Haploidentical Transplants Past, Present and Future

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Case

- 32 y/o hispanic man with Ph + ALL.
- Induction with Hyper-C-VAD regimen achieving CR.
- 1st relapse just before the last cycle of Hyper C-VAD.
- Re-induction with High-dose Ara-C/Idarubicin—CR
- Maintenance with Gleevec
- 2nd relapse. Re-induction with high dose VP-16/Cytoxan. No remission.
- Treated with Dasatinib with clinical response.
- Allogeneic stem cell transplant with a 1 Ag-mismatched unrelated donor. Thiotepa/TBI
- Mucosal/gastrointestinal/hepatic toxicities.
- Acute GVHD IV
- Died 87 days post transplant

- KPS- 90%

HLA typing all siblings
MUD search
Plans for AutologousBMT

- KPS-70%

- KPS- 70%
- KPS-60%

Donor identified
Not medically cleared
Donor identified
Not available

- KPS- 60%

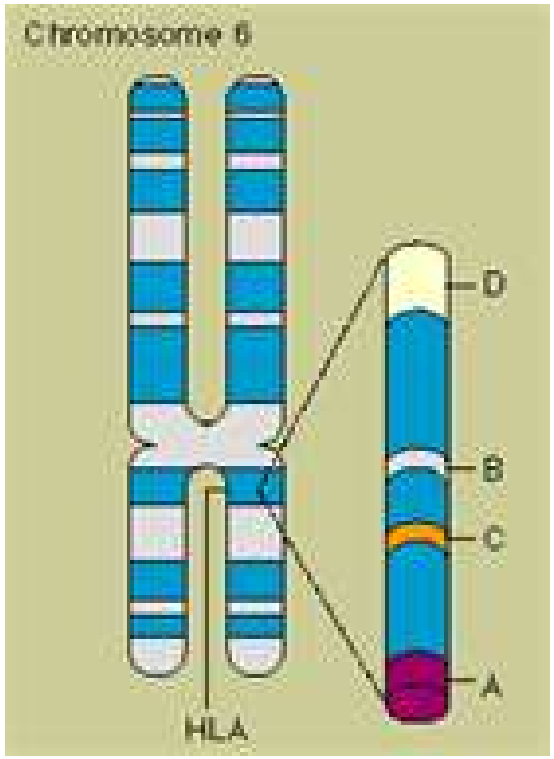
- KPS-60% CMV infection
- KPS-40%

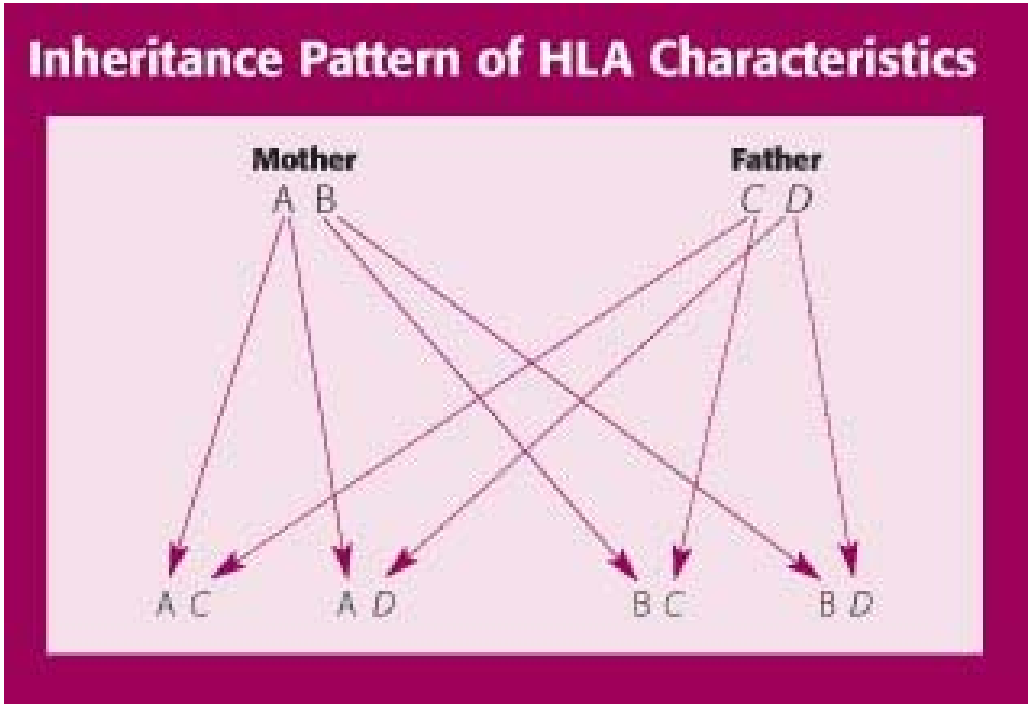
- KPS-30%

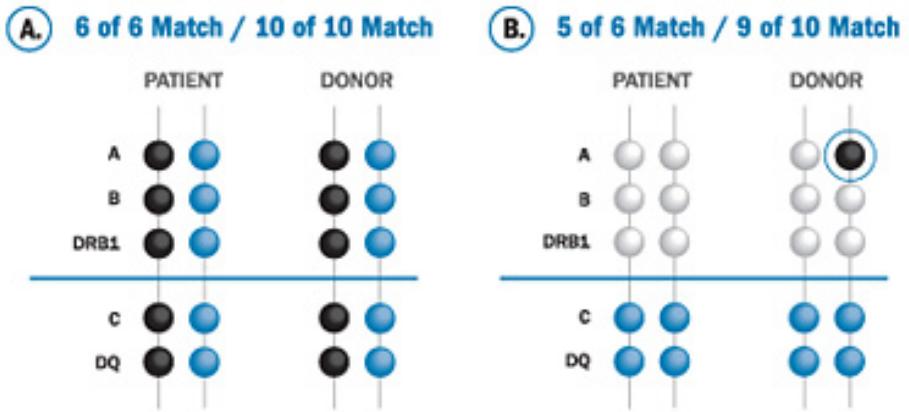
Questions

- Could the outcome of this patient be different if the transplant was done earlier?
  - Better disease status
  - Better performance status
- Donor availability as the limiting factor.

HLA Matching

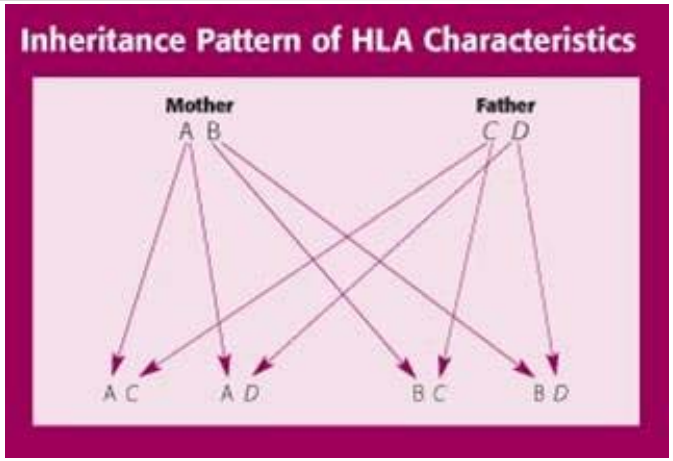


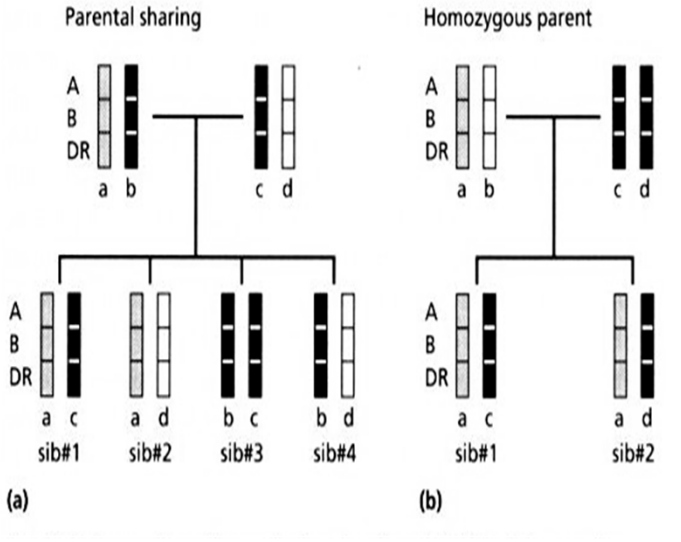




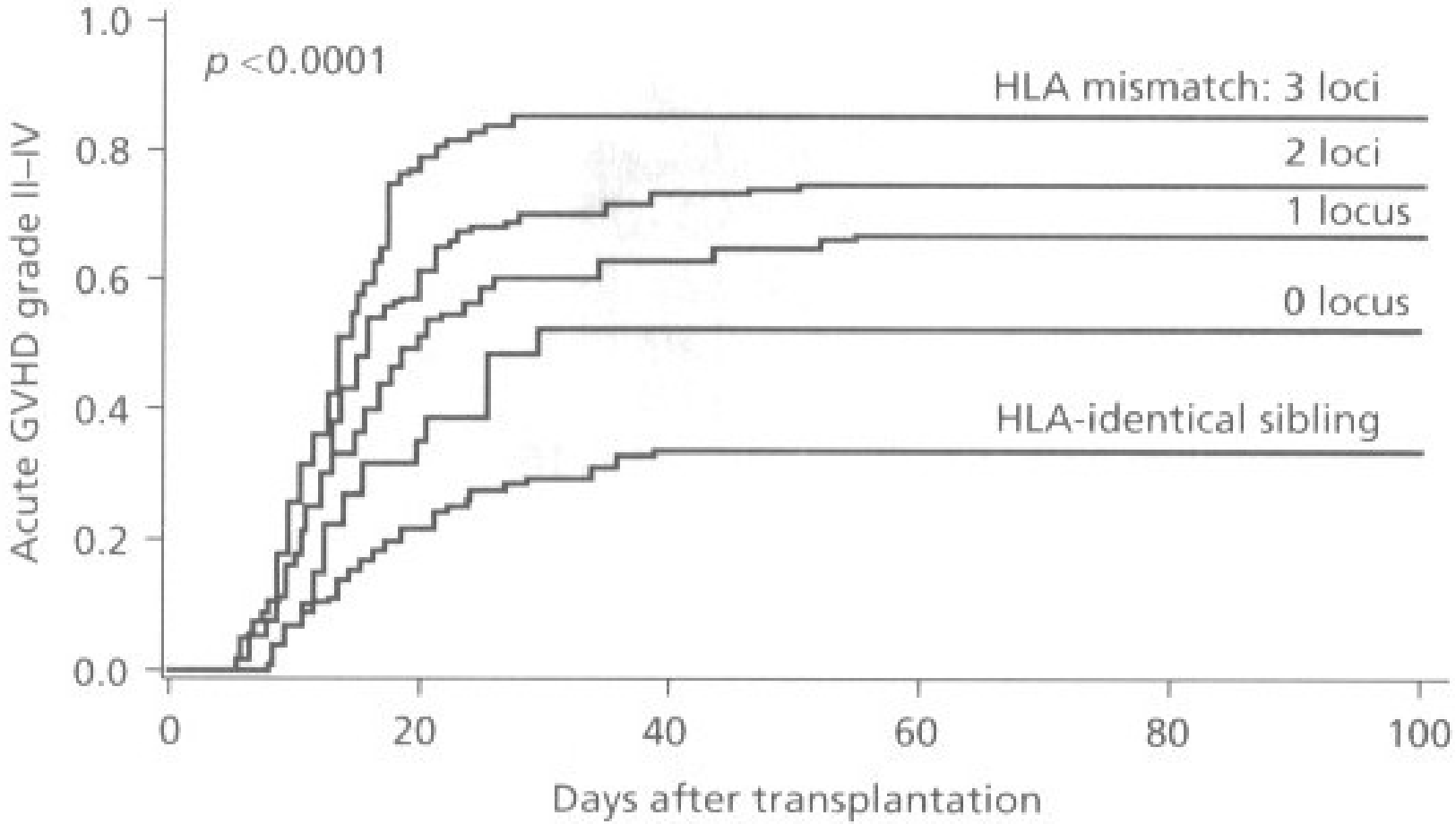
Donor selection

- Matched related donors
  - 25% chance that a sibling will be HLA-matched at the A, B, and DR loci
    - inherit the same HLA genes on chromosome 6
  - generally siblings
    - unless the parents happen to have very common haplotypes or there has been intermarrying
  - preferred donor source for an allogeneic transplant
  - Fewer than 30% of patients will have an HLA-matched sibling





HLA mismatch & GVHD



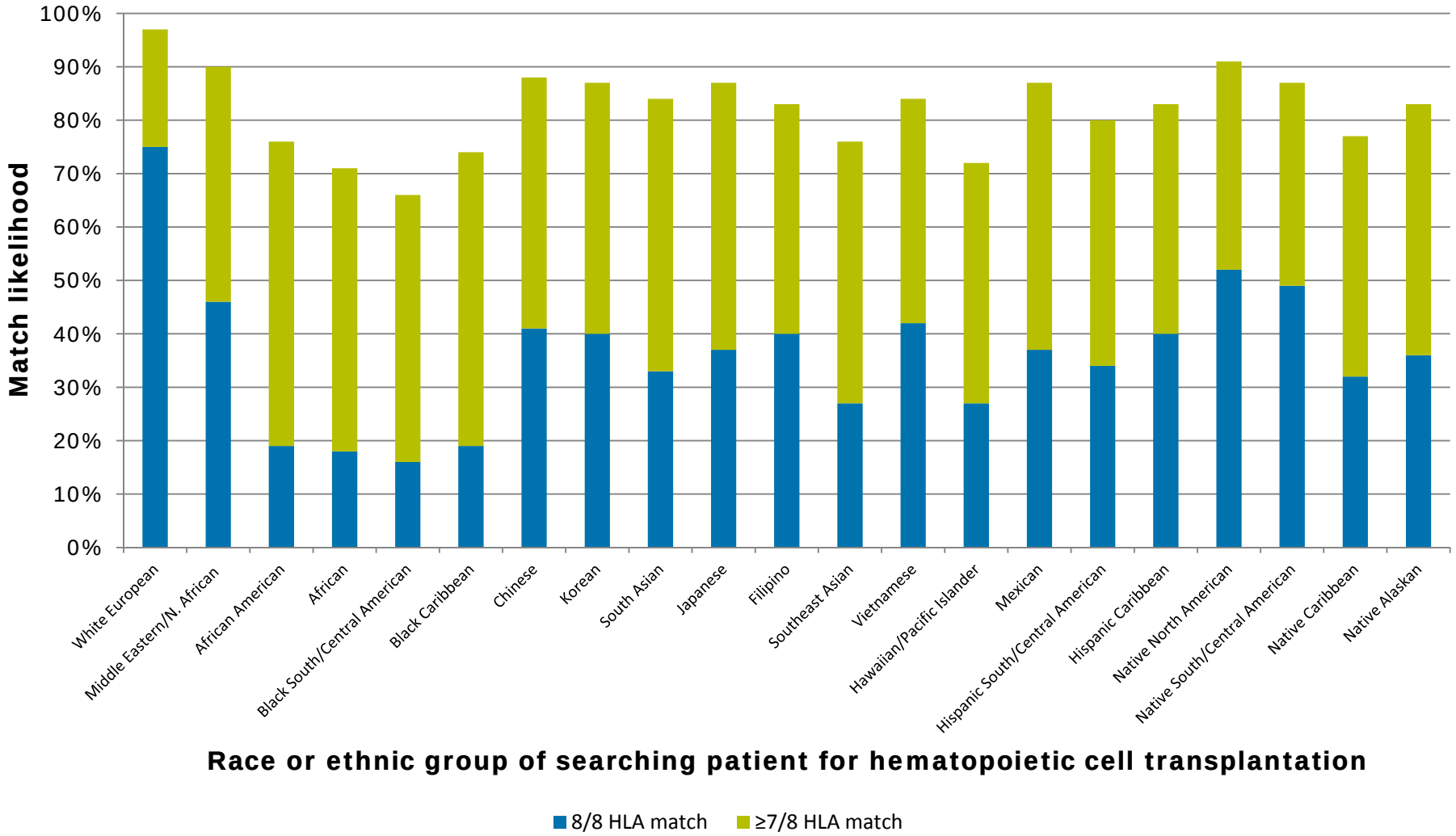
Pts received unmodified marrow and MTX + cyclosporine

Donor Selection

- Matched unrelated donors
  - In 1986 the National Marrow Donor Program (NMDP) was established as a repository for HLA-typing information
  - Over nine million donors registered in the NMDP data bank
    - Matched unrelated grafts have been made available for 90 percent of Caucasians compared to less than 10 percent of minorities
    - More polymorphisms with HLA
    - Relatively large number of haplotypes that are specific to their racial groups

Likelihood of finding matched unrelated adult donor

Range 66-97%: *Available suitable match, by race/ethnic group, Be The Match Registry®*



Gragert L, et al. N Engl J Med. 2014; 371(4): 339-348.

Why choose partial matches?

- Allogeneic HCT is an established curative therapy for a variety of hematologic malignancies
  - Genotypically HLA-identical sibling donors are available for about 30% of white patients
    - still regarded as the best donors for HCT
  - However, for the remaining 70% of patients HLA-A–, B-, C-, DRB1-, and DQB1-matched unrelated donors (MUDs) are meanwhile routinely accepted
  - Partially HLA-matched family donors other than HLA-identical siblings are another option

Perspective of haploidentical HCT

- Advantages of haploidentical HCT:
  - Nearly all patients have an immediately available donor
    - Parents
    - Children
  - Stronger graft vs. tumor effect with partial HLA disparity
- Disadvantages
  - GVHD, graft rejection, and delayed or incomplete immune reconstitution

Early years of haploidentical transplantation

- In 1983, Powles and colleagues transplanted 35 pts with advanced AML or ALL who received 1 to 3-antigen mismatched transplants
  - 12 pts died from an early syndrome
  - 10 pts had engraftment failure, requiring regrafting from same donor
  - 11 remaining were alive at the time of publication in 1983

Lancet 1983; 1:612

Disappointments

- Attempts to overcome GVHD using T-cell depletion
  - Results in comparison were complicated with a high risk of graft failure & recurrence of malignancy
  - EBV related post transplant lymphoproliferative disease also became apparent
- Treatment mortality focused also on prevention and treatment of opportunistic infections
- CMV serostatus recognized as important for screening

Focus on decreasing GVHD & graft failures

- Peripheral blood haploidentical transplants with “mega dose” (Aversa, et al.)
  - Stem cells: G-CSF, vigorously T-depleted
  - Recipient prep: TBI, thiotepa, fludarabine, ATG
- Results encouraging:
  - High rate of engraftment, little GVHD, minimal nonhematologic toxicity (mortality from nonleukemic causes ~40%)
  - Compared to historical controls

NEJM 1998; 339(17):1186

How does MFD compare?

- Ottinger, et al.
- Compared Matched Unrelated Donors (MUD), Mismatched Family Donor (MFD), & Identical Sibling Donor (ISD) in 325 pts (mostly with CML)
  - Retrospective, single center
- Analysis revealed the parameters of:
  - disease stage, patient age, time interval between diagnosis and transplantation, and donor age to be independent risk factors for OS
- Type of donor (ISD, MFD, or MUD) had no significant difference on OS after HCT

Blood 2003; 102:1131

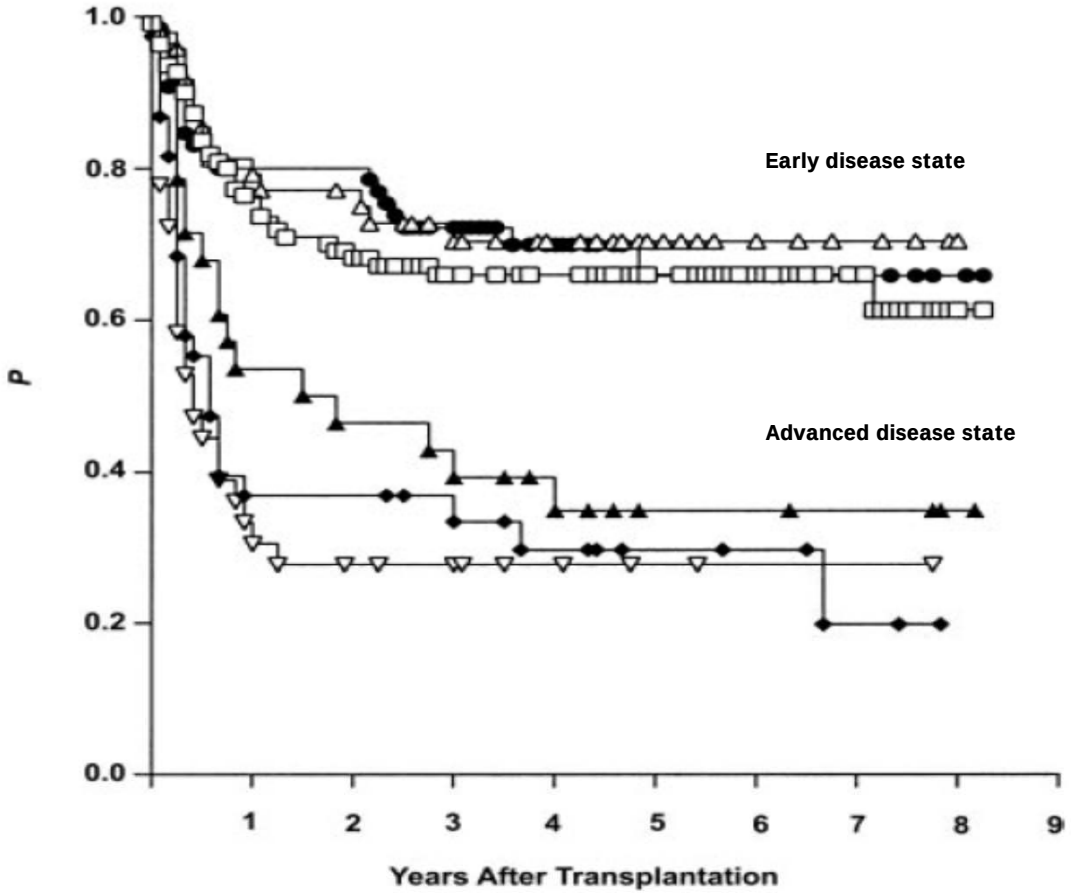


Figure 2. Overall survival (Kaplan-Meier estimates) after allogeneic hematopoietic stem cell transplantation from genotypically HLA-identical siblings (ISDs), alternative (partially) HLA-matched family donors (MFDs), and HLA-matched unrelated donors (MUD). Results are given after stratification for early (ear) and advanced (adv) disease stage. △ indicates MFD ear (n = 48); ●, MUD ear (n = 66); □, ISD ear (n = 110); ▲, ISD adv (n = 28); ▽, MUD adv (n = 35); and ◆, MFD adv (n = 38).

Blood 2003; 102:1131

GVHD

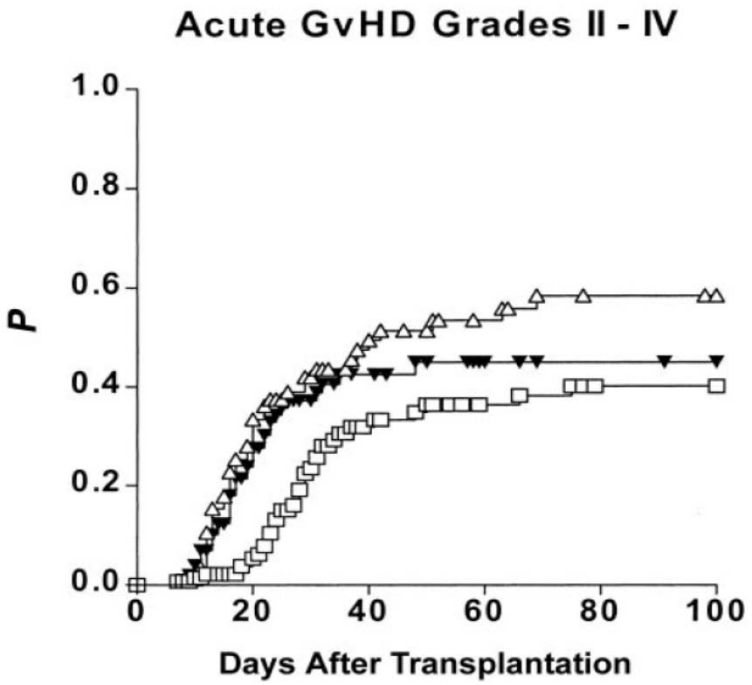


Figure 3. Risk of acute graft-versus-host disease (Kaplan-Meier estimates) after hematopoietic stem cell transplantation from genotypically HLA-identical siblings (ISDs), alternative (partially) HLA-matched family donors (MFDs), and HLA-matched unrelated donors (MUDs). □ represents ISDs; △, MFDs; and ▼, MUDs.

Blood 2003; 102:1131

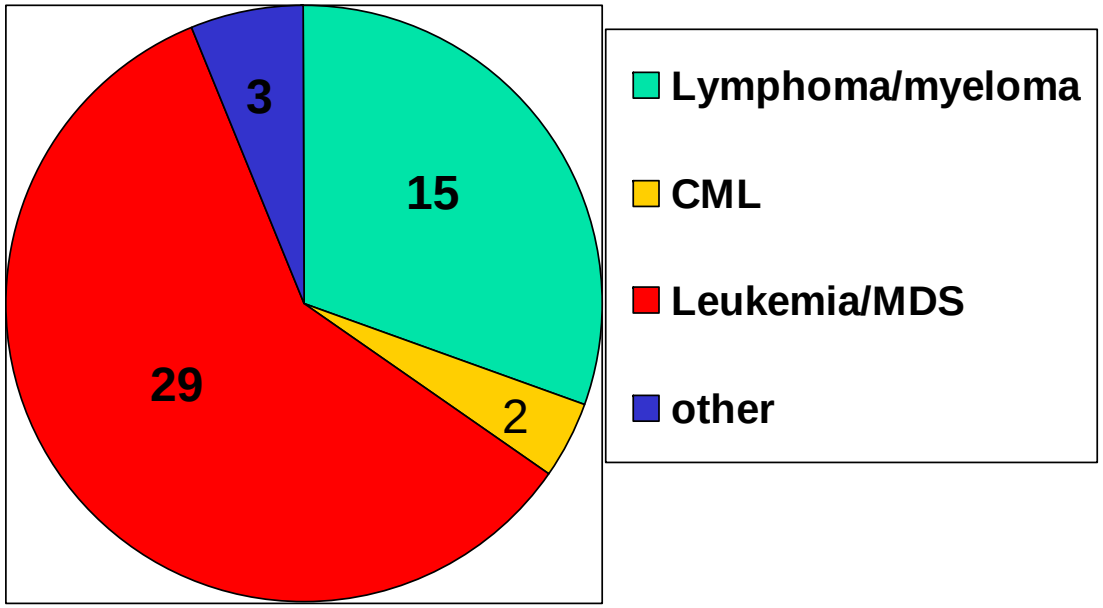
Newer approaches

- Partial T-cell depletion
  - CD-34 selection
- ATG
- Alemtuzumab-(Campath)
- Lymphocyte “add –back”
- Post transplant IL-2

- Regimen related toxicities
- Infections
- Relapse
- GVHD

Partially matched Non-ablative transplants

- 49 Patients
  - Median age 48 yrs
  - 30 (61%) refractory disease
    - 12 (24%) pts prior Auto BMT
  - 19 “standard risk”
    - 7 (14%) 1st remission or no tx



Rizzieri, D. A. et al. J Clin Oncol; 25:690-697 2007

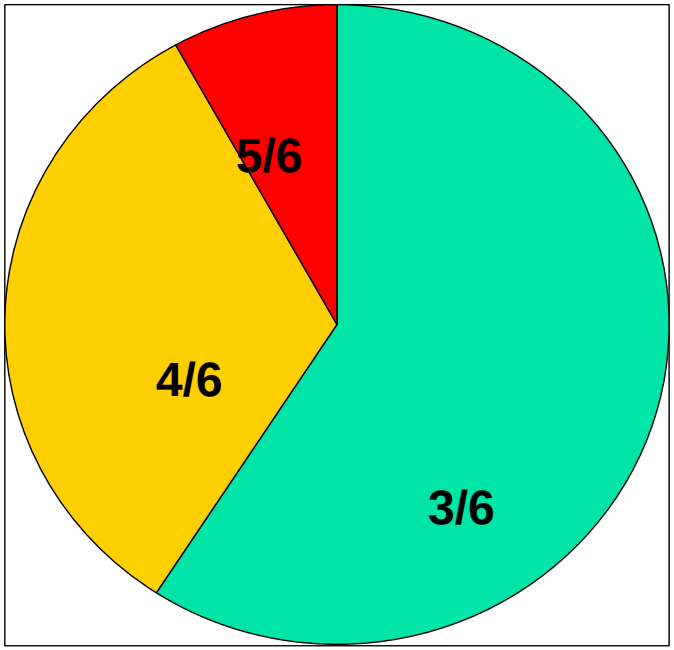
Treatment regimen

- Alemtuzumab 20 mg/d D-4 to 0.
- Fludarabine 30 mg/m2/d D-5 to D-2
- Cyclophosphamide 500 mg/m2/d D-5 to D-2
- Filgrastim 5 microg/m2 D+1
- GVHD
  - Cellcept+ CSA.

Rizzieri, D. A. et al. J Clin Oncol; 25:690-697 2007

HLA matching

- 3/6
  - Sibling 17
  - Parent/child 12
- 4/6
  - Sibling 8
  - Parent/child 7
  - Half-sibling 1
- 5/6
  - Parent/child 3
  - Cousin 1



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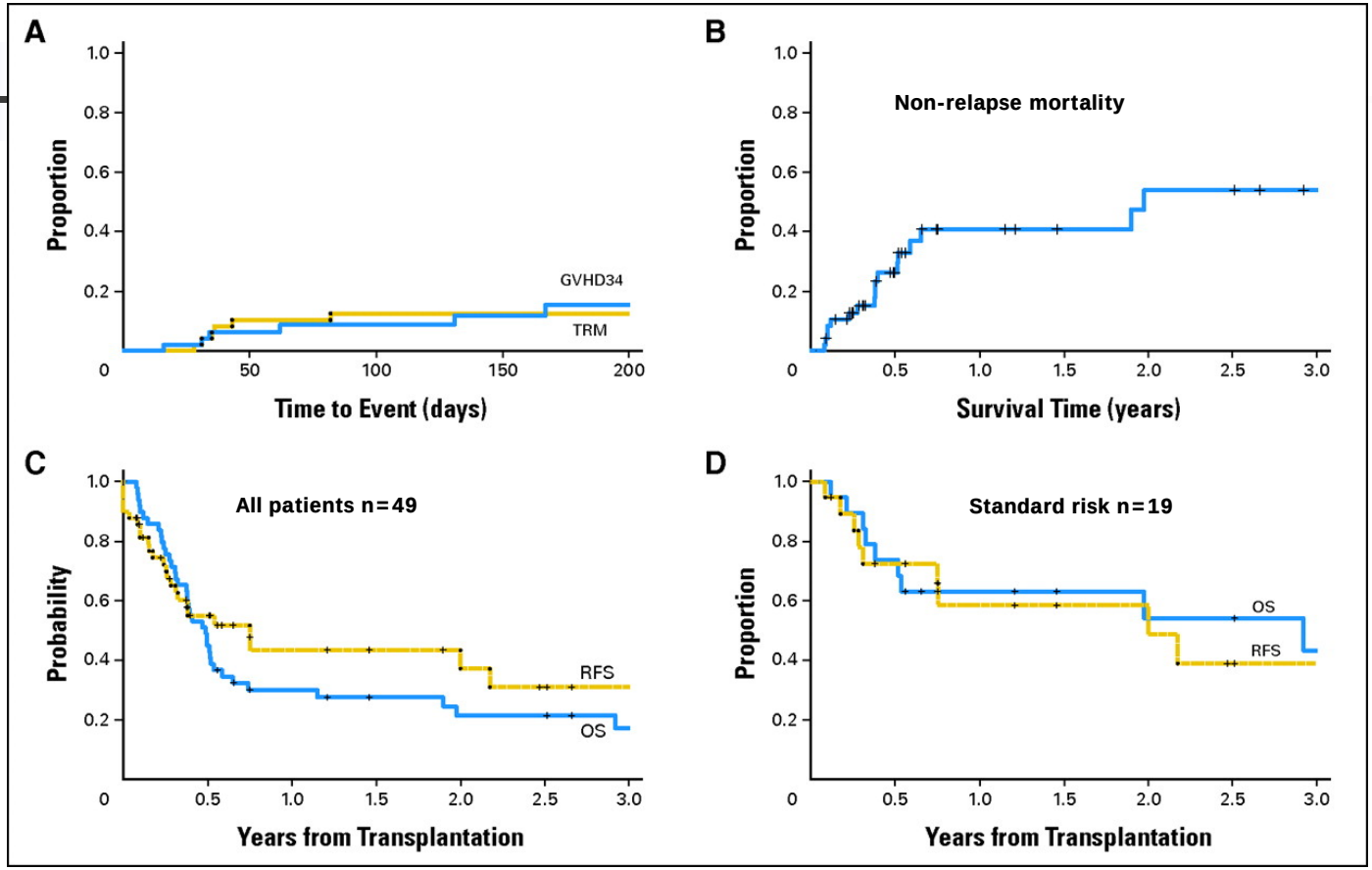
Results

- Response to transplant
  - CR: 37
  - PR: 5
  - SD/PD: 7
- Acute GVHD
  - 2 : 4
  - 3 : 3
  - 4 : 1
- Chronic GVHD
  - Limited : 5
  - Extensive : 2

- Cause of death
  - Progressive disease: 24
  - Infections: 11
  - Secondary CA: 2
  - Hemolytic anemia: 1
  - Neurotoxicity: 1

Rizzieri, D. A. et al. J Clin Oncol; 25:690-697 2007

Fig 1. Cumulative incidence graphs using Kaplan-Meier estimates



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Conclusions

- Clinical information needs to be considered when deciding to utilize alternative donors for allogeneic transplantation
- The timing of transplant seems to be an important predictor of transplant outcome
  - Haploidentical donors are readily available
- Haploidentical transplants should be considered as a treatment strategy in patients requiring an allogeneic transplant where no other donor is available
- Relapse and GVHD remain a problem in haploidentical transplants.

Cyclophosphamide post transplant

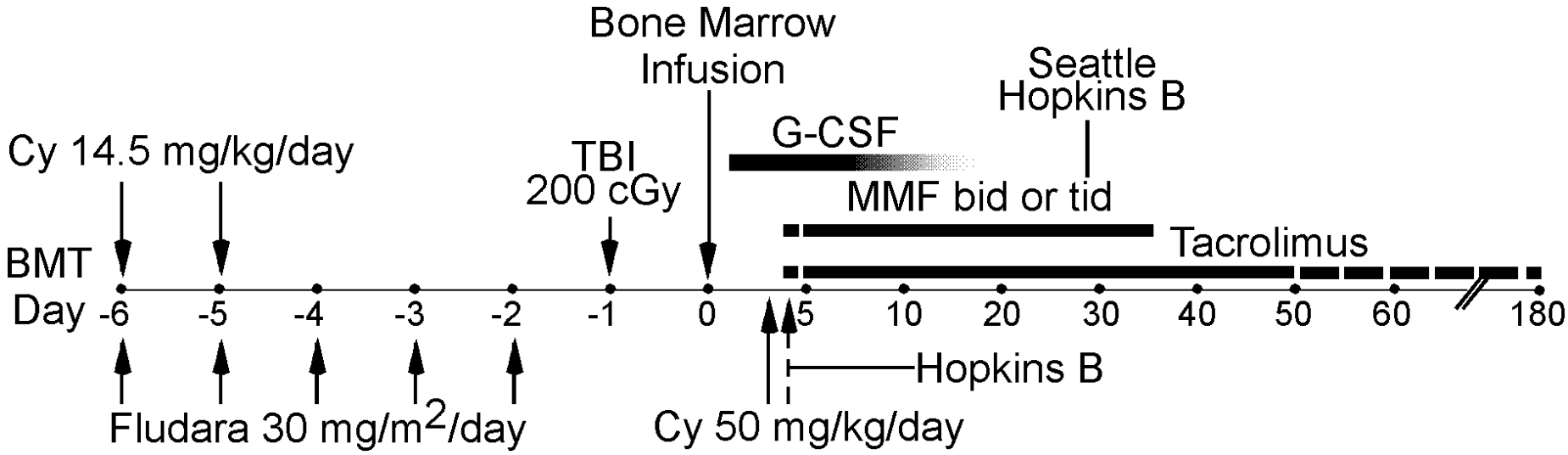
- Activated , alloreactive lymphocytes (cells most responsible for GVHD) are selectively sensitive to cyclophosphamide

- Engraftment of mismatched bone marrow in animals treated pre transplant with fludarabine /TBI and given post transplant cyclophosphamide

- HLA-Haploidentical Bone Marrow Transplantation for Hematological Malignancies Using Nonmyeloablative Conditioning and High-Dose , Posttransplantation Cyclophosphamide- Biology of Blood and Marrow Transplantation 2008 14(6):641

CTN trial-Background

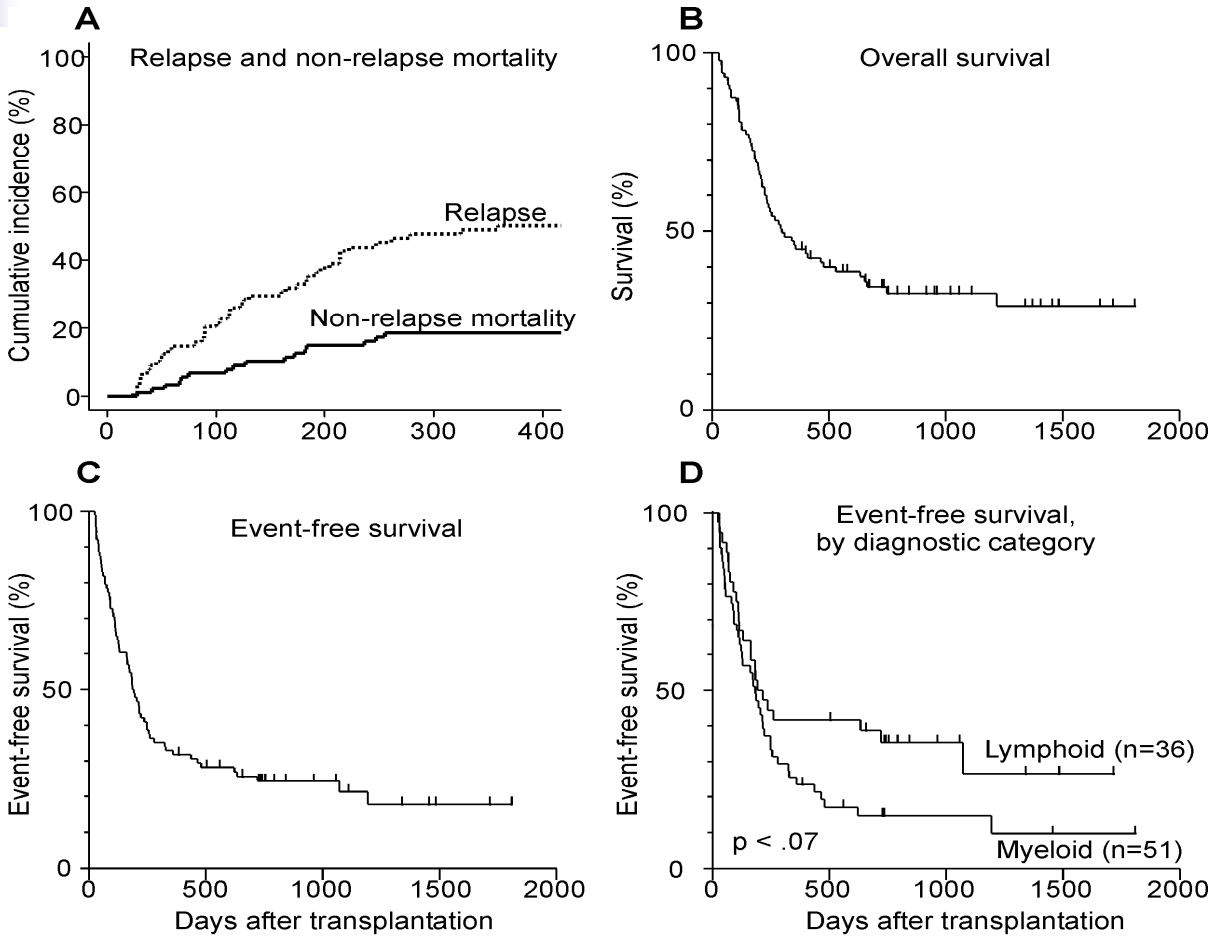
- 80 consecutive patients with hematological malignancies
- Treatment at Seattle and John Hopkins



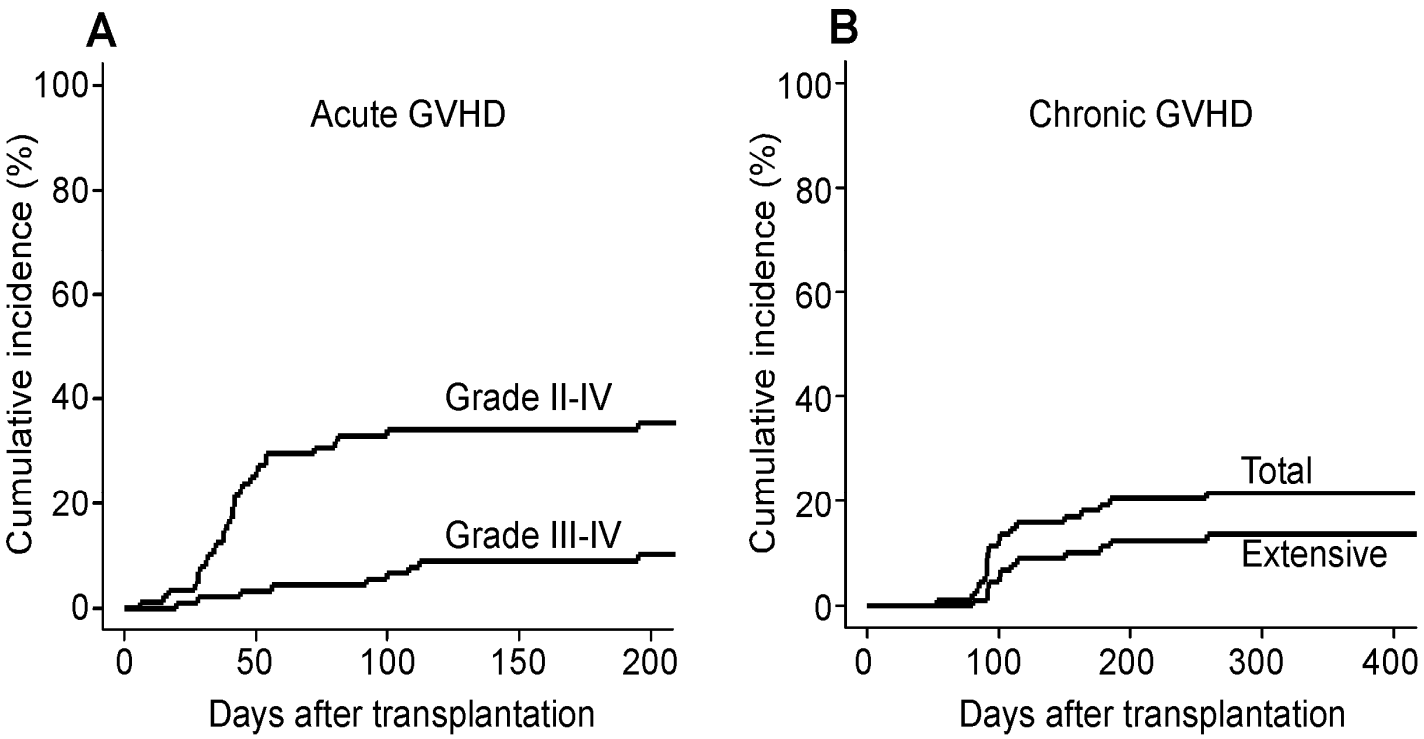
CTN trial-Background

- Neutrophil recovery – 15 days
- Platelet recovery 24 days
- Graft failure : 13%
- Lower incidence of Chronic GVHD
  - 2 vs 1 dose of Cy

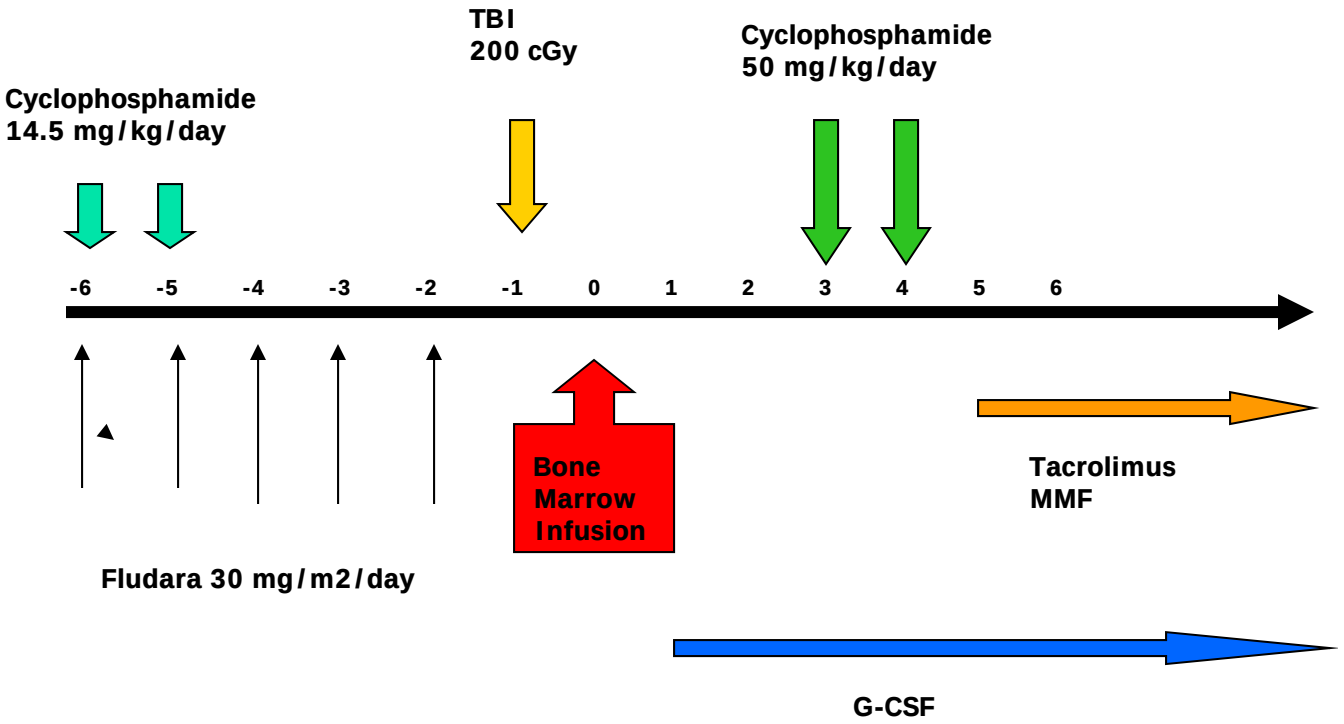
Haploidentical transplants



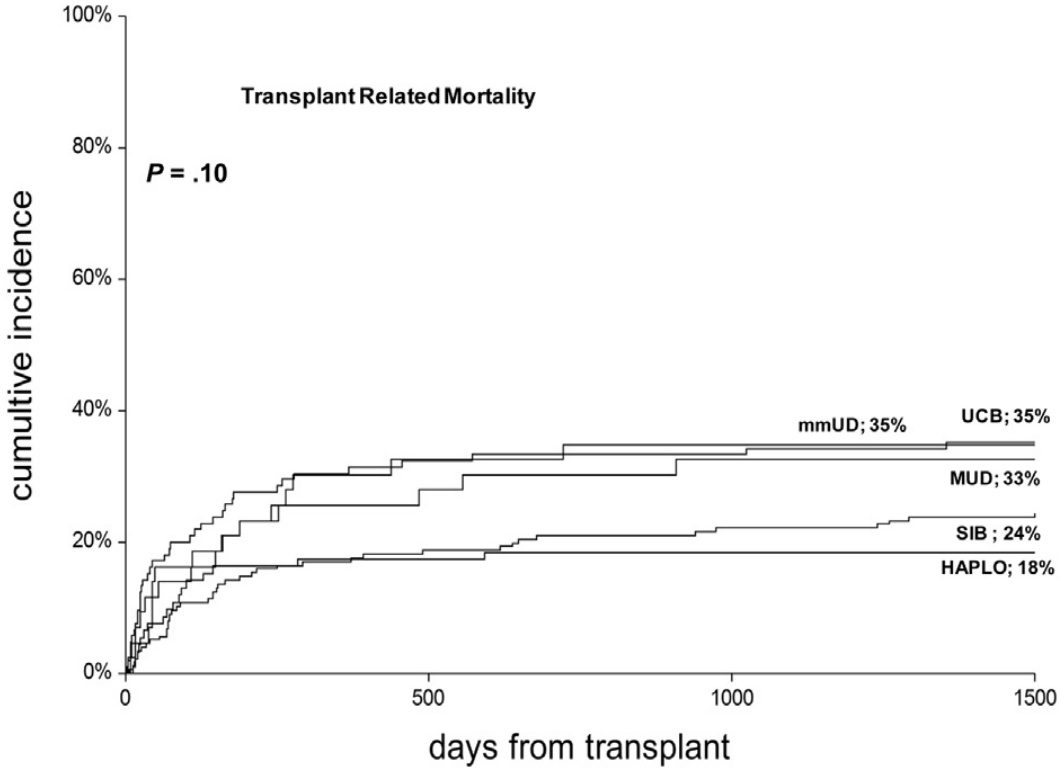
Haploidentical transplants



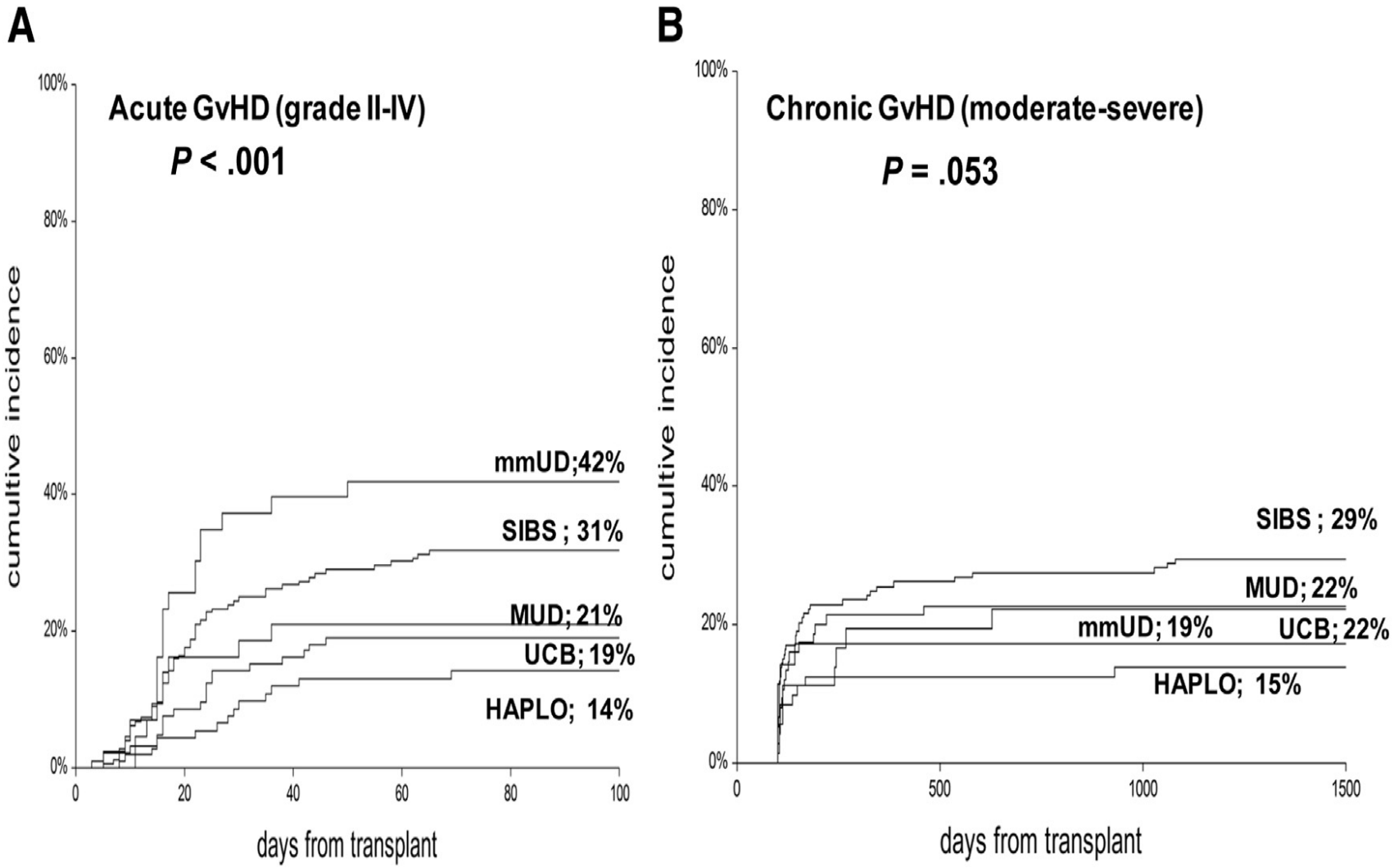
CTN 0603


TBI
200 cGy
Cyclophosphamide
50 mg/kg/day
Cyclophosphamide
14.5 mg/kg/day
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
Bone
Marrow
Infusion
Tacrolimus
MMF
Fludara 30 mg/m2/day
G-CSF

- Italian Retrospective study
- 459 Patients
- 176- Sibs
- 43- MUD
- 43- mmMUD
- 105- CORD
- 92-HAPLO



- Biology of Blood and Marrow Transplantation 2014(20):1573



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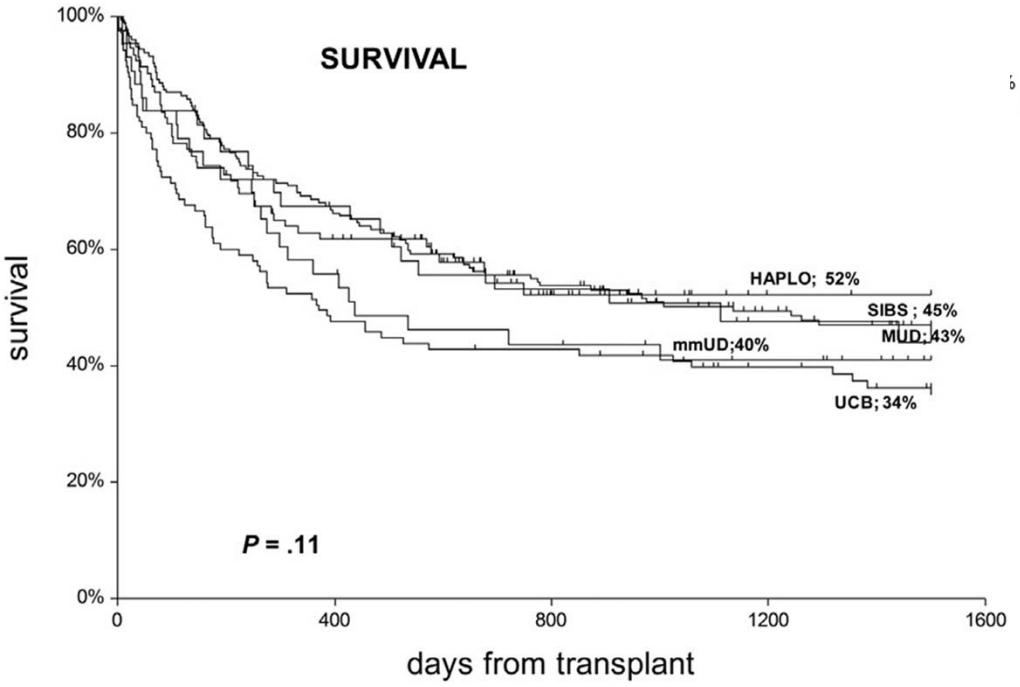

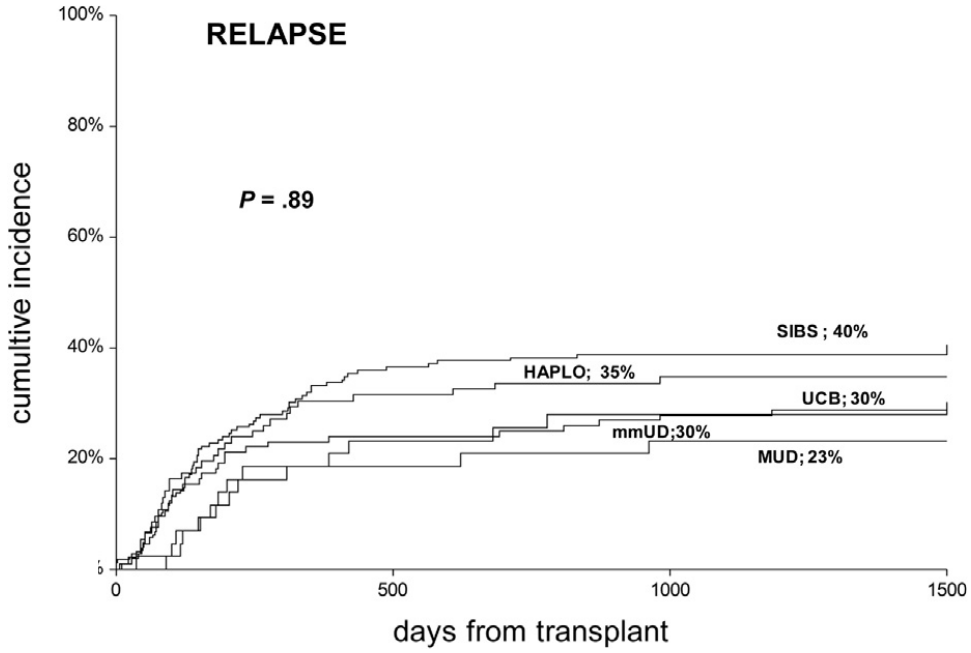

- Biology of Blood and Marrow Transplantation 2014(20):1573

PRESENT

- Several groups reported results using more intensive regimens---myeloablative
- Use of PBSC with similar results as compared to BM
- More widespread use as experience accumulates
- Earlier use
- Still requires longer follow up
- Comparative prospective trials are ongoing
  - Cord blood vs Haplo

FUTURE

- Non HLA factors to consider
  - Non-inherited maternal antigens
  - Natural Killer cell (NK) alloreactivity
- Graft engineering
  - Suicide gene insertion to T cells