Reduced Intensity Transplants in Pediatrics

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Why should we consider Reduced Intensity Transplants in Pediatric Patients

- We have done traditional transplants for 50 years still lousy results (ALL in CR2 short initial remission (30-40% 3 year EFS)
- As Pediatricians we would like to reduce long term effects
- To reduce up-front Transplant related mortality
- To induce Graft vs. Tumor effect with the ultimate goal to improve survival (CURE).


This is what we try to avoid

Traditional Allogeneic Transplantation

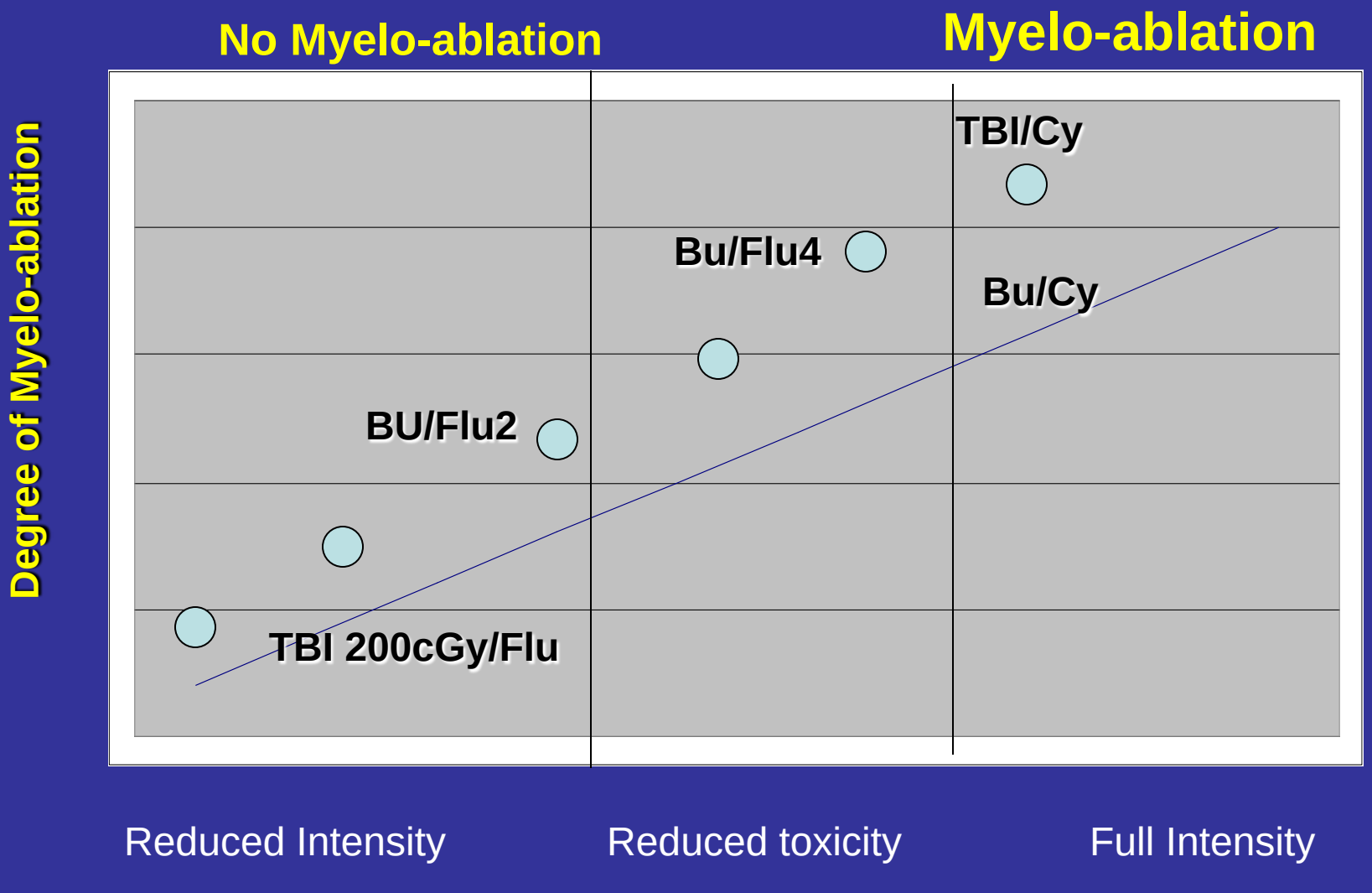
- Curative potential in most hematological malignancies and some solid tumors
- Conditioning regimens consist of high doses of chemotherapy with or without TBI
- Treatment is associated with high morbidity and mortality of 10-40%
- Limited to younger patients (<50 years).
- Approach is prohibitive in patients with a co-morbid illness or organ dysfunction.

What is a Reduced Intensity

So, Where are we exactly?

This is what we are trying to achieve

Reduced Intensity Transplants



Rationale for Allogeneic RIT

- The anti-tumor effect of donor immune cells (NK cells) is thought to play a major role in the curative potential of allogeneic transplant
- **Graft vs. Tumor Effect**
- Engraftment of donor cells can occur following conditioning regimens consisting of lower doses of therapy (immune-suppressive)
- RIT regimens are associated with less toxicity than standard myeloablative regimens

RIT
Pre-Clinical Studies

- Animal Studies:
  - **Chimeric engraftment was seen in 10/11 dogs following a single dose of TBI (2Gy) with infusion of identical DLA stem cells and GVHD prophylaxis with CSA and MMF (Storb et al.)**

RIT Studies: Hematological Malignancies

- **Giralt et al.:**
  - 13 patients with ANLL/ MDS (median age of 59 years)
  - Treatment: Fludarabine, Idarubicin, and Ara-C or melphalan plus PBSC
  - Outcome: all patients engrafted with 90% donor cells by day 14-30; only one toxic death.
- **Childs et al.**
  - 11 patients with hematological malignancies
  - Treatment: Cytoxan and Fludarabine and plus PBSC and CSA for GVHD prophylaxis.
  - Outcome: all patients engrafted; 4 patients develop severe GVHD.

RIT Studies: Hematological Malignancies (cont.)

- **Slavin et.al.**
  - 26 patients with hematological malignancies
  - Treatment: Fludarabine and Busulfan plus PBSC and ATG and CSA for GVHD prophylaxis.
  - Outcome:
    - All patients engrafted
    - No toxic deaths.
    - Partial chimera was seen in 9/26.
    - The estimated survival probability was 77%; 4 patients died of severe GVHD.

Review of The Literature

- Over 500 Abstracts last year submitted to ASH with multiple regimens and types of patients
- Many papers with small series or case reports.
- several Abstracts in Pediatric patients
- 1 full length paper using RIT in Pediatrics (Pulsipher et al 2009)

Differences Between RI and Full Intensity Allogeneic Transplants

Full Intensity

- high doses of chemotherapy and TBI
- lower numbers of stem cells infused
- intense GVHD prophylaxis
- inpatient hospital care
- high transplant related toxicity
- increase risk of GVHD

Reduced intensity

- lower doses of chemotherapy and TBI
- higher numbers of stem cells infused
- minimal GVHD prophylaxis
- outpatient care
- minimal transplant related toxicity
- Increase risk of cGVHD

Engraftment

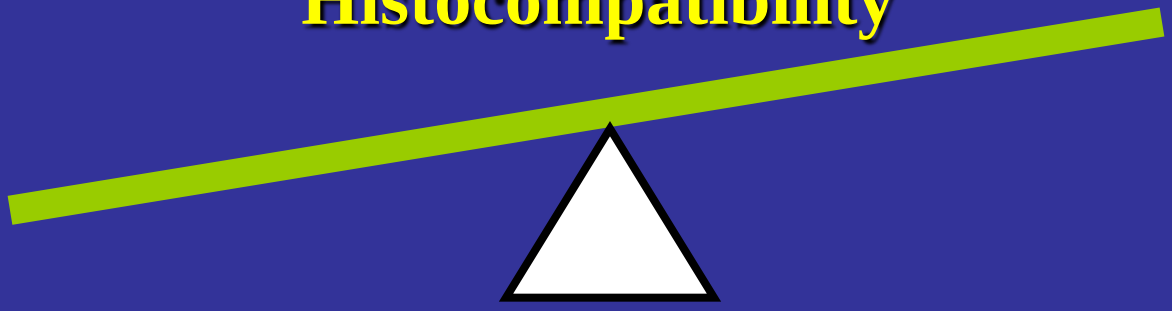
Graft

- Stem cell dose
- T-cell dose (CD8)
- Graft-facilitating cells
- Stromal stem cells?

Host

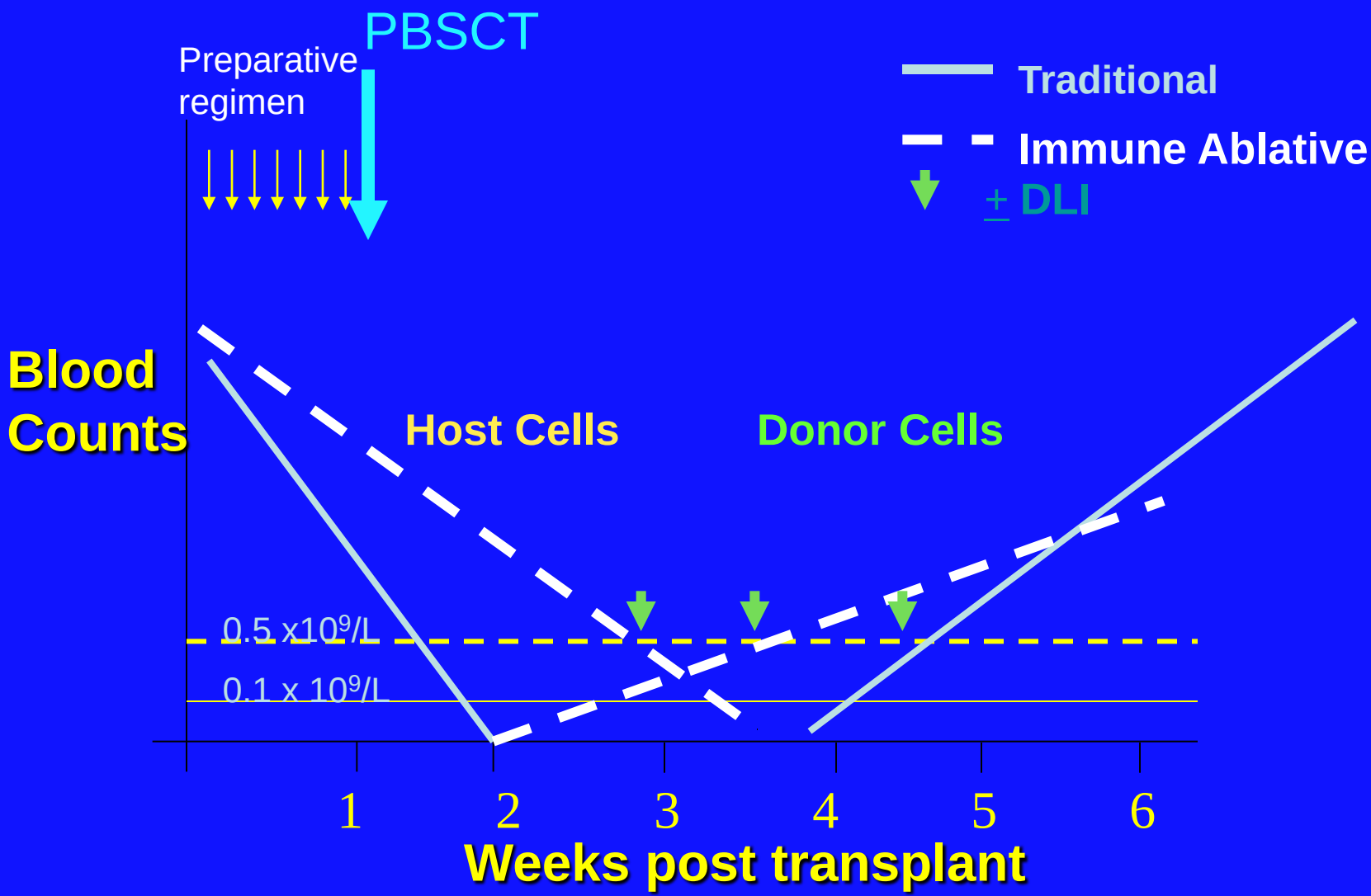
- Immunosuppression
- Preparative regimen
- Post-transplant Rx
- Disease effects
- Sensitization

Histocompatibility



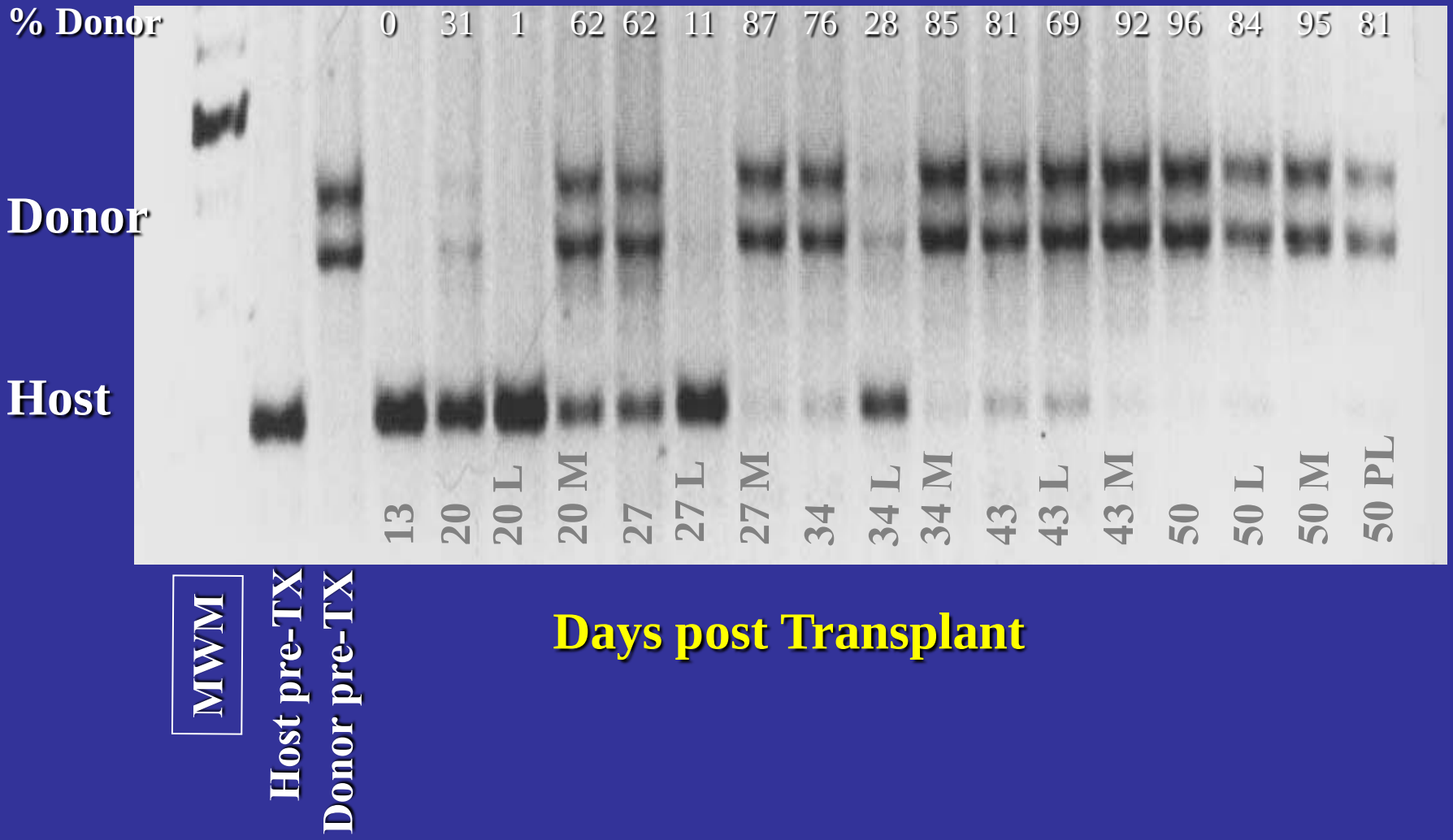
In RIT regimens the graft cells may inhibit rejection.

Hematological Reconstitution: Full vs. Reduced Intensity Transplant



Chimerism after an Reduced Intensity transplant

MWM= Molecular Weight Marker
TX= Transplant
L= Lymphoid (T cells)
M=Myeloid
PL= platelets



Before we continue we have to ask the following Question.

What role is the Myelo-ablation play in Disease Control?

EXPRESSION OF WT1 GENE AS A PREDICTOR OF OUTCOME IN PEDIATRIC PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTS (HSCT) FOR ACUTE LEUKEMIA.

***Morris Kletzel, Marie Olszewski, David Jacobsohn, Wei Huang, Roopa Seshadri, Reggie Duerst*.**

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Background

- **WT1 gene is a transcription factor located on chromosome 11p13, and is involved in the pathogenesis of Wilms tumor.**

- **Significant levels of expression of WT1 gene have been reported to be expressed in blast of adult patients with acute leukemia (ALL, AML).** Miwa et al1992, Miyagi et al 1993 and Menssen et al1995.

- **WT1 as a reliable tool for detection of MRD in Children.** Kletzel et al 2002

- **Prognostic significance of quantitative analysis of WT1 gene in adults with acute leukemia** Garg et al 2003

- **High levels of MRD (gene rearrangements) prior to HSCT predicts poor outcome in children with ALL** Krejsi BMT –MRD study group. 2003

Patients and Method

- 62 patients with acute leukemia
  (AML n=33), (ALL n=29)
- Median age 4.0 years (range .46-18.4)
- 36 males 26 females.
- Stem Cell Source
  UCB (n=33), MUD (n=13), MS (n=16)
- Race
  C (n=37), AA (n=8). H (n=14), O (n=3)

Patients and Methods

Full Intensity Conditioning:

fTBI 1200 cGy (8 fractions of 150 cGy) day -8 to -5.

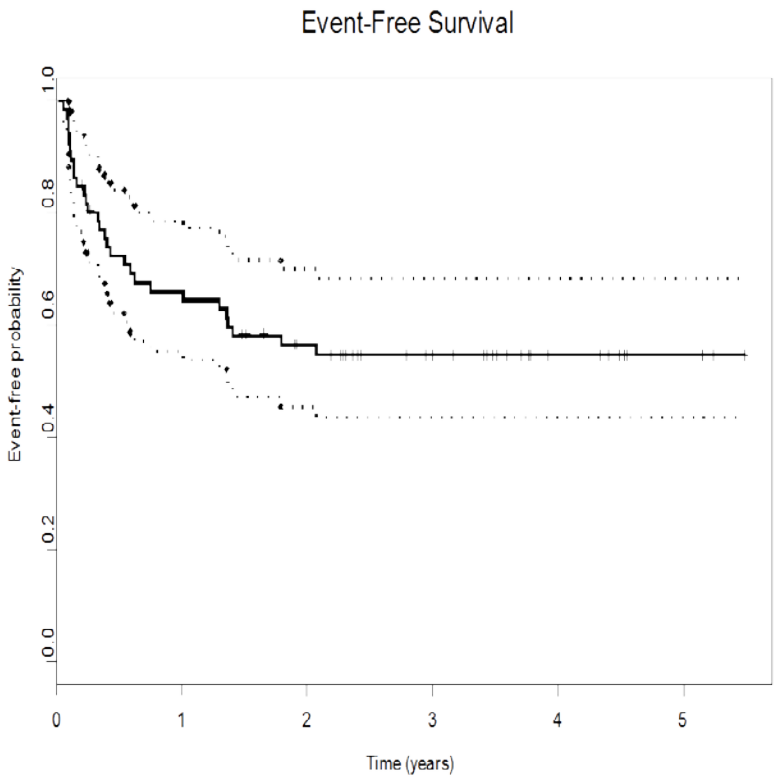
VP-16 1000mg/m^2 as an 8 hr infusion day -4

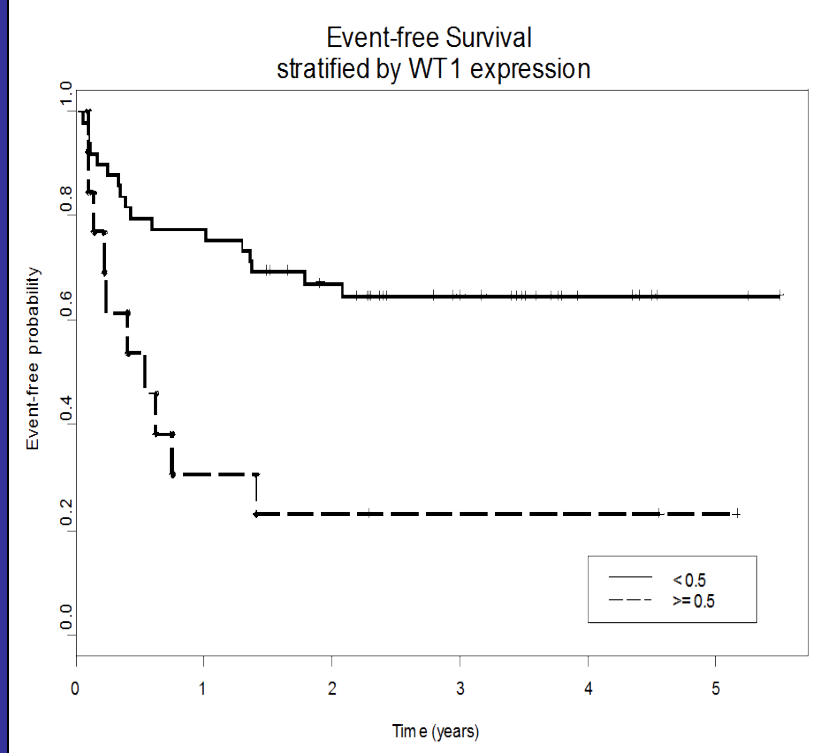
Cyclophosphamide 60 mg/kg/day x 3 days days -4 to -2

GVHD prophylaxis:

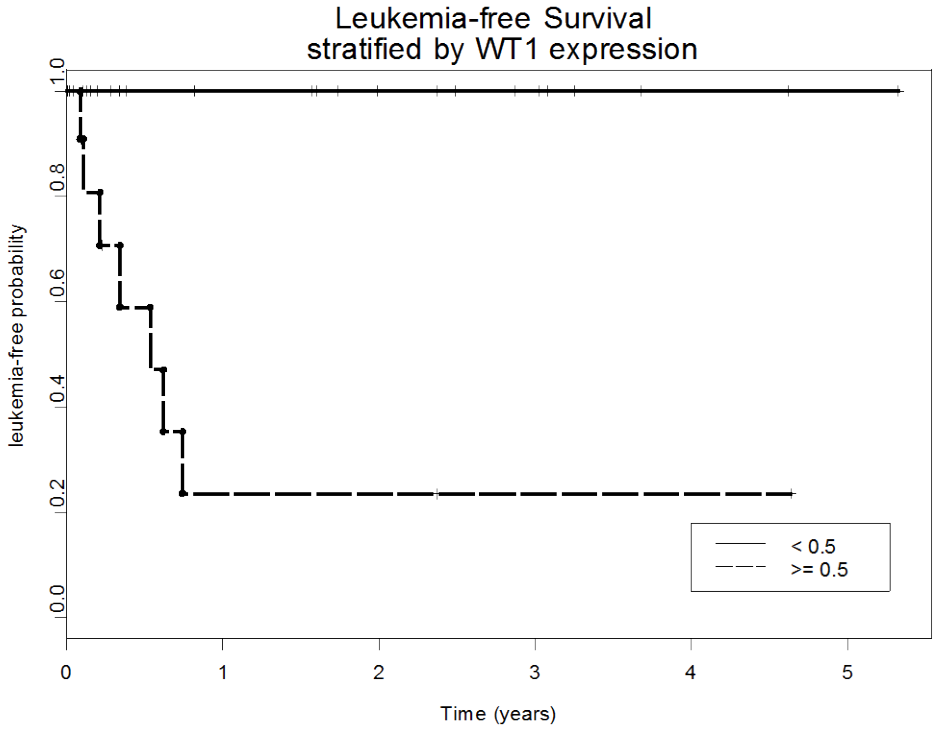
CSA, short course MTX (days 1,3 and 6) for the matched siblings and rabbit ATG (2mg/kg on days 1,3,5,7) was added to the alternative donors

Results


Event-Free Survival
Event-free probability
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Time (years)


Event-free Survival
stratified by WT1 expression
Event-free probability
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Time (years)
< 0.5
>= 0.5

Results


Leukemia-free Survival
stratified by WT1 expression
leukemia-free probability
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Time (years)
< 0.5
>= 0.5

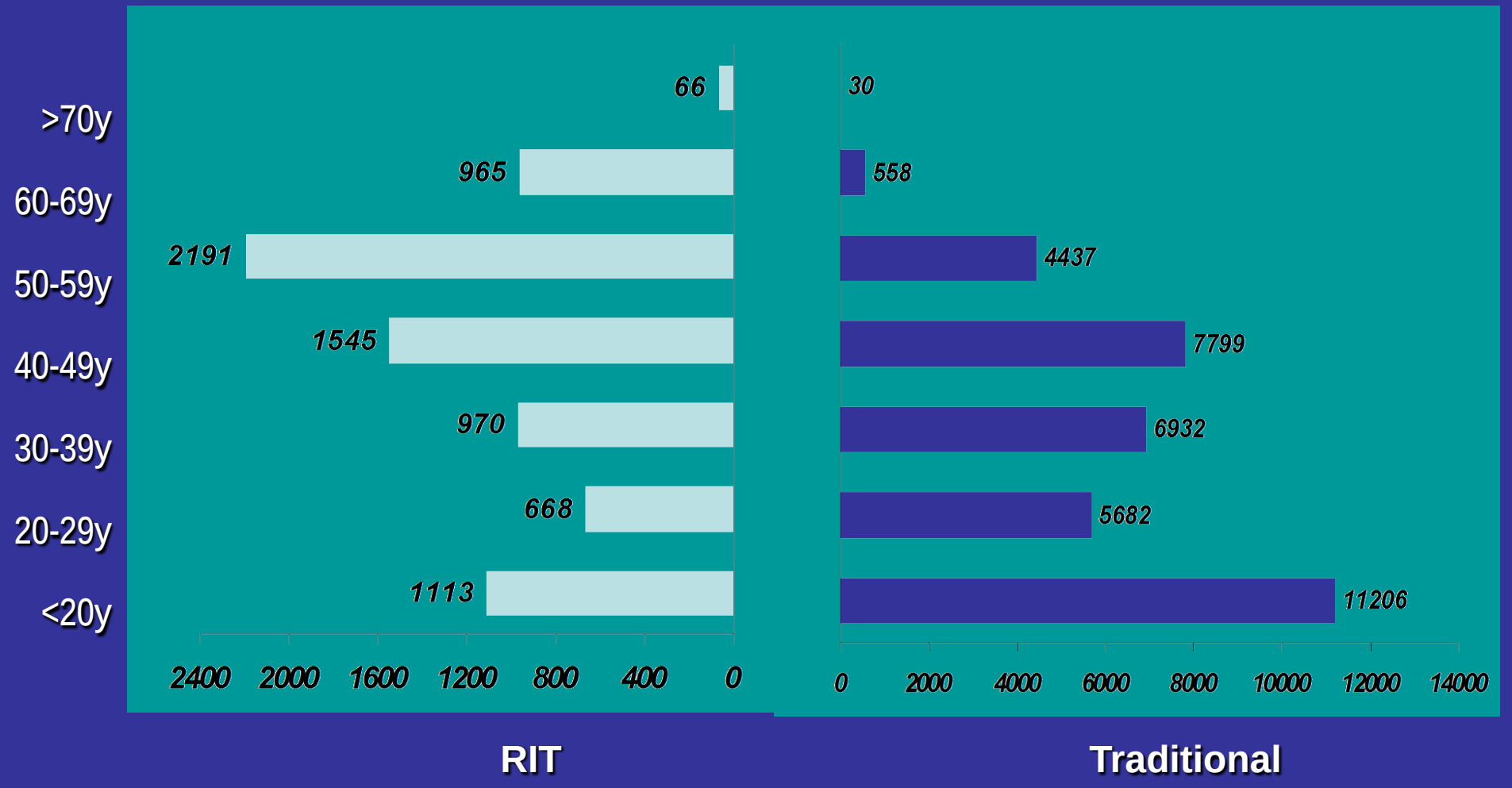
Conclusions

- Increase WT1 expression prior to HSCT is associated with relapse (p=0.003)
- Patients with amplified expression were 3.3 times more likely to have a relapse
  95%CI (1.5-7.3)
- The association does not change after controlling for:
  - Transplant type
  - Acute GVHD
  - Chronic GVHD
  - HLA antigen mismatch

RIC regimens

- TBI 200 cGy in one fraction
- Fludarabine based
- Sub-myeloablative based
- ATG supplementation
- Infusion of high numbers of CD34+ cells donor cells (6×10^6)

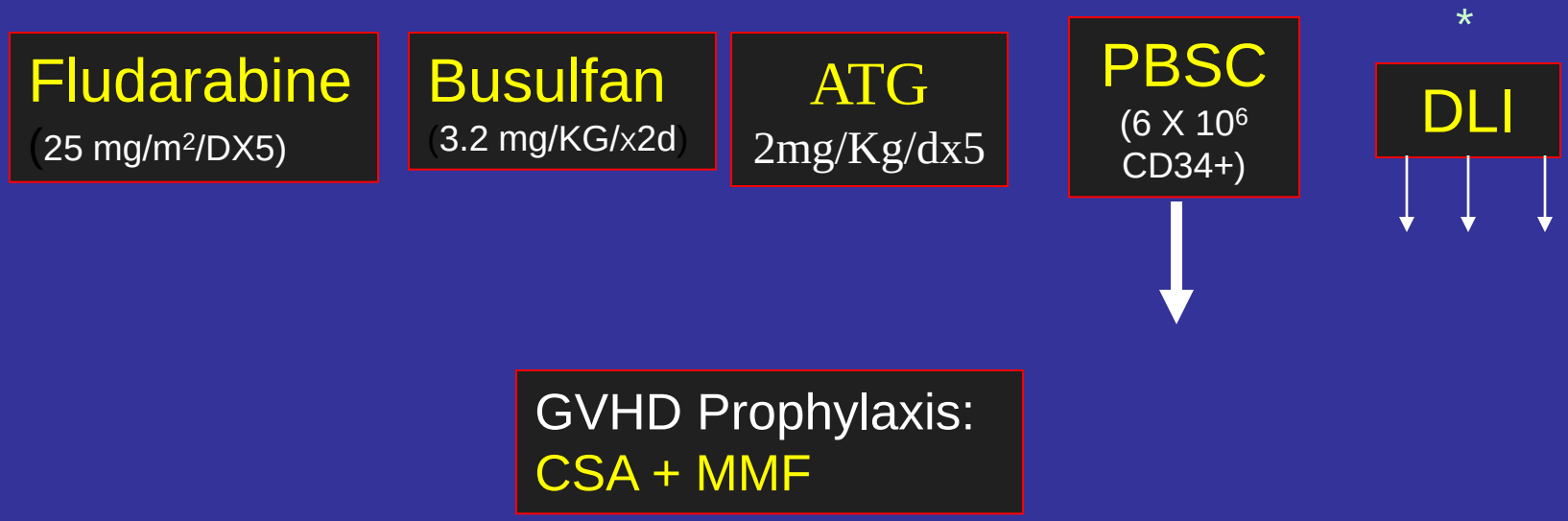
AGE OF ALLOTRANSPLANT RECIPIENTS REGISTERED WITH THE IBMTR, 1997-2002



RIC Schema at Lurie Children's

- **HLA-matched donor related or unrelated 7/8, 8/8**
- **Two antigen mismatched for UCB**

- **Regimen**



Note for the cord we have added a dose of Thio-Tepa 10 mg/Kg to improve engraftment

* Only to improve chimerism

Is There GVL effect in Lymphoid Leukemia's ?

Experience with ALL only patients

- ALL patients (16)
- CR2 (8)
- CR3 (3)
- CR4 (4)
- refractory Dz (1)
- males (11) females (5)
- Median age 8.9 years (1-16)
- Prior HSCT (7)
- PBSC (13) BM (3)

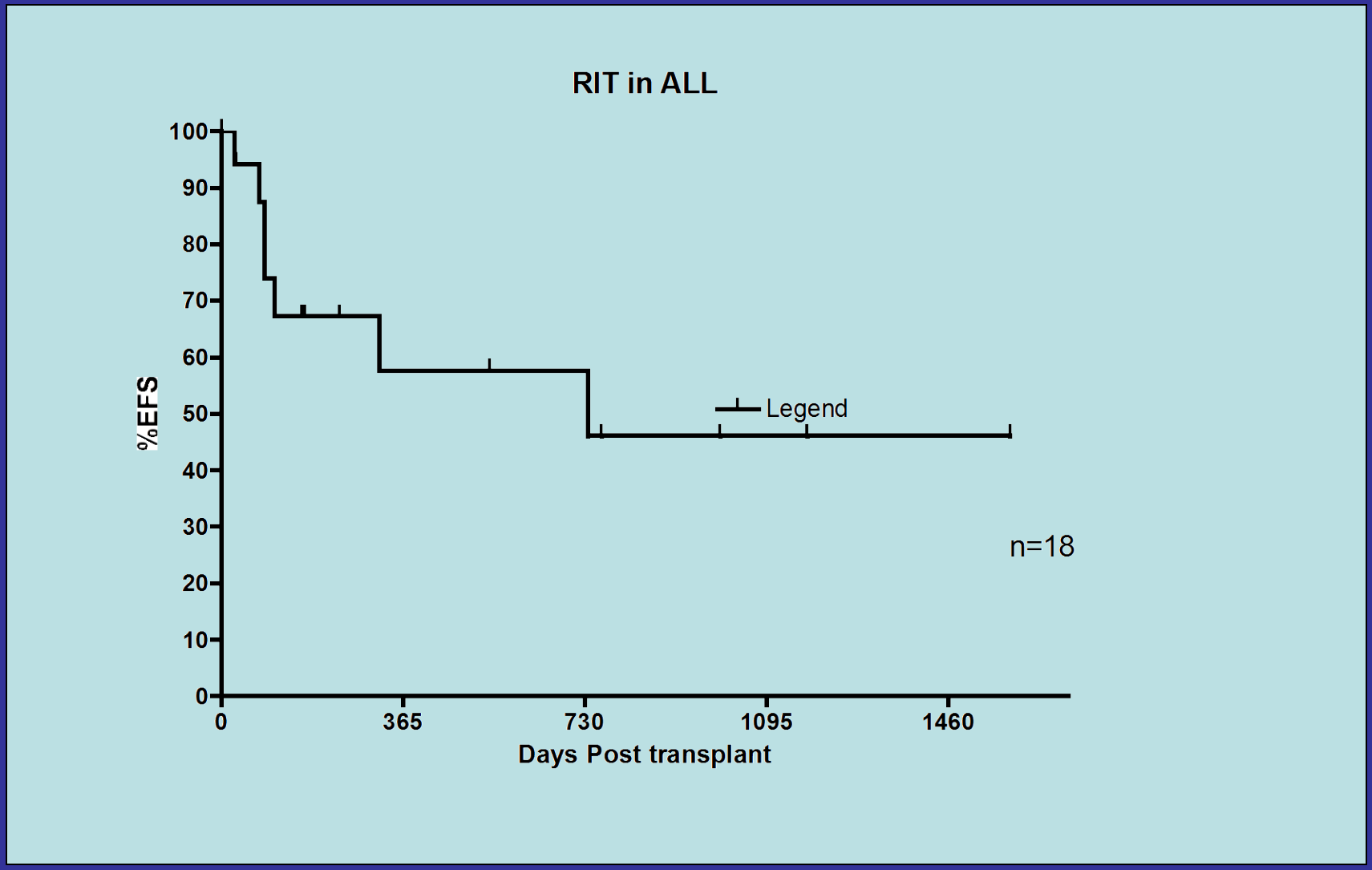
RIC in ALL

- RIC due to:
  - Prior aspergillosis (1)
  - PH+ (1)
  - Neurological Toxicity (2)
  - Infant CR2 (1)
  - Relapse post Myeloablative Tx (7)
  - No reason (6)

RIC in ALL

- Outcome
  - Cause of death
    - PD (1)
    - Infection (2)
    - Neuro (2)
  - Acute GVHD
    - Grade I (5)
    - Grade II (1)
    - Grade III (0)
    - Grade IV (2)
  - Chronic GVHD
    - Limited (2)
    - Extensive severe (1)

Experience with ALL patients only EFS



Conclusions

- Difficult to draw conclusions from the small numbers and the diversity of patients.
- Acute toxicity is minimal
- Engraftment is difficult in patients with hemoglobinopathies
- There is GVL effect in ALL patients
- Chimerism is good and sustained in all other patients.
- The source of Stem cells does not appear to create any problem but cord blood transplants may required extra myelosuppression
- Acute GVHD was not a problem
- Higher than expected incidence of cGVHD and this maybe a problem
- A larger number of patients are necessary to confirm this findings

How about RIC conditioning in patients who relapse after an Allogeneic transplant

- 13 patients (9 males and 4 females)
- Median age 9 years (1-16)
- Transplanted at Lurie Children's between 2002 and 2012
- All n=11 and AML n=2
- Source of Stem Cells
  - 1st transplant (8 MRS and 5 MUD including 2 UCB)
  - 2nd Transplant (5 MRS and 8 MUD)
- Conditioning Regimens
  - Regimen A fTBI 1200cGy (150cGy fractions day -7 to -4, VP-16 1000mg/m^2 on day -3 and cyclophosphamide 60 mg/kg day on day -3 to -1 (1st HSCT n=7 , 2nd HSCT n=6)
  - Regimen B Fludarabine 30 mg/m^2 day from -10 to -6, Busulfan dose based on results of PK of a test dose to achieve a AUC of 4000 µicroMol-min/day on days -5 ,-4, rabbit ATG 2 mg/kg on days -4 to -1 (1st HSCT n=3, second HSCT n=10)
  - GVHD prophylaxis for Reg A CSA/Tacro and short course MTX for Reg B CSA/Tacro MMF ± Extracorporeal photopheresis

Results of second Transplants after relapse using RIC

- Median time from diagnosis to 1st HSCT 202 days
- Median time from 1st HSCT to the second HSCT 531 days
- Median time to ANC >500 µl was 15 days (10-39) for the 1st HSCT vs. 18.5 (10-25) for the second (p=0.7)
- Median time to platelets >20.0 µl 16.5 days (1-54) for the 1st vs.19 days (0-54) for the second (p=0.8)
- Full donor chimerism was achieved at a median 34.5 days (12-63) in 13/13 pts. after the 1st HSCT and 44 days (22-108) after the second in 10-13 pts. (2 had partial chimerism)
- Median follow up after the 2nd HSCT 1259 (350-3508)
- All patients receive the 2nd transplant from a different donor
- The 3 and 5 year EFS is 69% and 43% respectively
- The 7 patients who are Alive and free of disease (1 with Partial chimerism** and 6 with full donor chimerism from the second HSCT)
- 6 pts. have expired 3 of complications of cGVHD in remission and 3 with progressive disease (2 of the 3 had a partial chimerism from the second HSCT)

** This patient has a full donor chimerism of the 1st donor (graft failure second donor)

Conclusions of second Transplants after relapse using RIC

- Pts. who relapse after a 1st myeloablative HSCT can be successfully treated with a second transplant from a different donor
- Pts. who did not achieved a full donor chimerism from the second donor were at higher risk of relapse
- The only exception was the patient who had a graft failure from the second transplant but has a full donor chimerism from the first.
- There was an increase incidence of cGVHD in this cohort and pts. those with extensive and severe cGVHD died fro complications of GVHD and not relapse.
- All but one of the surviving patients have cGVHD which may explain that there is The biologic effect of GVL in this group of patients.
- Evaluation of chimerism can be difficult in this group of patients since the evaluation has to be made with the recipient and each one of the donors

Outcome of Second Transplants in Pediatric Patients with Acute Leukemia after a Hematopoietic Stem Cell Transplant (HSCT) from a Different Donor. Assessment of Chimerism by Real -Time PCR to determine the Risk of Relapse

Sana Khan[1], Marie Olszewski[1], Morris Kletzel[1,2]

Purpose

To assess the Survival and Efficacy of a second HSCT from a different donor in patients who relapse after the 1st allo HSCT using Chimerism to assess the risk of relapse

A retrospective analysis

Patients and Methods

- 13 patients (9 males and 4 females)
- Median age 9 years (1-16)
- ALL (n=11) AML (n=2)
- Donor Source
  - 1st Tx MRS (n=8) Alternative Donors (n=5 2 cords)
  - 2nd Tx MRS (n=5) Alternative donors (n=8)
- Conditioning regimens
  - Reg A fTBI, VP-16, Cytoxan
  - Reg B Fludarabine, Busulfan ATG

Patients and Methods

- Conditioning regimens
  - 1st Tx regimen A (n=7) regimen B (n=6)
  - 2nd Tx regimen A (n=4) regimen B (n=9)
- GVHD prophylaxis
  - Reg A CSA/Tacro short course MTX ± ATG
  - Reg B CSA/Tacro, MMF ± ECP
- Chimerism was evaluated by RT-PCR
  - Full donor >98% ± 1%

Results

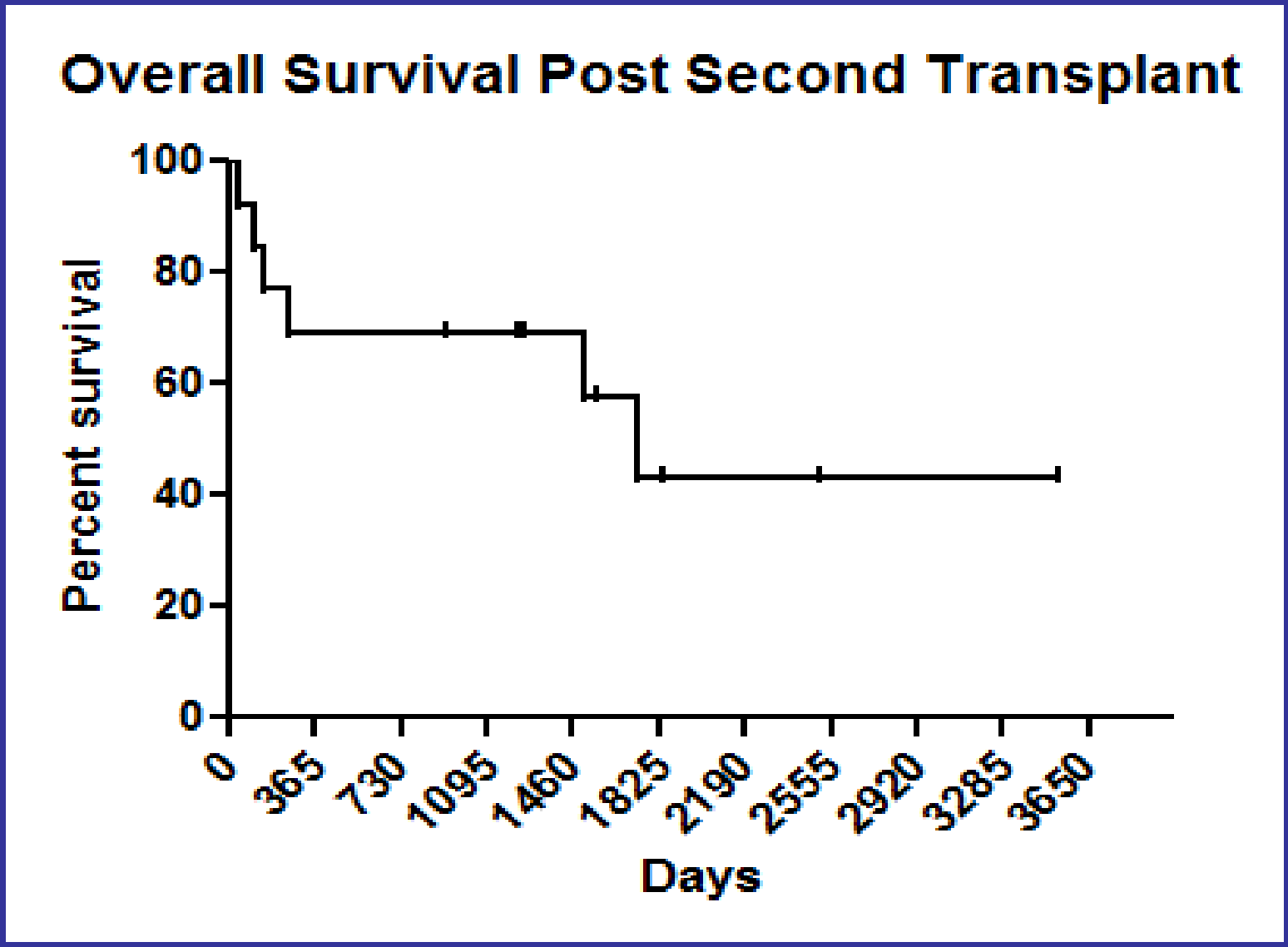
- Median time from Dx to 1st transplant 202 days
- Median time from 1st to 2nd HSCT 531 days

	1st TX	2nd Tx	P value
ANC>500	15 (10-39)	18.5(10-25)	0.7
Plat >20.0	16.5 (1-54)	19 (0-54)	0.8
Full donor Chimerism	34.5 (12-63) 13/13	44(22-108) 10/13	

Results

- Median follow up after 2nd Tx 1259 days

Survival


Overall Survival Post Second Transplant
Percent survival
100
80
60
40
20
0
0
365
730
1095
1460
1825
2190
2555
2920
3285
3650
Days

Survival

- 7 patients are alive (1 with Partial Chimerism and 6 full donor Chimerism) all but one have cGVHD the one without cGVHD had graft failure of the second donor but full donor Chimerism of the 1st donor***
- 6 patients have died (3 full donor Chimerism with complications of cGVHD and 2 partial Chimerism from relapse, one full donor Chimerism patient died of relapse.

Conclusions

- Pts who relapse after 1st allo transplant can be successfully treated with a second HSCT from a different donor
- Pts who did not achieve a full donor Chimerism after the second HSCT were at higher risk of relapse
- All but one surviving pts have cGVHD
- Patient who died from complications of cGVHD were in remission