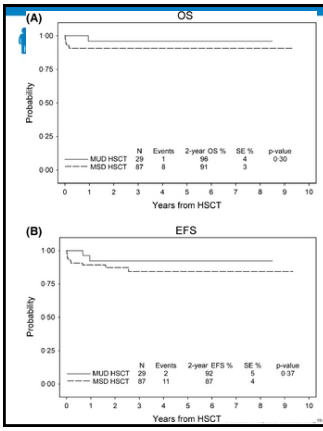
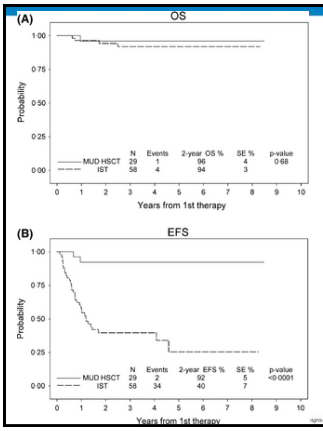
METHODS: Dufour et al. BJH 2015

- **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
upfront MSD VS
upfront MUD

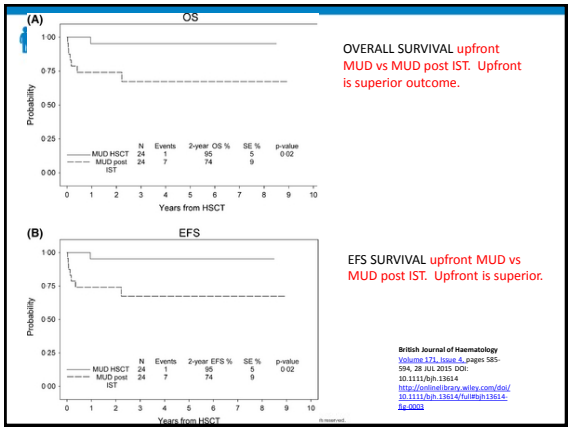
EVENT-FREE SURVIVAL
upfront MSD VS
upfront MUD



OVERALL SURVIVAL
MUD vs IST
using eATG and CSA

EFS SURVIVAL
MUD vs IST
using eATG and CSA

British Journal of Haematology
Volume 171, Issue 4, pages 585-594, 28 JUL 2015 DOI: 10.1111/bjh.13614
http://onlinelibrary.wiley.com/doi/10.1111/bjh.13614/full#bjh13614-fig-0002



OVERALL SURVIVAL upfront MUD vs MUD post IST. Upfront is superior outcome.

EFS SURVIVAL upfront MUD vs MUD post IST. Upfront is superior.

British Journal of Haematology
Volume 171, Issue 4, pages 585-594, 28 JUL 2015 DOI: 10.1111/bjh.13614
http://onlinelibrary.wiley.com/doi/10.1111/bjh.13614/full#bjh13614-fig-0003

Dufour et al. BJH 2015 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.

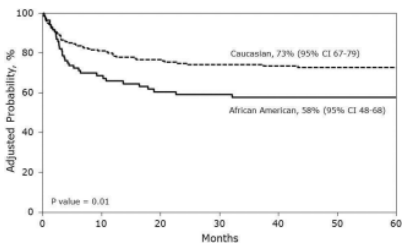
Are all BMT outcomes for SAA as wonderful as the European Data?

- 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)

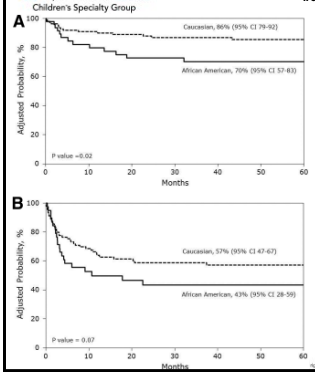
Effect of race on outcomes after allogeneic hematopoietic cell transplantation for severe aplastic anemia



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).

American Journal of Hematology
Volume 89, Issue 2, pages 125-129, 15 NOV 2013 DOI: 10.1002/ajh.23594
http://onlinelibrary.wiley.com/doi/10.1002/ajh.23594/full#ajh23594-fig-0001

Effect of race on outcomes after allogeneic hematopoietic cell transplantation for severe aplastic anemia



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?

Alternative, Alternative Donor Transplant: Everyone has a donor!

- Haplo "Post Transplant Cyclophosphamide" Experience
  - DeZern et al BBMT 3/2017
  - N=15 (primarily adults)
- With a median follow-up of 21 (range, 3 to 64) months (by reverse Kaplan-Meier method), all patients are alive, transfusion independent, and without evidence of clonality.
- No severe acute GVHD or extensive chronic GVHD.
- Very little GVHD.
- No significant viral infection complications.
- By 6 months after transplantation, all patients were back to their baseline Karnofsky or better and off prescription prophylaxis.

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., Phillip 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., Xingmin Feng, M.D., Ph.D., Jay Lozier, 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

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Patients (N = 26)
Age — yr	
Median	44
Range	18–77
Race or ethnic group — no. (%)†	
White	12 (46)
Black	7 (27)
Asian	1 (4)
Hispanic	6 (23)
Male sex — no. (%)	14 (54)
Time since diagnosis — mo	
Median	26
Range	13–138
Time since last intensive IST — mo	
Median	14
Range	6–117
Prior courses of intensive IST — no.	
Median	2
Range	1–4
Response to prior intensive IST — no. (%)‡	
Primary refractory	23 (88)
Relapsed refractory	3 (12)
Transfusions required — no. (%)	
Packed red cells	22 (85)
Platelets	26 (100)
PNH clone — no. (%)§	
≥1%	8 (31)
<1%	17 (65)
Laboratory values	
Platelets — $\times 10^{-3}$/mm^3	
Median	9
Range	5–15
Neutrophils — $\times 10^{-3}$/mm^3	
Median	0.8
Range	0.1–2.8
Hemoglobin — g/dl	
Median	[illegible]
Range	[illegible]–13.8
Thrombopoietin — pg/ml	
Median	2767
Range	1615–4618

Table 2. Clinical and Laboratory Adverse Events.*

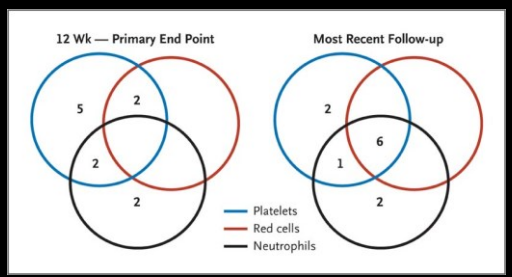
Event	Patients (N = 26)
	no. (%)
Upper respiratory infection	3 (12)
Fever	
Without culture-confirmed infection†	3 (12)
With culture-confirmed bacteremia‡	3 (12)
Musculoskeletal pain	2 (8)
Orthostatic hypotension	2 (8)
Rash	2 (8)
Shingles	1 (4)
Clostridium difficile colitis	1 (4)
Cellulitis	1 (4)
Abdominal pain	1 (4)
Nausea and vomiting	1 (4)
Viral hepatitis	1 (4)
Elevation of liver-enzyme levels	1 (4)
Gingival bleeding	1 (4)
Depression	1 (4)
Weakness	1 (4)
Myositis	1 (4)

* Adverse events of grade 2 or higher that occurred while the patient was receiving eltrombopag or within 30 days after discontinuation of the drug are listed. Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3), regardless of the likelihood that the event could be attributed to the study treatment.

† Patients who were classified as having fever without confirmed infection had fever that resulted in hospitalization owing to neutropenia and were treated with empirical antibiotics, without identification of the causative organism.

‡ Patients who were classified as having confirmed bacteremia had catheter-related *Staphylococcus aureus* infection, *Klebsiella pneumoniae* bacteremia, urinary tract infection with *Escherichia coli*, or *Pasteurella multocida* bacteremia.

Lineage Characteristics of Responses to Eltrombopag.



Olnes MJ et al. N Engl J Med 2012;367:11-19

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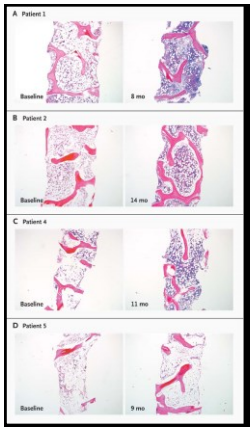

Bone Marrow Cellularity at Baseline and at 8 Months or Longer in Four Patients with Trilineage Responses to Eltrombopag.

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

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Conclusions

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

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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…"

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.

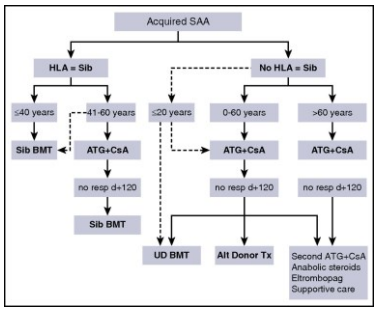
Treatment Algorithm for SAA (Korthof et al for the EBMT. BMT 2013)

- 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

Treatment strategy in patients with acquired aplastic anemia.



Andrea Bacigalupo Blood 2017;129:1428-1436

blood

THERAPY OF IDIOPHATIC PRCA

Idiopathic PRCA:

Primary

- CsA +/- Prednisone: minimum 3 months: monitor levels and retic
- Cytoxan po +/Predisone: 6-8 weeks start with 25mg increase to 50mg monitoor Ptl and neutrophils, response may occurr when drug d/c due to myelotoxicity

Salvage

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

Salvage in patient with MGUS:

- Velcade + decadrone

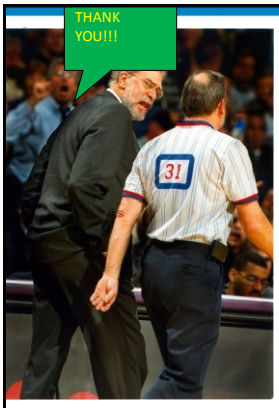
Salvage in patients with hypoglobulinamia:

- IvIG

Children's Hospital of Wisconsin
Children's Specialty Group

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.



- AAMDS for the invitation to speak.
- Our patients and their families.
- Our Advanced Practice Providers and nurses at the MACC Fund Center within Children's Hospital of Wisconsin.
- My local mentors Dr. Bruce Camitta and Dr. Jim Casper.
- Long distance mentors, colleagues and friends including Dr. Neal Young, Dr. Andre Bacigalupo, Dr. Judy Marsh, Dr. Regis Peffault de Latour amongst others ☺