Living with Aplastic Anemia

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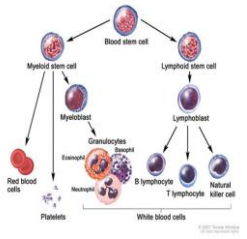
The function of the bone marrow

Bone Marrow Stem Cells Mature into Blood Cells



Mature Blood Cells and Health

Type	Function	Term
Red Cells	Carry oxygen	Anemia
Platelets	Prevent bleeding	Thrombocytopenia
White Cells		
Lymphocytes		
Monocytes		
Neutrophils	Prevent bacterial infections	Neutropenia
Eosinophils		
Basophils		

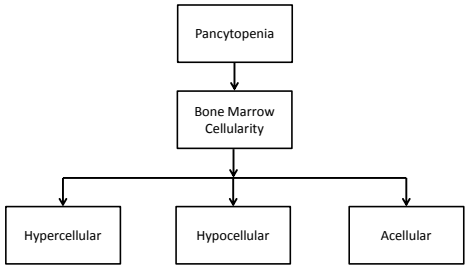
Symptoms and signs of bone marrow failure

- Anemia
  - Fatigue, shortness of breath, racing heart
- Neutropenia
  - Fever, skin or nail infections, ulcers
- Thrombocytopenia
  - Bruises, nose bleeds, gum bleeding

A Case Study - I

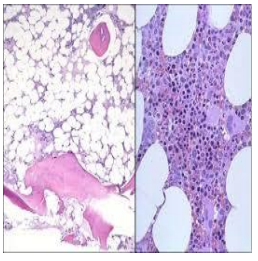
- JW is a 52 year old previously healthy man who presents with fatigue, low-grade fevers, and a large bruise on his thigh
- Complete blood count demonstrates pancytopenia
  - Hgb 6.9 gm% (Normal 13.6 – 17.0)
  - Neutrophils 500 per cu mm (normal 3.6 – 10.5)
  - Platelets 22,000 per cu mm (normal 150 – 450)
- Referred for further evaluation

Bone marrow cellularity is an essential clue



Hypocellular bone marrow failure

The Bone Marrow Biopsy



The Possible Explanations

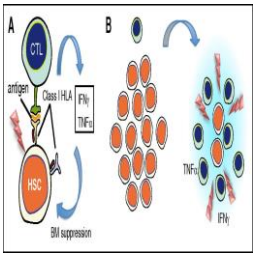
- Normal Stem Cells
  - Inadequate supplies
  - Hostile environment
- Damaged Stem Cells
  - Temporary
  - Permanent
- A combination

A Case Study - II

- Vitamin B12 and folate levels normal
- Bone marrow biopsy 10% cellular without dysplasia in residual marrow tissue
- Cytogenetics: 46 XY [12 metaphases]
- Additional tests:
  - PNH –
  - Chromosome breakage assay –
  - Genomic sequencing –
  - Flow cytometry –

What is going on?

Immune system – marrow interactions



Immune-Mediated Aplastic Anemia

- A very rare disease (2 per million)
  - Compare to MDS (70 per million to 350 per million adults 60 – 69 years)
- Toxins or infections rarely identified
- A diagnosis of exclusion

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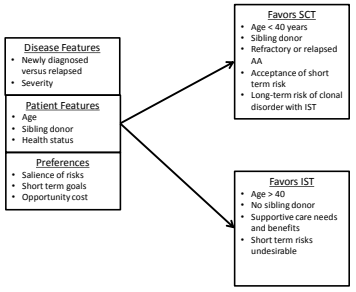
Decision making process: SCT or IST?



Best Supportive Care - I

- Supportive care has contributed to a progressive improvement in survival in all patients
- Do not delay instituting optimal therapy waiting to see if there is a response to growth factors
- Limit transfusions in younger patients headed to SCT
- Regularly scheduled evaluations more accurate than waiting for symptoms

Best Supportive Care - II

- Neutropenia – risk of infection
  - Prophylaxis practice varies substantially
  - Avoid steroids: reduce risk of invasive fungal infections
- Anemia – fatigue, increased cardiac demand
  - Monitor response to red cell transfusions and identify meaningful trigger
- Thrombocytopenia
  - Trigger < 10,000 per microliter

What are the options?

- Anti-thymocyte globulin
  - Horse
  - Rabbit
- Cyclosporine A
- (Prednisone or other corticosteroids)
- Cyclophosphamide
- Alemtuzumab
- Danazol
- Hematopoietic growth factors

Living with Aplastic Anemia

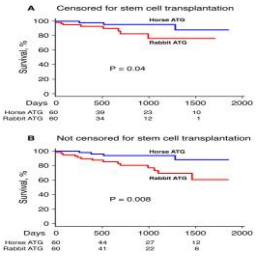
IMMUNOSUPPRESSIVE THERAPY

Randomized trial of horse versus rabbit ATG

Clinical Outcomes

	Horse	Rabbit	P-value
Number	60	60	NS
Idiopathic	58	58	NS
Age (mean, yrs)	37	31	NS
ANC (mean/ cu mm)	408	356	NS
PLT (mean/ cu mm)	16,000	12,600	NS
PNH clone < 1%	35 (58%)	41 (68%)	NS
Response at 3 m	37 (62%)	20 (33%)	.002
Response at 6 m	41 (68%)	22 (37%)	.001
Clonal evolution	21%	14%	NS
Overall survival	96%	76%	.04

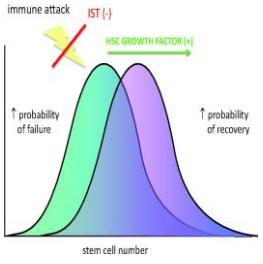
Survival Curves



Scheinberg P 2011 NEJM 365 430

Phase I/II trial of Eltrombopag and IST

Immune Suppression and Stem Cell Exhaustion



Neal S. Young Hematology 2013;2013:76-81

Rationale for combined Rx

- Intensive immune suppressive therapy alleviates the T-cell mediated destruction of stem cells
- Hematopoietic growth factors encourage the stem cells to mature into peripheral blood cells

Townsley DM 2017 NEJM 376 1540

Phase I/II trial of Eltrombopag and IST

Rationale for TPO-mimetic

Phase I/II compared to prior experience

	2017	Horse	P-value
Number	92	60	No formal comparison possible
Age (mean, yrs)	32	37	
ANC (mean/ cu mm)	310	408	
PLT (mean/ cu mm)	9,000	16,000	
PNH clone < 1%	53 (63%)	35 (58%)	
Response at 3 m	74 (80%)	37 (62%)	
Response at 6 m	80 (87%)	41 (68%)	
Clonal evolution	8 %	21%	
Overall survival	97%	96%	

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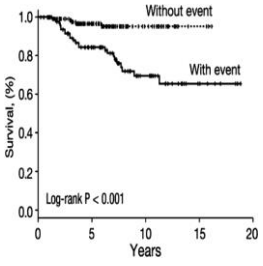
Life after IST

Long-term survival after IST



Neal S. Young Hematology 2013;2013:76-81

What are the events?

- Recurrence of immune-mediated aplastic anemia
- Emergence of "clonal disorder"
  - MDS
  - Acute Leukemia
- Other

What about people…

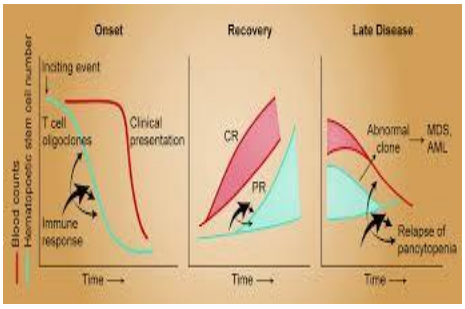
…who don't benefit?

- Repeat IST
- Further evaluation for an alternative disorder
  - Emerging data on "late presentations" of constitutional mutations
- Allogeneic SCT
- Best supportive care

…who experience recurrent pancytopenia?

- Further evaluation for an alternative disorder
  - Emerging data on constitutional mutations and late presentations
- Tapered off of CSA?
- If AA – repeat IST, SCT?
- If MDS, Rx per standards

Recurrent cytopenias – late clonal disorder



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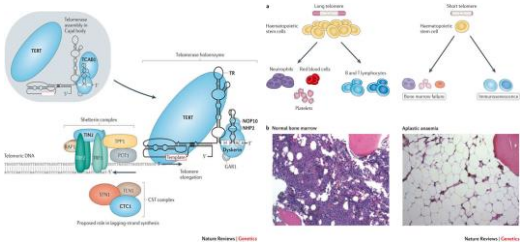
SPECIAL TOPICS

Genomic sequencing and bone marrow failure

- Acquired mutations
  - Associated with MDS or AML
- Constitutional – present at birth
  - Current screen sequences 59 genes
- Late onset but constitutional – atypical features

Telomeres and bone marrow failure

DNA-Protein Complex **Shortened Telomeres and AA**



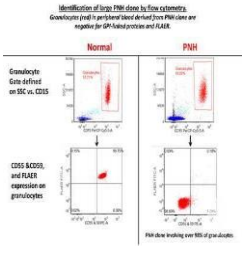
Armanios M 2012 Nat Rev Gen 13 693

Paroxysmal Nocturnal Hemoglobinuria

PNH

- Acquired mutations of the PIGA gene →increased sensitivity to complement-mediated lysis
- Clinical syndrome(s)
  - Unexplained hemolytic anemia
  - Unusual thrombosis
  - Bone marrow failure

Laboratory Test



PNH and bone marrow failure

- It is possible to detect PNH clones in up to 70% of patients with bone marrow failure (including AA or MDS)
- The clone is less than 1% in the majority
- Overtime the clone may…
  - Expand
  - Persist
  - Disappear
- The clinical significance remains undetermined

Pure Red Cell Aplasia

Clinical presentation and Rx

- "Isolated Anemia"
  - Absent or damaged erythroid precursors
- Rx depends on cause:
  - Thymoma – resection?
  - B19 – intravenous immunoglobulin
  - LGL – MTX?
  - Idiopathic – prednisone or cyclosporine

Potential Causes

- Constitutional
  - Diamond-Blackfan Syndrome
- Acquired
  - In the setting of a chronic hemolytic anemia
  - Viral infection: parvovirus B19
  - Malnutrition
  - Thymoma
  - Idiopathic
  - Immune disorder: LGL