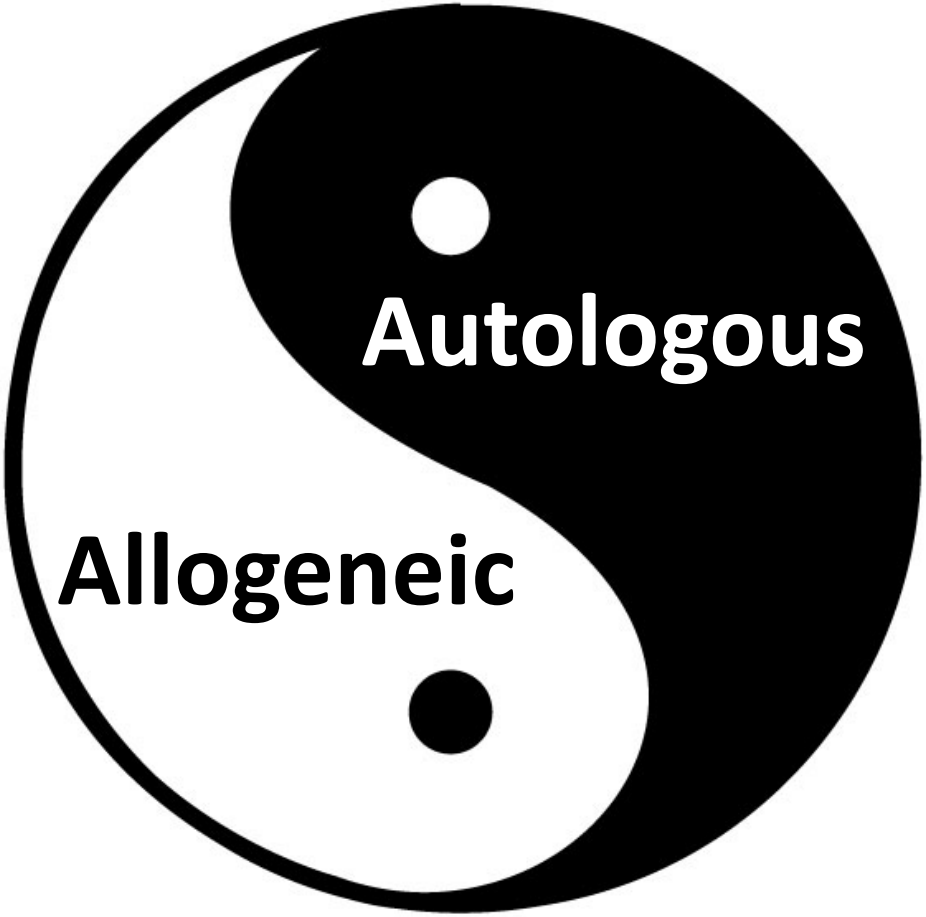
TRANSPLANTATION

20  14

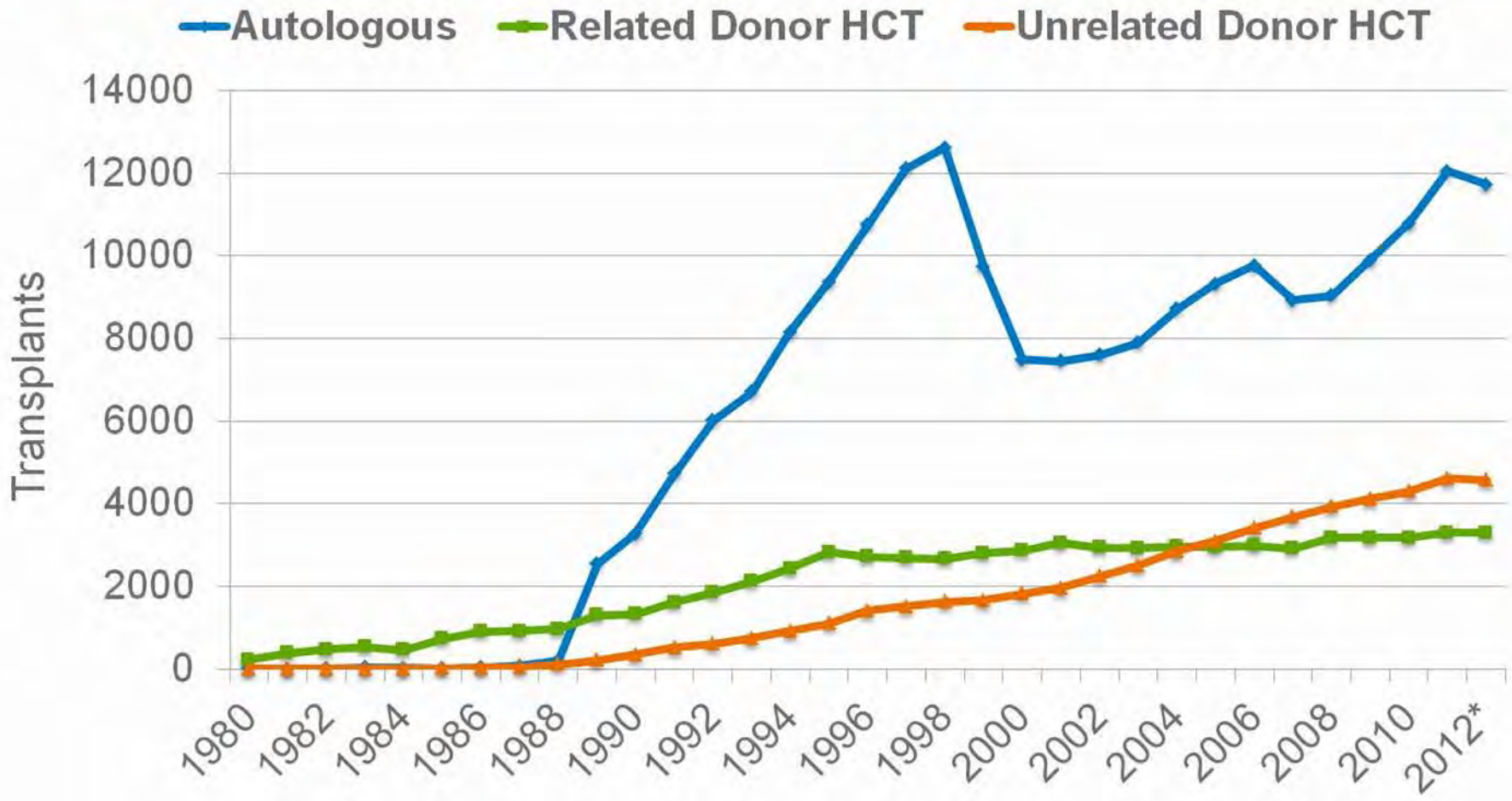
Matthew Lunning D.O.*

*I have no relevant conflicts of interest

By the end….

- List 3 conditioning regimens commonly used in stem cell transplantation.
- Appreciate disease and patient characteristics that may influence the type of blood stem cell transplant and preparative regimens utilized for transplantation.
- List 3 non-malignant disorders that could be treated by stem cell transplantation.

Trends in Transplantation



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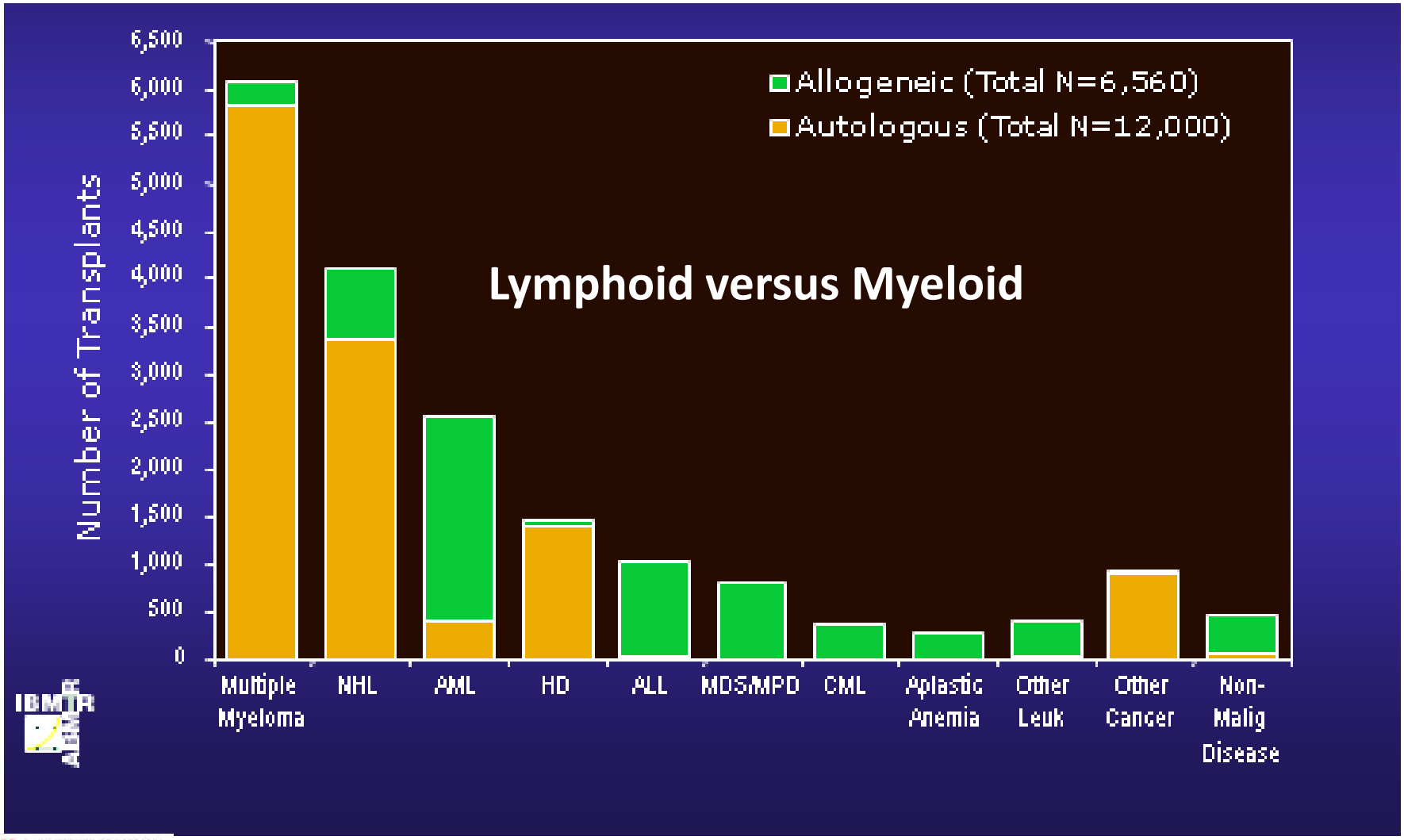
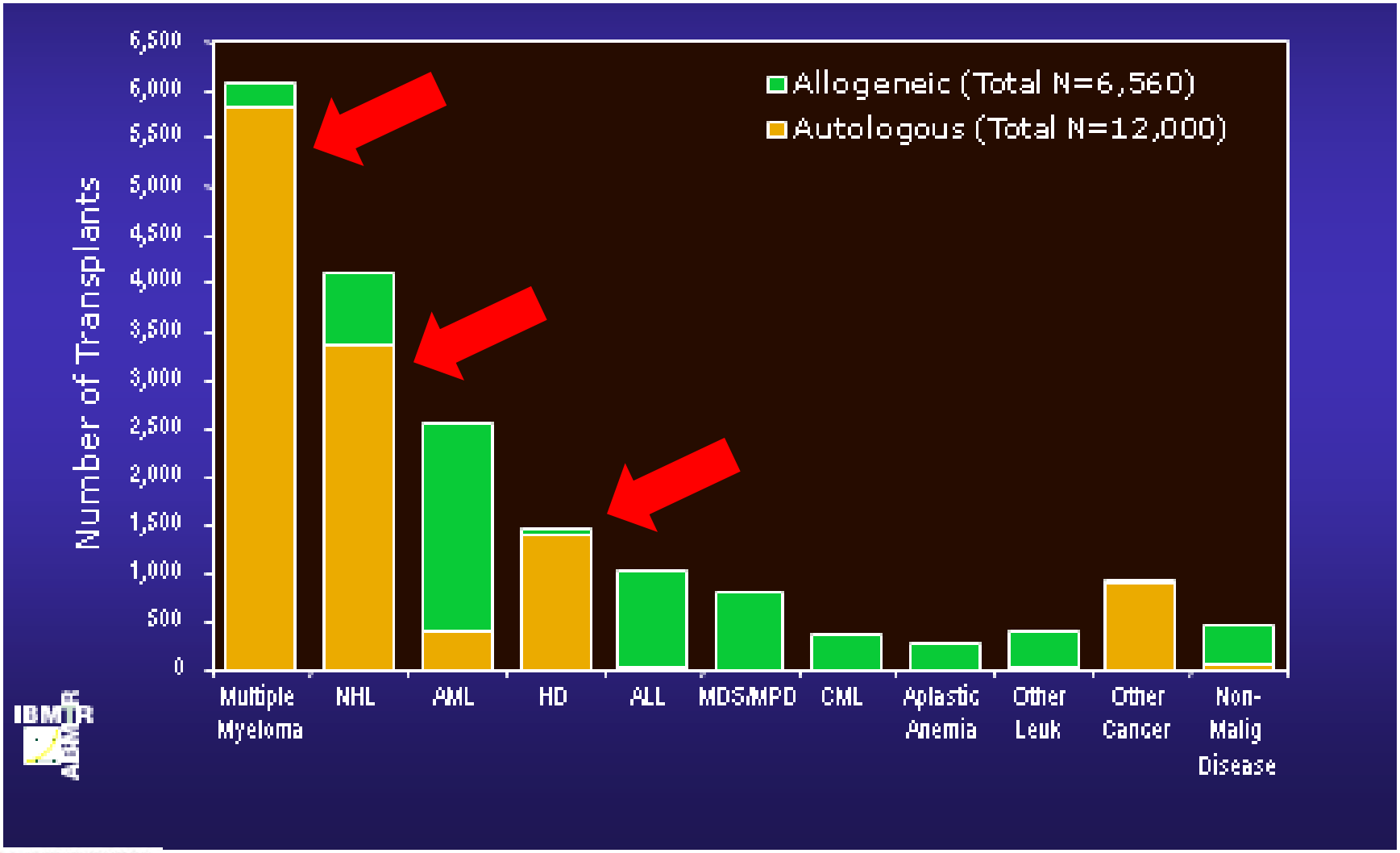
*Data incomplete

Trends in Transplantation



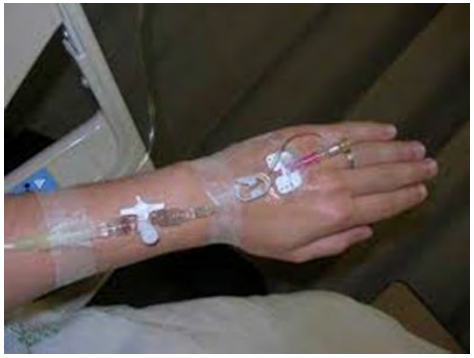

Autologous
Allogeneic

Who gets an “auto”?

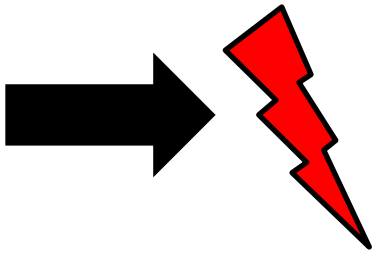


Autologous “Transplantation”: A Modern Misnomer

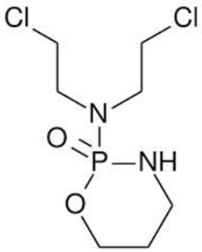
Collection



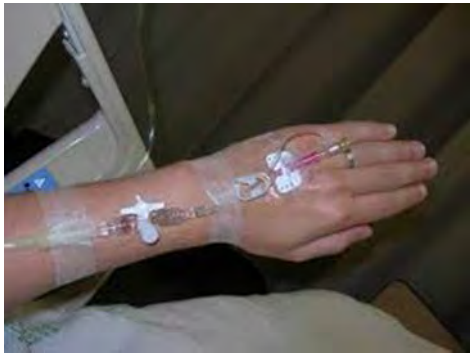
High dose therapy



OR

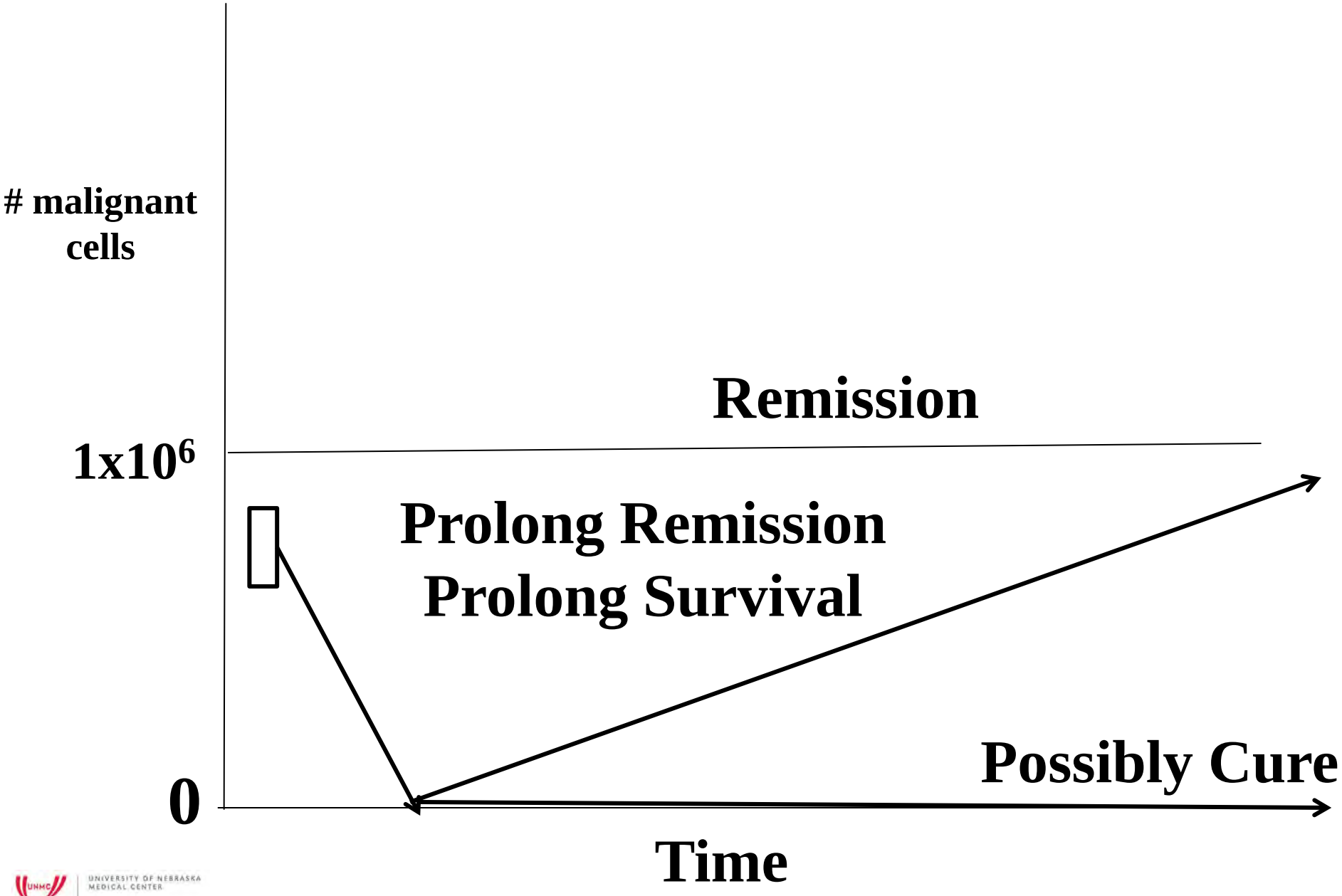


Stem cell Rescue



High dose therapy (HDT) and autologous stem cell RESCUE (ASCR)

Goal of HDT-ASCR



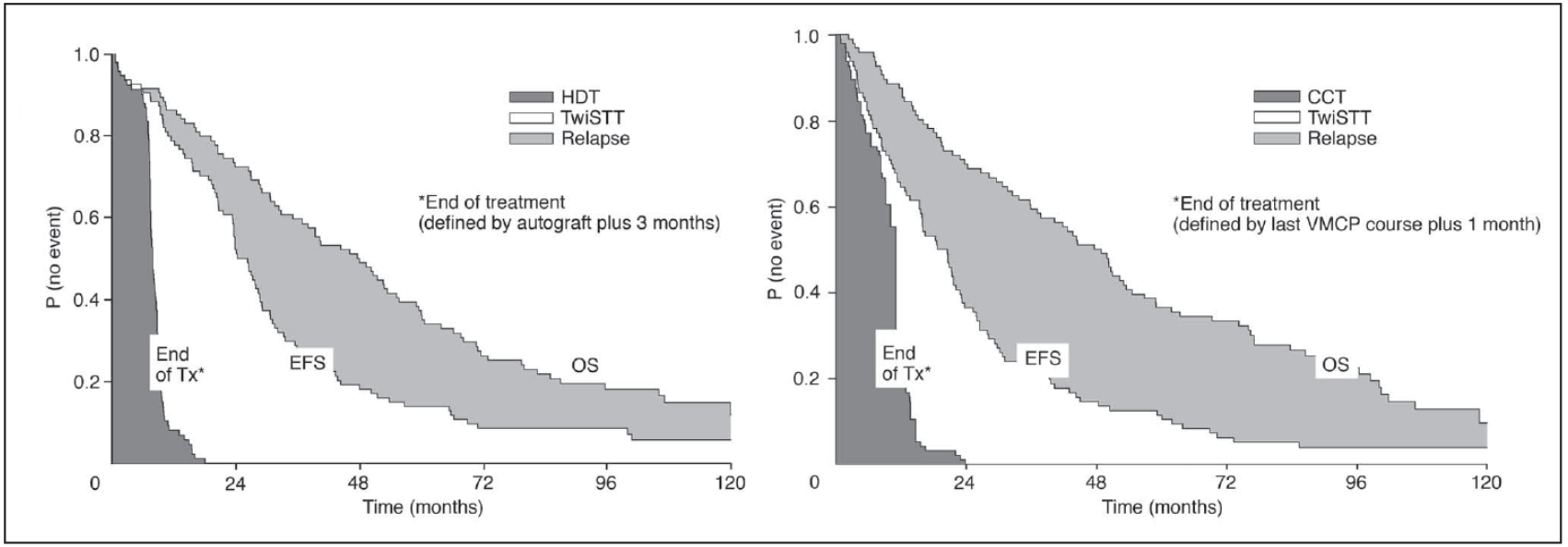
HDT-ASCR Check Boxes

- Right disease
  - Multiple Myeloma (MM), Diffuse large B-cell lymphoma (DLBCL), Mantle cell lymphoma (MCL), Peripheral T-cell lymphoma (PTCL)
- Right response
  - Chemosensitive (complete response—CR; partial repsonse—PR)
- Ability to collect
  - Chemotherapy, GCSF, Plerixafor
- Comorbidities
  - CAD, COPD, CKD, Obesity
- Conditioning
  - Melphalan, BEAM, CBV

HDT/ACSR in Multiple Myeloma

- Most common reason to do HDT-ASCR
- Often requires at least a partial response (PR) by International Myeloma Working Group (IMWG) criteria
  - Greater 50% reduction in monoclonal protein
- Comorbidities
  - Obesity
  - CKD
- Mobilization and collection with GCSF +/- cyclophosphamide (Cy) +/- plerixafor
- Most common conditioning regimen
  - High dose Melphalan (200 mg/m^2 or 140 mg/m^2)

Why HDT-ASCR in Multiple Myeloma?



Fermand et al. JCO 2005

- Well established that likely provides an event free survival advantage but arguable if there is an overall survival advantage.
- Modern upfront triplet regimens (RVD & CyBorD)
  - More patients in at least a PR >95% fast response
  - Able to mobilize more people (stay fit during induction)

WHO Classification of Lymphoid Neoplasms (2008)

Precursor

- B lymphoblastic leukaemia/lymphoma
- B lymphoblastic leukaemia/lymphoma, NOS
- B lymphoblastic leukaemia/lymphoma
- with recurrent genetic abnormalities
- B lymphoblastic leukaemia/lymphoma
- with t(9;22)(q34;q11.2); *BCR-ABL1*
- B lymphoblastic leukaemia/lymphoma
- with t(v;11q23); *MLL* rearranged
- B lymphoblastic leukaemia/lymphoma
- with t(12;21)(p13;q22); *TEL-AML1*
- *(ETV6-RUNX1)*
- B lymphoblastic leukaemia/lymphoma
- with hyperdiploidy
- B lymphoblastic leukaemia/lymphoma
- with hypodiploidy (hypodiploid ALL)
- B lymphoblastic leukaemia/lymphoma
- with t(5;14)(q31;q32); *IL3-IGH*
- B lymphoblastic leukaemia/lymphoma with
- t(1;19)(q23;p13.3); *E2A-PBX1*
- (*TCF3-PBX1)*
- T lymphoblastic leukaemia/lymphoma

Indolent B

- Chronic lymphocytic leukaemia/ small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- *Splenic lymphoma/leukaemia, unclassifiable**
- *Splenic diffuse red pulp small B-cell lymphoma*
- *Hairy cell leukaemia-variant*
- Lymphoplasmacytic lymphoma
- Waldenström's macroglobulinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- *Paediatric nodal marginal zone lymphoma*
- Follicular lymphoma
- *Paediatric follicular lymphoma*
- Primary cutaneous follicle centre lymphoma

Aggressive B

- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
- T-cell/histiocyte rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- *EBV positive DLBCL of the elderly*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- *B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma*
- *B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma*

Mature T/NK

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- *Chronic lymphoproliferative disorder of NK-cells*
- Aggressive NK cell leukaemia
- Systemic EBV positive T-cell lymphoproliferative
- disease of childhood
- Hydroa vaccineforme-like lymphoma
- Adult T-cell leukaemia/lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous CD4 positive small/medium T-cell lymphoma*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, *ALK* positive
- *Anaplastic large cell lymphoma, ALK*

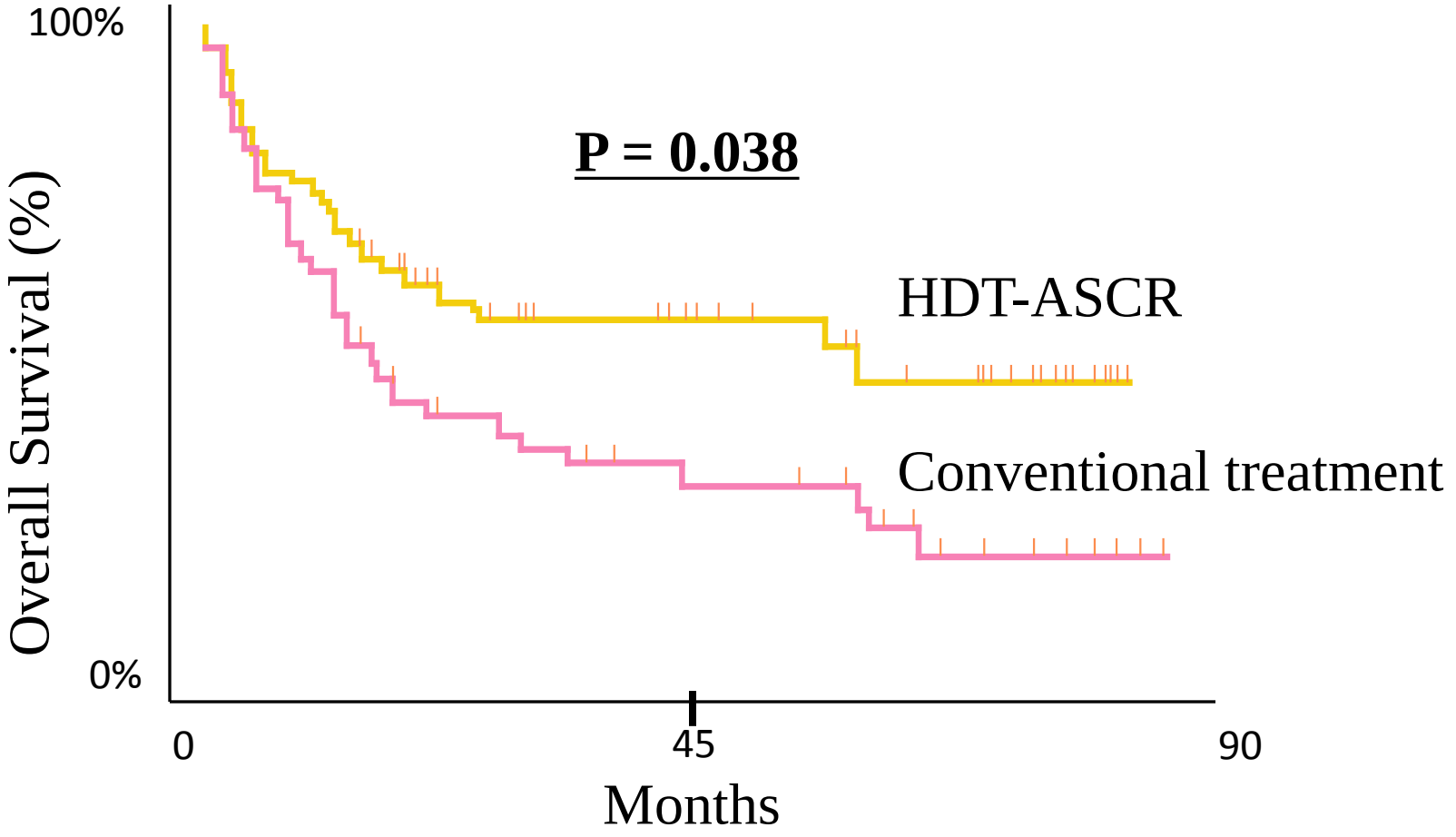
HL and PTLD

- HODGKIN LYMPHOMA
  - Nodular lymphocyte predominant Hodgkin lymphoma
  - Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte depleted classical Hodgkin lymphoma
- POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)
  - Early lesions
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like PTLD
  - Polymorphic PTLD
  - Monomorphic PTLD (B- and T/NK-cell types) #
  - Classical Hodgkin lymphoma type PTLD

HDT/ACSR in Non-Hodgkin Lymphoma

- Diffuse large B-cell lymphoma (DLBCL)
  - Most common NHL
- Mantle cell lymphoma (MCL)
- Peripheral T-cell Lymphoma (PTCL)

PARMA Trial (1995): HDT-ASCR vs. Conventional Treatment

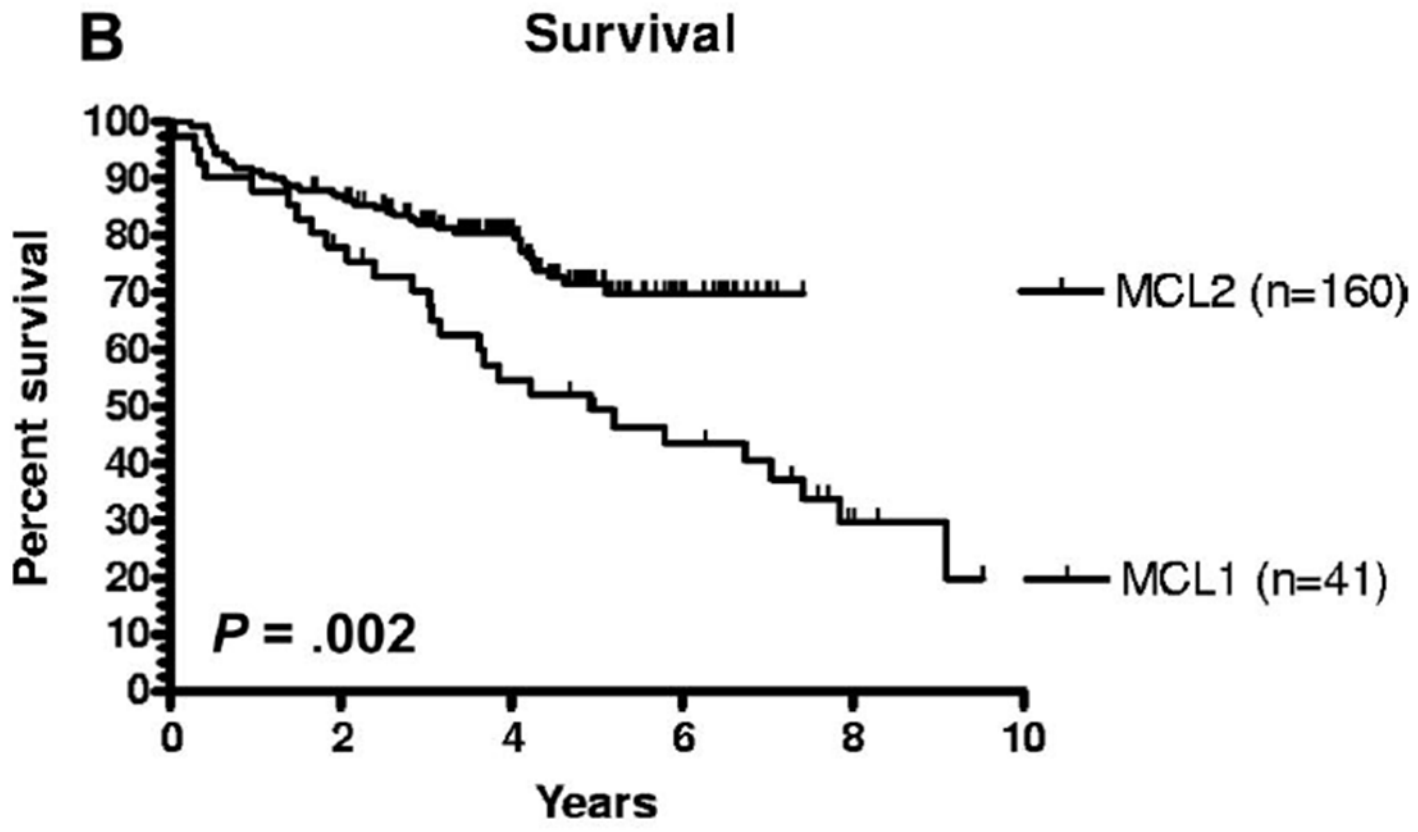


Phillip et al. N Engl J Med ***1995****;333:1540*

HDT-ASCR for DLBCL

- HDT-ASCT remains the standard of care in relapsed/refractory disease
  - No role for up-front consolidation
  - Chemosensitive disease matters
- RICE or DHAP are equivalent salvage therapies
  - Coral Study: 3-year EFS by intent to treat with contemporary salvage: 31%
  - Poor risk factors
    - Relapse < 1 year from dx
    - Rituximab exposed…. **3-year EFS→ 20%**
- BEAM remains the best condition regimen
- Relapsed/Refractory DLBCL is less chemosensitive in the rituximab era

MCL: Up-Front consolidation



Adding rituximab and cytarabine…deeper responses pre-transplant

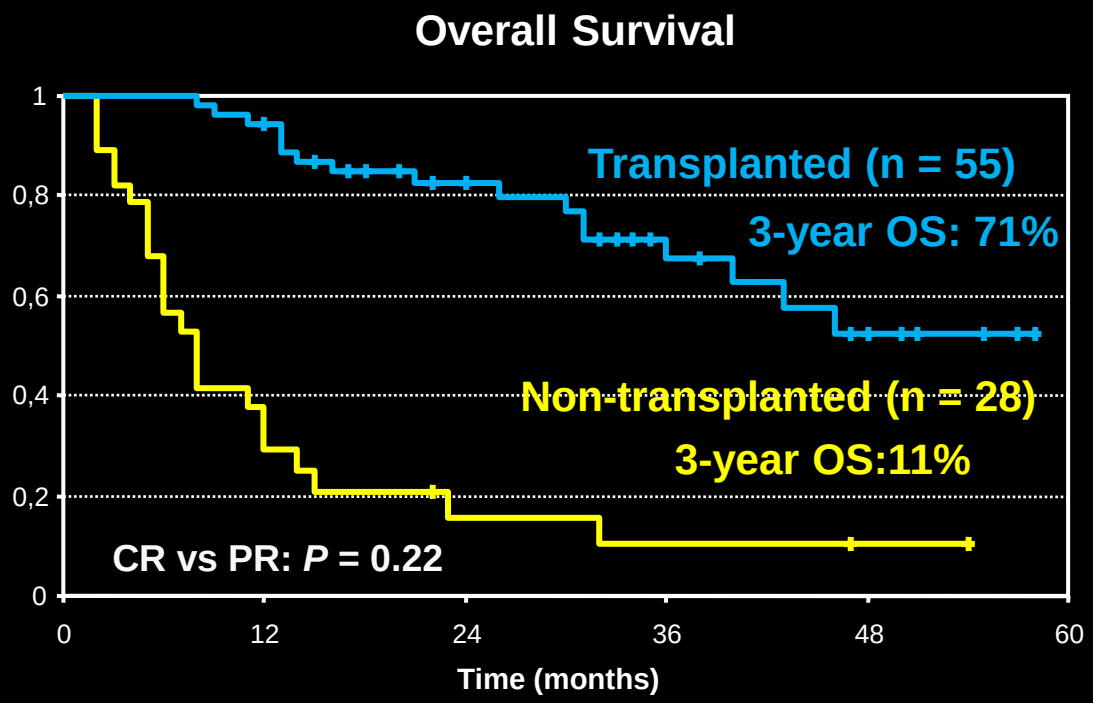
PTCL: Up-Front Consolidation

PTCL
(N = 83)

→ CHOP x 4-6 →

CR (39%)
PR (40%)

→ HDT-ASCR
TBI + CY-ASCT
66%



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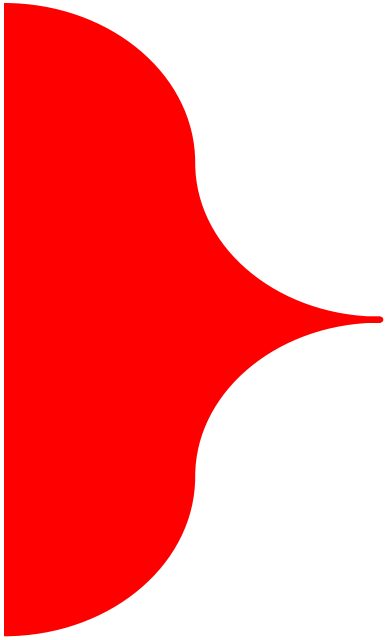
Reimer P, et al. *J Clin Oncol.* 2009;27:106-113.

HDT-ASCR Toxicity

- BEAM
- Pulmonary toxicity (BCNU)
- Cardiac- atrial fibrillation
- Mucositis (melphalan)
- **Cytopenias**
  - **Hemorrhage**
  - **Febrile neutropenia/sepsis**
    - **Bacterial**
    - **Candida**
- Nausea/vomiting



TRM 1-4%

- Day +10-14 day hematopoietic recovery time
- Late infections:
  - Zoster
  - herpes simplex

HDT-ASCR Summary

- Autologous stem cell transplantation
  - Misnomer
  - Happen faster with less logistical issues
  - Little to no graft versus tumor effect
- Multi-step process
  - Right disease (MM, DLBCL, MCL, PTCL)
  - Right response (chemosensitive)
  - Ability to collect (chemo, GCSF, plerixafor)
  - Comorbidities (CAD, COPD, CKD, Obesity)
  - Conditioning (Melphalan, BEAM)


Autologous
Allogeneic

Over 50 years of transplant

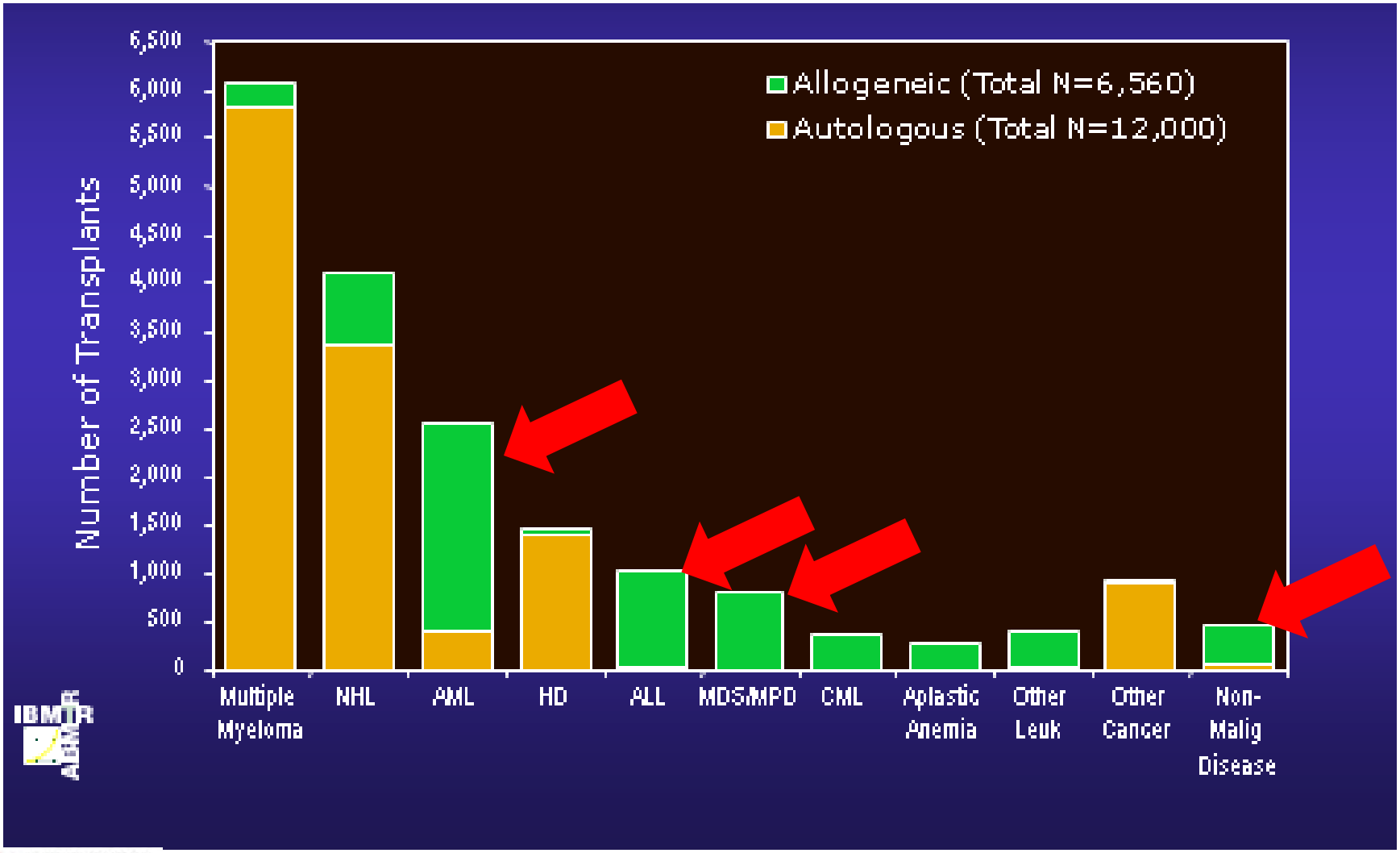
1957: First allogeneic BMT (Thomas ED)

1963: First long-term engraftment (Mathe)

1977: First large trial (100 patients) (Thomas ED)

1998: Non-myeloablative or reduced intensity transplant regimens

Who gets an “allo”?

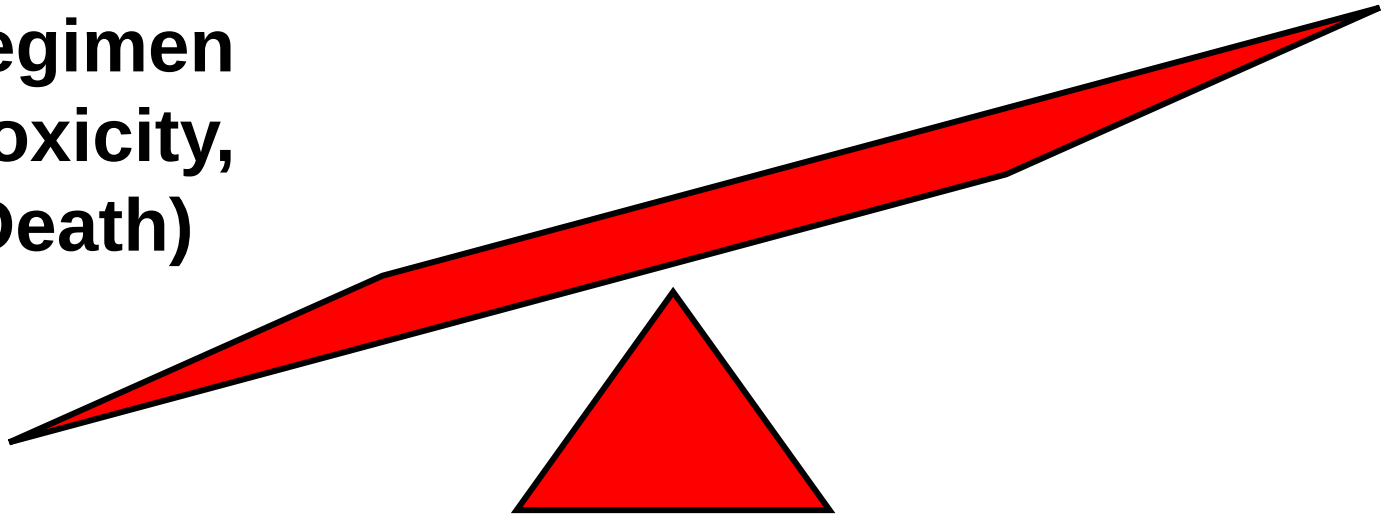


Pre-Transplantation Variables

Patient/Donor
Age
Disease
Co-morbidities
Chemosensitivity

Benefit (Cure, Live Longer, Feel Better)

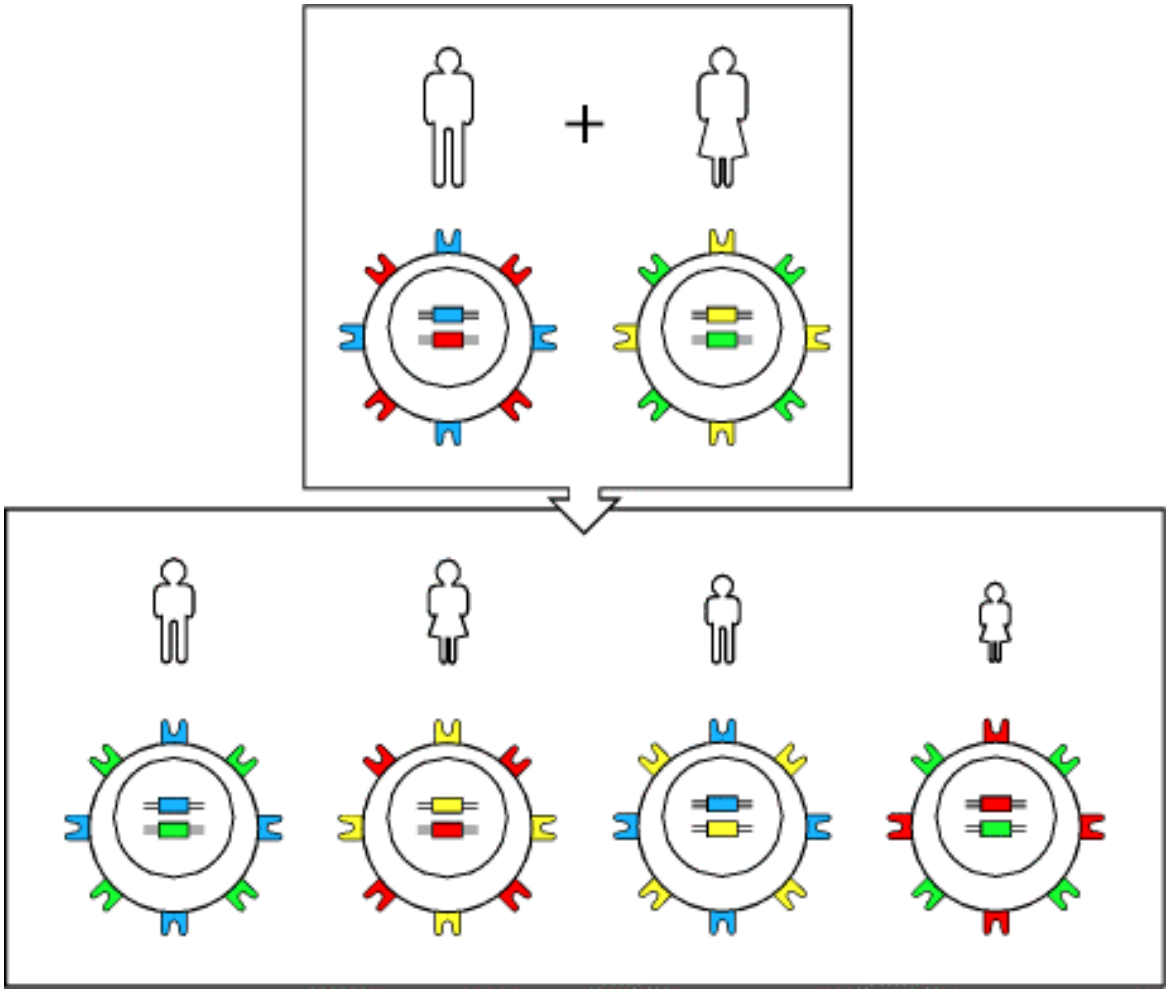
Regimen (Toxicity, Death)



Donor Search

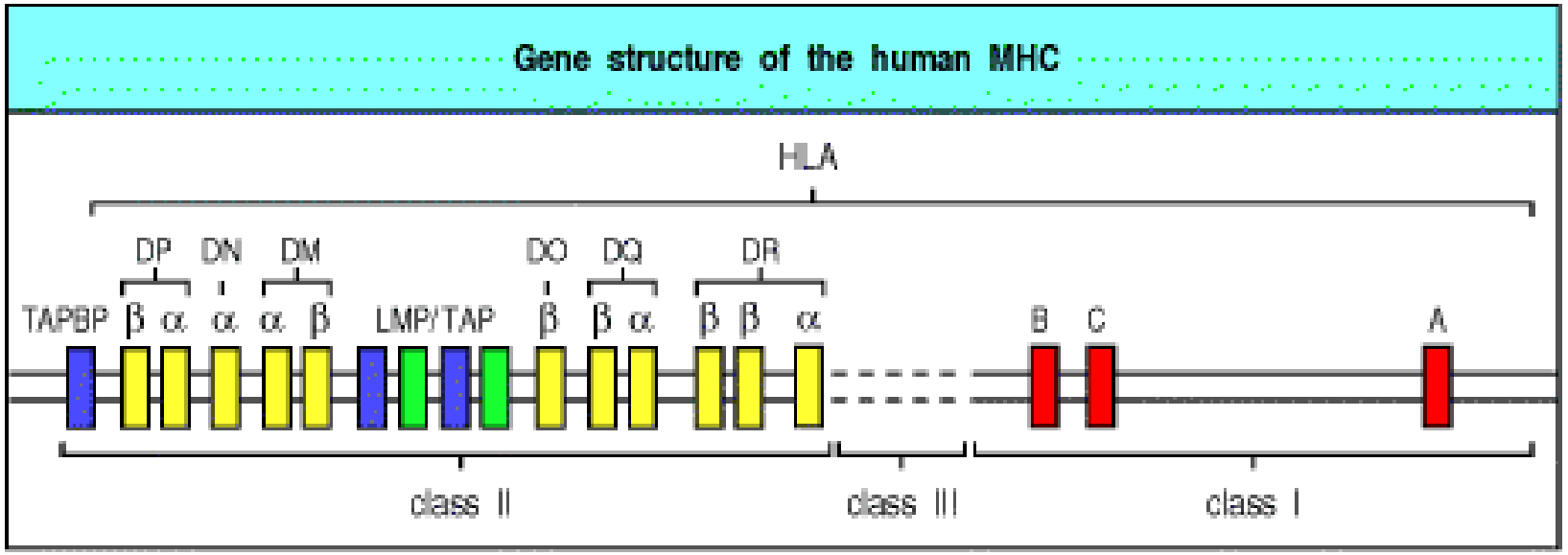
Donor Collection

Related Donors



1 in 4 (25%) chance of being a match regardless of age, gender, or race

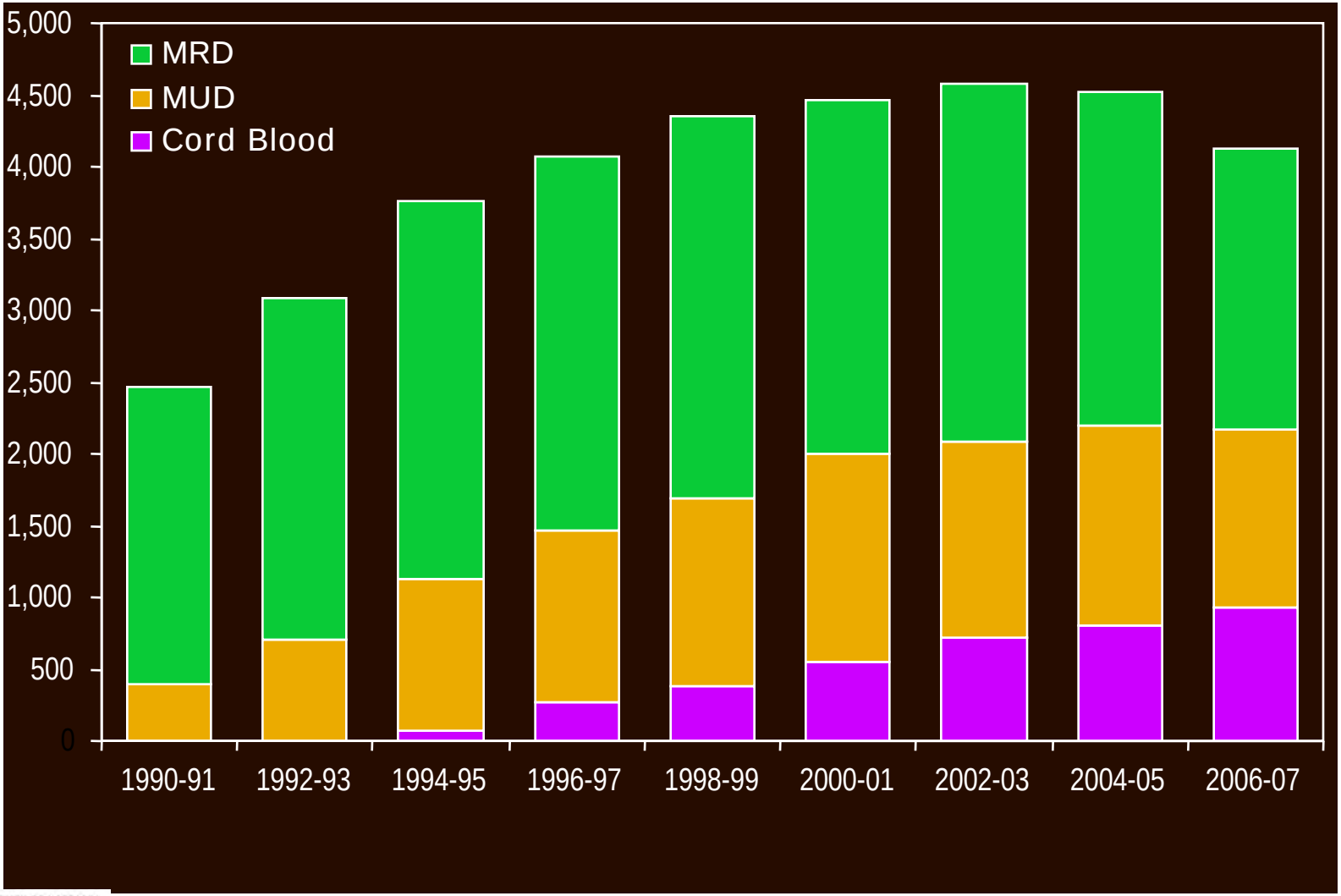
The Molecular Doppelganger Effect



Meaning of a MATCH

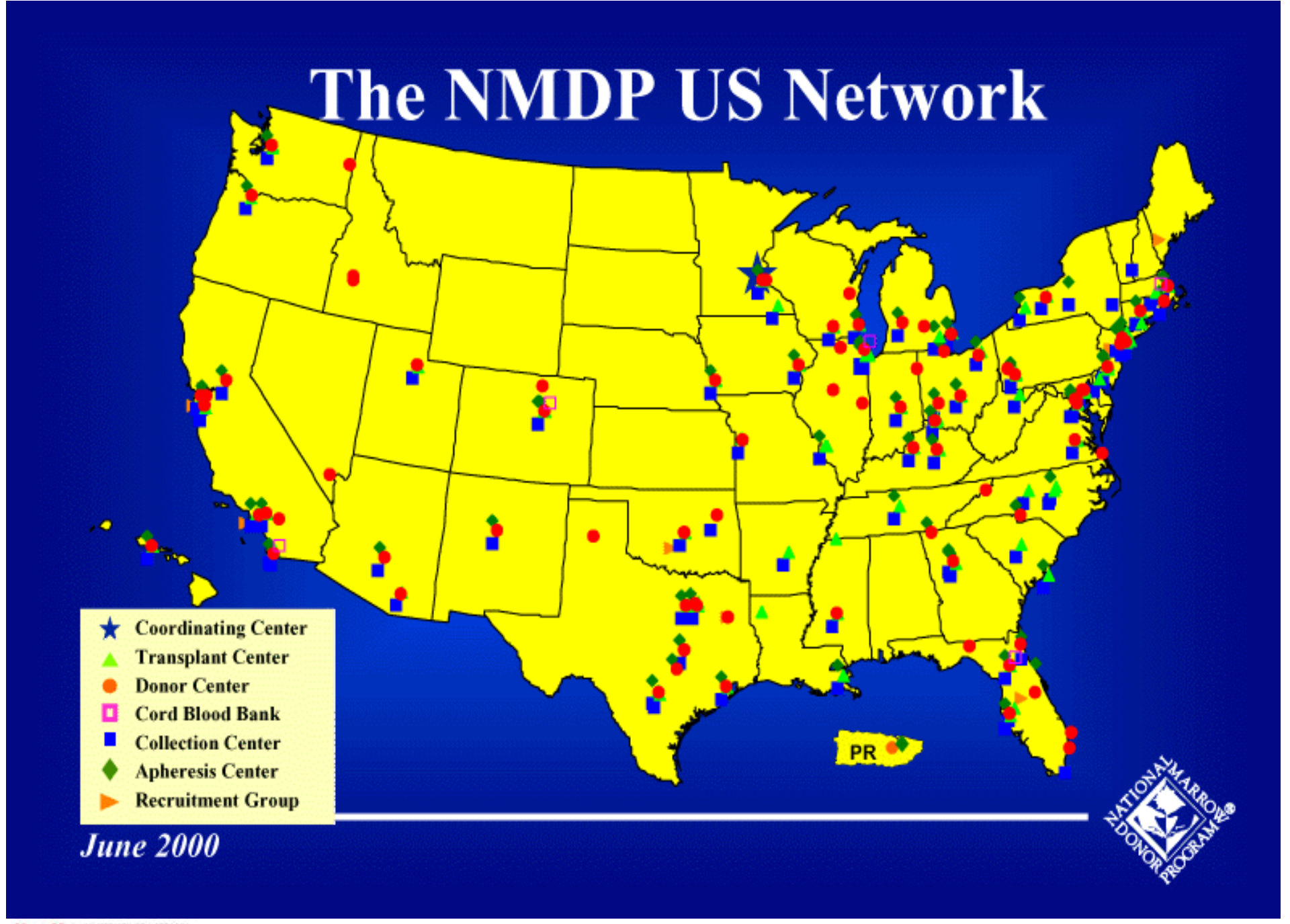
- Match:
  - GENOTYPIC match = patient and donor have SAME PARENTS; Ex: matched related donor (MRD)
  - PHENOTYPIC match = patient and donor share alleles, but do NOT have same parents; Ex: matched unrelated donors (MUDs)
- Degree of Match
  - "6 of 6": HLA-A, B, and DRB1 alleles (3 pairs x 2 co-dominant alleles each = 6 co-dominant Ags or alleles
  - "10 of 10": HLA-A, B, and DRB1 *plus* HLA-C and DQB1 (5 pairs x 2 alleles each, all co-dominant)

What Donor Source Are We Using?



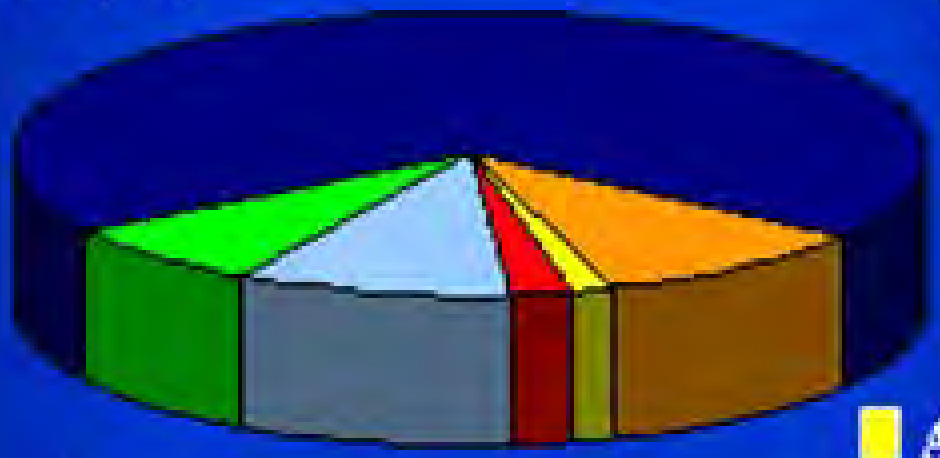
CIBMTR 1990-2007

The NMDP US Network



NMDP Volunteer Donors

Distribution of NMDP Volunteer Donors



Caucasian
2,247,800 (69%)

Asian/Pacific Islander
241,532 (7%)

Hispanic
325,178 (10%)

African American
319,346 (10%)

American Indian/
Alaska Native
53,540 (2%)

Multiple Race/Other
70,731 (2%)

June 2000, donors with race/ethnicity data = 3,258,127

Patient/Donor Match Matters

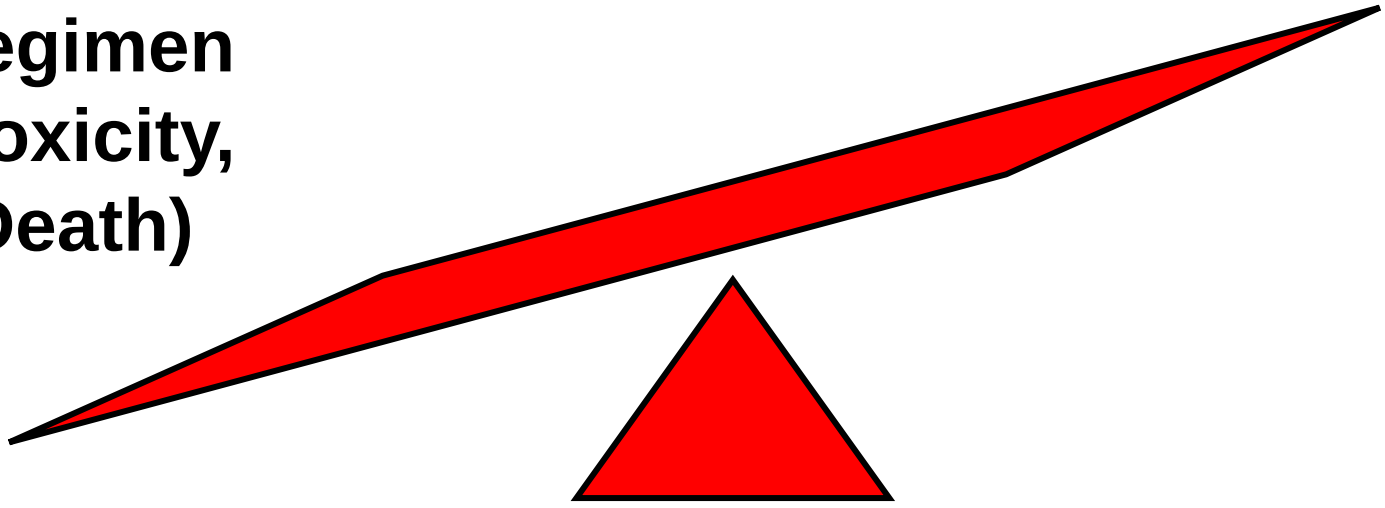
HLA MATCH	GRAFT FAILURE (%)	GRADE III-IV aGVHD (%)
Genotypic Match	2	7
Phenotypic Match	7	7
Mismatch – 1 locus	9	32
Mismatch – 2 or 3 locus	21	62
Matched unrelated	3	36
Mismatched unrelated – 1 locus	5	51

Pre-Transplantation Variables

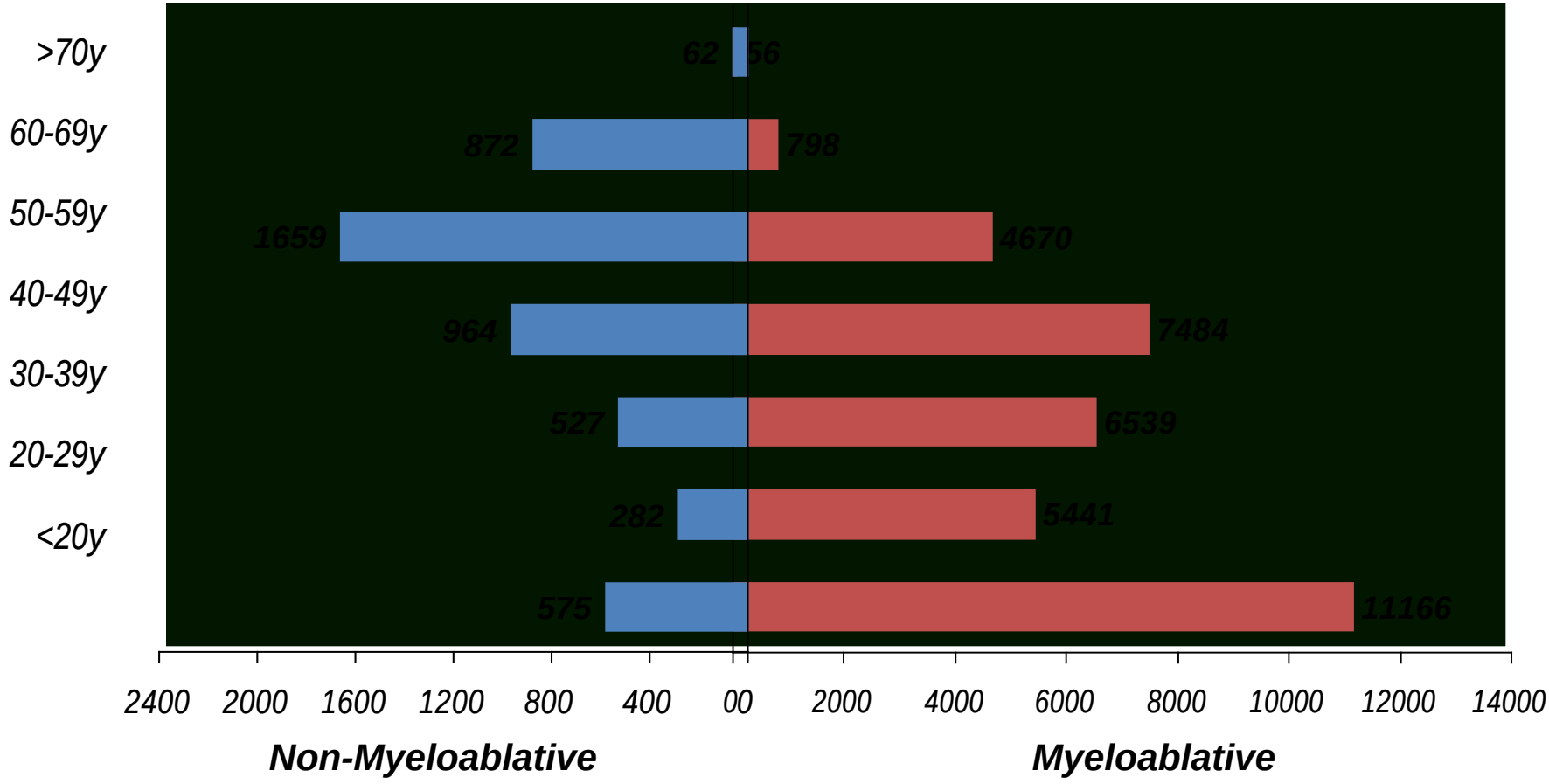
Donor
Age
Disease
Co-morbidities
Chemosensitivity

Benefit (Cure, Live Longer, Feel Better)

Regimen (Toxicity, Death)



AGE OF ALLOTRANSPLANT RECIPIENTS



IBMTR/ABMTR data

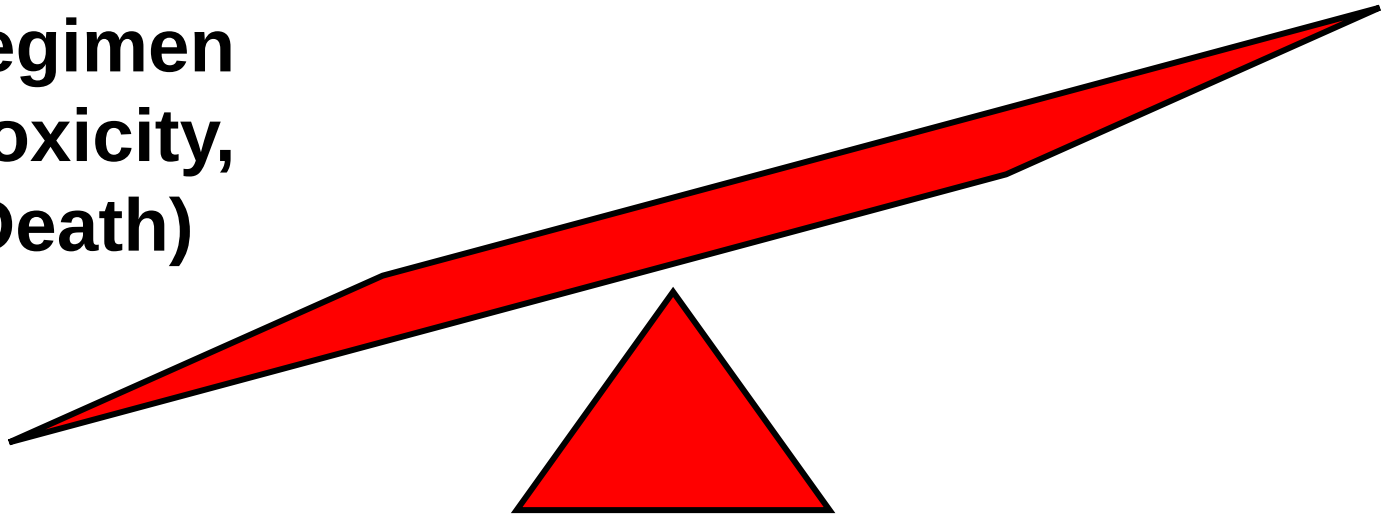
1998-2003

Pre-Transplantation Variables

Donor
Age
Disease
Co-morbidities
Chemosensitivity

Benefit (Cure, Live Longer, Feel Better)

Regimen (Toxicity, Death)



The Disease Matters

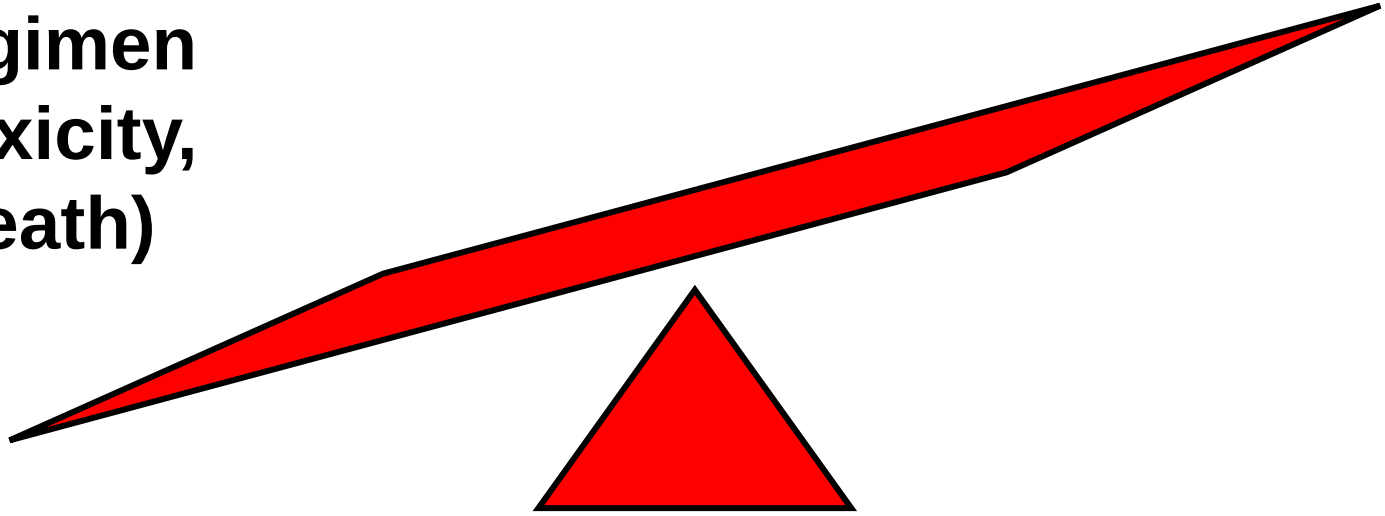
- Myeloablative
  - AML
  - ALL
  - CML
  - MDS
  - NHL (LL, DLBCL)
- Reduced Intensity
  - CLL
  - NHL (low grade)
  - HL
  - MM

Pre-Transplantation Variables

Donor
Age
Disease
Co-morbidities
Chemosensitivity

Benefit (Cure, Live Longer, Feel Better)

Regimen (Toxicity, Death)



Pre-Transplant Comorbidity Index

Table 4. Definitions of comorbidities included in the HCT-CI and HCT-CI scores compared with original CCI scores

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores	Original CCI scores*
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1	0
Cardiac‡	Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF ≤ 50%	1	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1	0
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1	1
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	1	Not included
Hepatic, mild‡	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	1	1
Obesity†	Patients with a body mass index > 35 kg/m^2	1	Not included
Infection†	Requiring continuation of antimicrobial treatment after day 0	1	Not included
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2	1
Peptic ulcer	Requiring treatment	2	1
Moderate/severe renal‡	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2	2
Moderate pulmonary‡	DLco and/or FEV_1 66%-80% or dyspnea on slight activity	2	1
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3	2
Heart valve disease	Except mitral valve prolapse	3	0
Severe pulmonary‡	DLco and/or FEV_1 ≤ 65% or dyspnea at rest or requiring oxygen	3	1
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	3	3

To convert creatinine from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 88.4.

EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLco, diffusion capacity of carbon monoxide.

*Definitions of comorbidities included in the original CCI are defined in the appendix of a prior publication.[8]

†Newly investigated comorbidities.

‡Comorbidities with modified definitions compared with the original CCI.

§One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.

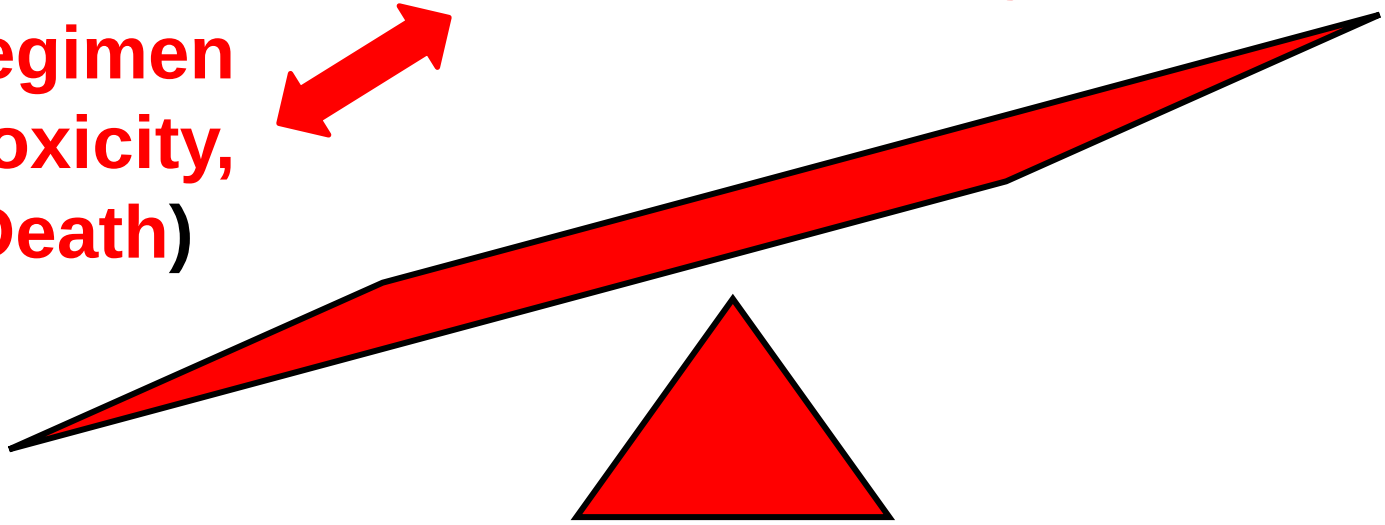
Sorror *Blood* 2005;106:2912

Pre-Transplantation Variables

Donor
Age
Disease
Co-morbidities
Chemosensitivity

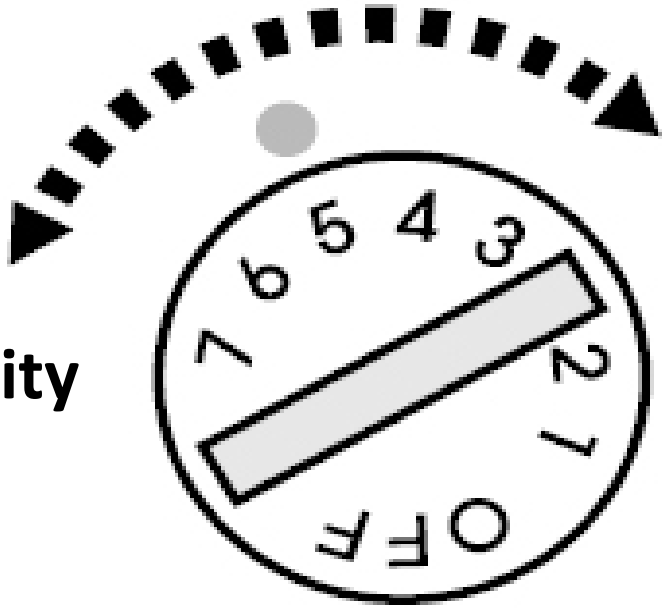
Benefit (Cure, Live Longer, Feel Better)

Regimen (Toxicity, Death)



Type of Conditioning

Reduced Intensity



Myeloablative

Determine by total dose of chemotherapy or radiation

Myeloablative

- Total Body Irradiation (TBI)-based:
  - TBI: 1375 rads (125 cGy tid x 4 days)
  - Lungs are shielded after 800 cGy

AND

  - Cyclophosphamide
- Non-TBI based
  - Busulfan (with dilantin or Keppra)
  - Cyclophosphamide

OR

- Fludarabine

Reduced-Intensity Conditioning

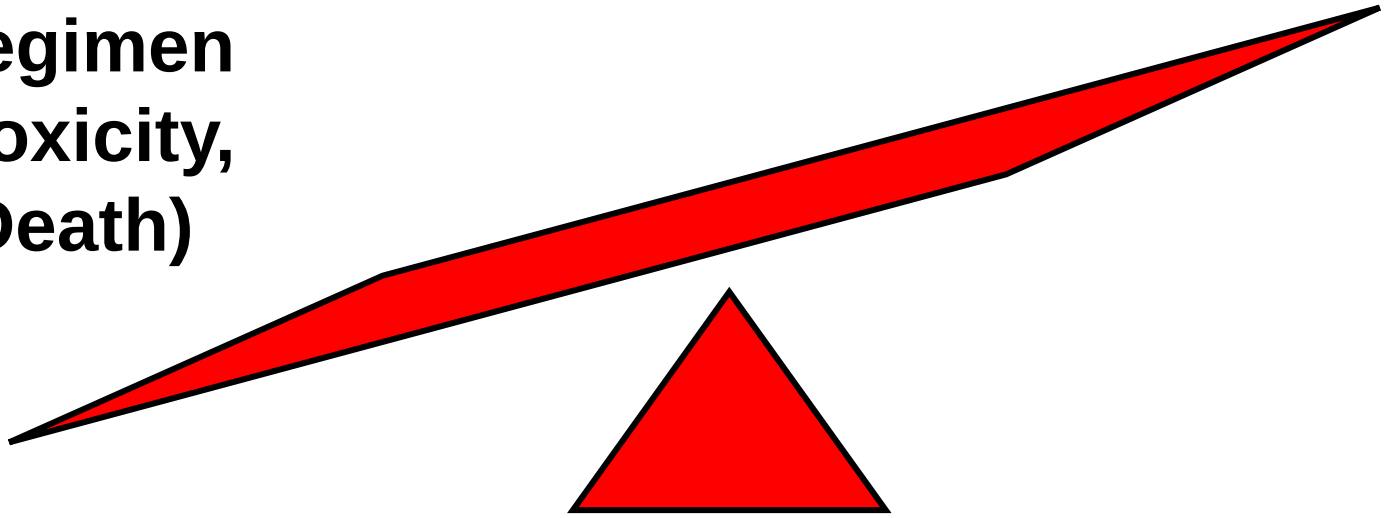
- Busulfan, Fludarabine
- Melphalan/Fludarabine 125 mg/m^2
- Fludarabine/Cyclophosphamide, lower dose TBI

Pre-Transplantation Variables

Donor
Age
Disease
Co-morbidities
Chemosensitivity

Benefit (Cure, Live Longer, Feel Better)

Regimen (Toxicity, Death)



Day=0: Let's Drive a Race Car

Demonstrating Allogeneic Graft Versus Malignancy Effects

Indirect Evidence

- Reduction in relapse rates
- Existence of a plateau on EFS curves
- Remission inversion after prior HDT-ASCR
- Reduction in relapse rates with GVHD
- Effects of withdrawal of immunosuppression
- Effects of Donor Lymphocyte Infusions
- Donor cytotoxic effector cells at sites of disease

Direct Evidence

Post Txp Risks of Allogeneic Transplantation

Early (Day=0) → **Late (yrs)**

Mucositis

Infections during neutropenia

Hemorrhagic Cystitis

Cardiomyopathy

Veno-occlusive disease (VOD)

Graft rejection

Graft Versus Host Disease (GVHD)

Opportunistic infection (CMV, etc)

EBV-lymphoproliferative disorder

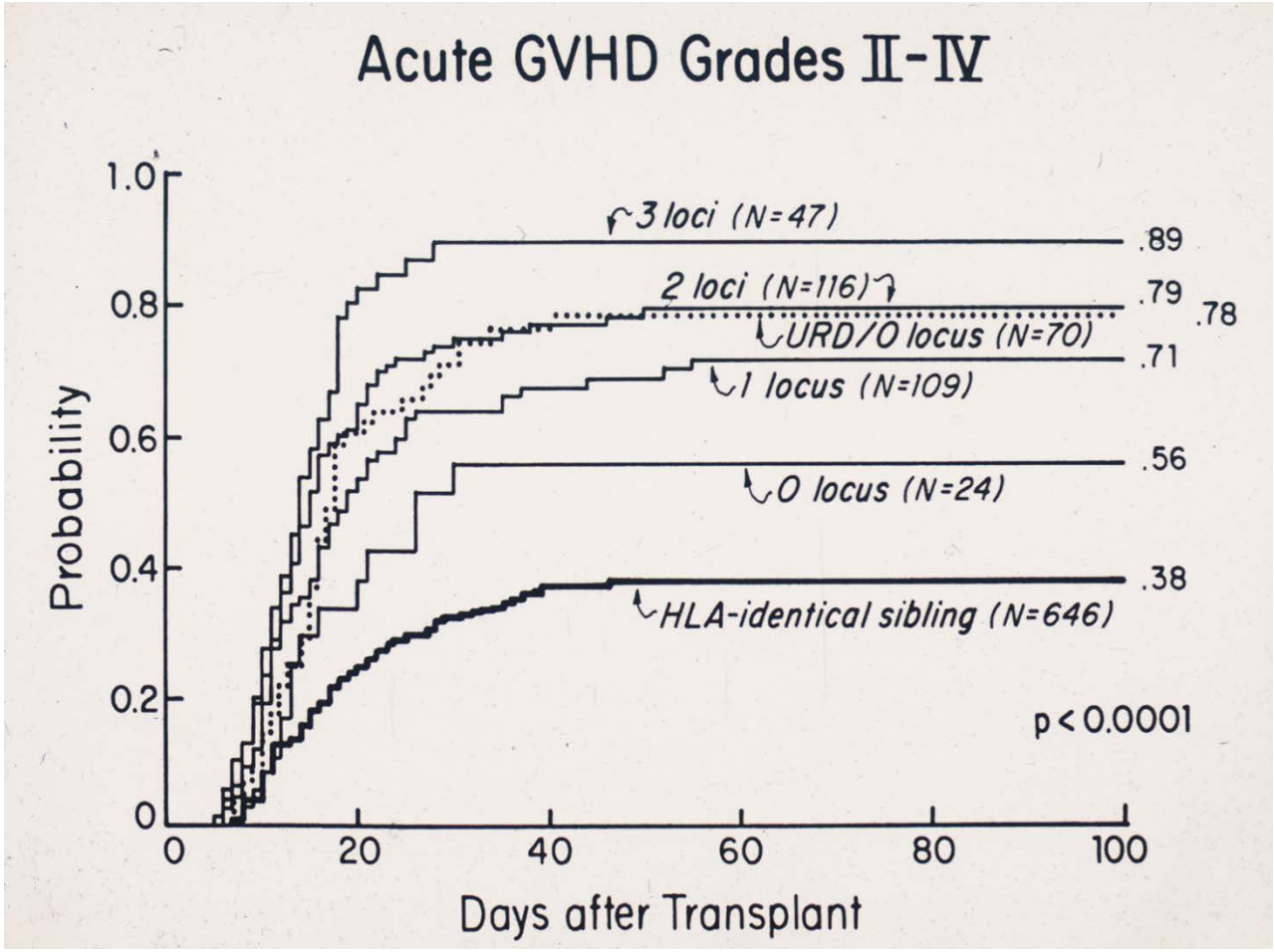
Disease Relapse

Infertility

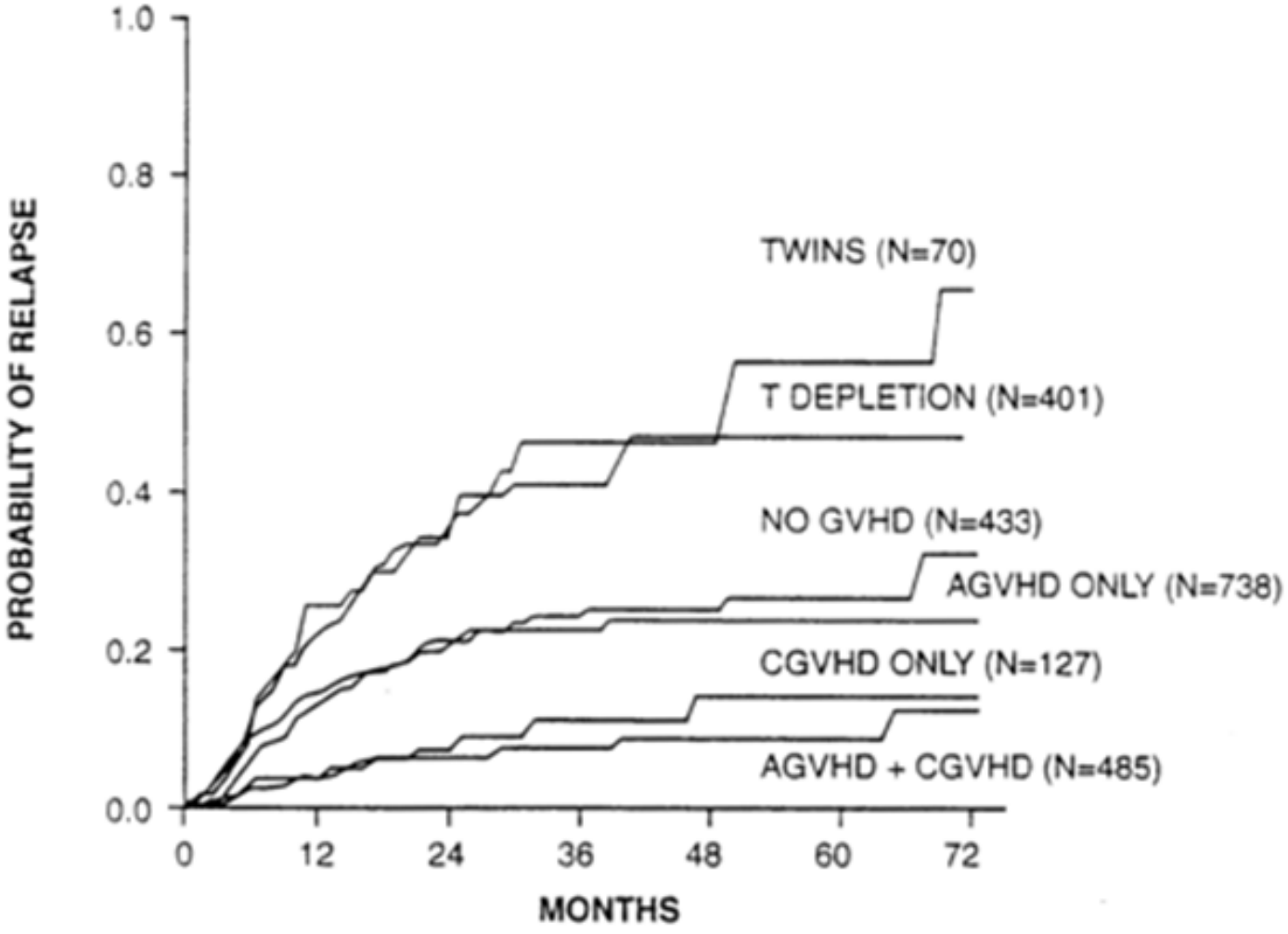
Cataracts, Dental caries

Secondary Malignancies

Graft versus Host disease (GVHD)



Probability of Relapse



Brakes: GVHD Prophylaxis

- HLA match does not mean immunologic equivalence (minor alleles)
- Differences in other HLA antigens
- Graft not immunologically "controllable" once in recipient
  - Cyclosporine/Methotrexate
  - Cyclosporine/Mycophenolate
  - Tacrolimus/Mycophenolate
  - Tacrolimus/Sirolimus
  - T-Cell Depletion

Acute Graft versus Host Disease (aGVHD)

- Occurs in 40-70% of allogeneic transplants
- More common in older patients and mismatched donors
- Acute diarrhea, skin rash, liver function abnormalities
- Dx: clinical plus biopsy of affected system
- Rx: High-dose steroids + immunosuppression + commonly oral budesonide for GI

Acute Graft Versus Host Disease

- Response in 70-80% of patients
- Taper steroids by 50% first 10 days then 10% per week in responsive patients
- Increased risk of infection:
  - Bacterial
  - Fungal
- Steroid Resistant
  - 20-30% of aGVHD
  - No standard therapy
    - ATG, infliximab, etancercept, photophoresis
    - Profound immunosuppression
    - Infectious deaths common

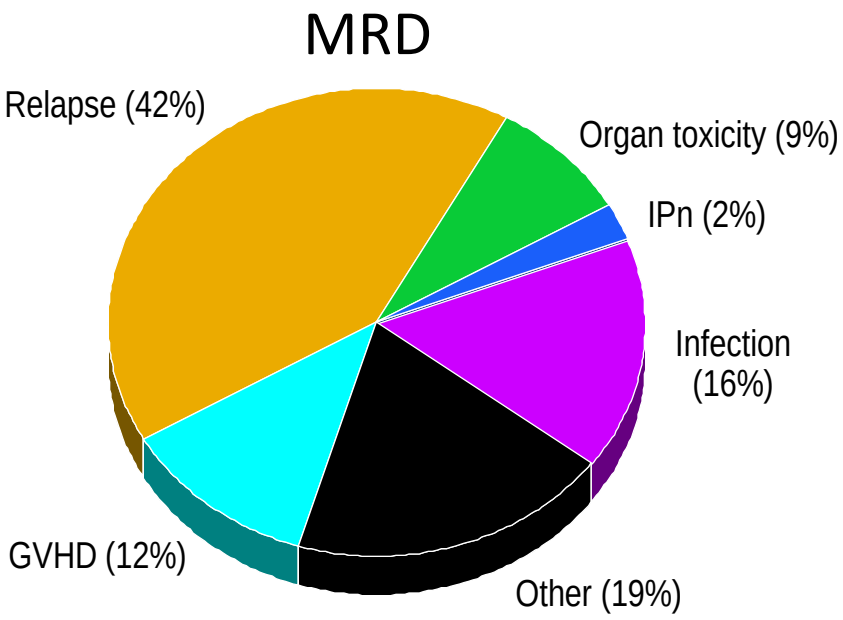
Chronic Graft versus Host Disease

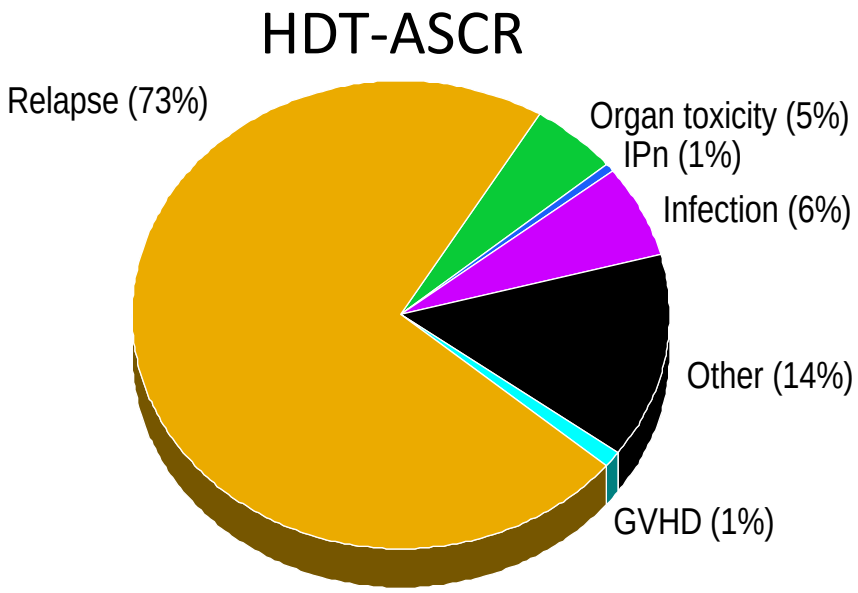
- Distinct entity from aGVHD
- Features in common with autoimmune disorders (Rhuematology)
  - Ocular, oral, pulmonary, cutaneous (scleroderma-like), hepatic
  - Diarrhea unusual, weight loss possible
- Dx: biopsy, clinical
- Rx: High-dose steroids, tacrolimus, cyclosporine, rituximab, MMF, photophoresis, imatinib, dasatinib

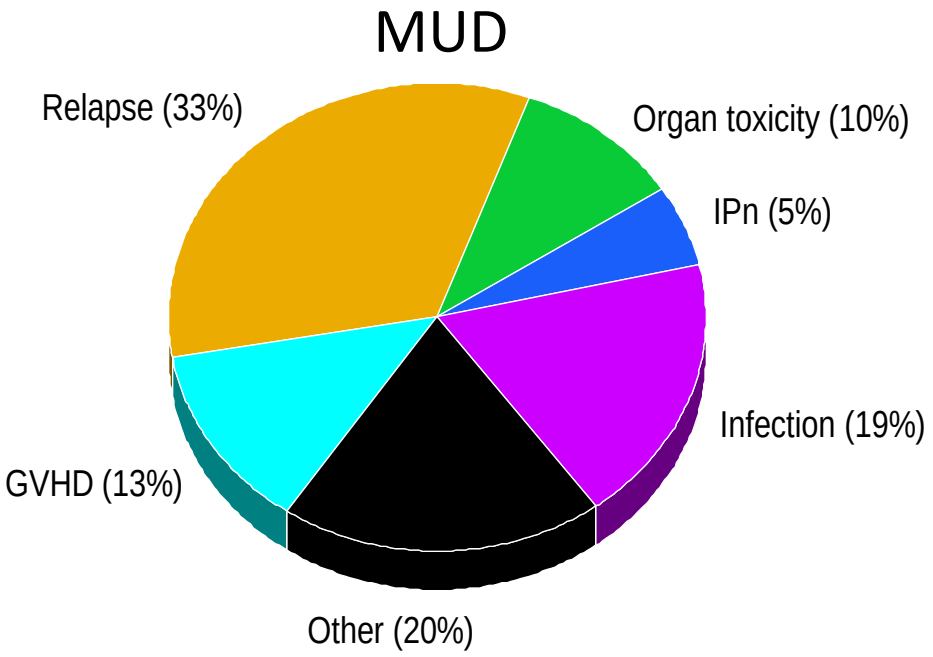
Immunologic Tolerance

- Donor T-cells re-educated by processing through the thymus
- Allows for reduction/elimination of GVH therapy eventually in many patients
- May take years
- Lifelong immunosuppression not necessary in all patients

Causes of Death after Transplantation







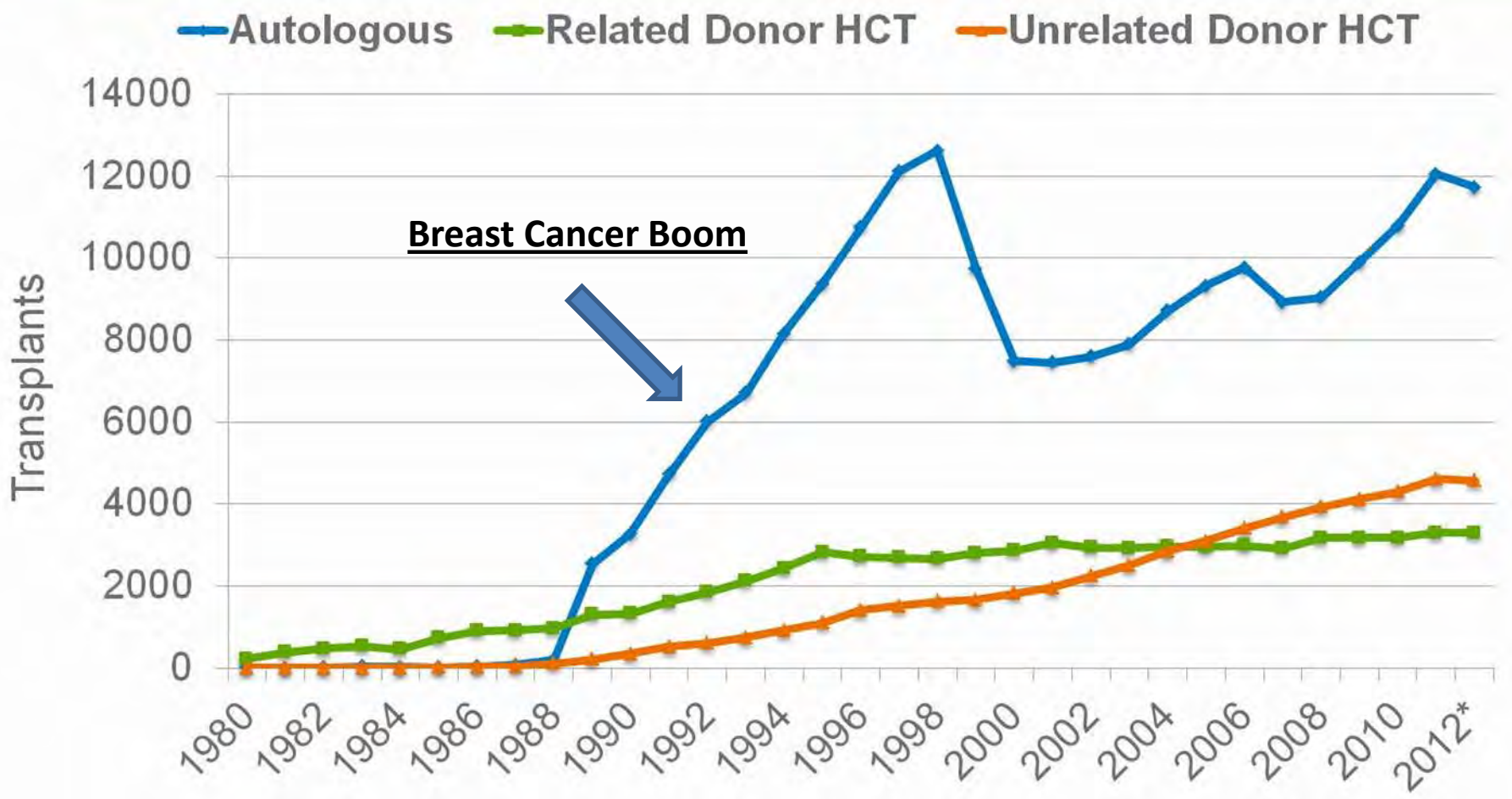
2002-2007

Disclaimer

I am a “transplanter” who looks for diseases that may benefit from HDT-ASCR or transplant…

I am NOT an expert in the next 3 diseases

Non-Malignant Transplantation



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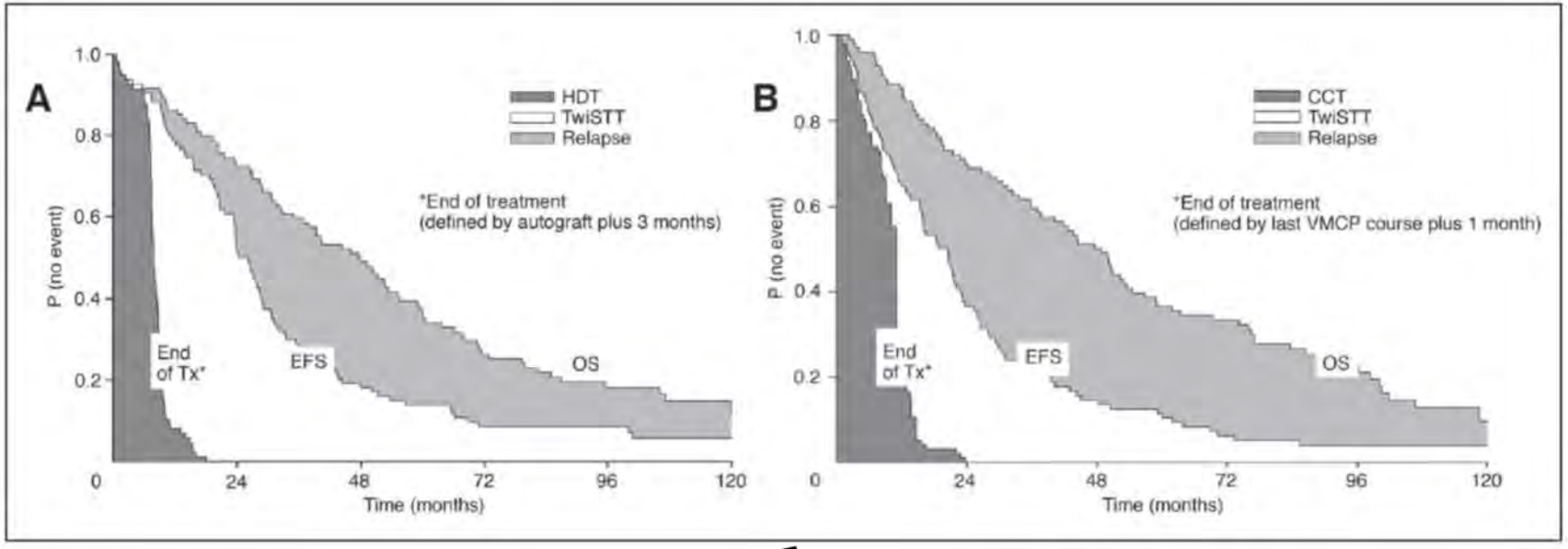
*Data incomplete

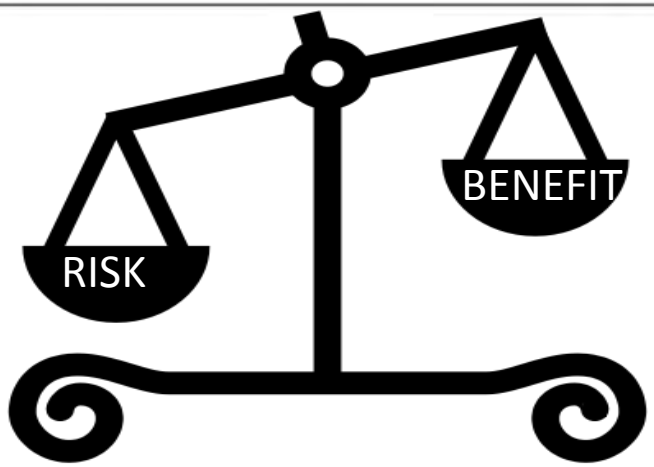
Non-Malignant Transplantation

- Autologous
  - Multiple Sclerosis
  - Systemic sclerosis (Scleroderma)

- Allogeneic
  - Sickle cell anemia

HDT-ASCR: Logic in non-malignant conditions?





Multiple Sclerosis

- Multiple Sclerosis: Etiology exactly unclear but possible related to autoimmune destruction of myelin sheath (insulation of nerves)
- Four clinical scenarios of MS:
  - relapsing remitting
  - secondary progressive
  - primary progressive
  - progressive relapsing

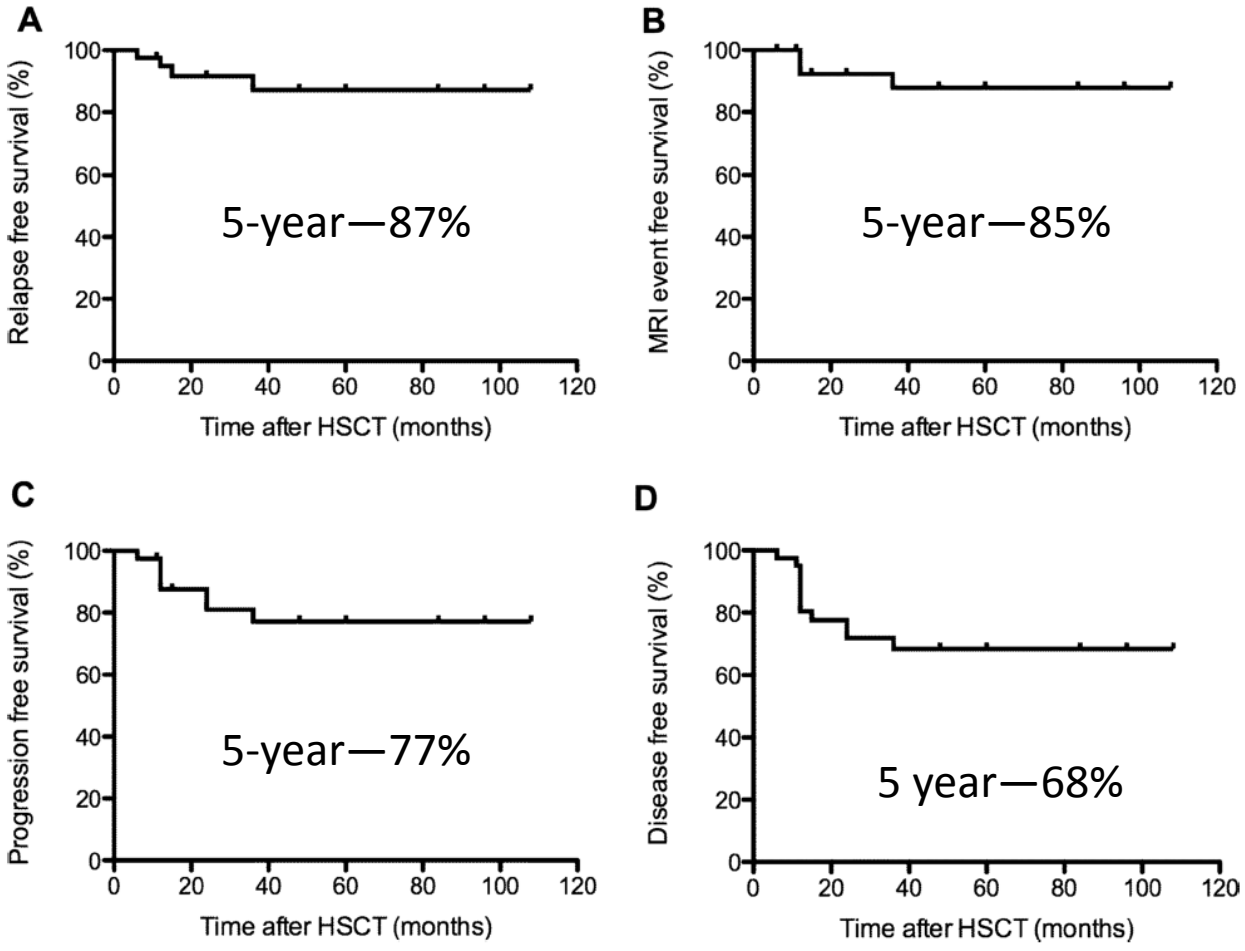
Swedish Observation Study

- Aggressive relapsing remitting MS (RRMS)
  - Aggressive disease with high relapse frequency
  - Short duration of aggressive disease
  - Potential for recovery
  - Failure of conventional therapy
- 48 patients enrolled
  - Mobilized GCSF+Cy
  - Conditioning (BEAM-ATG or Cy-ATG)

Burman et al. J Neurol Neurosurg 2014

HDT-ASCR: Multiple Sclerosis

Median age 31; Median follow-up: 48 months



No transplant mortality

Systemic Sclerosis (Scleroderma)

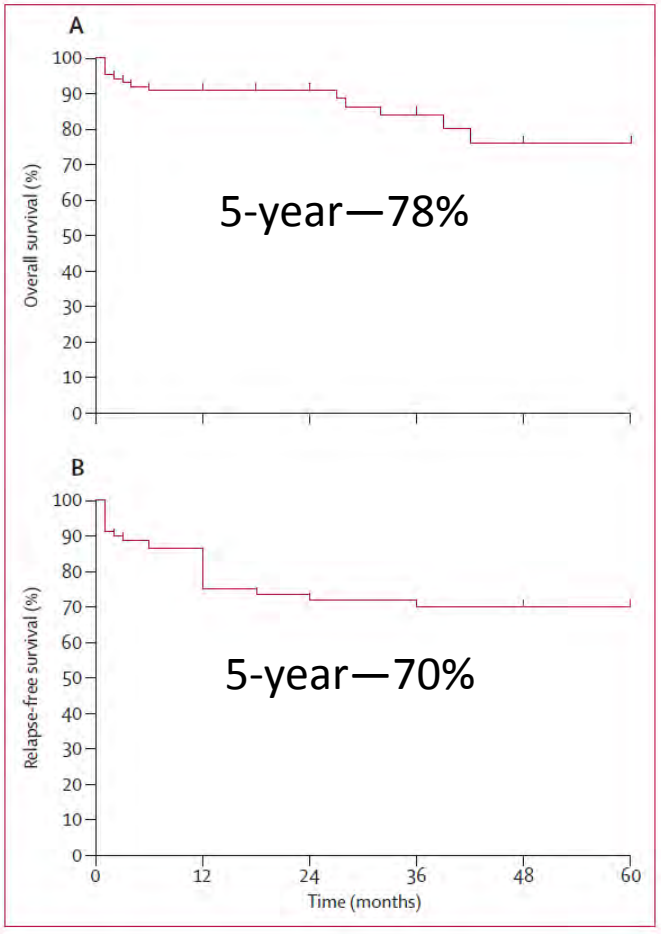
- Autoimmune disease that causes hardening of the skin
  - Localized
  - Diffuse
- Immunosuppression is mainstay treatment options for systemic sclerosis with supportive treatment of affective organs
- ASSIST trial showed improve skin sclerosis and improve pulmonary function.
- Previously with high-transplant related mortality

Northwestern/Sao Paulo Experience

- 90 patients screened in the study
- Mobilized with Cy+GCSF
- Conditioning Cy+ATG; divided over 4 days

Burt et al. Lancet 2013

Results



	Normal echocardiogram or electrocardiograph or female sex	Abnormal echocardiogram or electrocardiograph or male sex	p value*
DLCO			
Group: echocardiogram	Normal 71·3% (3·1)	Abnormal 56·7% (3·8)†	0·0045
Group: electrocardiograph	Normal 73·3% (4·6)	Abnormal 62·0% (3·0)‡	0·045
Group: sex	Female 66·3% (2·8)	Male 64·5% (4·9)	0·75
FVC			
Group: echocardiogram	Normal 70·8% (3·2)	Abnormal 68·4% (2·4)	0·58
Group: electrocardiograph	Normal 73·6% (4·6)	Abnormal 68·2% (2·1)	0·28
Group: sex	Female 66·1% (2·5)	Male 66·3% (3·1)	0·95
Total lung capacity			
Group: echocardiogram	Normal 80·3% (3·4)	Abnormal 78·8% (2·3)	0·70
Group: electrocardiogram	Normal 81·9% (4·4)	Abnormal 78·7% (2·1)	0·51
Group: sex	Female 75·8% (2·4)	Male 75·2% (3·0)	0·80
mRSS			
Group: echocardiogram	Normal 16·1 (1·7)	Abnormal 18·2 (1·3)	0·33
Group: electrocardiograph	Normal 16·1 (2·4)	Abnormal 17·8 (1·1)	0·51
Group: sex	Female 17·0 (1·4)	Male 16·4 (2·1)	0·77

Transplant related mortality—6%

Randomized Clinical trial: ASTS and SCOT not reported

Sickle Cell Disease

- Results from a single amino acid substitution in the beta chain of hemoglobin.
- Leads to polymerization of hemoglobin proteins.
  - Sickle shape of RBCs
- Consequences
  - Anemia
  - Increased hemolysis
  - Acute and chronic occlusive disease

Sickle cell and transplantation

- More common indication in children.
- Resulted in a 95% disease free survival.
- In those children with mixed-chimerism still led to a reduction sickling and its complications.

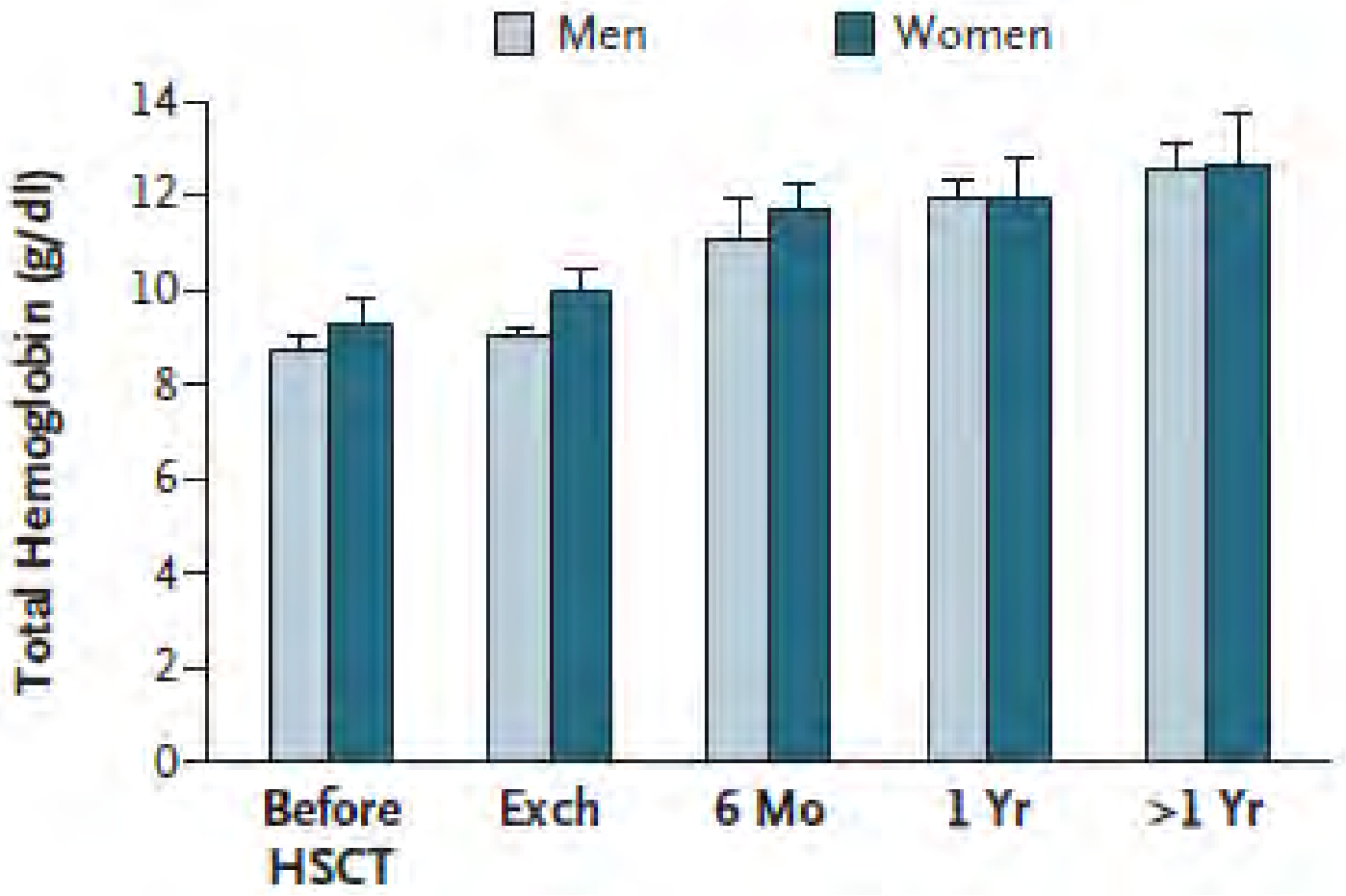
- Can this be achieved in adults?

Allogeneic Transplantation in Adults

- 10 patient study
- Must have:
  - Hemoglobin SS or SC
  - Severe disease (refractory to hydroxyurea)
  - Matched related donor
- Reduced-intensity conditioning
  - Alemtuzumab + total body irradiation
- GVHD prophylaxis: Sirolimus

Hsieh et al. NEJM 2009

Improvement in Hemoglobin



MOST PATIENTS HAD MIXED CHIMERISMS

At the end….

- List 3 conditioning regimens commonly used in stem cell transplantation.
- Appreciate disease and patient characteristics that may influence the type of blood stem cell transplant and preparative regimens utilized for transplantation.
- List 3 non-malignant disorders that could be treated by stem cell transplantation.

We've come a long way....