An Overview of Aplastic Anemia in Adults

AAMAC Education Day

October 24, 2009

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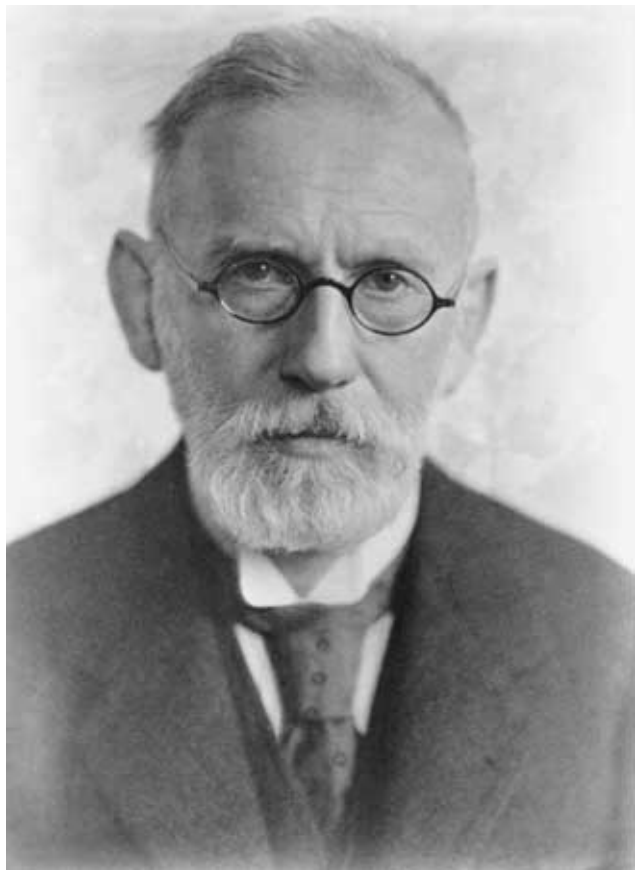
Objectives

- Review the epidemiology, clinical presentation and diagnosis of aplastic anemia in adults

- Discuss the therapy of aplastic anemia in adults

Introduction

- Bone marrow failure syndrome
  - pancytopenia
  - bone marrow hypocellularity
- First described by Paul Ehrlich in 1888



Introduction

- Epidemiology
  - likely ~ 2/million in Western populations
    - Studies from Spain, France, UK, Scandinavia and Brazil
  - higher incidence in Asia
  - gender ratio 1:1
  - 2 age peaks
    - young adults, elderly

Incidence of Aplastic Anemia, Spain

Table 1. Incidence of aplastic anemia according to age and sex.

	Age at diagnosis (years) 2-14	15-24	25-44	45-64	≥65	N. of cases	Total incidence[a]
Male							
N. of cases	17	25	22	28	31	123	
Incidence	1.92	2.83	1.52	2.56	5.89		2.54
Female							
N. of cases	12	11	15	31	43	112	
Incidence	1.43	1.41	1.00	2.58	4.89		2.16
Total							
N. of cases	29	36	37	59	74	235	
Incidence	1.68	2.16	1.26	2.57	5.33		2.34

[a]*Number of cases per one million people per year.*

Montane, E. et al. Haematologica 2008;93:518-523

haematologica
the hematology journal

Clinical Presentation

- Secondary to decreased blood cells
  - anemia (low red cells)
    - fatigue, chest pain and shortness of breath with exertion, palpitations
  - thrombocytopenia (low platelets)
    - bleeding, bruising, petechiae
  - leukopenia (low white blood cells)
    - infections

Approach to Aplastic Anemia

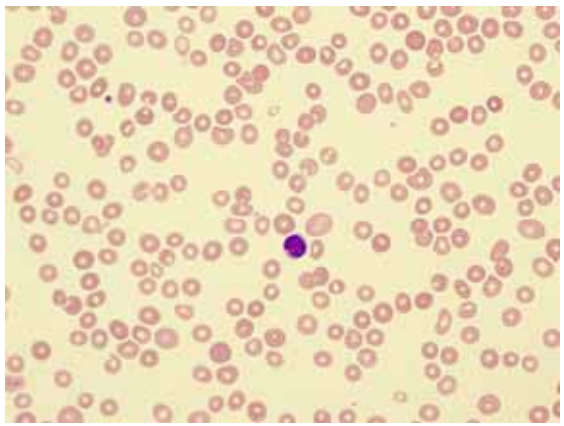
- Confirmation of the diagnosis

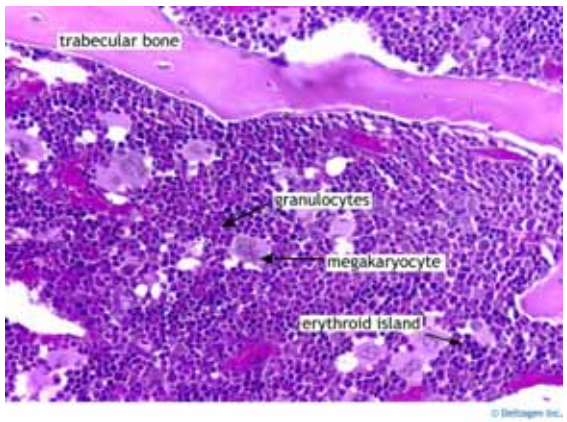
- Define the disease
  - acquired or congenital
  - cause
  - disease severity

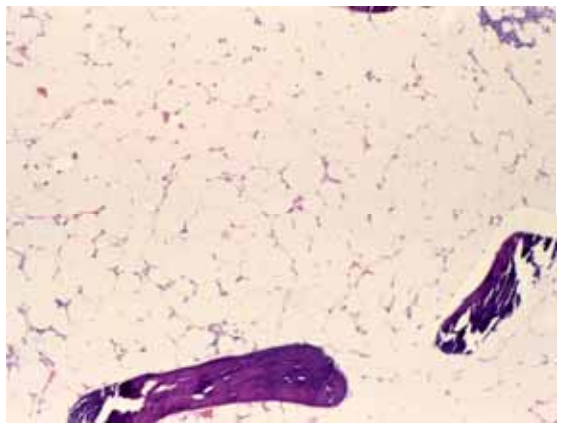
Approach to Aplastic Anemia

- Traditional definition
  - pancytopenia with hypocellular bone marrow
  - normal hematopoietic tissue replaced by fat cells
  - absence of abnormal infiltrate in the bone marrow or increased reticulin (fibrosis or scar)
  - at least 2 of hemoglobin < 100 g/L, platelets < 100, absolute neutrophil count < 1500

Approach to Aplastic Anemia







Approach to Aplastic Anemia

- Is the diagnosis really aplastic anemia?
  - Exclude:
    - hypocellular MDS
    - myelofibrosis
    - lymphoma
    - atypical mycobacterial infection
    - anorexia nervosa

Approach to Aplastic Anemia

- Is the disease an inherited bone marrow failure syndrome?
  - Fanconi anemia
  - Dyskeratosis congenita
  - Shwachman-Diamond syndrome

Approach to Aplastic Anemia

- What is the cause?
  - idiopathic
  - post-hepatitic
  - drugs, chemicals, environmental exposures
  - PNH
  - pregnancy
  - thymoma

Approach to Aplastic Anemia

- How severe is the disease?
  - Severe aplastic anemia
    - Bone marrow cellularity < 25%
    - 2/3: ANC < 500, platelets < 20, reticulocytes < 20
  - Very severe aplastic anemia
    - As above except ANC < 200

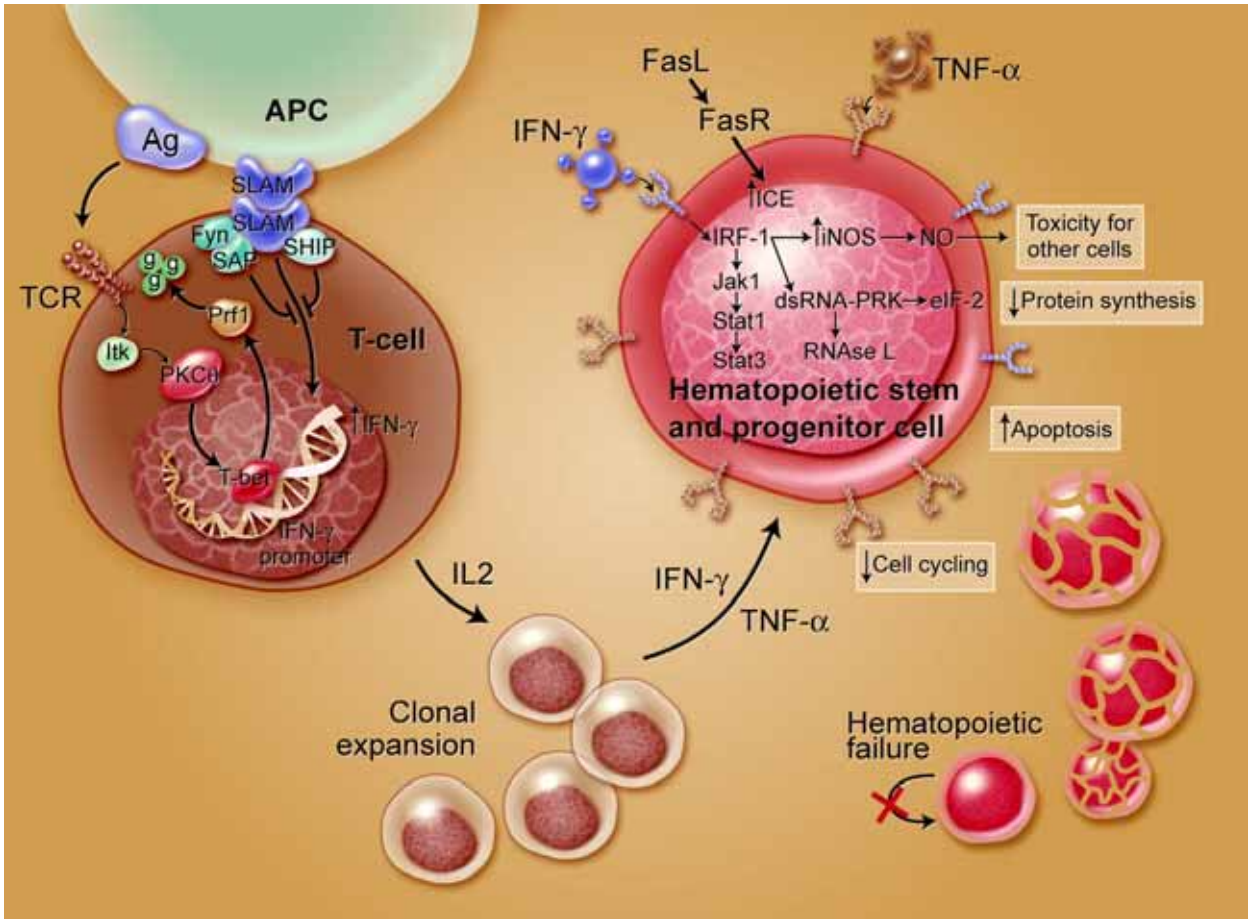
What is the cause of idiopathic aplastic anemia?

- Immune mediated disease

- Variability
  - environmental exposures
  - patient risk factors
  - differences in immune response

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Immune destruction of hematopoiesis



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

Treatment

- Depends on severity of disease
  - Nonsevere aplastic anemia
    - follow expectantly
  - Severe aplastic anemia
    - immunosuppression versus allogeneic bone marrow transplant

Immunosuppression

- Reducing the activation or effectiveness of the immune system

- If aplastic anemia is an autoimmune disease, “shutting down” the immune system is logical

Immunosuppression

- Standard therapy
  - antithymocyte globulin (ATG) and cyclosporin

Immunosuppression

- ATG
  - injection of human lymphocytes into an animal
  - animal makes antibodies against the lymphocytes
  - the antibodies attack the lymphocytes in the patient

ATG

- Side effects
  - allergic reaction
  - cytokine release syndrome
  - serum sickness
  - infections

Cyclosporin

- Inhibits T lymphocytes

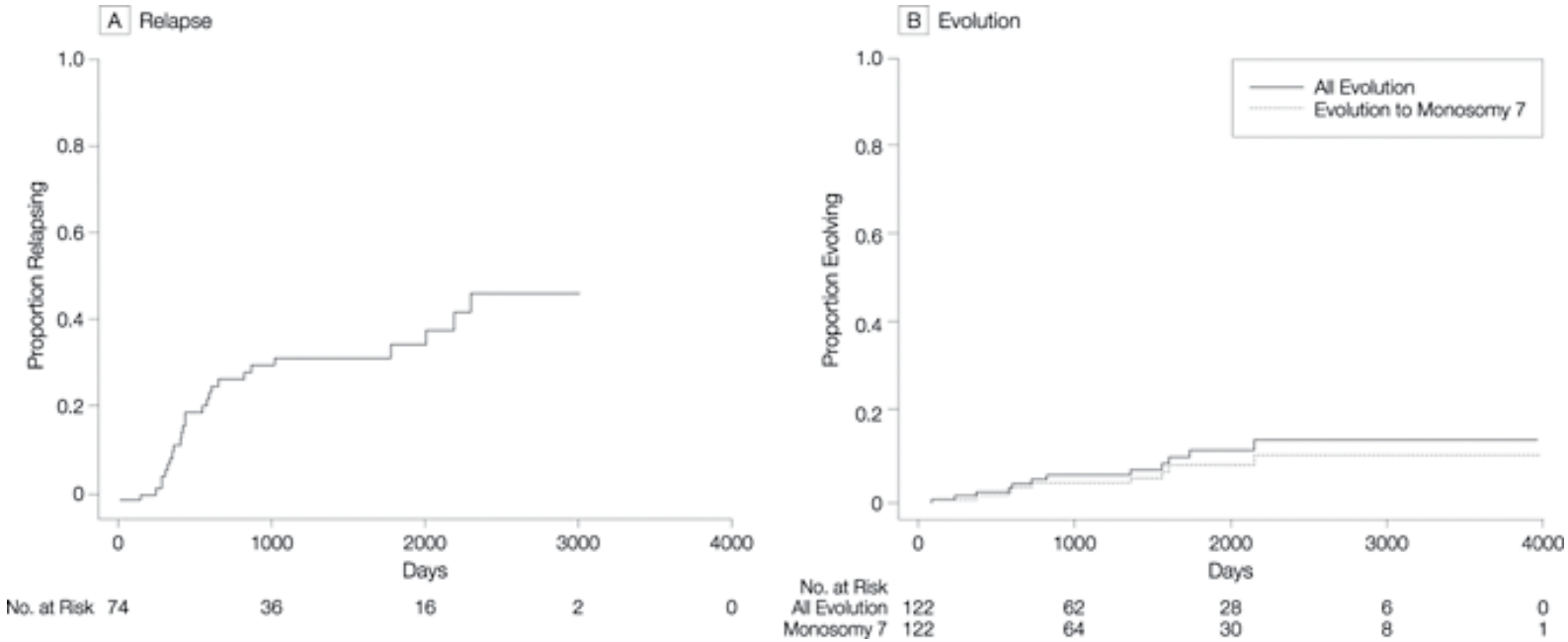
- Side effects
  - kidney problems
  - high blood pressure
  - metabolic problems
  - infections

Immunosuppression

Study Group	N	Median Age	Response (%)	Relapse (%)	Clonal Evolution (%)	Survival (%)
German	84	32	65	19	8	58(11yrs)
EGBMT	100	16	77	12	11	87(5 yrs)
NIH	122	35	61	35	11	55(7 yrs)
Japan	119	9	68	22	6	88(3 yrs)
NIH	104	30	62	37	9	80(4 yrs)

Adapted from Young et al Blood 2006

Late Events After Immunosuppressive Therapy



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

JAMA

Relapse after ATG + Cyclosporin

- High risk of relapse
  - 20-40%
- Treat with second course of ATG
  - 50-60% will respond to second course
- No prospective trial comparing horse to rabbit ATG; choice depends on:
  - whether a severe reaction occurred with first course
  - centre practice
  - drug availability

Bone Marrow Transplant

- Background
  - curative therapy
  - 1961
    - first successful transplant using a syngeneic (identical twin) donor
  - 1972
    - first successful transplant using a matched, unrelated donor
  - 1976
    - randomized prospective trial showed survival advantage of matched related donor over standard of care

Bone Marrow Transplant

- Transplanted bone marrow stem cells replaces the failing bone marrow cells

- Stem cells reconstitute all the normal cells
  - new immune system
  - new red cells
  - new platelets

Bone Marrow Transplant

- Potential cure but…

- Complications
  - side effects from chemotherapy
  - graft rejection
  - graft versus host disease
  - long term complications

Bone Marrow Transplant

- Acute complications
  - nausea, vomiting, diarrhea, mucositis
  - organ damage
  - infections
  - bleeding

Bone Marrow Transplant

- Graft failure
  - central problem in aplastic anemia
  - reported in up to 5-15% of patients
  - why?
    - conditioning regimens are nonmyeloablative (chemotherapy not as strong as other transplants)
    - immune activity rejects the graft

Bone Marrow Transplant

- Graft versus host disease
  - acute versus chronic
    - At least 20-40% of patients
  - can be difficult to treat and associated with significant morbidity and decreased quality of life

Long-term Complications

- Toxicities from treatment regimens
- Immune deficiency
- Autoimmune syndromes
- Infectious complications
- Endocrine disturbances
- Chronic GVHD
- Second malignancies
- Cognitive dysfunction
- Psychosocial adjustment
- Decreased quality of life

Bone Marrow Transplant

- Source of stem cells
  - unmanipulated bone marrow first choice
  - peripheral blood stem cells
    - faster engraftment, but increased GVHD and lower survival
  - umbilical cord blood
    - little data

Syngeneic Allogeneic BMT

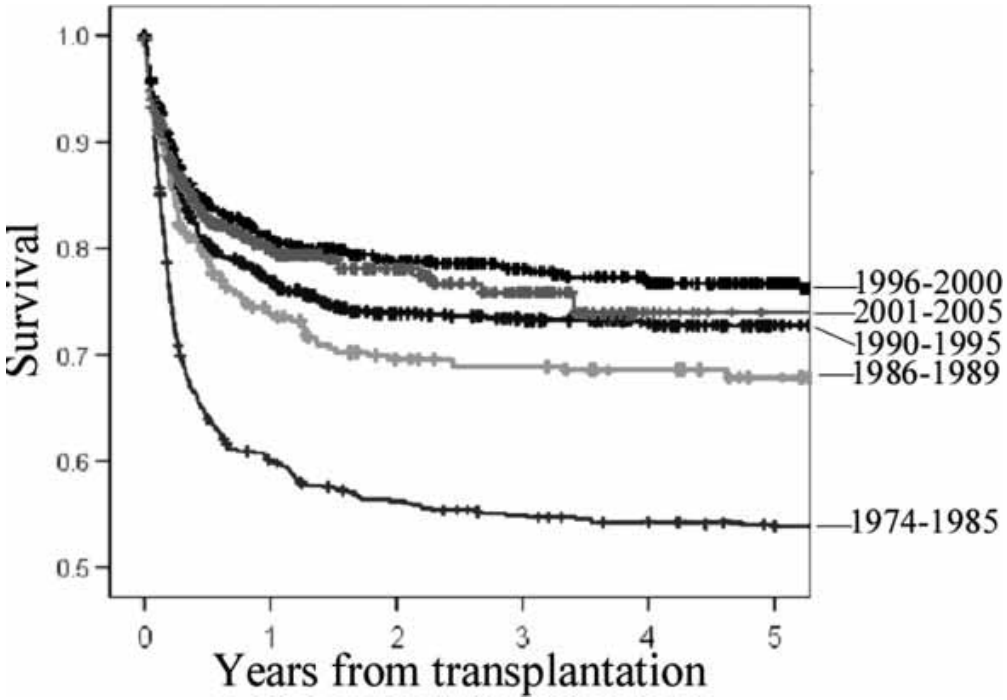
- Ideal donor is an identical twin
  - no need for graft versus tumor effect
  - minimizes risk of graft failure
  - no GVHD

  - survival rates of 70-90%

Sibling Allogeneic BMT

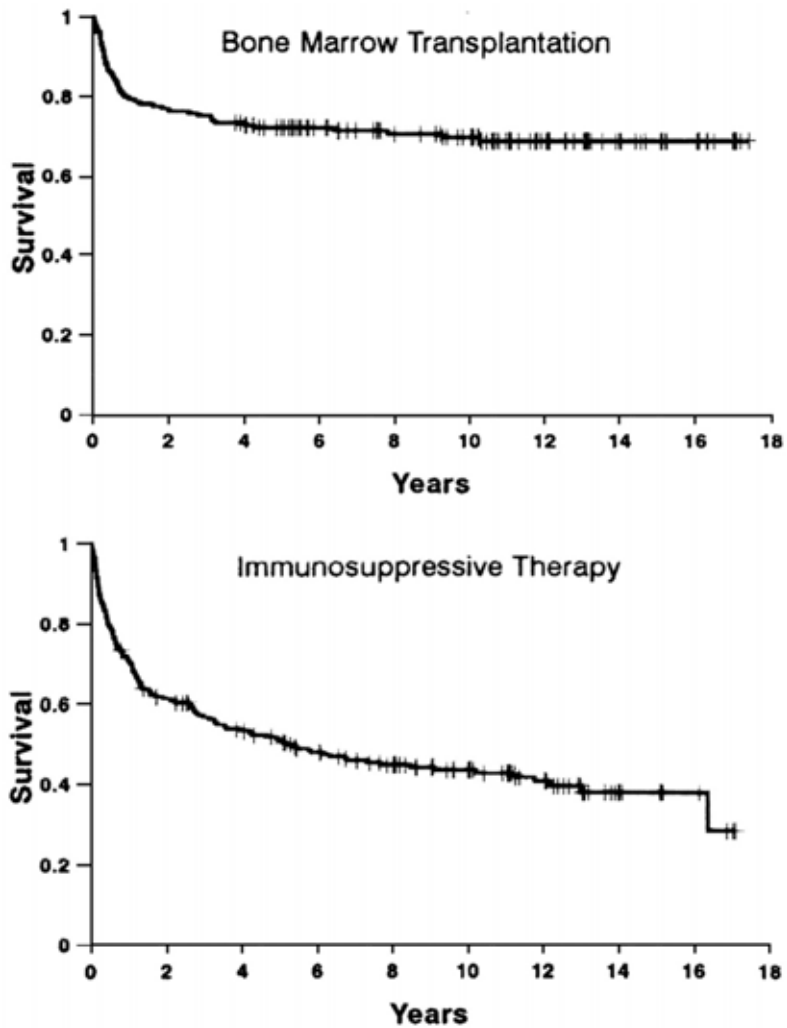
- Few prospective studies
- Important to consider sibling BMT early
- Steady improvement in outcome over time

Sibling Allogeneic BMT



Passweg Aplastic Anemia Working Party EBMT

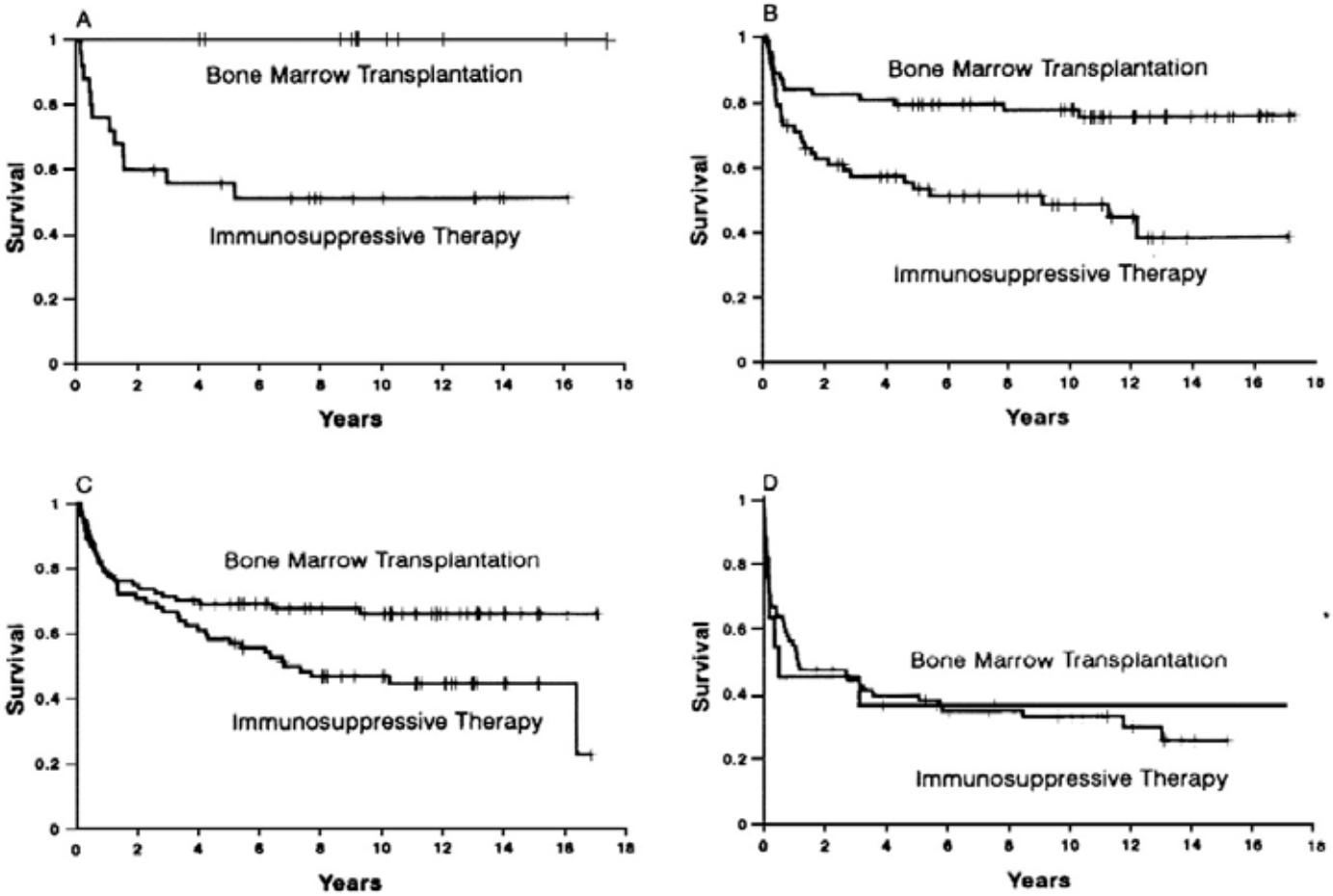
Sibling BMT compared to Immunosuppression



Doney, K. et. al. Ann Intern Med 1997;126:107-115

Annals of Internal Medicine

Effect of patient age on survival by treatment group



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Annals of Internal Medicine

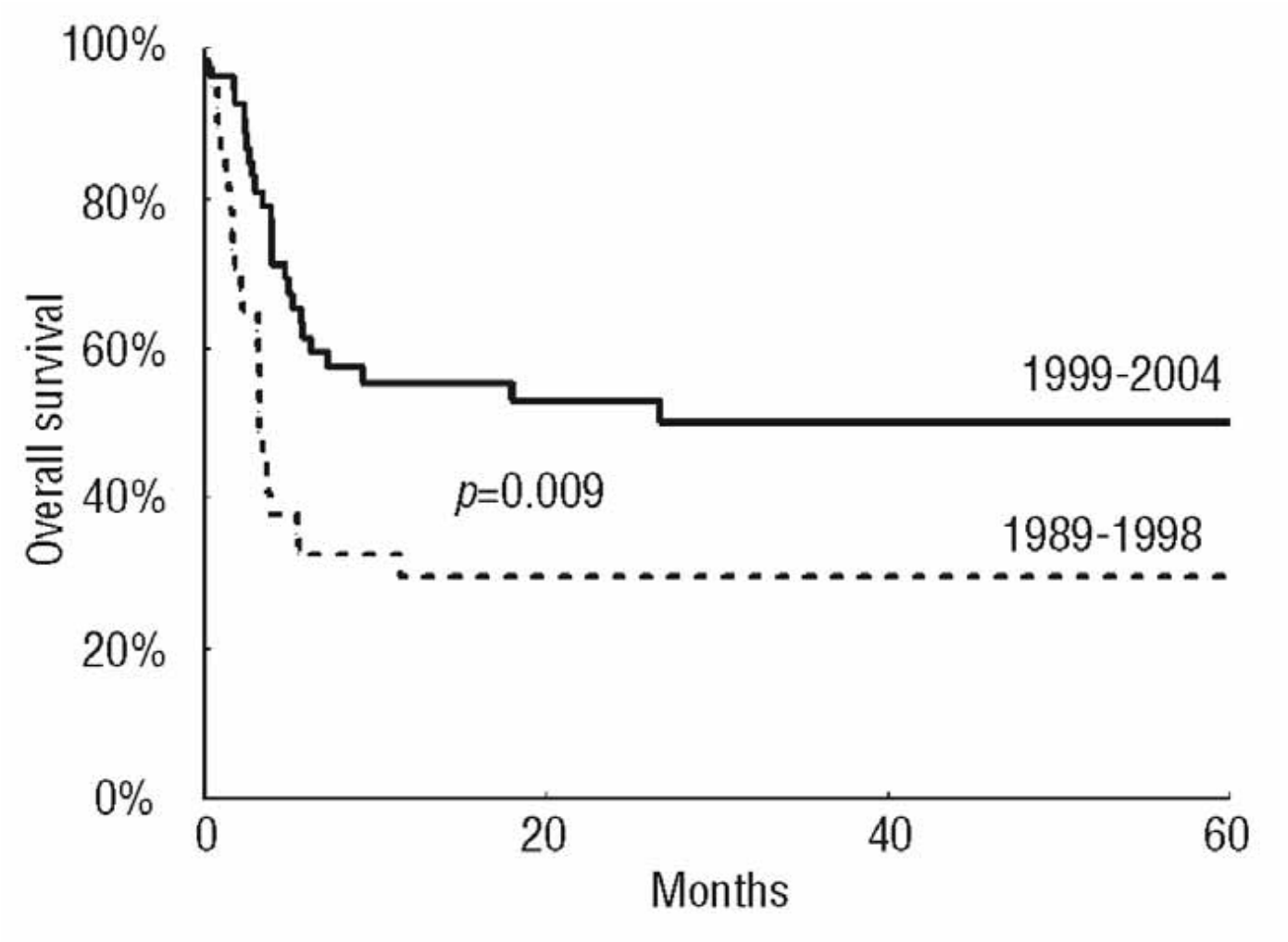
Sibling Allogeneic BMT

- Recommendations
  - younger adults with a sibling donor should be treated with allogeneic BMT over immunosuppressive therapy
  - transfusions prior to transplant should be minimized
  - conditioning generally with cyclophosphamide + ATG

Matched, unrelated BMT

- Little prospective data
- Higher morbidity and mortality than sibling BMT
- Improved survival over time

Impact of Better HLA Matching in MUD BMT



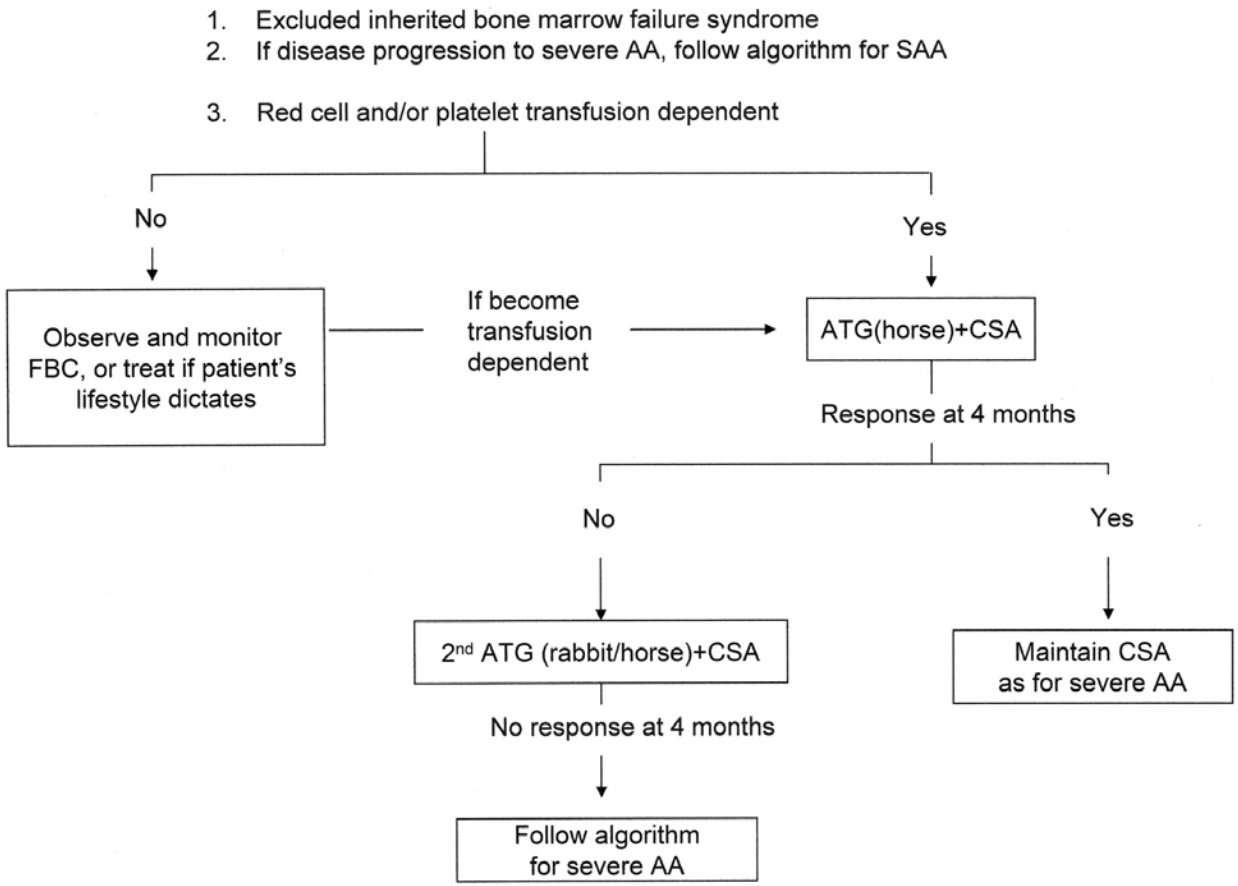
Maury, S. et al. Haematologica 2007;92:589-596

haematologica
the hematology journal

Matched, unrelated BMT

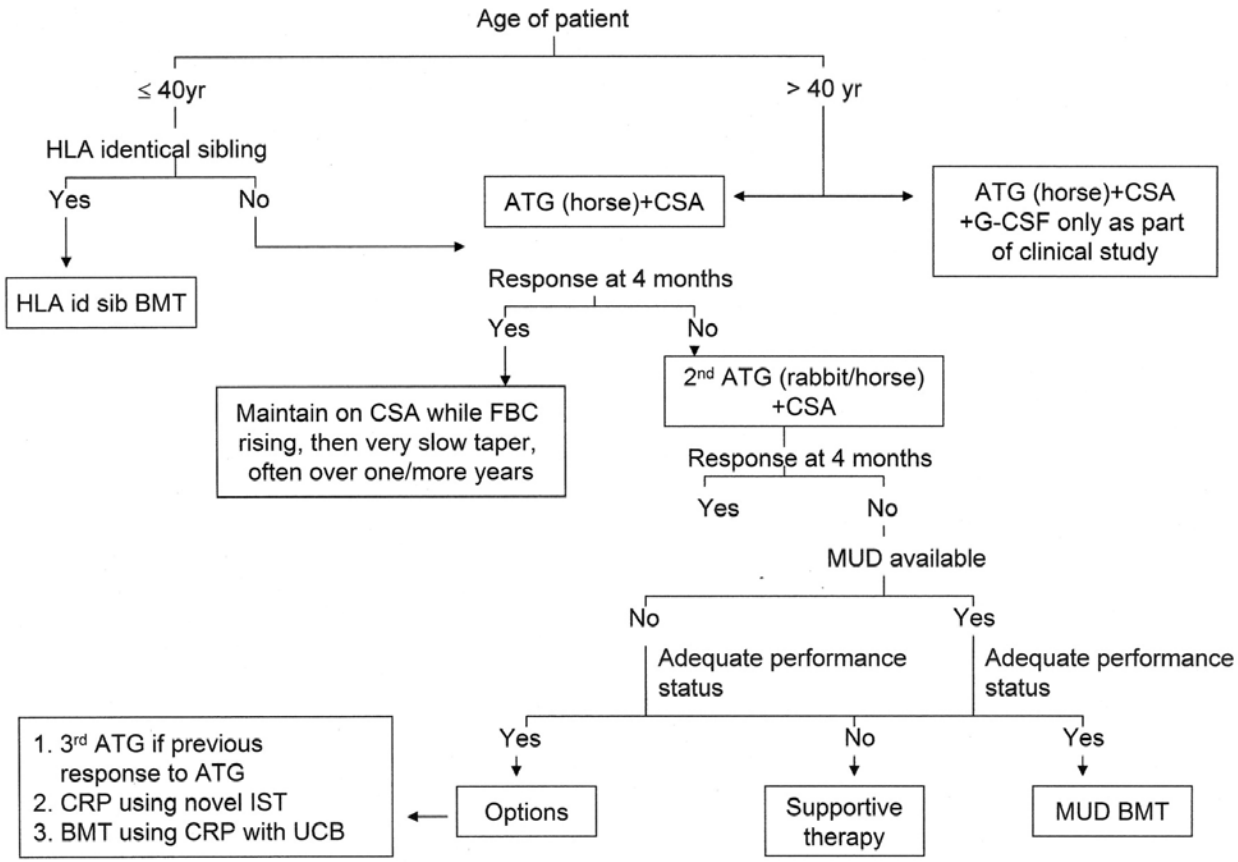
- Recommendations
  - at least 2 courses of immunosuppression should be given before considering proceeding with a MUD BMT

Approach to Treatment



Marsh, J. Hematology 2006;2006:78-85

Approach to Treatment



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- Thank you!
- Questions?