Congential and Acquired Aplastic Anemia

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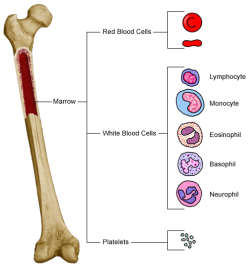
HSCT Basics

- **Restoration of a properly functioning bone marrow**
- **Restoration of a properly functioning immune system**



Neutropenia

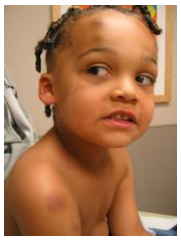
Table 9-9. Management of Neutropenic Patient[a]

1. Admit to hospital for persistent fever over 101°F.
2. Obtain appropriate cultures (blood, throat, urine, infected area) and sensitivity.
3. Administer parenteral antibiotics (Chapter 26)
   a. If an organism is isolated, 10–14 days' intravenous treatment is required.
   b. If no organism is isolated, antibiotic is continued until afebrile or neutropenia is resolved.
4. Place on reverse isolation to prevent superinfection with antibiotic-resistant organisms.
5. Observe strict hand-washing procedures.
6. Wash skin carefully with a Povidine-containing solution before all skin puncture procedures.
7. Minimize manipulation of skin, oral mucosa, perineum, and rectum; rectal temperatures and enemas are contraindicated.
8. Treat mouth ulcerations and gingivitis with appropriate systemic antibiotics if secondary bacterial infection is found and 3% hydrogen peroxide–1% alum mouthwash, which usually produces symptomatic relief.
9. Administer recombinant human G-CSF (rHu-GCSF)[b] for treatment of Kostmann disease (severe congenital agranulocytosis), Shwachman–Diamond syndrome, other congenital neutropenias, and severe neutropenia following chemotherapy (the starting dose is 5 μg/kg SC with dose modification according to the patient's absolute neutrophil count).

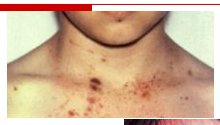
[a]Neutrophil count less than 500 cells/mm³.
[b]G-CSF specifically stimulates myeloid progenitor cells in the bone marrow and enhances neutrophil production and function.

Manual of Pediatric Hematology-Oncology

Thrombocytopenic Bleeding

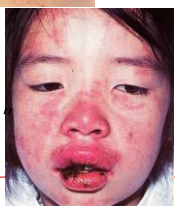


Bruises and "Dry Purpura"



Petechiae

Hemorrhagic "Wet Purpura"



Transfusional Iron Overload

- 1 unit PRBCs contains ~ 200 to 250 mg of iron
- No physiologic mechanism exists for iron excretion
- With repeated blood transfusions, iron accumulates
- Signs of iron overload can be seen after 10-20 transfusions

Congenital: Inherited Bone Marrow Failure Syndromes

Inherited Bone Marrow Failure Syndromes

Pancytopenias

Fanconi anemia (FA)
Dyskeratosis congenita (DC)
Shwachman Diamond syndrome (SDS)
Cartilage hair hypoplasia
Pearson syndrome
Reticular dysgenesis
Congenital amegakaryocytic thrombocytopenia
Familial marrow dysfunction
Down, Dubowitz, Seckel, or Noonan syndrome

Single Cytopenias

Red blood cells
Diamond-Blackfan anemia (DBA)
Congenital dyserythropoietic anemia (CDA)
White blood cells
Severe congenital neutropenia (Kostmann)
Platelets
Thrombocytopenia with absent radii (TAR)
Leukoerythroblastosis
Osteopetrosis

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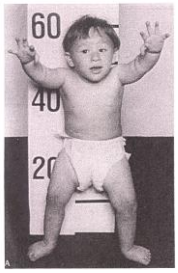
Fanconi Anemia Clinical presentation

- Short stature, microcephaly, elfin face
- Thumb and radial anomalies
  - Thenar hypoplasia
  - Clinodactyly of 5th digit
  - Syndactyly
  - Hyperextensible thumbs
  - Absence or hypoplastic radius
- Renal and ureter abnormalities
- Hypogonadism
- Gastrointestinal abnormalities
- Hearing deficit
- No physical abnormalities



Fanconi Anemia Endocrinopathies

- GH deficiency (not all patients)
- Hypothyroidism
- Glucose intolerance
- Premature menopause
- Decreased fertility, hypogonadism

Fanconi Anemia Molecular Biology

- G_2M arrest
- Apoptosis
- Increased DNA breaks
- DNA repair defect
- Chromosomal instability

Fanconi Anemia
Diagnostics

- Chromosome breaks in lymphocytes (Di-epoxybutane, mitomycin C)
- Flowcytometry (G2/M arrest)
- Fibroblast cultures (chromosome breaks)
- Complementation analysis
- Gene mutation cloning

Aberrations during DNA-replication phase

Broken chromatids in metaphase

Misrepair leads to chromatid interchange figures, quadriradials

Arrest/delay in late S- or G2 phase

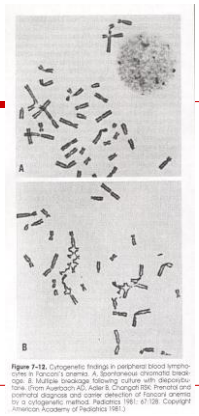


Figure 7-12. Cytogenetic findings in peripheral blood lymphocytes in Fanconi's anemia. A. Spontaneous chromatid breakage. B. Multiple breakage following culture with diepoxybutane. (From Auerbach AD, Adler B, Chaganti RSK: Prenatal and postnatal diagnosis and carrier detection of Fanconi anemia by a cytogenetic method. Pediatrics 1981; 67:128. Copyright American Academy of Pediatrics 1981.)

Table 1. *FA complementation groups and FA genes*

FA complementation group	FA gene	Approximate frequency in FA patients (%)	Chromosomal location	Protein product (kDa)	Reference
A	*FANCA*	60%	16q24.3	163	Lo Ten Foe et al. 1996
B	*FANCB*	Rare	Xp22.31	95	Meetei et al. 2004
C	*FANCC*	15%	9q22.3	63	Strathdee et al. 1992b
D1	*BRCA2*	5%	13q12.3	380	Howlett et al. 2002
D2	*FANCD2*	5%	3p25.3	155, 162	Timmers et al. 2001
E	*FANCE*	Rare	6p21.3	60	de Winter et al. 2000a
F	*FANCF*	Rare	11p15	42	de Winter et al. 2000b
G	*FANCG*	10%	9p13	68	de Winter et al. 1998
I	Unknown	Rare	Unknown	Unknown	Unknown
J	*BRIP1*	Rare	17q23.2	130	Levitus et al. 2005
L	*FANCL*	Rare	2p16	52	Meetei et al. 2003a
M	*FANCM*	Rare	14q21.2	250	Meetei et al. 2005

Disease Course

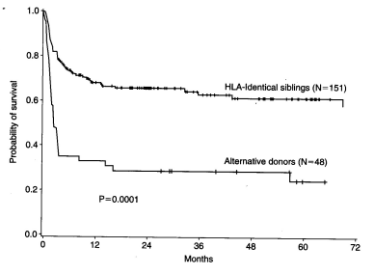
- Heterogeneous
- If no treatment
  - Development of pancytopenia; transfusion dependent in 5 to 10 years
- Cytogenetic abnormalities
- MDS, AML (M6)
- Solid tumors: squamous cell carcinoma (head and neck), GU, liver
- Median age of survival 20 yrs; 25% live beyond 31 yrs

Treatment Approaches

- HLA identical BMT
- If no HLA-identical donor
  - Yearly checks
  - Bone marrow morphology, cytogenetics
  - Await development of cytopenias
  - G-CSF
- Androgens ??
- Alternative donor BMT

Overall Survival after BMT

Horowitz MM et al. 1995



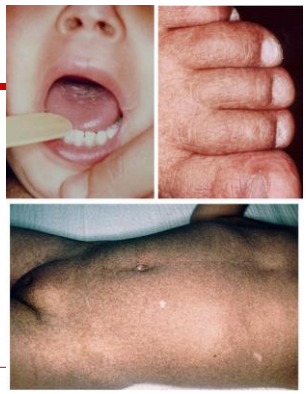
BMT in Fanconi Anemia

- Future directions:
  - Avoid irradiation (reduce cancer risk)
  - Improve immunosuppression (reduce GVHD)
  - Avoid previous treatment with androgens, heavy transfusion history
  - Avoid infections (pre-treatment with Voriconazole for 4 wks)

Dyskeratosis Congenita

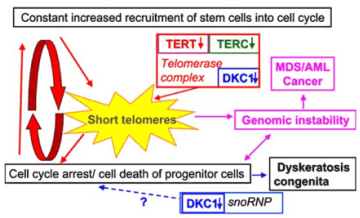
- Underrecognized in pediatrics
- Physical findings with increasing age
  - Lacey reticulated pigmentation
  - Dysplastic nails
  - Oral leukoplakia
- Autosomal recessive, autosomal dominant, X-linked

Dyskeratosis Congenita



Dyskeratosis Congenita

- Short telomere length in all leukocyte subsets (flowcytometry with flourescence in-situ hybridization FISH)



Dyskeratosis Congenita

- Marrow failure 94% at age 40y
- Malignancy 35%
- Treatment similar to Fanconi anemia:
  - HLA-matched stem cell transplant
    - Increased risk of pulmonary and liver fibrosis
  - GCSF ?
  - Androgens ?

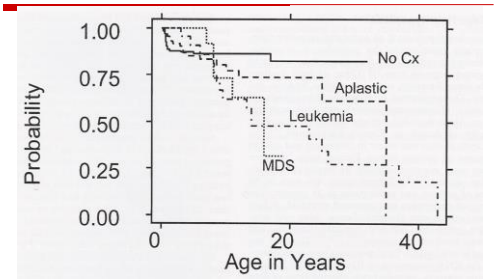
Shwachman Diamond Syndrome

- Classical triad
  - Exocrine pancreas insufficiency in early infancy
  - Neutropenia (early infancy, skin infections)
  - Metaphyseal dysostosis
- Malnourishment, short stature, developmental delay, protuberant abdomen

Shwachman Diamond Syndrome

- **SBDS gene mutation 7p12-q11 (95% of patients)**
- **Chromosome 7 (75%)**
  - **40% Isochromosome 7 (7q(i(7q))**
    - **Rare in AML, MDS, ALL**
    - **No progression to MDS or AML**
  - **60% Other chromosome 7 abnormalities**
    - **Monosomy 7**
    - **Monosomy 7+ i(7q)**
    - **Del 7q**
    - **translocation 7**
- **Chromosome 20**
  - **Del(20q)(q12)**
  - **Rare in SDS, 4% MDS**
  - **Spontaneous resolution**

SDS Survival



Nathan & Oski's 2003

Shwachman Diamond Syndrome

- Pancreatic enzyme replacement
- GCSF
- Hematopoietic stem cell transplantation
  - Bone marrow stroma defect?
  - Increased cardiac toxicity

Congenital Amegakaryocytic Thrombocytopenia

- Thrombocytopenia (median age 7 days)
- Develop aplastic anemia (age 5 yrs) 91% , AML (age 17 years) 55%

- No characteristic physical abnormalities
- Absent or abnormal megakaryocytes
- MPL mutation (thrombopoietin receptor)
- Autosomal recessive

- Hematopoietic stem cell transplant (aplastic anemia protocol)

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Diamond Blackfan Anemia

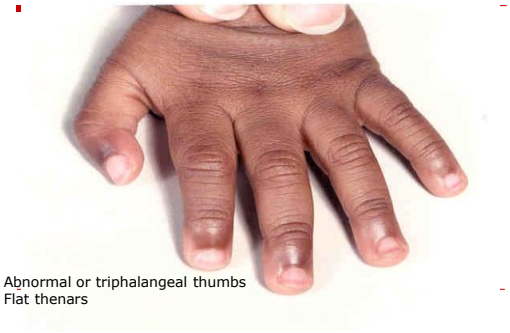
- Childhood pure red cell aplasia

- Macrocytic anemia
- Reticulocytopenia
- Normal bone marrow cellularity with paucity of erythroid precursors

Diamond Blackfan Anemia compared to Transient Erythroblastopenia of Childhood

	DBA	TEC
Diagnosis (median)	2.5 mo	23 mo
Age > 1 yr	12%	83%
Etiology	Inherited ?	Acquired
Antecedent History	None	Viral illness
Abnormal physical findings	24%	< 1%
Red cell adenosine deaminase (ADA)	Increased	Normal
MCV increased (at dx)	80%	8%
Hb F increased (at dx)	100%	25%
i Antigen increased (at dx)	100%	20%

Clinical Features



Abnormal or triphalangeal thumbs
Flat thenars

Table 7-28. PHYSICAL ABNORMALITIES IN DIAMOND-BLACKFAN ANEMIA

Abnormality	Males	Females	Total
No. of patients	254	226	527
Birth-weight, ≤2500 g	6%	11%	7%
Head, face, palate	7%	14%	10%
Upper limbs	7%	10%	8%
Short stature	12%	14%	13%
Eyes	6%	7%	6%
Renal	4%	4%	4%
Neck	0.4%	2%	1%
Hypogonadism	5%	0%	3%
Retardation	2%	4%	2%
Lower limbs	0%	1%	1%
Cardiopulmonary	2%	2%	2%
Nose	1%	1%	1%
Other skeletal	4%	6%	4%
Other anomalies	6%	5%	5%
At least one abnormality*	22%	28%	24%

*Excludes low birth-weight as the only finding. Several patients had more than one birth defect.

Diamond Blackfan Anemia

- Autosomal dominant
- RPS19, RPS24, RPS17 mutation – 30%
- Encode for ribosomal proteins
- Precise mechanism not elucidated

- Red cell transfusion therapy
- 79% steroid responsive
- 17% steroid non-responsive
- 25% improve ("spontaneous remission")

- Steroids: cushingoid features, fractures, cataracts

Diamond Blackfan Anemia

- HLA-identical stem cell transplantation
  - Actuarial survival 72 ± 10%
- Alternative donor transplantation
  - Actuarial survival 19 ± 11%

- Cancer up to 50%, median age 23 years
- MDS, Leukemia, Osteosarcoma

Severe Congenital Neutropenia

- Early onset neutropenia (<0.5 x 10^9/L)
  - Exclude cyclic neutropenia
- Pyogenic infections (fever, gingivitis)
- Marrow maturation arrest at promyelocytes
- No characteristic physical abnormalities

- Accelerated apoptosis in promyelocytes
- ELA2 mutation in 50% - autosomal dominant
- Other: WAS, GFI1
- Kostmann syndrome, HAX1 – autosomal recessive

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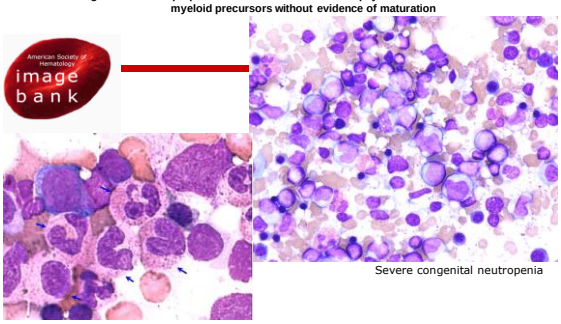
Figure 2. A touch preparation done on the marrow biopsy shows a marked increase in myeloid precursors without evidence of maturation



Lazarchick, J. ASH Image Bank 2005;2005:101290

Severe Congenital Neutropenia

- >95% respond to GCSF
- 50% reduction in infections
- 21% MDS/AML at 10 years
- Role of GCSF unclear
  - GCSF-unresponsive patients may have higher potential for MDS/AML (40% vs. 10%)
- Consider stem cell transplant for unresponsive patients

Thrombocytopenia and Absent Radii

Thrombocytopenia and Absent Radii

- Bilateral absence of radii with presence of thumbs
- Shortened humeri and clavicles
- Purpura, petechiae
- Thrombocytopenia 80% <50 x 10^9/L
- Leukemoid reaction
- Absent, decreased, or immature megakaryocytes

Thrombocytopenia and Absent Radii

- Platelet count increases to >100 x 10^9/L by 1 year of age
- Preleukemic condition
- Genetics unclear, deletion on 1q21.1 is not sufficient (bigenic?)

Bone Marrow Failure is a Risk Factor for Clonal Evolution

	FA	DC	DBA	SDS	SCN	CAMT	TAR
Leukemia MDS	35%	5%	20% ?	71%	55%	53%	14%
Solid tumors	Head & neck, gyn, brain	Head & neck	Osteo-sarcoma	-	-	-	-
Age at cancer median, range	15 y (0.1-48)	28 y (1.5-68)	23 y (1.2-44)	18 y (2-43)	14 y (2-26)	12 y (1.6-17)	5.3 y (0-67)
Cancer by age 40-50y	85%	35%	52%	71%	55%	53%	14%

Acquired Aplastic Anemia

Epidemiology

- Incidence 2 cases/10^6
  (International Aplastic Anemia and Agranulocytosis Study 1980-1984, Israel, Europe)
- Age 15-25 yrs, >60 yrs
- More common in Asia (4-7/$10^{6)}$
- No sex or racial differences
- Geographic variation is most likely due to environmental causes

Epidemiology

- Genetic association:
  - HLA-DR2, class II haplotype DRB*1501 is 2x more frequent than in normal population (cyclosporine-responsiveness) (Nakao S 1994; Nakao S 1992)

Etiology

- Determination of the actual cause in an individual patient is virtually impossible
- Idiopathic

Etiology – Secondary Drugs, toxins, radiation

TABLE 7-3. Classification of Drugs and Chemicals Associated with Aplastic Anemia*

AGENTS THAT REGULARLY PRODUCE MARROW DEPRESSION

Antibiotics: daunorubicin, doxorubicin hydrochloride (Adriamycin), chloramphenicol
Antimetabolites: antifolic compounds, nucleotide analogs
Antimitotics: vincristine, vinblastine, colchicine
Benzene and chemicals containing benzene: carbon tetrachloride, chlorophenols, kerosene, Stoddard's solvent
Cytotoxic cancer chemotherapy alkylating drugs: busulphan, melphalan, cyclophosphamide

AGENTS POSSIBLY ASSOCIATED, WITH LOW PROBABILITY RELATIVE TO USE

Chloramphenicol
Insecticides: chlordane, chlorophenothane (DDT), γ-benzene hexachloride (lindane), parathion
Anticonvulsants: carbamazepine, hydantoins, phenacemide
Nonsteroidal anti-inflammatory agents: indomethacin, ibuprofen, oxyphenylbutazone, phenylbutazone, sulindac
Antihistamines: cimetidine, chlorpheniramine, ranitidine
Antiprotozoal drugs: quinacrine, chloroquine
Sulfonamides: some antibiotics, antidiabetics (chlorpropamide, tolbutamide), antithyroidal drugs (methimazole, methylthiouracil, propylthiouracil), carbonic anhydrase inhibitors (acetazolamide, methazolamide)
Penicillamine
Metals: gold, arsenic, bismuth, mercury

AGENTS MORE RARELY ASSOCIATED

Allopurinol (may potentiate marrow suppression by cytotoxic drugs)
Antibiotics: flucytosine, mebendazole, methicillin, sulfonamides, streptomycin, tetracycline, trimethoprim/sulfamethoxazole
Carbimazole
Guanidine
Lithium
Methyldopa
Potassium perchlorate
Quinidine
Sedatives and tranquilizers: chlordiazepoxide, chlorpromazine, meprobamate, methyprylon, piperacetazine, prochlorperazine
Thiocyanate

Nathan & Oski 2003

Etiology - Secondary

- Viruses
  - Non-A non-B hepatitis (0.07%; 2-5% of all pts with AA, up to 10% in Asia; male; <20 yrs old)
  - Epstein-Barr virus
  - Flavivirus
    - Arbovirus hemorrhagic fever; dengue
    - Lymphocyte activation, marrow-suppressive cytokine release
  - Cytomegalovirus, Human Herpesvirus 6
    - Graft failure in bone marrow transplant patients
  - Human Immunodeficiency virus (rare)

Etiology - Secondary

- Immune diseases
  - Eosinophilic fasciitis
  - Hypogammaglobulinemia
  - Thymoma
  - Post-transfusion GvHD in immunodeficiencies
- Paroxysmal nocturnal hemoglobinuria
- Myelodysplasia/Myelofibrosis/Osteopetrosis
- Pregnancy

Presentation and Evaluation

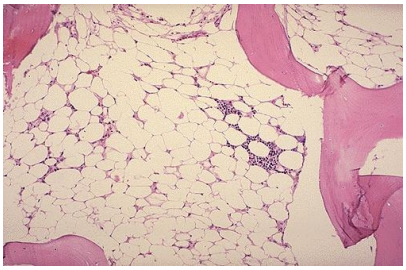
Bleeding	41%
Anemia	27%
Infection	5%
Combination	20%
Routine examination	8%

Williams DM et al. 1973

Presentation and Evaluation

- CBC
  - Morphology, reticulocyte count
- Bone marrow aspirate and biopsy
  - Morphology, cytogenetics, culture
- Peripheral blood chemistry
  - LDH, LFTs, renal parameters
  - Viral serologies
  - PNH studies
  - Chromosome breakage studies
  - HLA typing
  - Autoimmune disease evaluation

Guinan EC, 1997



Presentation and Evaluation

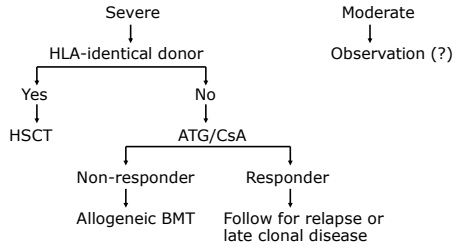
- Severe aplastic anemia
  - Bone marrow cellularity <25%
  - Two of three peripheral blood criteria
    - ANC <500/cu.mm.
    - Platelets <20,000/cu.mm.
    - Reticulocytes <40,000/cu.mm.
  - No other hematologic disease
- Moderate aplastic anemia
  - Bone marrow cellularity <50%
  - 2 or 3 cytopenias for >6 weeks
    - ANC <1,500/cu.mm.
    - Platelets <100,000/cu.mm.
    - Reticulocytes <40,000/cu.mm.

Camitta BM et al. 1976, Khatib Z et al. 1994

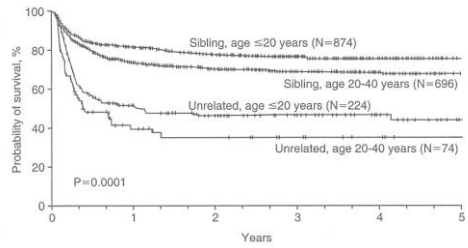
Treatment and Outcomes

- Therapy
  - Bone marrow transplantation
  - Immunosuppression
  - Other
    - Growth factors, androgens, steroids, splenectomy
    - New therapeutic approaches

Treatment Algorithm



Bone Marrow Transplantation



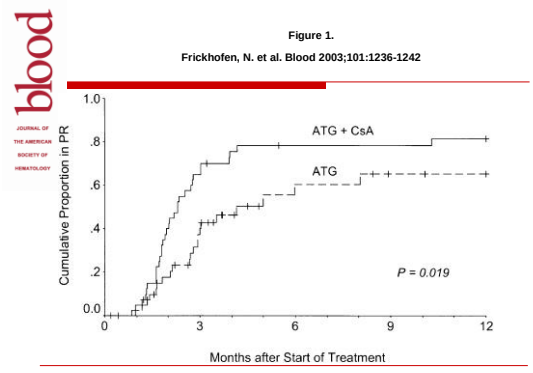
Horowitz MM 2000: BMT after aplastic anemia 1991-1997, IBMTR

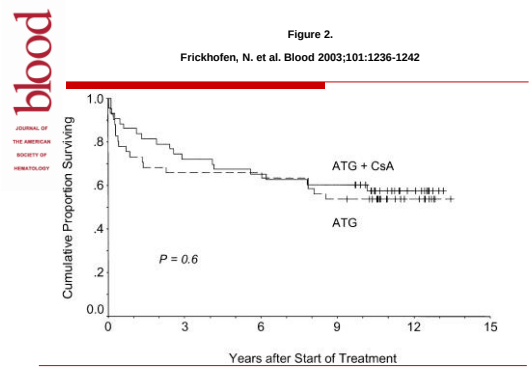
Bone marrow transplantation Alternative donor

- Benesch M et al. 2004
  - Highly purified, positively selected CD34+ stem cells
  - 4 m unrelated, 4 mm unrelated, 1 mm related
  - 8 pts (89%) in CR at 47 months
  - 1 pt died of GVHD
- Woodard P et al. 2003
  - Positively selected CD34+ stem cells
  - 4 haploidentical, 1 unrelated
    - 3 successful, 1-2.5 years
    - 2 graft rejection with positive HLA crossmatches with the donors

Immunosuppressive Therapy

- "Standard"
  - Anti-thymocyte globulin (Prednisone)
    - 40 mg/kg/d x 4 days
  - Cyclosporine
    - Therapeutic level until transfusion-independence for 2 months
  - G-CSF or GM-CSF or no growth factor
    - Kojima S et al. 2000: no difference in survival, but difference in time to neutrophil recovery

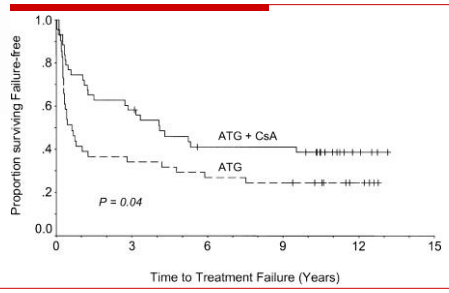




blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Figure 3.

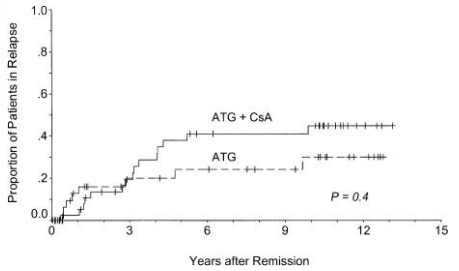
Frickhofen, N. et al. Blood 2003;101:1236-1242



blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

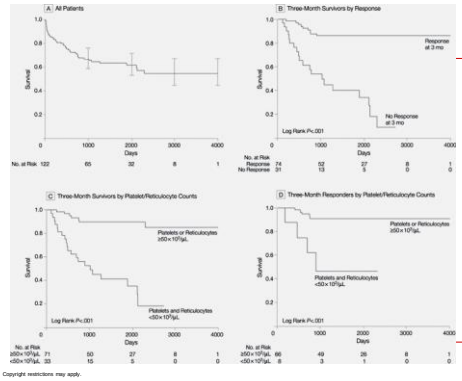
Figure 4.

Frickhofen, N. et al. Blood 2003;101:1236-1242



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

Survival for Entire Cohort



JAMA

High dose cyclophosphamide

- Tisdale JF at al. 2002
  - Randomized trial HD CY vs. ATG/CsA

Table 1. Results at median follow-up of 38 months

	ATG/CSA (%)	Cy/CSA (%)
Overall response	13/16 (81)	8/15 (53)
CR	10 (63)	6 (40)
PRi	3 (18)	2 (13)
Relapse	6/13 (46)	2/8 (25)
Cytogenetic evolution	2/14 (14)	1/12 (8)

Overall responses are shown by type and overall percentage and do not differ between arms. Complete responses have been observed in 6 of 8 responders or 75% in the Cy arm and 10 of the 13 responders or 77% in the ATG arm (40% Cy and 63% ATG, overall complete response rates). No patients remain in the PRd response group. Relapse rates do not differ between arms (P = .38) with 6 among 13 responders and 2 among 8 responders relapsing in the ATG and Cy arms, respectively.

High dose cyclophosphamide

Brodsky A et al. 2004

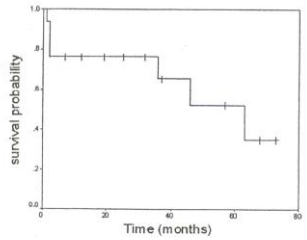


Figure 1. Kaplan-Meier probability of survival.

Late Clonal Disease

- Rosenfeld S et al. 2003
  - Chromosomal abnormalities 12/122 pts
  - Risk of PNH 10% at 2 yrs, remaining stable for 7 yrs
- Frickhofen et al. 2003
  - PNH 10% at 11 yrs (5 pts, 2 clinical sx)
  - MDS/Leukemia 8%, duration 6.6-9.5 yrs
  - Solid tumor 11%, duration 1-11 yrs

Pathophysiology

- Overlap of hematopoietic defect with paroxysmal nocturnal hemoglobinuria
- T-cell mediated, organ-specific attack of cytotoxic lymphocytes on CD34 hematopoietic stem and progenitor cells.

Paroxysmal nocturnal hemoglobinuria

- PNH
  - Absent or diminished surface expression of proteins with GPI (glycosylphosphatidylinositol) anchors
  - CD55, CD59, CD14, CD66, Campath-1
  - Acquired mutations in the X-linked PIG-A gene
  - Clinical PNH: Hemolysis, bone marrow failure, thromboses

Paroxysmal nocturnal hemoglobinuria

- Pathogenetic link between PNH and AA
  - Occurrence of PNH cell clones at presentation or with/without symptoms after immunosuppressive therapy
    - Tichelli A et al. 1988: 13/103, 13% pts
    - Schrezenmeier H et al. 1995: 27/52, 52% pts
    - Wang H et al. 2001: 31/35, 89% pts
    - Maciejewski JP et al 2001: 30% pts
  - May represent immunologic pressure to normal hematopoietic cells and lead to positive selection of PNH+ cells
  - Change in PNH cell clone after treatment is not consistent

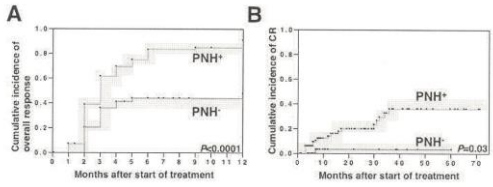
Paroxysmal nocturnal hemoglobinuria

- Sugimori C et al. 2005
  - 122 patients, mean age 56 years
  - High-resolution two color flowcytometry to quantifiy CD55-CD59- granulocytes and RBCs
  - 68% PNH+ (0.005-23.1% GPI-AP$^-$ cells)
  - Improved response rate in PNH+ pts, independent of magnitude of PNH- clones (91% vs. 48%)
  - Increased failure-free survival at 5 yrs (64% vs. 12%)
  - No difference in overall survival

Paroxysmal nocturnal hemoglobinuria

- Sugimori C et al. 2005

Figure 3. Response to immunosuppressive therapy.



New therapeutic approaches

- Anti-IL2 receptor antibody
- Mycophenolate mofetil
- Tacrolimus
- Rapamycin
- Eltrombopag
- Extracorporeal photopheresis
- Alternative bone marrow transplantation