Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Inherited and Acquired Marrow Failure

Comprehensive Hematology & Oncology Review Course

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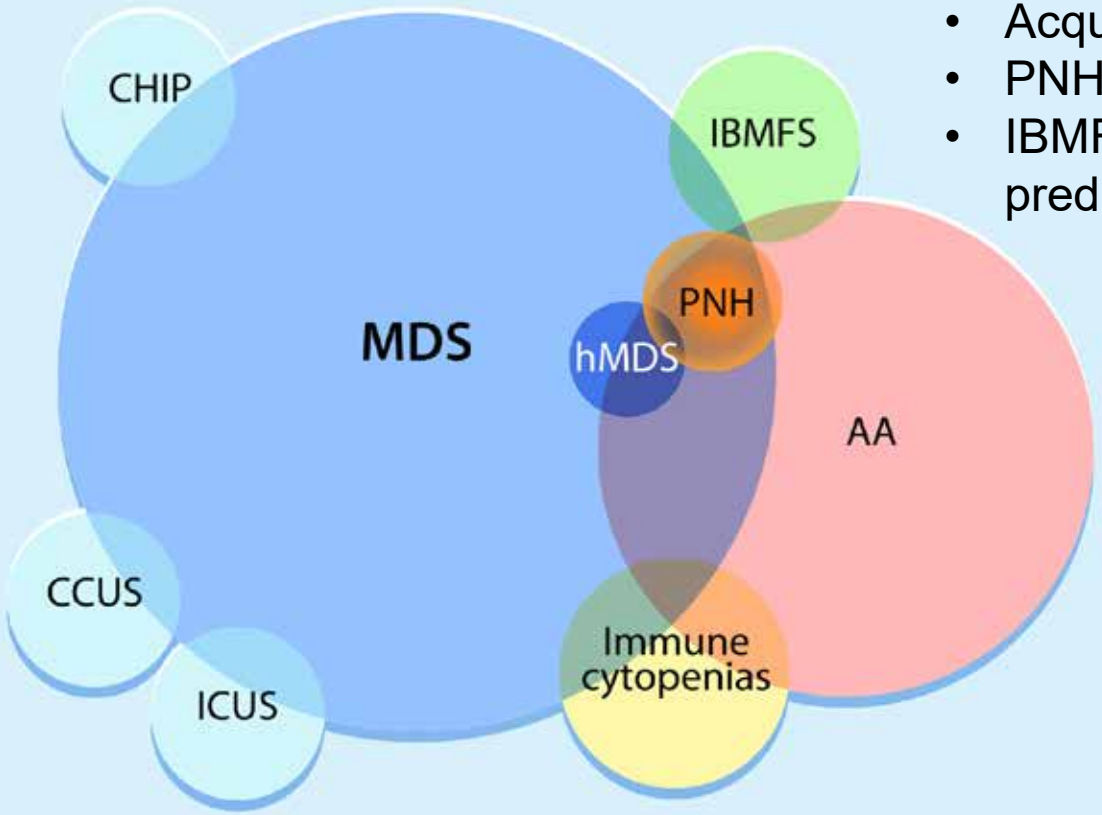
Marrow failure

- Inability of hematopoiesis to meet physiologic demands for the production of healthy blood cells.



- Acquired aplastic anemia
- PNH
- IBMF/hematopoietic malignancy predisposition syndromes

Diagnostic work-up of hypocellular marrow + cytopenias

Pancytopenia
Exclude known causes, e.g, B12/ folate deficiency, medication

↓

BM aspirate/biopsy
(chromosome analysis, cytology, flow cytometry, iron stain)

↓

Hypocellullar

↓

Peripheral blood
- HSCT candidate consider HLA typing
- **Chromosomal breakage study**
  (+ skin fibroblast testing if suspicion is high)
- Reticulocyte count
- Flow cytometry for GPI-anchored proteins
- Consider telomere length testing
- Consider genetic testing

Consider underlying genetic cause

- Younger age
- Personal history of congenital anomalies or extra-hematologic manifestations
- Family history
- Member of family with genetically defined IBMF/AL-MDS
- Antecedent macrocytosis or cytopenias
- Monosomy 7 & trisomy 8 MDS in peds/young adults
- Absence of a PNH clone[1]

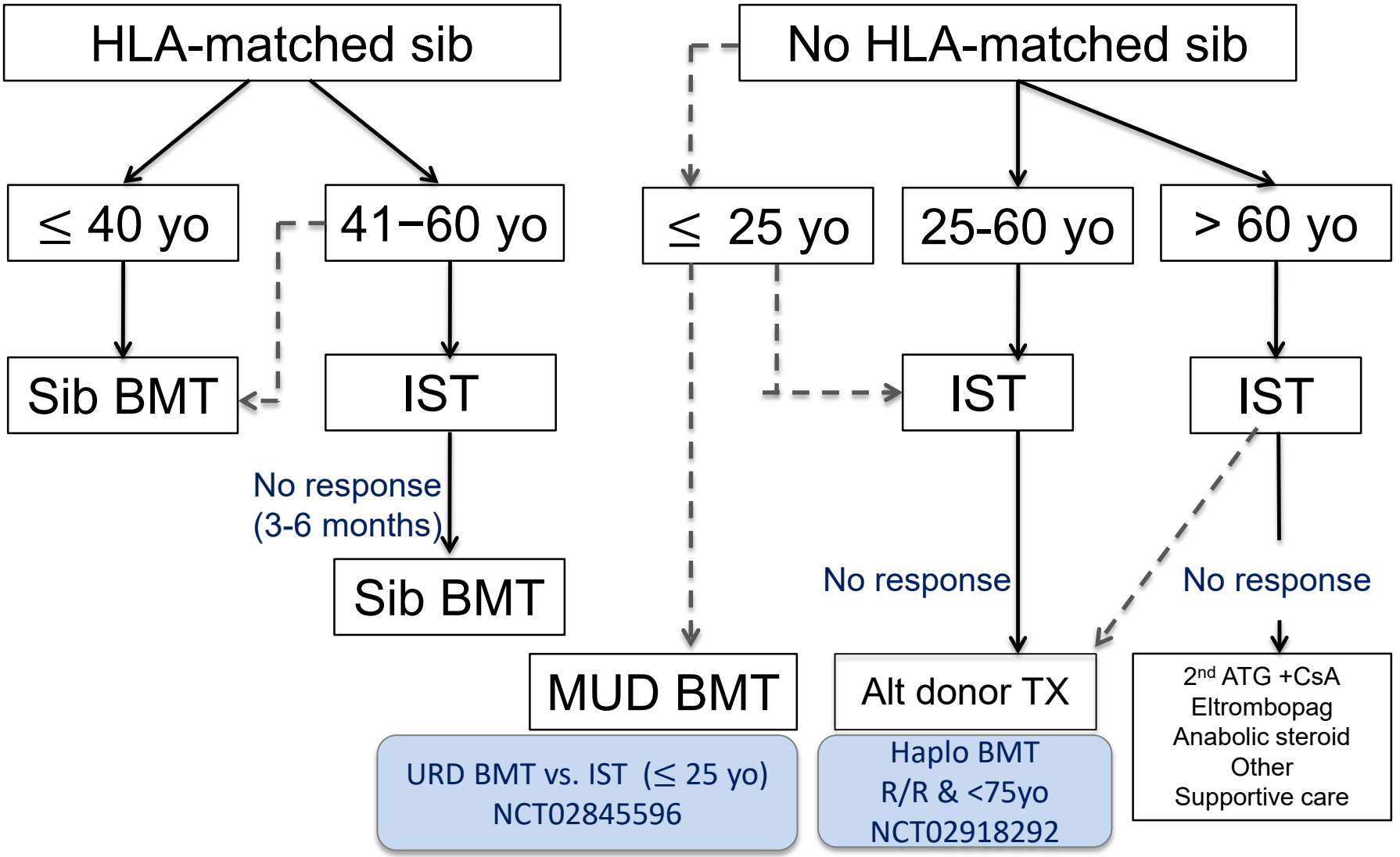
1. DeZern A. et al. Eur Journal Hematology 2014: 92.

Idiopathic acquired aplastic anemia

- Biphasic age distribution
  - Young adults and > 60 yo
- Presumed 2^{ndary} to immunologic destruction of hematopoietic stem cells
- Severity - Camitta's criteria[1]
  - Severe
    - BM cellularity <25% or 25-50% w/ <30% residual hemat. cells
    - 2/3 of the following
      - ANC <500/uL
      - Plts < 500/uL
      - Absolute retic count <20,000/uL (some use <60,000/uL[2])
  - Very severe - ANC<200/uL
  - Non-severe (moderate) - better than severe

1. Camitta BM. Blood 1976: 48(1). 2. Killlick S. BJH 2016: 172.

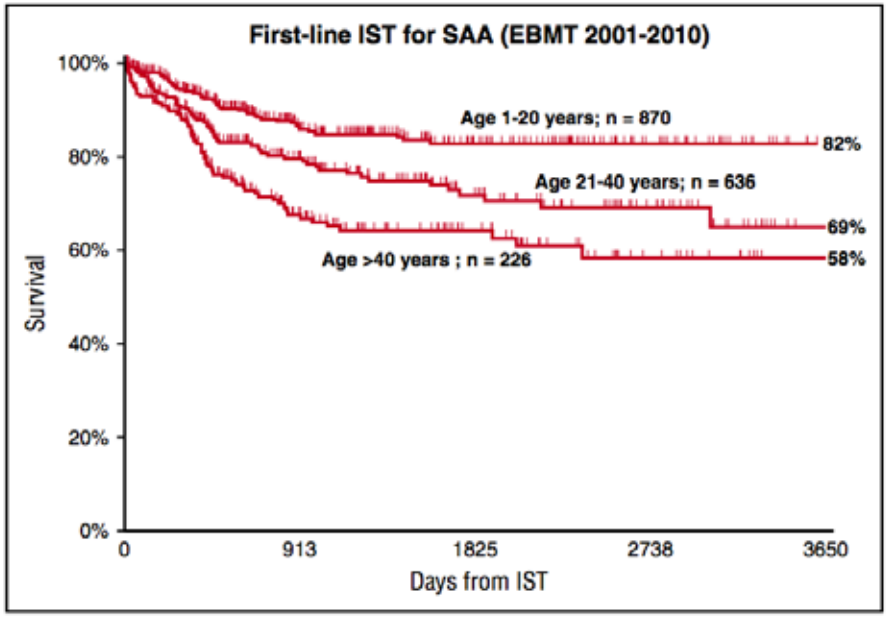
Severe idiopathic acquired aplastic anemia

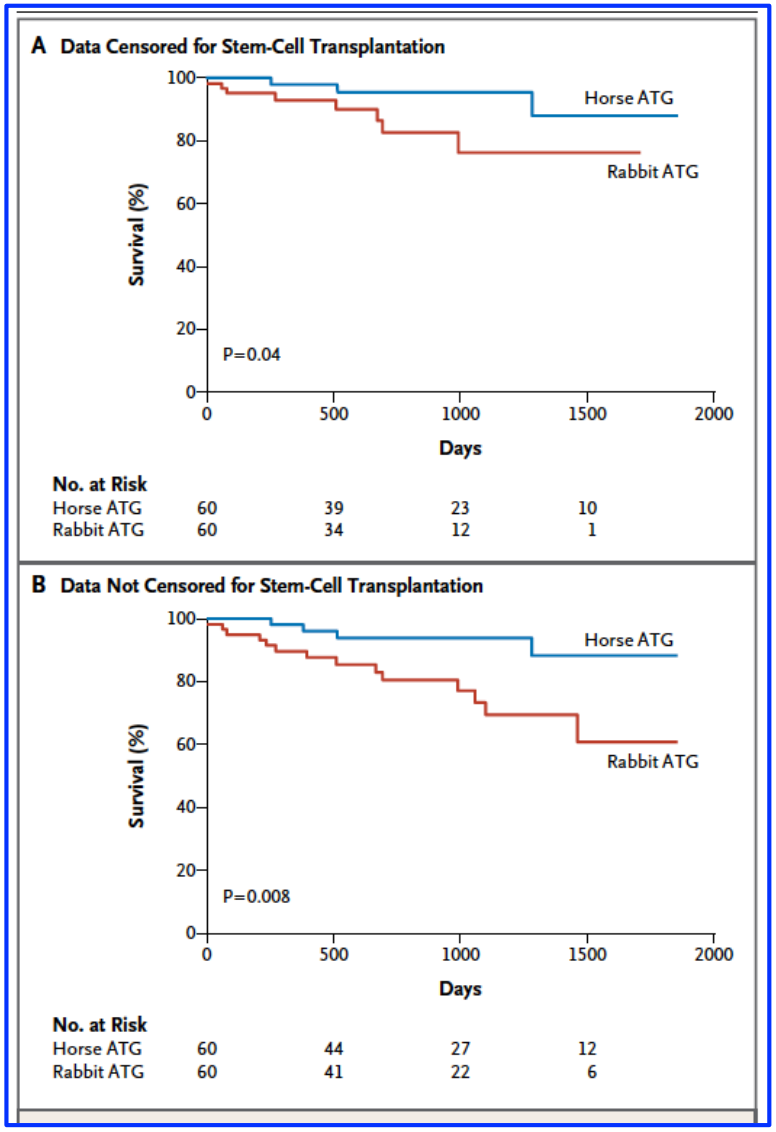


Nice review in Georges G. et al. Blood Advances 2018: 2(15).

Immune suppressive therapy (IST)

- **Horse is better than rabbit ATG[1]**
- **Response to IST is age-dependent[2]**
- Adding GM-CSF, G-CSF, and IL-3 doesn't improve response or survial[3]





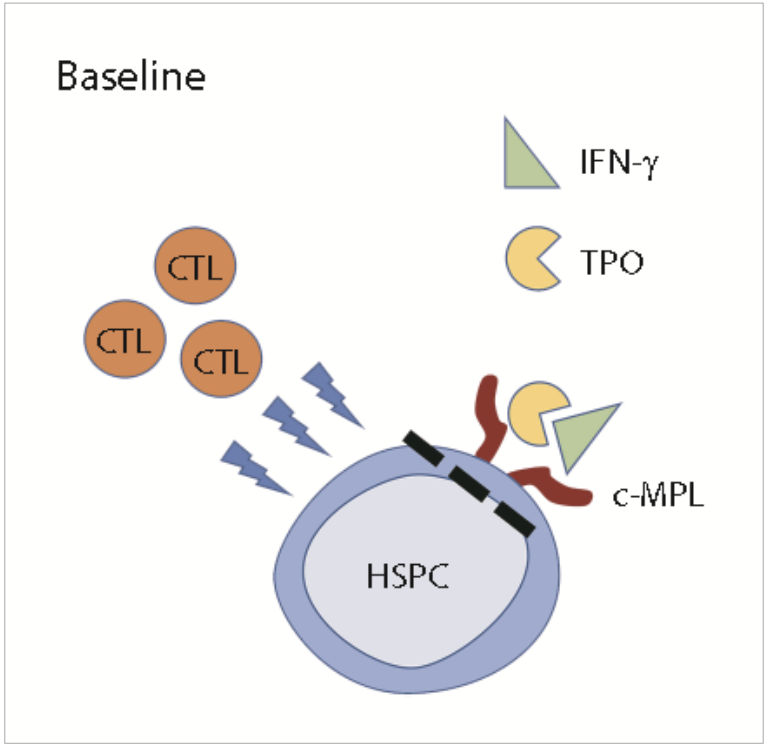
1.Scheinberg P et al. NEJM 2011: 365(35). 2. Bacigalupo A. Blood 2017: 129 (11).
3. Gurion R. et al. Haematologica 2009: 94(5). 4. Young N. et al. Blood 2006: 108(8).

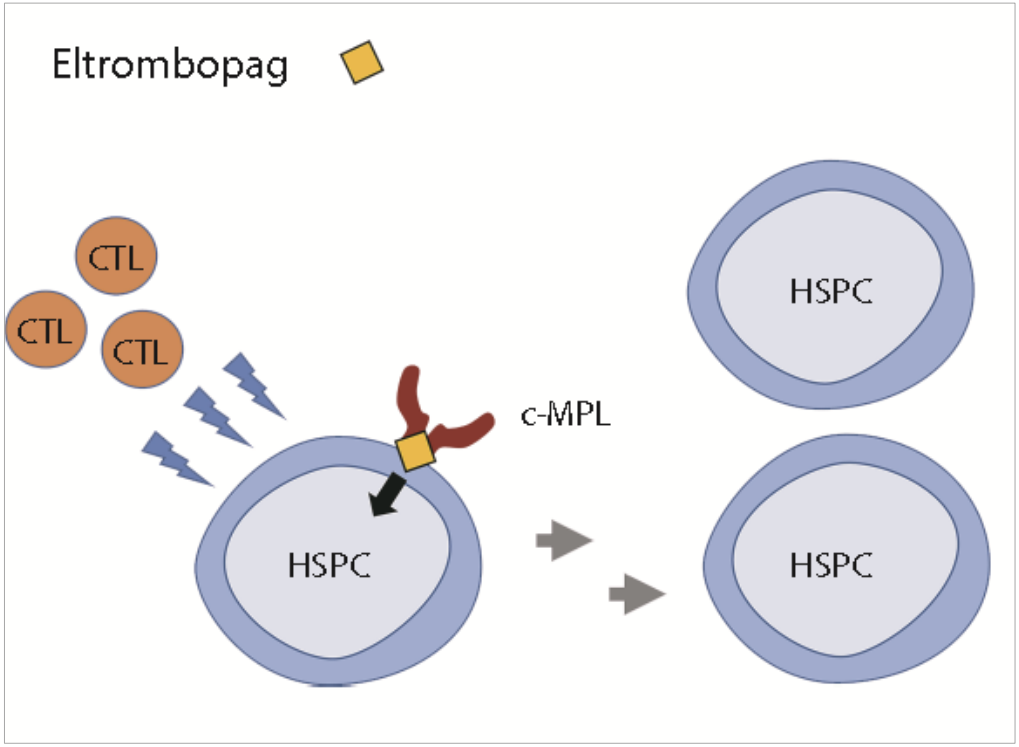
Late complications of IST treated patients

- Relapse in ~ 1/3 of responders[1]
- MDS/AML evolution in 10-15% of cases[1,2]
- Only 29% (24/84) with normal blood counts and off all IST after long-term follow-up (median follow-up 11.3 yrs)[2]

1. Young N. et al. Blood 2006: 108(8). 2. Frickenhofen N. et al. Blood 2003: 101(4).

Eltrombopag (Epag) improves trilineage hematopoiesis in patients with acquired AA





From Bubushok DV. Blood 2019: 133(24).
Mechanism in Alvarado et al. Blood 2019: 139(19).

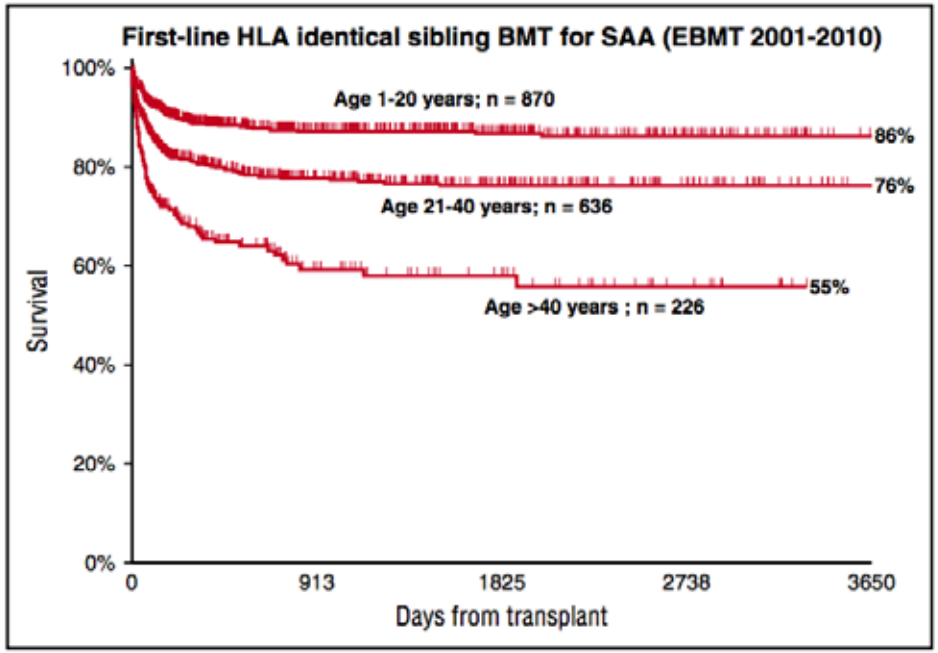
Epag added to standard IST for AA

- Relapsed/refractory[1]
  - Phase 2 study; 25 patients
  - Epag 150 mg po daily
    - Hematologic response 44% @ 12 wks
- Upfront therapy[2]
  - Phase 1-2 study; 92 patients; median f/up 2 yrs
  - Epag 150 mg po daily D1-6 months + hATG/CsA
    - CR 58% and OR 94% @ 6 months
  - **RCT IST vs IST+Epag (NCT02099747, >15 yo)**
- Impact on malignant evolution uncertain
  - 19% (16/83) of rSAA treated with single-agent Epag early cytogenetic clonal evoluation[3]

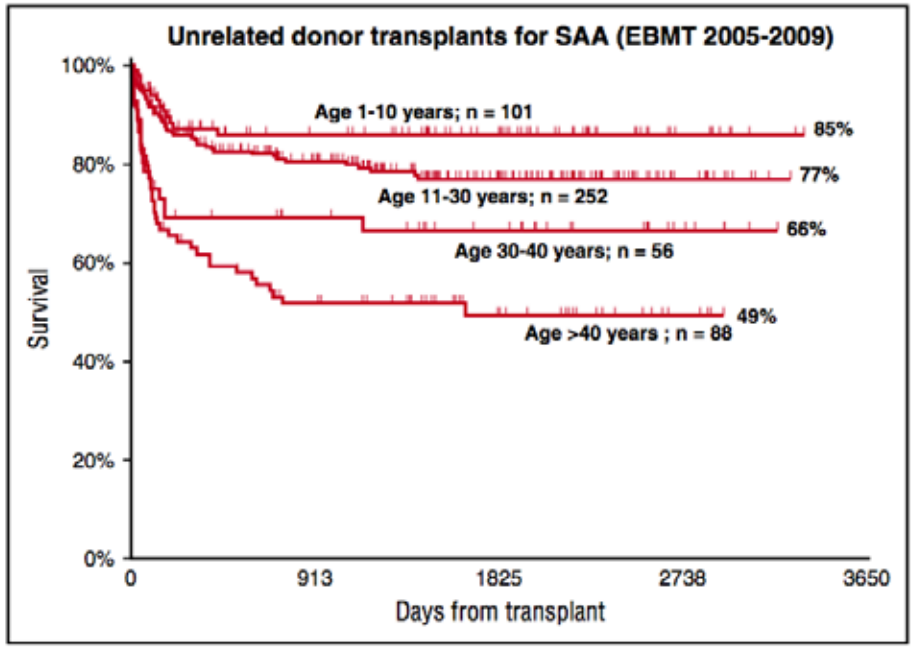
1. Olnes MJ. et al. NEJM 2011: 371(1). 2. Townsley M et al. NEJM 2017: 376(16). 3. Winkler T. et al. Blood 2019; 133(24).

BMT for severe AA

HLA-matched sib



MURD



Data from EBMT Registry reviewed in Bacigalupo A. Blood 2017: 129 (11).

Hopkins Phase II trial of Haplo BMT for SAA

Relapsed/refractory trial (20 patients)

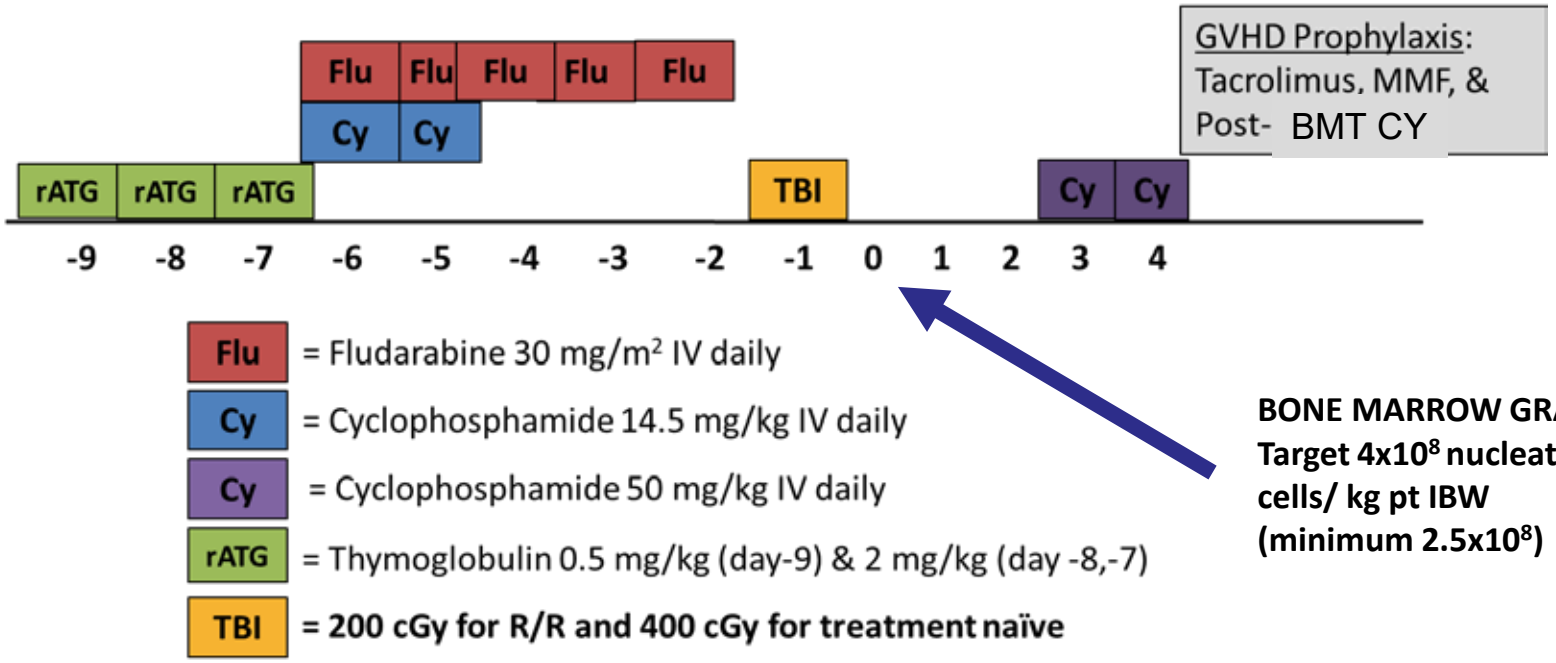
- SAA and ≥3 months after IST & no sib donor
- Median age 29 yo (5-69)

Treatment naïve trial (17 patients)

- SAA and untreated & no sib donor
- Median age 22 yo (3-63)

DeZern A. Blood Adv 2020: 8(4).

Conditioning and GVHD Prophylaxis

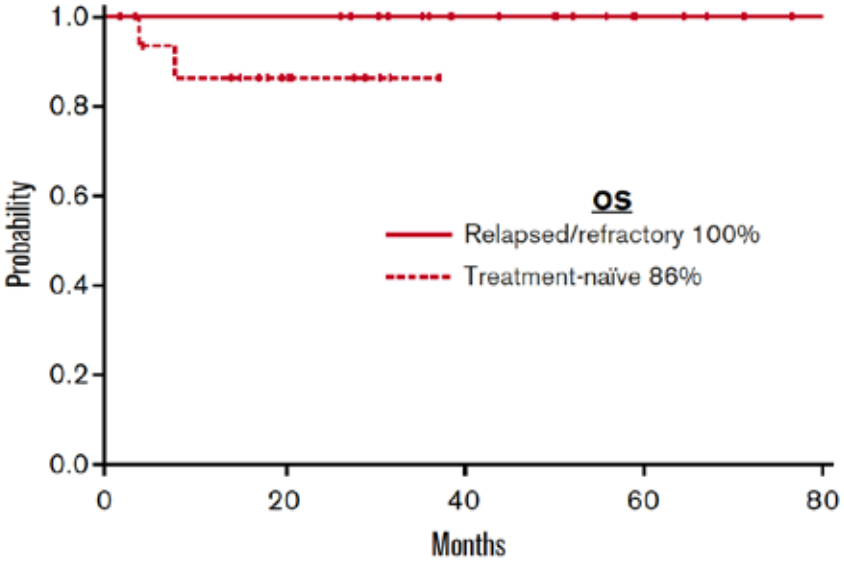


BONE MARROW GRAFT:
Target $4x10^8$ nucleated cells/ kg pt IBW (minimum $2.5x10^8$)

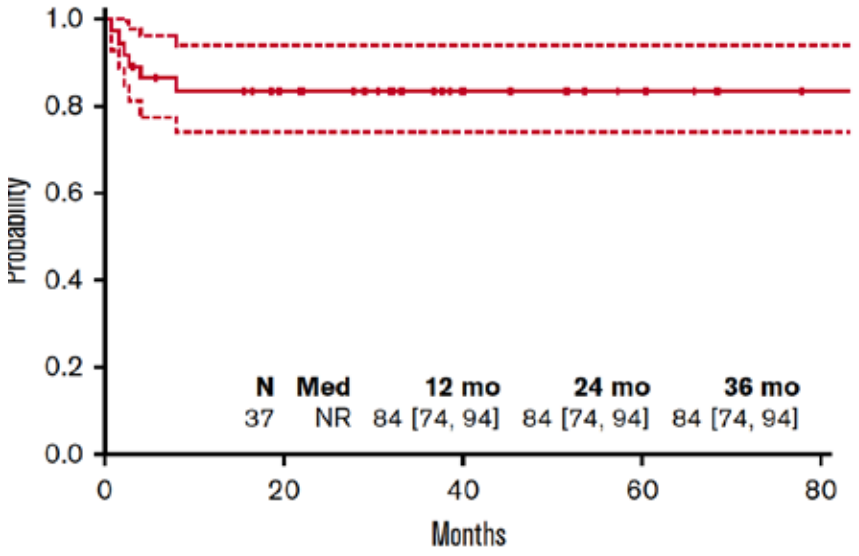
**** After initial 7 treatment-naïve patients treated at 200 cGy, increase TBI to 400 cGy**

DeZern A. Blood Adv 2020: 8(4).

Overall survival



GVHD-free survival



DeZern A. Blood Adv 2020: 8(4).

- CTN 1502 CHAMP study NCT02918292 (relapsed/refractory SAA up to 75 yo)

Paroxysmal nocturnal hemoglobinuria

- Nonmalignant clonal expansion of HSCs with a somatic mutation of *PIGA*
- PNH cells lack surface proteins that require a GPI anchor which normally protect against complement-mediated hemolysis

CD59

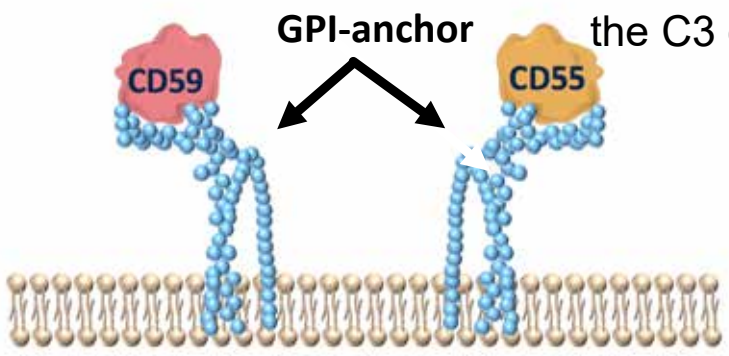
Membrane inhibitor of reactive lysis (MIRL)

Inhibits assembly of the membrane attack complex

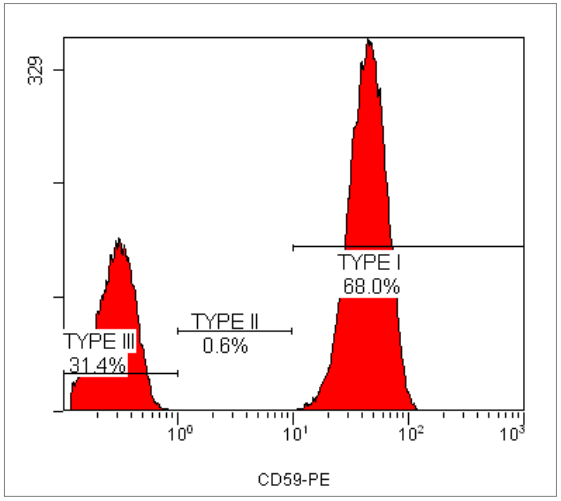
CD55

Decay accelerating factor (DAF)

Inhibits the formation and stability of the C3 convertases



Classical PNH



Clinical triad

1. Intravascular hemolysis
2. Thrombosis
3. Bone marrow failure

Diagnosis - Absent or reduced GPI-linked proteins

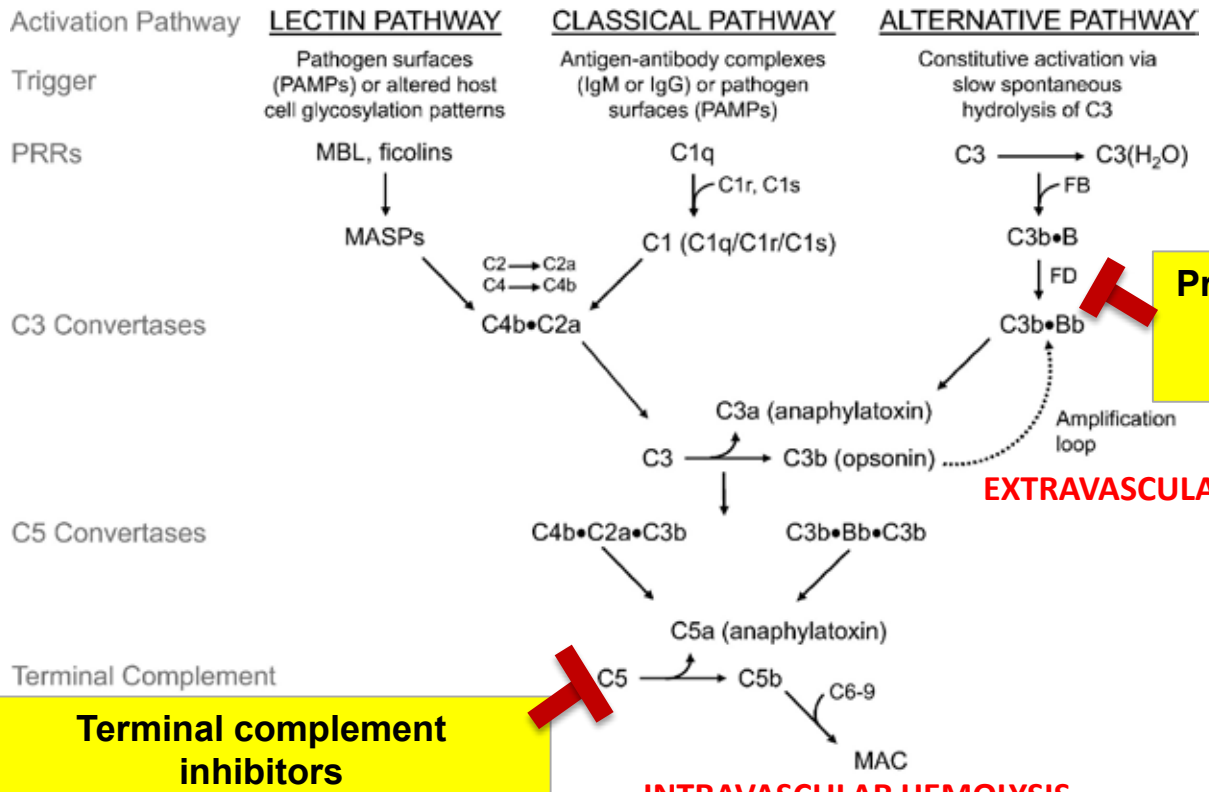
Treatment

- Folic acid ± iron supplementation, role for prophylactic anticoagulation unclear

- Eculizumab or ravulizumab[1,2] treatment indicated for significant disease manifestations attributable to hemolysis
  - Consider d/c anticoagulation in patients on therapy
  - **ACIP recommends meningococcal vaccination**
    MenACWY and MenB vaccines
    Consider antimicrobial prophylaxis for duration of ecu/ravulizumab txt
    Vaccination does not eliminate risk

1. Lee JW. Blood 2019; 133(6). 2. Kulasekararaj AG. et al. Blood 2019; 133(6).

Complement pathways and PNH



Proximal complement inhibitors in clinical trials
(target C3, factor B, factor D)

Terminal complement inhibitors
(target C5)
Eculizumab, **Ravulizumab**

Baines and Brodsky, Blood Reviews 2017: 31.

Potential causes of persistent anemia on eculizumab

- ~70% of patients on eculizumab do not normalize their hemoglobin[1]

Cause	Mechanism	Therapeutic approach
Intravascular hemolysis	Inherited C5 variants (rare)	Switch agent
	Inadequate plasma level of eculizumab	Decrease dosing interval
	Massive complement activation	Avoid triggers, maybe switch agent
Extravascular hemolysis	**C3-mediated (C3-fragment opsonization)***	Maybe proximal complement inhibitors
Bone marrow Disorders	Bone marrow failure	Aplastic anemia treatment
	Clonal evolution	Myeloid malignancy treatment

* Not uncommon and significantly contributes to the residual anemia

Modified from Ristano et al. Frontiers in Immunology 2019: 10.

IBMF/AL-MDS predisposition syndromes

Classical inherited bone marrow failure syndromes

- Congenital neutropenia
- Diamond Blackfan anemia
- Fanconi anemia
- Telomere biology disorders
- Shwachman-Diamond syndrome

Germline predisposition for hematopoietic malignancy

- *CEPBA*
- *DDX41*
- *14q32.2* genomic duplication *(ATG2B/GSKIP)*

Germline predisposition for hematopoietic malignancy with pre-existing cytopenia(s) and/or other organ dysfunction prior to hematopoietic malignancy presentation

- *ANKRD26*
- *ETV6*
- GATA2 Deficiency Syndrome
- *RUNX1* - Familial platelet disorder with associated myeloid malignancy
- *SAMD9* - MIRAGE syndrome; *SAMD9L* - Ataxia Pancytopenia Syndrome
- *SRP72*

Germline predisposition for myeloid neoplasms and solid tumor cancers

- Constitutional mismatch repair deficiency
- Hereditary breast and ovarian cancer (e.g., *BRCA1, BRCA2*)
- Li-Fraumeni syndrome
- RASopathies
- Other rare DNA repair syndromes (e.g., *BLM)*

Modified from 2019 NCCN MDS Guidelines (mutations associated with hereditary myeloid malignancy)

NCCN National Comprehensive Cancer Network®

Inherited BMF syndrome	Genetics	Classical findings	Hematology & oncology	Diagnostic tests	Solid tumors
Fanconi anemia	AR and x-linked recessive DNA repair genes (e.g., *FANCA*)	Congenital anomalies (1/3 lacking)	Macrocytosis, cytopenias, hypocellular marrow/AA, MDS, leukemia, solid tumors	Increased chromosome fragility	SCC (head/neck/ vulva/vagina) Hepatocellular carcinoma
Dyskeratosis congenita/ Telomere biology disorders	AD, AR, x-linked recessive Telomere maintenance genes (e.g., *DKC1*,*TERC, TERC*)	Dystrophic nails, lacey reticular rash, oral leukoplakia Adult presentations – immune deficiency, liver cirrhosis, premature graying, pulmonary AVMs, pulmonary fibrosis	Macrocytosis, cytopenias, hypocellular marrow/AA, MDS, leukemia, solid tumors	Very short telomeres for age	SCC (head & neck) ,
Diamond-Blackfan anemia	AR Ribosomal proteins (e.g. *RPS19*)	Short stature, Cathie's facies	Macrocytosis, erythroid hypoplasia, MDS, leukemia, solid tumors	Elevated erythrocyte adenosine deaminase	Sarcomas
Shwachman-Diamond syndrome	AR *SBDS, EFL1, DNAJC21*	Exocrine pancreatic insufficiency, short stature, skeletal abnormalities	Macrocytosis, cytopenia (especially neutropenia), hypocellular marrow/AA, MDS, leukemia	Low pancreatic isoamylase (adults) and serum trypsinogen (children) Low fat soluble vitamin levels	

Why care about IBMF/AL-MDS predisposition syndromes?

- Not so rare
- Informs clinical care
  - HSCT donor selection, timing and preparatory regimen
  - Cancer and end organ damage surveillance programs
  - Appropriate family counseling
  - Incorporation of genetic predisposition in 2016 WHO myeloid neoplasm and AL classification[1] and NCCN MDS and European LeukemiaNet guidelines[2]
- Informs mechanisms of clonal hematopoiesis and potential MDS/leukemia treatment strategies[3,4,5,6]

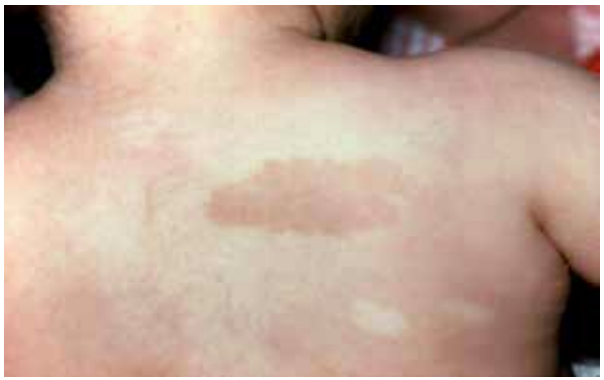
1. Arber D. et al. Blood 2016: 127. 2. Dohner H. et al. Blood 2017: 129. 3. Hinds DA et al. Blood 2016: 128. 4. Loh PR et al. Nature 2018: 559. 5. Farmer H. et al. Nature 2005: 434. 6. Bryant HE. rt al. Nature 2005: 434.

Fanconi anemia

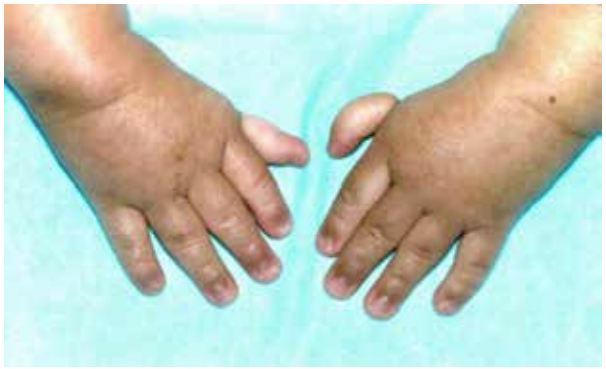
- Autosomal recessive; FANC B is x-lined recessive
- Many Fanconi genes
- Function in DNA repair
- Congenital anomalies
  - ~1/3 lack congenital anomalies
- Hypocellular marrow ± cytopenias
- Predisposition to cancer (AML; oral, esophageal, vulvar SCC, HCC)
- Radiosensitivity (DNA damage)

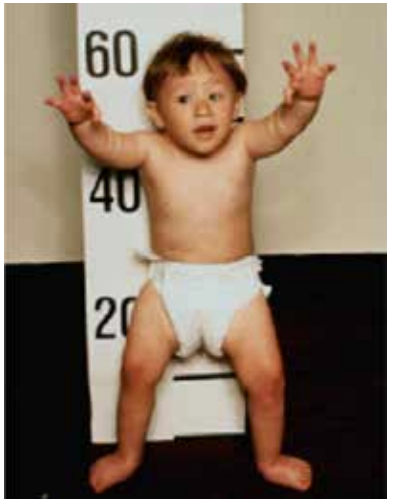
short stature

café au lait spot



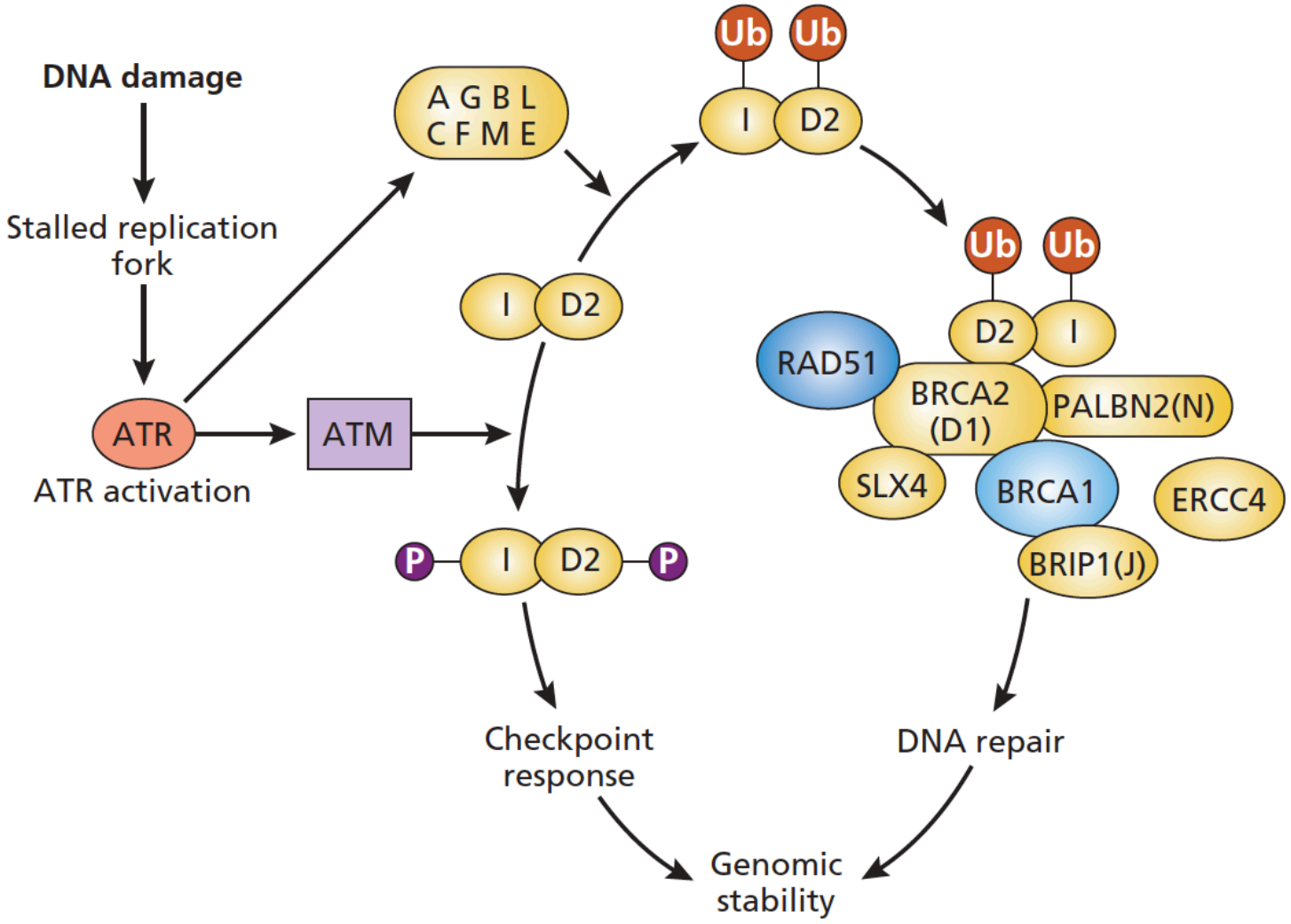
thumb abnormalities





Alter BP, Young NS. In Nathan DG, Oski DA, eds. Hematology of Infancy and Childhood 1993.

Fanconi anemia – hallmark is hypersensitivity to genetic damage induced by DNA damaging and cross-linking agents



From ASH SAP 2016 Chapter 15
Berturch A. and Dokal I.

FA-diagnosis – Chromosome fragility testing

- Based on the hallmark of genomic instability in FA cells[1,2]
  - 20% have mosaic lymphocytes (genetic reversion)[3,4]

    If clinical suspicion is high → test skin fibroblasts

    Back mutation has been reported in a hematopoietic stem cell.[5]
- Genetic testing
- Flow cytometry for G2 arrest
- Western blot for ubiquitinated D2
- Retroviral FA gene correction of FA phenotype

+MMC

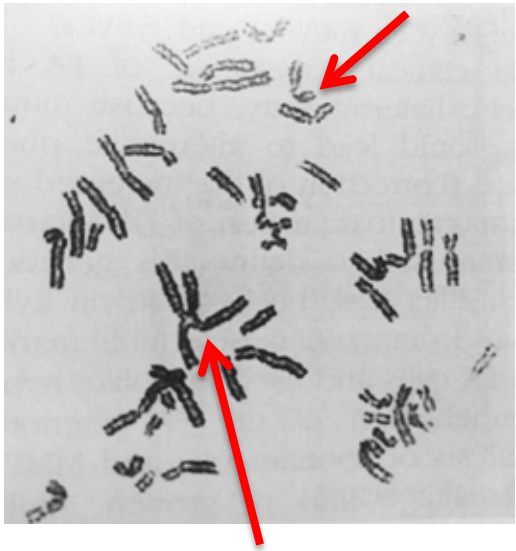


Image from Clinical Hematology
Edi Young N, Gerson S, High K. 2006.

1. Schroeder TM. Humangenetik 1966: 2. Sasaki MS. Et al. Cancer Res 1973: 33. 3. Soulier et al. Blood 2005: 105.
4. Lo Ten Foe JR, et al. Eur J Human Genet 1997: 5. Gregory J, et al. PNAS 2001: 98.

FA treatment and surveillance

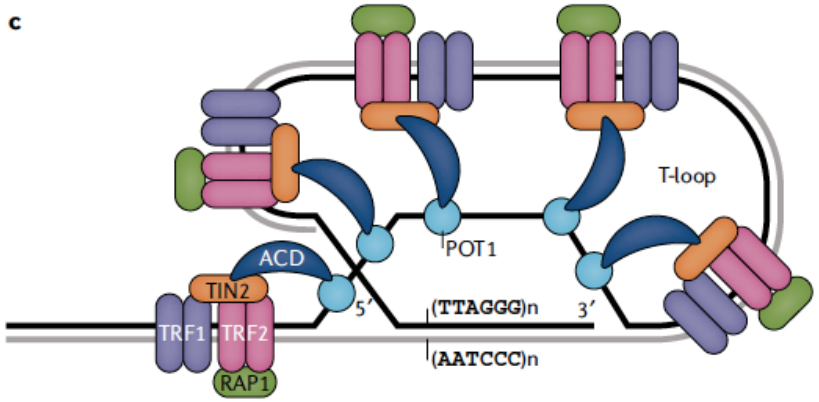
- Androgens improve hematopoiesis (oxymethalone 0.5-1 or danazol 2-4 mg/kg/day)
  - Stimulates erythroid progenitors and increases telomerase gene expression[1]
  - Erythroid and trilineage responses in ~ 60-80%[2]
  - Monitor LFTs, liver US (hepatic adenomas and peliosis hepatis), virilization
- HSCT
- Special consideration of potential treatment-related toxicities when treating solid tumors
- Monitor bone marrow failure and leukemia/MDS
- Avoid tobacco
- Surveillance for solid tumors in all adults

Fanconi anemia guidelines for diagnosis and management
https://www.fanconi.org/images/uploads/other/Guidelines_4th_Edition.pdf

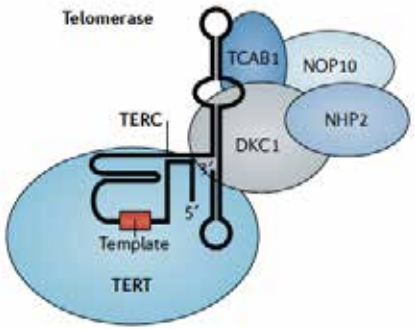
1. Calado RT et al. Blood 2009: 114. 2. Calado RT and Cle D. ASH Education Book 2017. Bone Marrow Failure: Inherited.

Human telomere complex

Telomeres



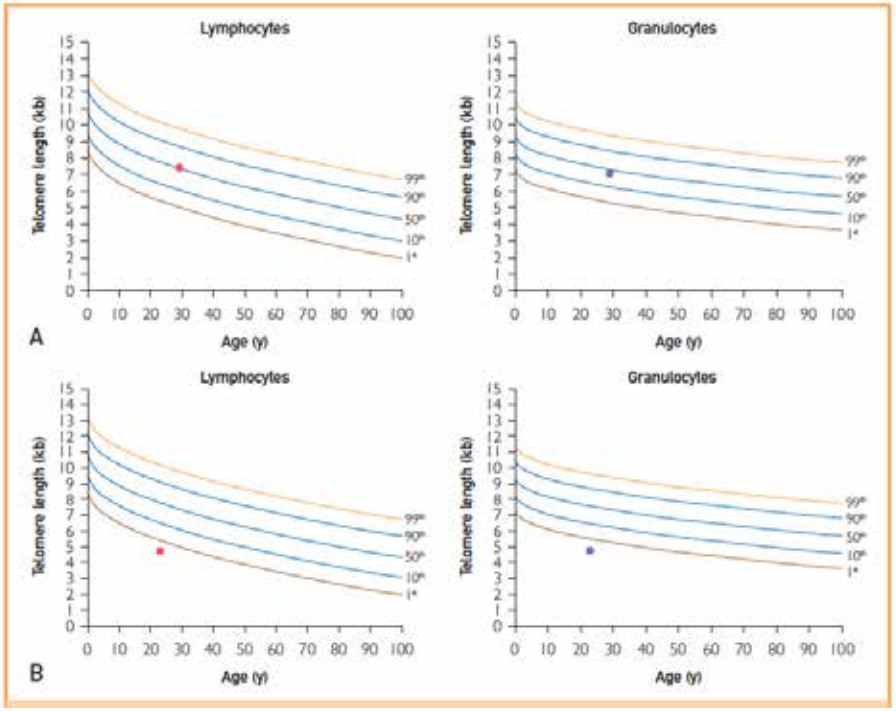
Telomerase



Clinical measurement of telomere lengths - Flow-FISH

Control

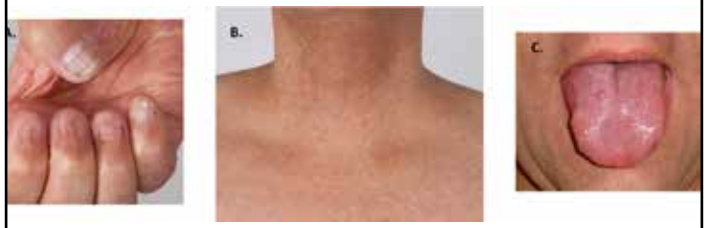
Suspected STS



From Shay JW and Wright WE Nature Reviews 2019: 20.

From Mangaonkar A. et al. Mayo Proceedings 2018: 93..

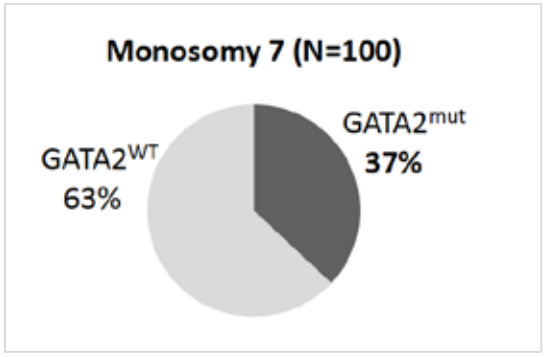
Spectrum of Telomere Biology Disorder phenotypes

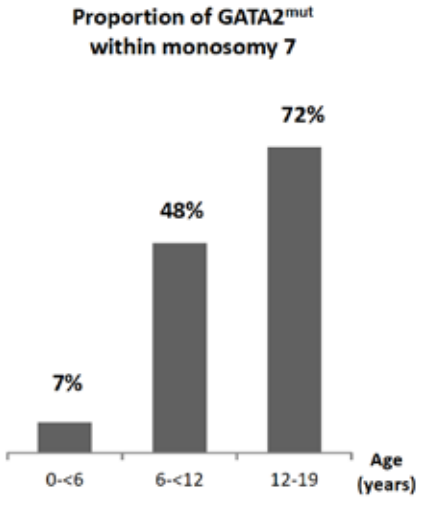
Representative disorders	Key clinical features
Dyskeratosis congenita (DC) 	Mucocutaneous triad (nail dysplasia, abnormal skin pigmentation, and oral leukoplakia), bone marrow failure, pulmonary fibrosis, pulmonary arteriovenous malformations, liver disease, avascular necrosis of hips or shoulders , urethral stenosis, lacrimal duct stenosis, esophageal stenosis, cancer, and/or developmental delay
Aplastic anemia*	Progressive multi-lineage cytopenias, non-immune mediated
MDS and AML*	
Hepatic disease*	Cryptogenic cirrhosis, noncirrhotic portal hypertension (nodular regenerative hyperplasia), hepatopulmonary syndrome
Idiopathic Pulmonary Fibrosis*	May occur in absence of DC-associated features. ~25% of familial IPF and 1–3% of sporadic IPF. Other pulmonary phenotype – pulmonary AVMs

* **May occur in absence of DC-associated features** - Important to recognize in adult patients as subclinical disease can exist concurrently in multiple organs, even when symptoms related to a single disorder predominate.

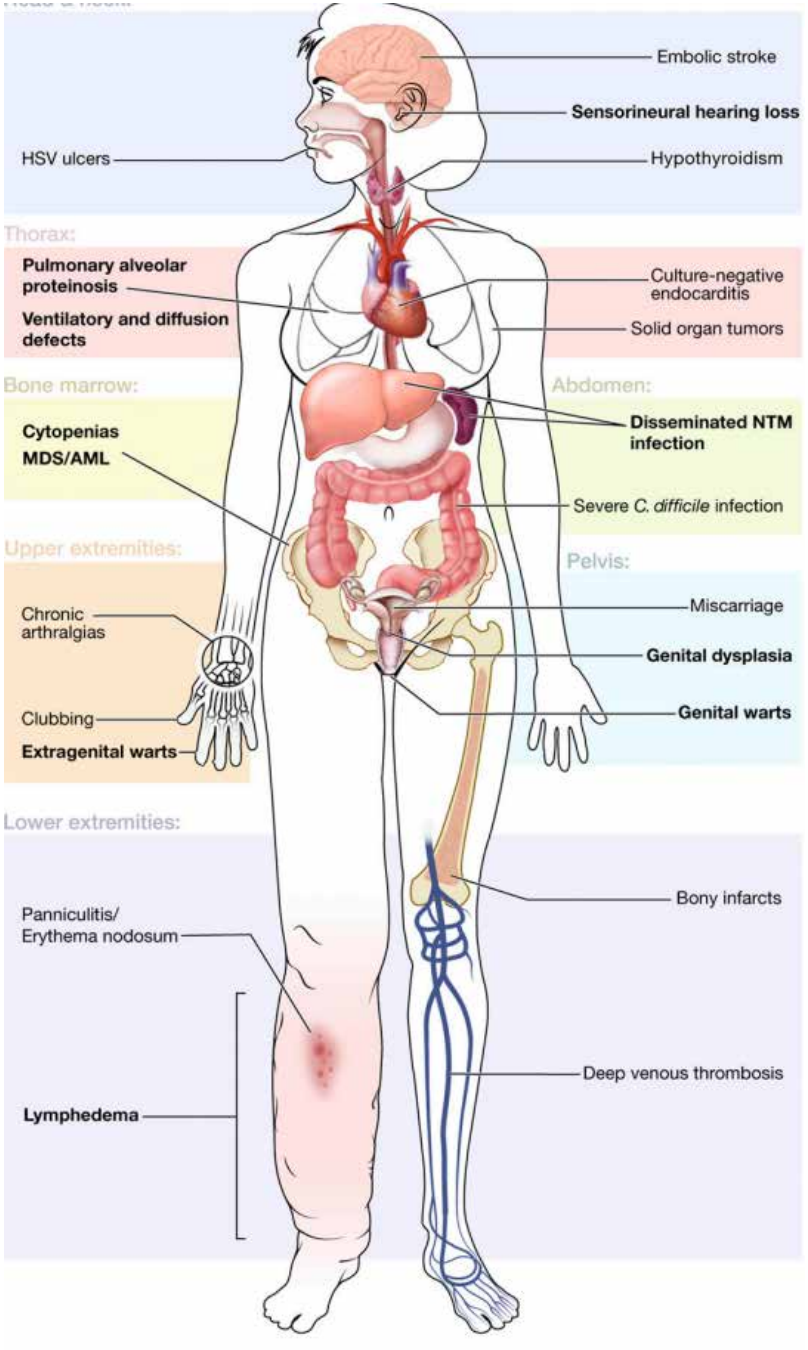
GATA2 deficiency syndrome

- Autosomal dominant familial AML/MDS
- Multiple clinical syndromes
  - MonoMac
  - Familial MDS/AML
  - Emberger's syndrome
  - Isolated cytopenias
  - Immunodeficiency (in all patients)
- Hints – disseminated NTM infection, Monosomy 7 MDS in young adults
  - Family history is not reliable - many de-novo mutations
- High risk of developing AML/MDS





Wlodarski MW et al. Blood 2016:127(11).



Spinner M et al. Blood 2014:123(6).

Familial Platelet Disorder with Associated Myeloid Malignancy: RUNX1 disorder

- Autosomal dominant
- Mild/moderate thrombocytopenia
- Hints - mild bleeding tendency – plt dense granule deficiency, family history of MDS/AL
- High risk of developing MDD/AML

High-yield pearls

- Randomized control study data demonstrates superior response and survival with horse ATG/CsA compared to rabbit ATG/CsA in upfront therapy of sAA
- Recognition of an underlying inherited myeloid malignancy predisposition syndrome is important.
- It is important to differentiate somatic from germline genetic variants in clonal hematopoietic states
- Consider GATA2 deficiency in patients presenting with disseminated nontuberculous mycobacterial infections or monosomy 7 MDS in young adults.