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Transplantation for Thalassaemia and Sickle Cell Disease

Dr Victoria Potter
Kings College Hospital

The Holy Grails

- Malignant disease ➔beneficial GVL without detrimental GVHD
- Non-malignant disease ➔ sustained engraftment without GVHD

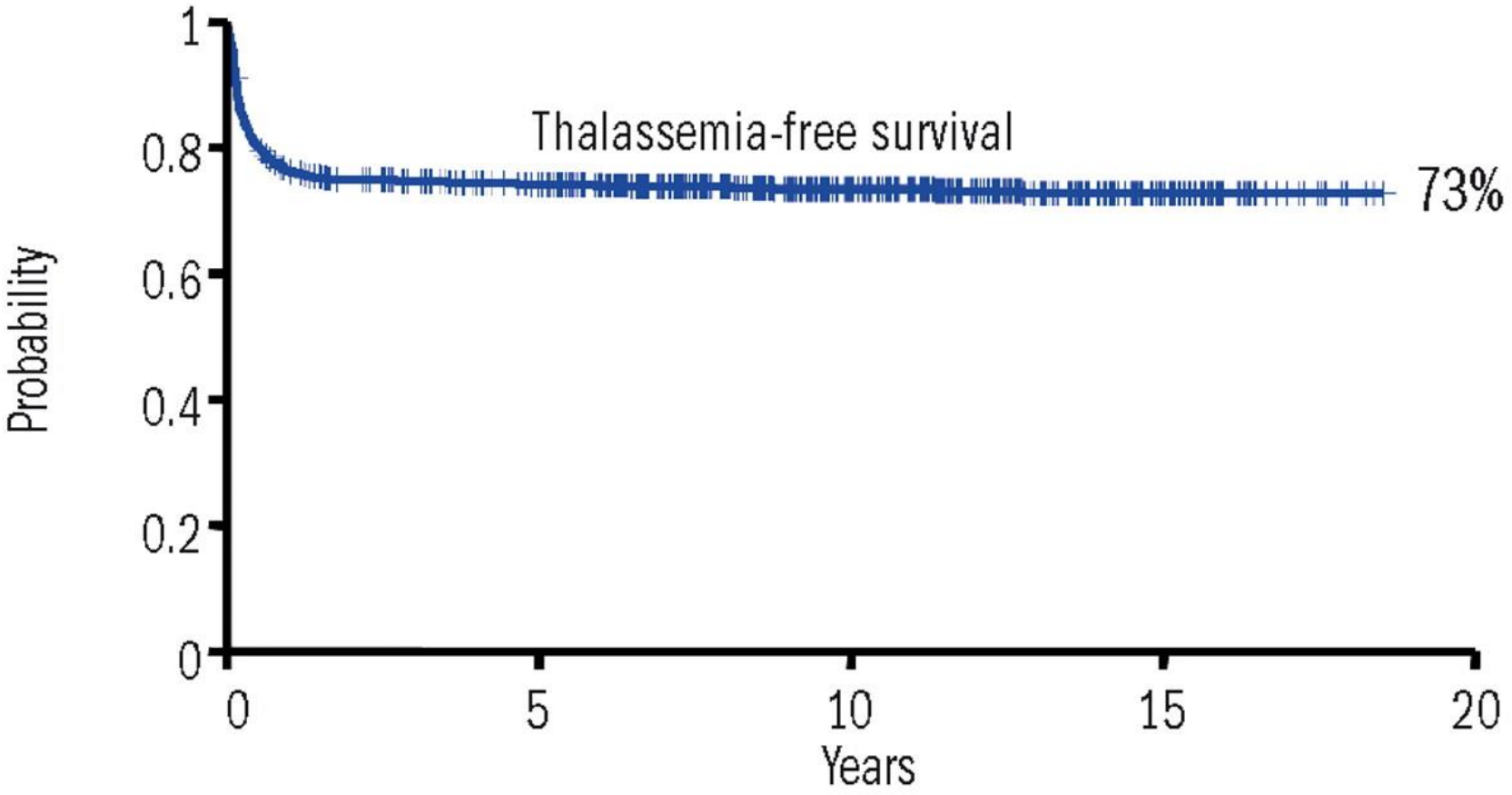
What are the goals of HSCT in non-malignant disease

Minimal toxicity from conditioning regimen
Sustained haematological engraftment: • *Full donor chimerism* • *Stable mixed chimerism?*
Absence of any chronic GVHD
Minimal long term complications

Thalassaemia

- HSCT only curative therapy
- >3000 transplants reported
- HSCT indicated for those with transfusion dependency if sibling or well matched HLA unrelated donor
- HSCT indicated early prior to development of transfusion related complications

Results of hemopoietic stem cell transplantation in 900 consecutive patients, aged 1–35 years, transplanted from an HLA identical sibling in Pesaro since December 1981.



Emanuele Angelucci, and Donatella Baronciani
Haematologica 2008;93:1780-1784

haematologica
the hematology journal

Prognostication

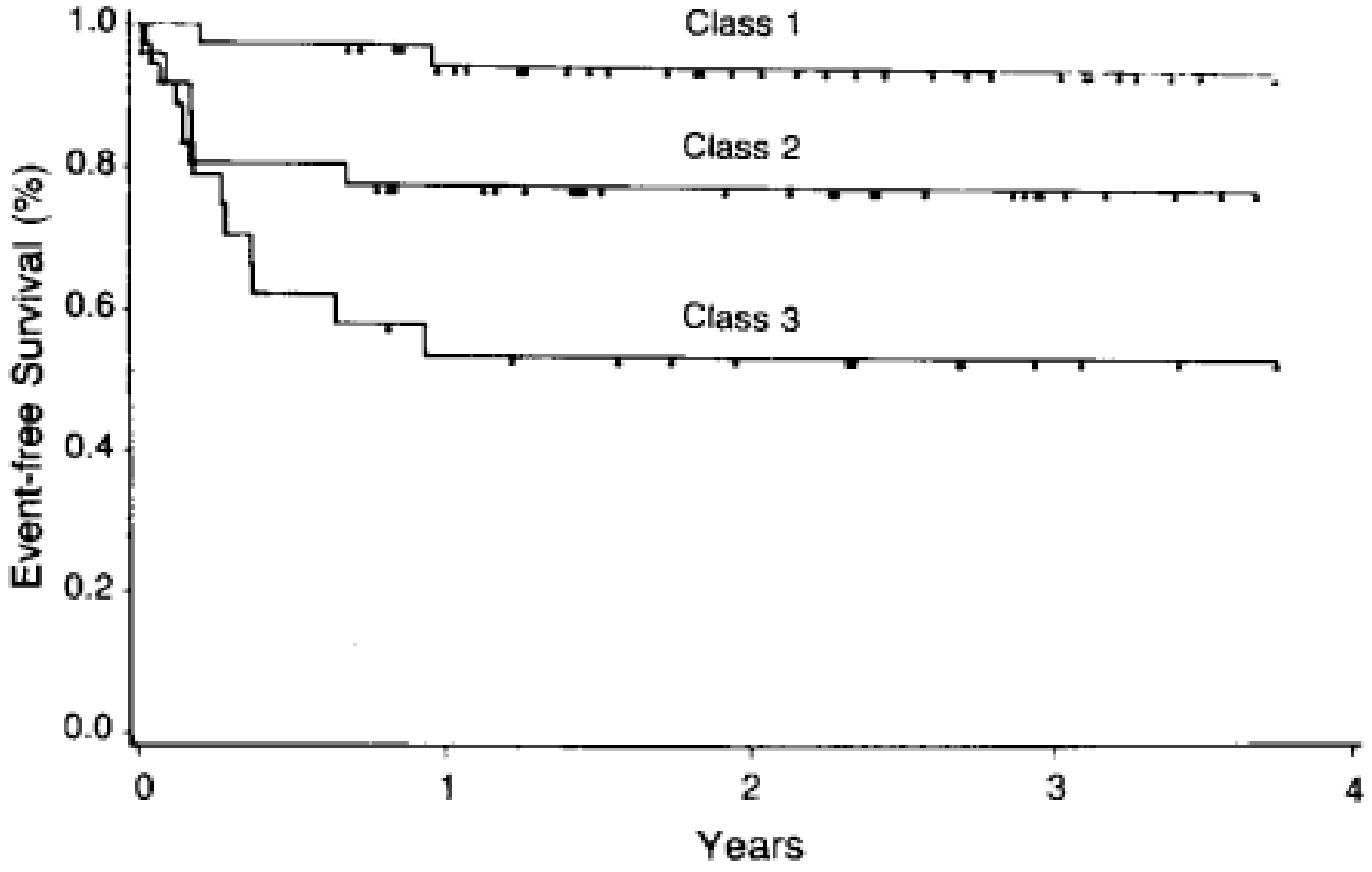
- Degree of iron overload is critically important to outcome
- Lucarelli et al 1990
  - Three variables all related to iron burden

1. Lifetime quality of chelation received prior to transplantation (regular versus non-regular)

2. Hepatomegaly (defined as more than 2 centimeters below the costal margin)

3. Presence of liver fibrosis pre-transplant, as determined by hepatic biopsy examination

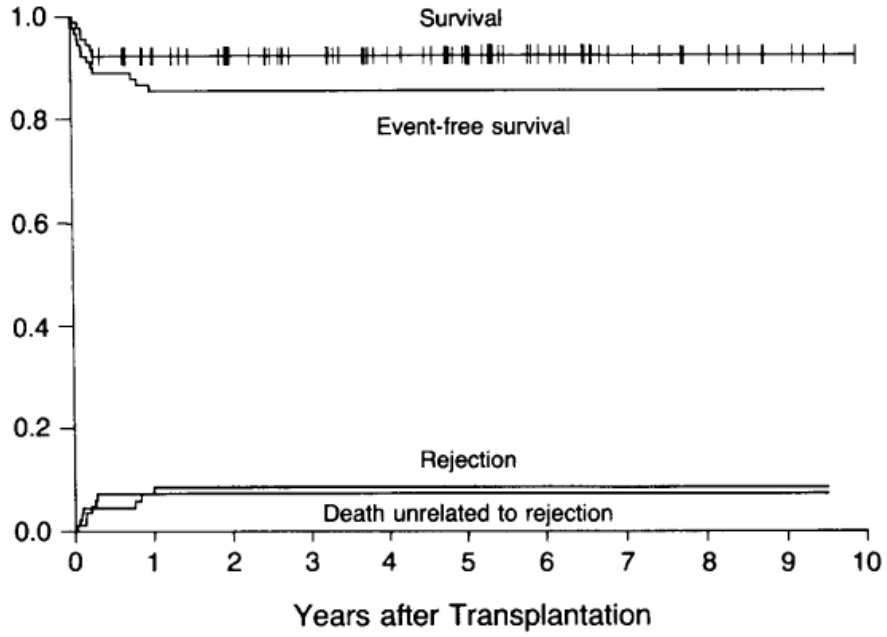
Survival according to risk factors



Lucarelli et al NEJM 1990

Survival in Class 1 patients

Lucarelli et al NEJM 1993

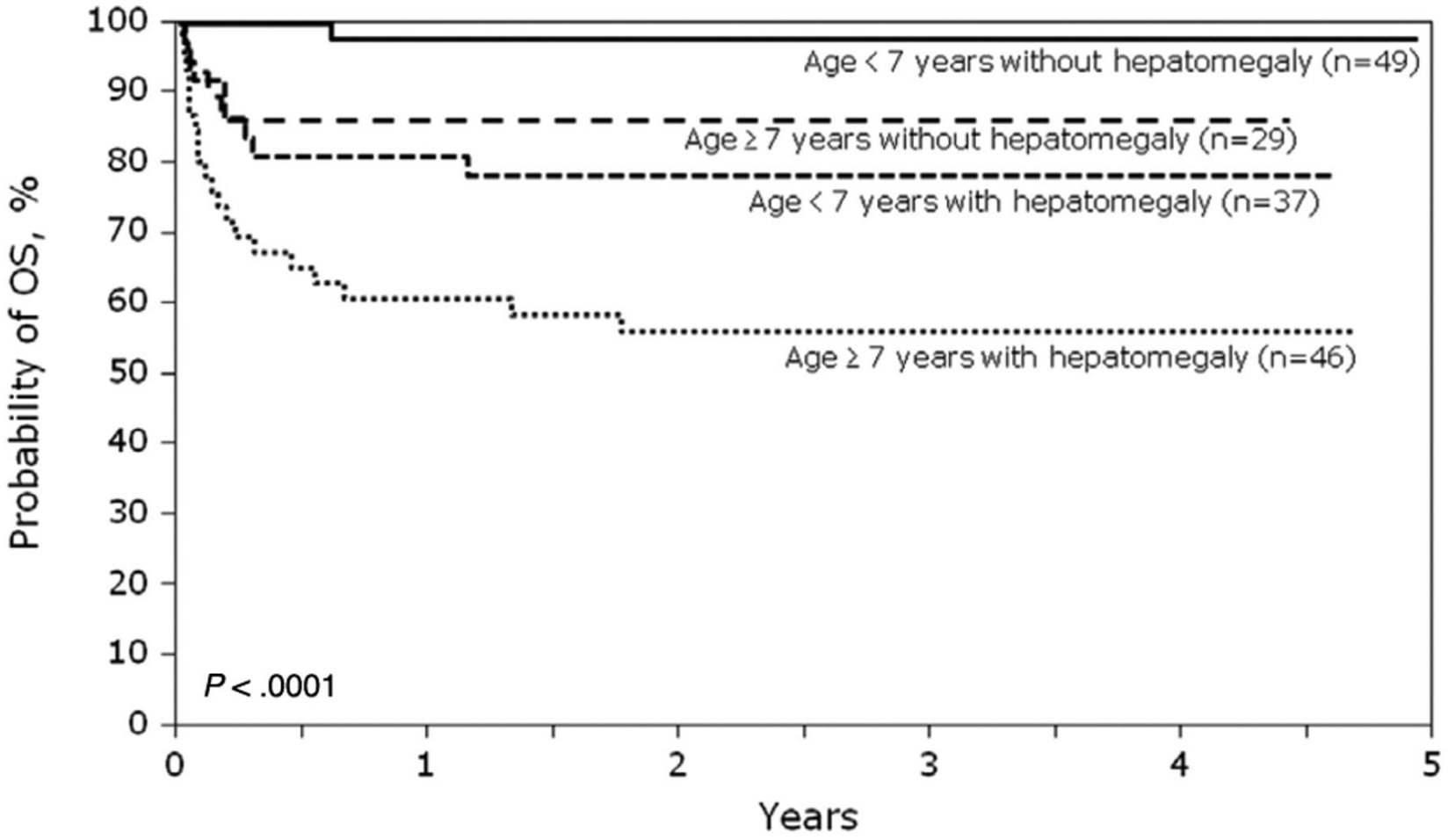


Current Expectations of Outcomes

Class I ➔ 95% OS, 90% TFS
Class II ➔ 85% OS, 80% TFS
Class III ➔ 75-80%, 65-70% TFS
Adult ➔ 70-75%

Taken from Transplantation chapter in Guidelines for the management of transfusion dependent thalassaemia, Cappellini et al

Probability of OS by age and hepatomegaly.

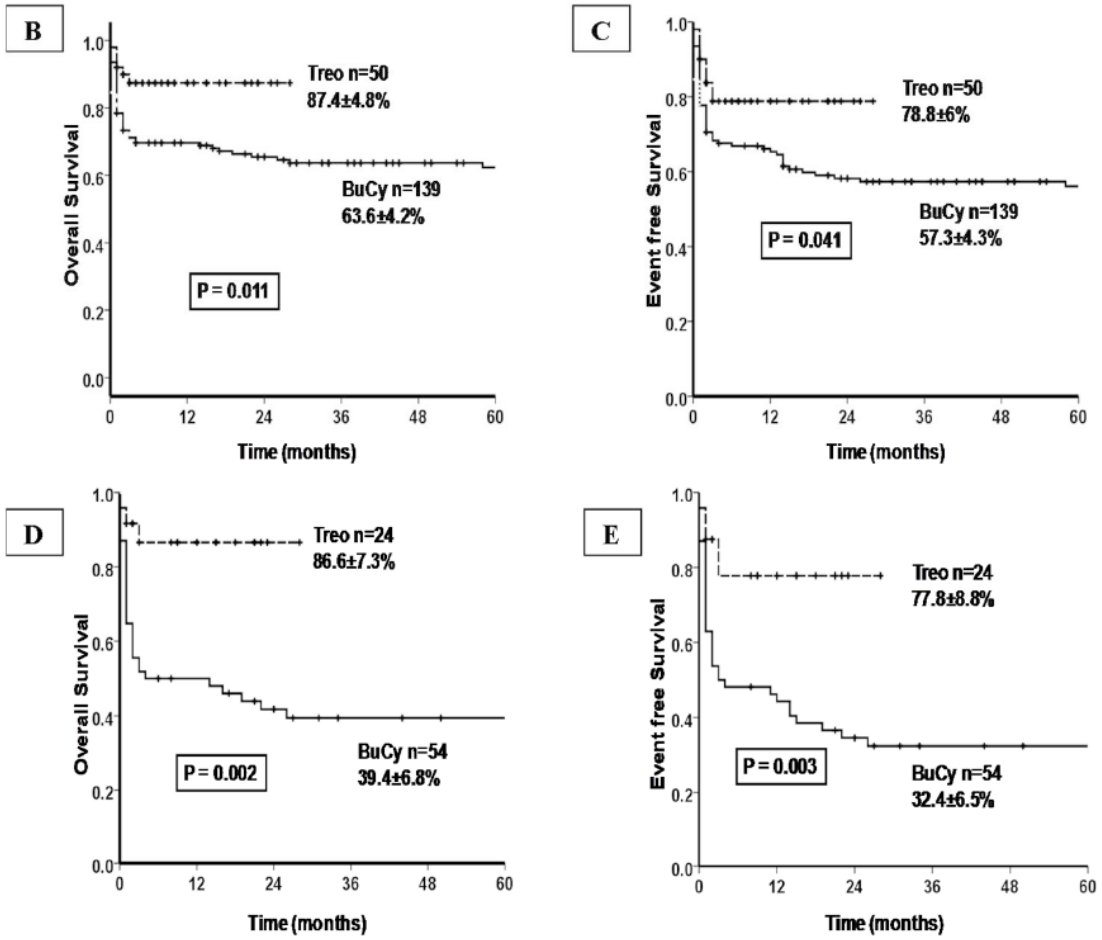


Mitchell Sabloff et al. Blood 2011;117:1745-1750

Conditioning

- Bu-Cy considered standard
- Avoid TBI
- Newer protocols developed using treosulfan demonstrate improved toxicity profile in high risk patients

Treosulfan based conditioning in high risk patients



Matthews et al PloS 1 2013

Alternative donor and graft sources

HLA matched sibling remains preferred donor

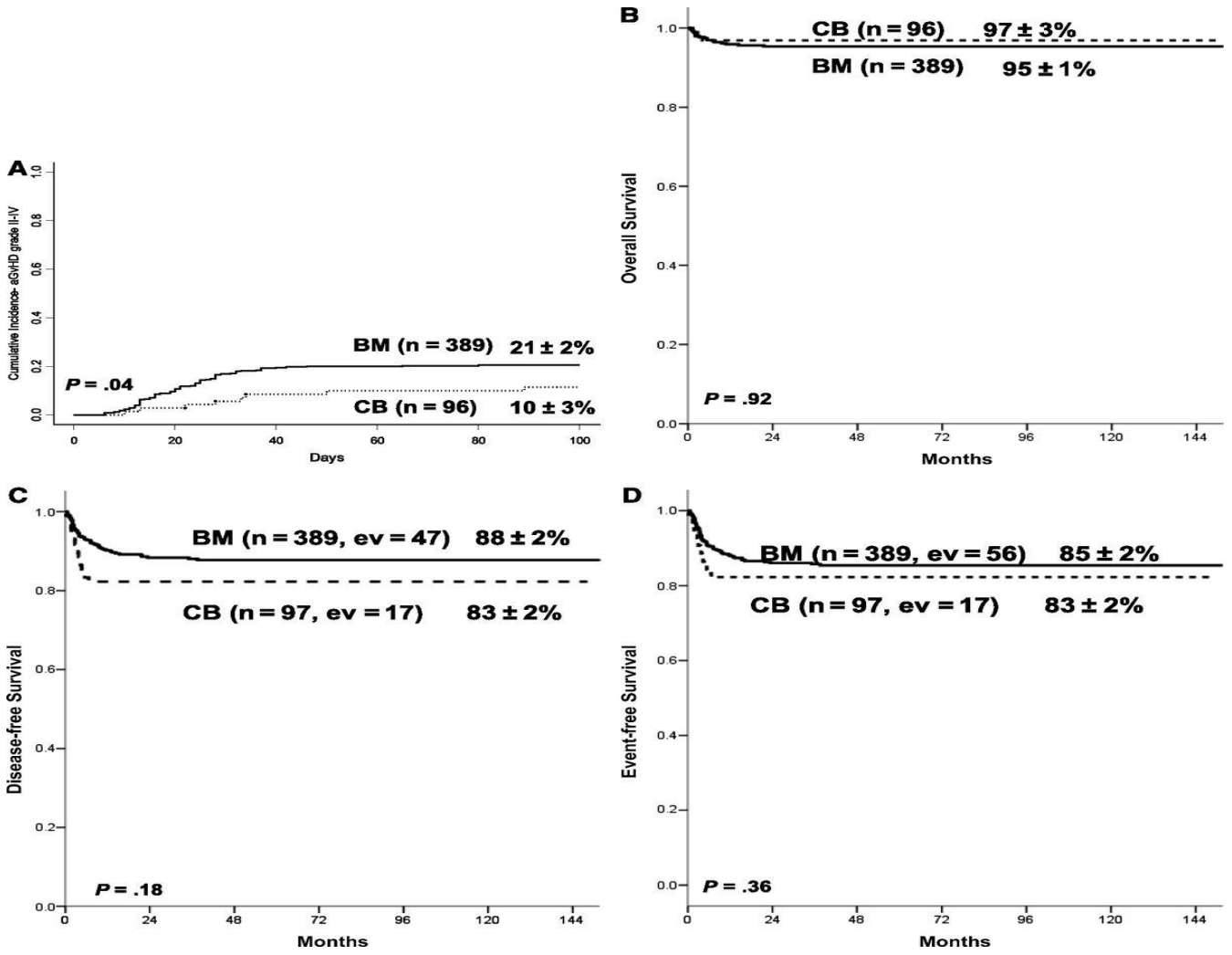
Related cord blood an acceptable alternative

Well matched HLA unrelated donor is second choice

Unrelated cord and haploidentical transplantation considered developmental

BM remains the preferred graft source due to lower risk of GVHD

Cumulative incidence of grade II-IV acute GVHD and Kaplan-Meier estimates of OS, DFS and EFS. (A) Cumulative incidence of grade II-IV acute GVHD (aGVHD) for patients given BM and CB transplantation.

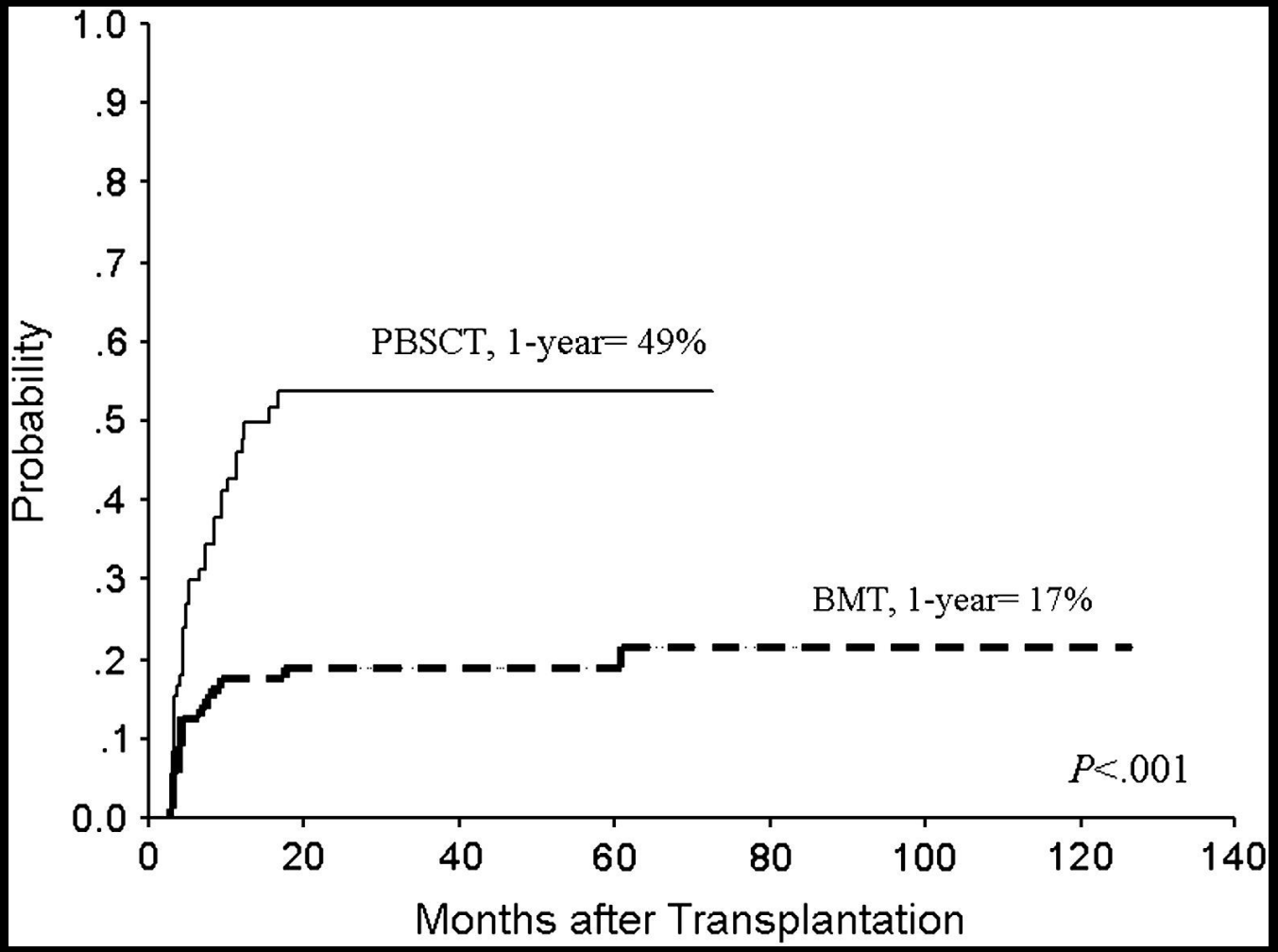


Franco Locatelli et al. Blood 2013;122:1072-1078

PBSC vs BM and GVHD

- 4 studies reported so far
- 3 demonstrate higher GVHD rates with PBSC compared to BM
- 1 demonstrated similar results in a Chinese population
- Current recommendations remain that BM remains preferred graft source

Figure 2



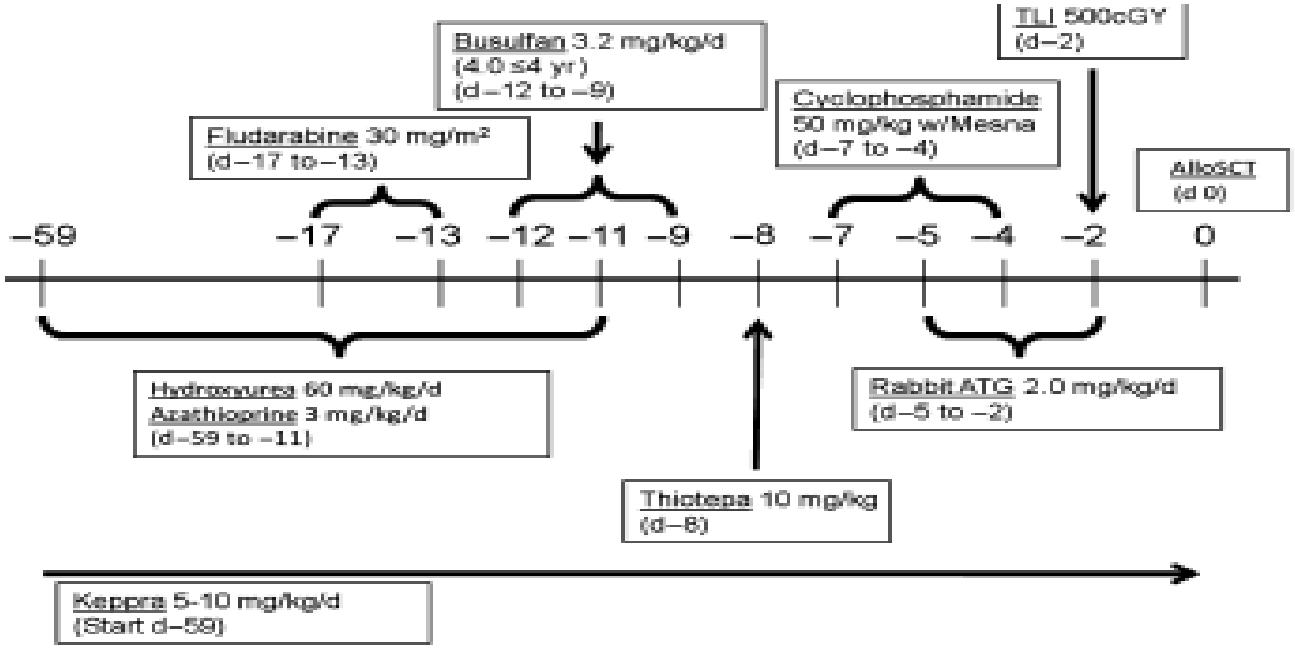
Biology of Blood and Marrow Transplant 2008 14, 301-308DOI: (10.1016/j.bbmt.2007.12.491)

Unrelated cord

- Jaing et al 2012
  - Single centre analysis
  - 35 patients
  - OS 88%, DFS 74%, TRM 11%
  - High CD34 dose (7.8) likely contributed to results
- Ruggeri et al BBMT 2011
  - Combined data from three registries
  - OS 62%
  - Graft failure 51%

Haplo

Limited experience so far

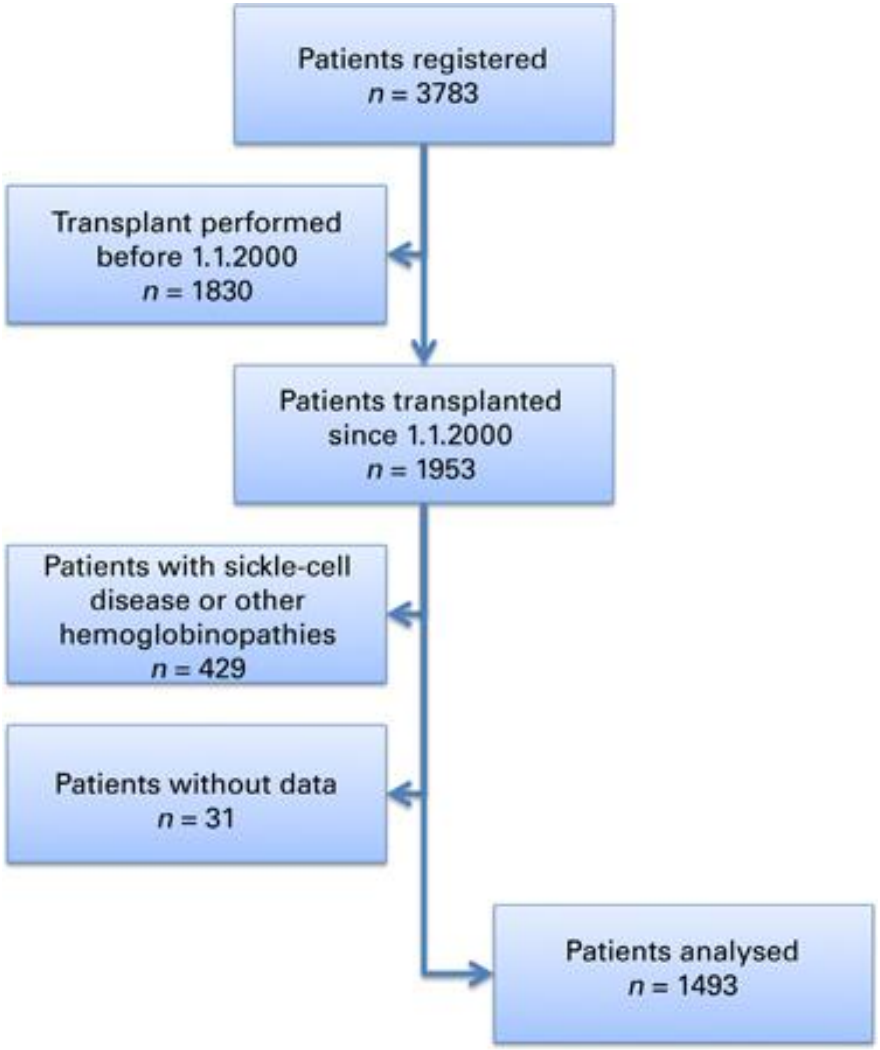


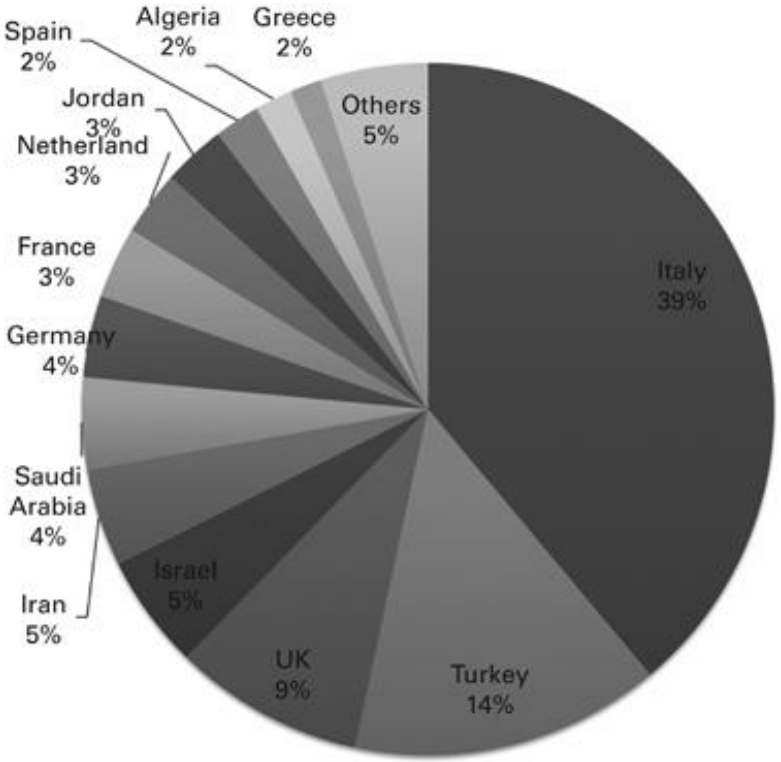
Sodani et al Blood 2010
22 patients
CD34 selection ➔ median dose 14.2x10^6/kg
Controlled CD3 addback
Engraftment in 16 patients with no aGVHD
OS = 90%

What about adults?

- Limited data
- RIC protocols have been associated with poor rates of engraftment
- Current recommendations remain early transplantation for those requiring

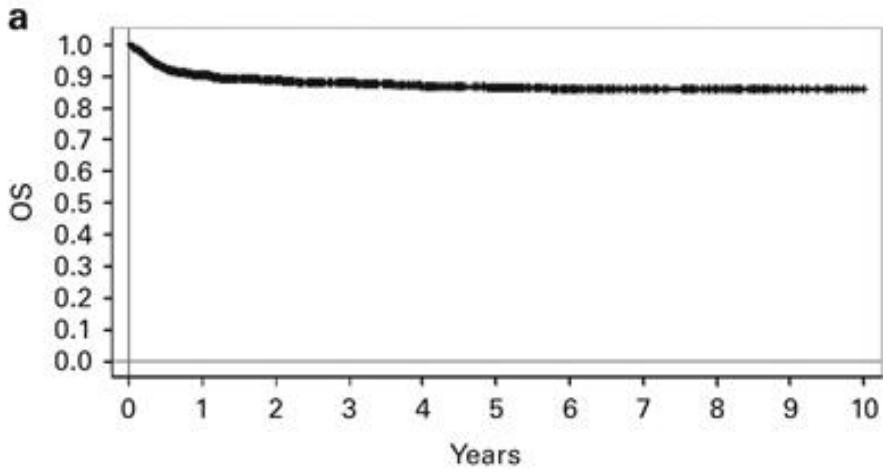
Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000–2010

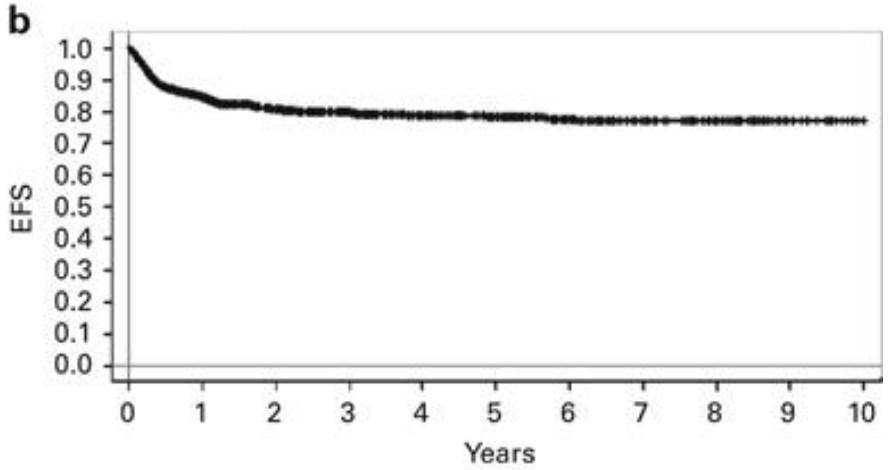




Baronciani et al BMT 2016

Survival rates for 1943 transplants from 2000-2010

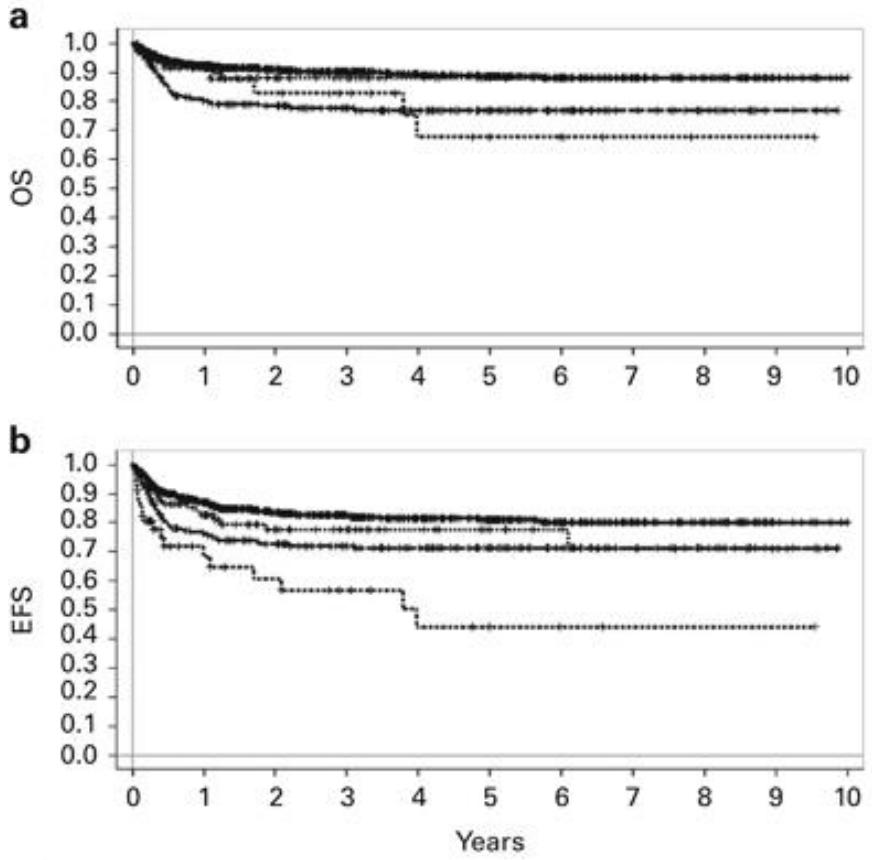




	Patients	Events	*Probability*
A) Overall survival	1493	154	0.88±0.01
B) EFS	1493	253	0.81±0.01

Baronciani et al BMT 2016

OS and EFS by donor

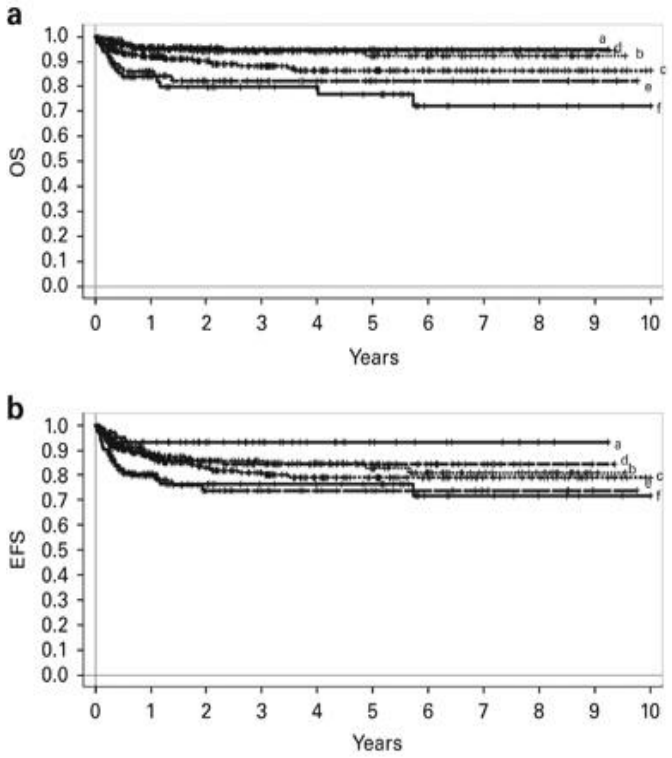


	Patients	A) OS Events	A) OS 2-year OS	B) EFS Events	B) EFS 2-year EFS
a) MSD	1061	88	0.91±0.01	151	0.83±0.01
b) MFD	127	11	0.88±0.04	22	0.78±0.05
c) MMFD	57	8	0.68±0.11	8	0.68±0.11
d) UD	210	43	0.77±0.03	43	0.77±0.03
P-value		<0.001		<0.001	

*donor information missing in 38 cases (2.5%)

Baronciani et al BMT 2016

OS and EFS by age



	Patients	A) OS Events	A) OS 2-yrs. OS	B) EFS Events	B) EFS 2-yrs. pEFS
a) < 2 years	66	3	0.95±0.03	4	0.93±0.03
b) 2-<5 years	266	13	0.94±0.02	32	0.86±0.03
c) 5-<10 years	352	33	0.90±0.02	52	0.83±0.02
d) 10-<14 years	197	8	0.96±0.02	24	0.86±0.03
e) 14-<18 years	97	14	0.82±0.04	20	0.74±0.05
f) ≥18 years	82	16	0.80±0.05	18	0.76±0.05
P-value (for trend)		<0.001		<0.001	

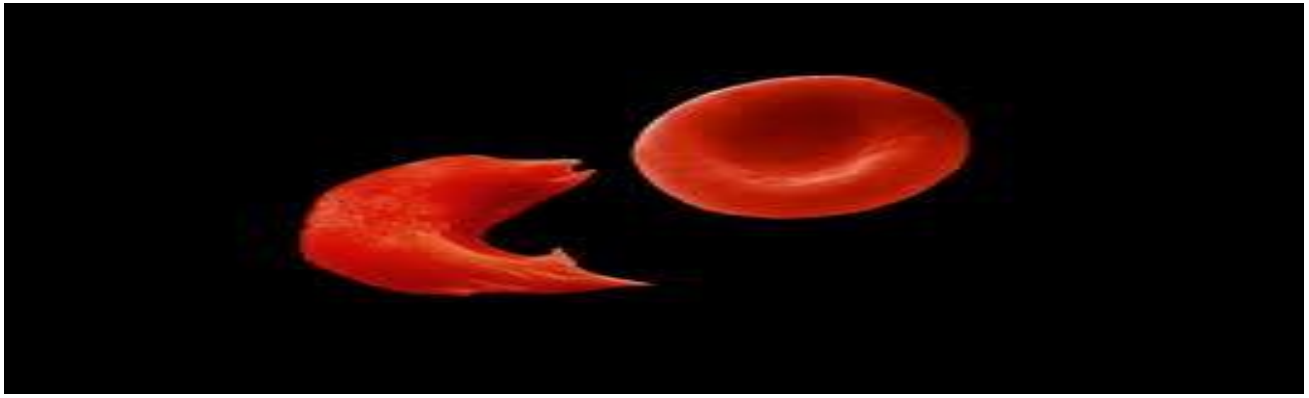
Baronciani et al BMT 2016

blood

2011 118: 1197-1207
doi:10.1182/blood-2011-01-332510 originally published online May 31, 2011

Allogeneic hematopoietic stem cell transplantation for sickle cell disease: the time is now

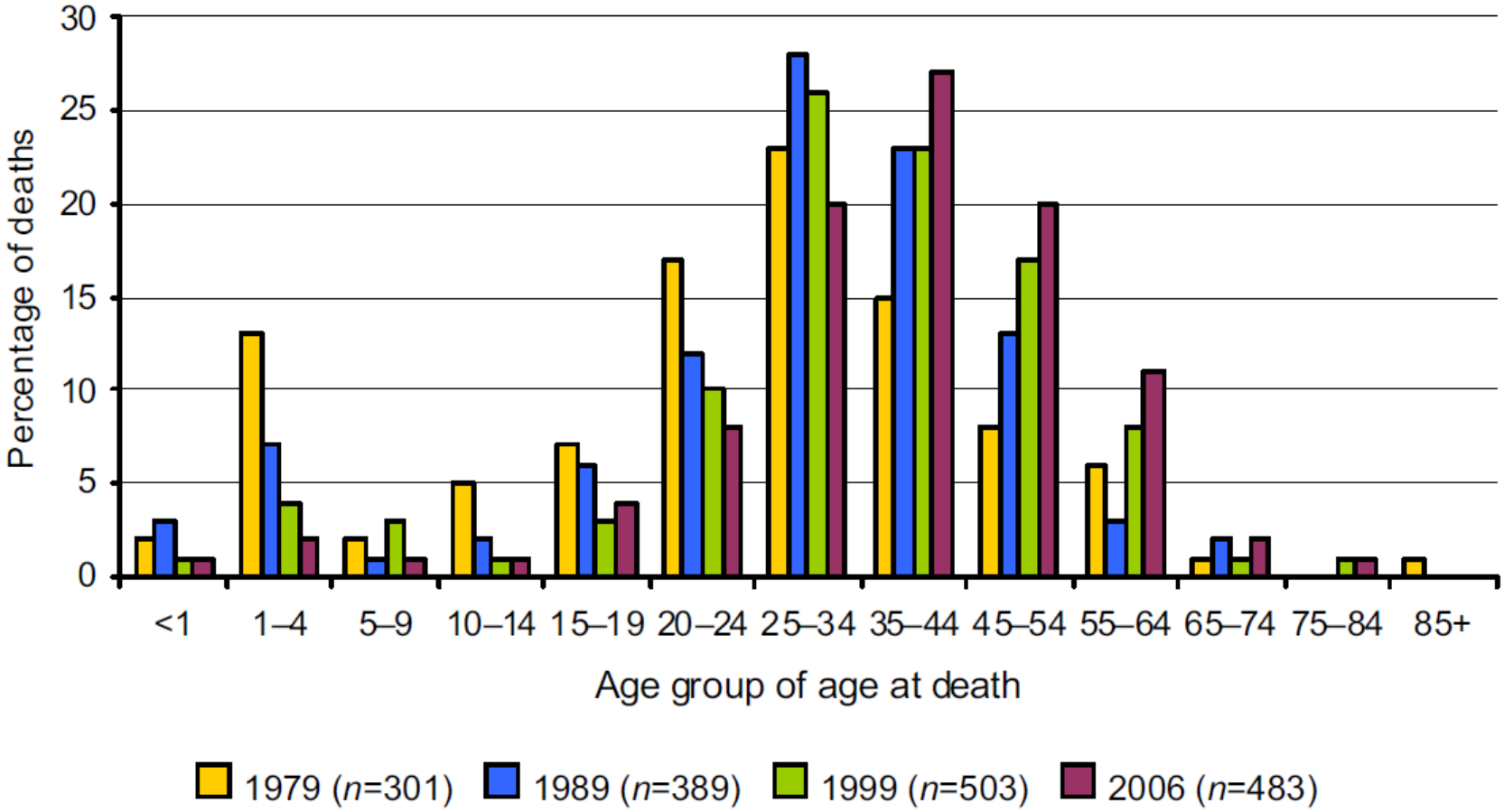
Matthew M. Hsieh, Courtney D. Fitzhugh and John F. Tisdale



Sickle cell disease –why?

- Despite some advances in care and intro of HU life expectancy remains shortened in patients with SCD
- There is no curative therapy
- Significant morbidity occurs in those with SCD related complications
- Resource implications are large

Age at death for individuals with SCD from CDC compressed mortality reports



Hassell, K.L. (2010) AJPM, 38, S512–S521.

Principles for HSCT in Adults

- HSCT is the only curative therapy for SCD
- Advances in transplant conditioning have improved the applicability of this procedure
- RIC protocols are important for adult patients with SCT given accumulated comorbidities
- A state of mixed chimerism indicating tolerance may be desirable
- GVHD has no advantage for non-malignant conditions

Indications for HSCT in SCD

- Patients with sickle cell disease at high risk for disease related morbidity or mortality defined by end organ damage
  - Overt CVA
  - Abnormal TCD on transfusion therapy
  - Pulmonary hypertension
  - Sickle related renal insufficiency
  - Sickle hepatopathy
- Patients with potentially reversible complications not ameliorated by hydroxycarbamide
  - Vaso-occlusive crises and/or acute chest syndrome (>/=1 hospital admission per year while on maximal tolerated dose of hydroxycarbamide)
  - Red cell alloimmunisation (Hb increase <1g/dL while on hydroxycarbamide)
  - Osteonecrosis of mutliple joints (Hb increase <1g/dL while on hydroxycarbamide)

"HSCT Indications remains a fluid paradigm based on the natural history of SCD, newer transplant approaches and changing outcomes"

Table 1. "Stringent" and "extended" indications for HSCT by donor availability based on a positive risk-benefit ratio

Matched sibling donor	MUD or minimally mismatched good quality cord product	Minimally mismatched donor, double cord product, haploidentical donor
Stroke	Stroke	Recurrent stroke despite adequate chronic transfusion therapy
Elevated TCD velocity	Elevated TCD velocity	
Recurrent acute chest syndrome	Recurrent acute chest syndrome despite supportive care	
Recurrent VOC	Recurrent severe VOC despite supportive care	
Pulmonary hypertension	Red cell alloimmunization and hemolysis and established indication for chronic transfusion therapy	
Tricuspid regurgitation	Pulmonary hypertension	
Osteonecrosis/AVN		
Red cell alloimmunization		
Silent stroke especially with cognitive impairment		
Recurrent priapism		
Sickle nephropathy		

Shenoy S Ther Adv Hematol. Oct 2013; 4(5): 335–344

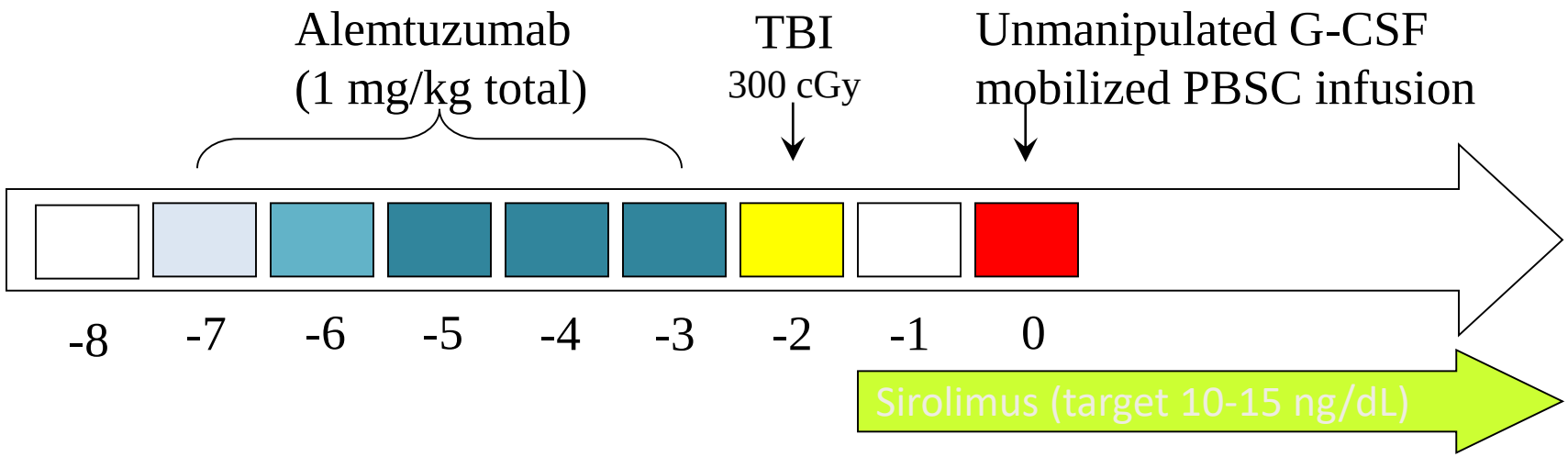
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 10, 2009 VOL. 361 NO. 24

Allogeneic Hematopoietic Stem-Cell Transplantation for Sickle Cell Disease

Matthew M. Hsieh, M.D., Elizabeth M. Kang, M.D., Courtney D. Fitzhugh, M.D., M. Beth Link, R.N., Charles D. Bolan, M.D., Roger Kurlander, M.D., Richard W. Childs, M.D., Griffin P. Rodgers, M.D., Jonathan D. Powell, M.D., Ph.D., and John F. Tisdale, M.D.

NIH protocol 03-H-0170
non-myeloablative stem cell transplant



- Hydroxyurea is continued through day -8
- Red cell exchange to lower HbS ~ 30%
- Platelet transfusion threshold is 50k/uL (to prevent CNS bleeding)
- Taper immunosuppression planned at 1 year post transplant, if CD3 donor chimerism is >50%

Hsieh et al. N Engl J Med 2009;361:2309-17.

Table 1. Characteristics of 10 Patients Undergoing Nonmyeloablative Hematopoietic Stem-Cell Transplantation (HSCT).*

Patient No.	Age at HSCT	Sex	Type of Sickle Hemoglobin	Coexisting Conditions and Indications for HSCT	Medical Management before HSCT
	yr				
1	24	F	SS	Recurrent TIA and stroke, elevated TRV	Simple and exchange red-cell transfusions
2	27	M	SS	Frequent VOC, priapism, proteinuria (1.7 g/24 hr)	Hydroxyurea, simple and exchange red-cell transfusions
3	21	F	SS	TIA, frequent VOC, acute chest syndrome	Hydroxyurea, exchange red-cell transfusions
4	16	M	SS	Frequent VOC, acute chest syndrome, narrow CNS arteries on MRA	Hydroxyurea, exchange red-cell transfusions
5	21	M	SS	Frequent VOC, acute chest syndrome	Hydroxyurea
6	40	M	SC	Frequent VOC, priapism, narrow CNS arteries on MRA, lacunar infarcts	Hydroxyurea
7	26	F	SS	Frequent VOC, elevated TRV	Hydroxyurea
8	26	F	SS	Frequent VOC, elevated TRV	Hydroxyurea and simple red-cell transfusions
9	45	F	SS	Sickle-cell–related FSGS (baseline creatinine, 2.5–2.7 mg/dl [221–239 μmol/liter]), elevated TRV, acute chest syndrome, frequent VOC, red-cell alloimmunization, hepatitis C	Hydroxyurea, simple and exchange red-cell transfusions, darbepoetin
10	26	M	SS	Sickle-cell–related nephrotic syndrome, elevated TRV, acute chest syndrome	Hydroxyurea, simple red-cell transfusions, prednisone

Hsieh MM et al. N Engl J Med 2009;361:2309-2317.

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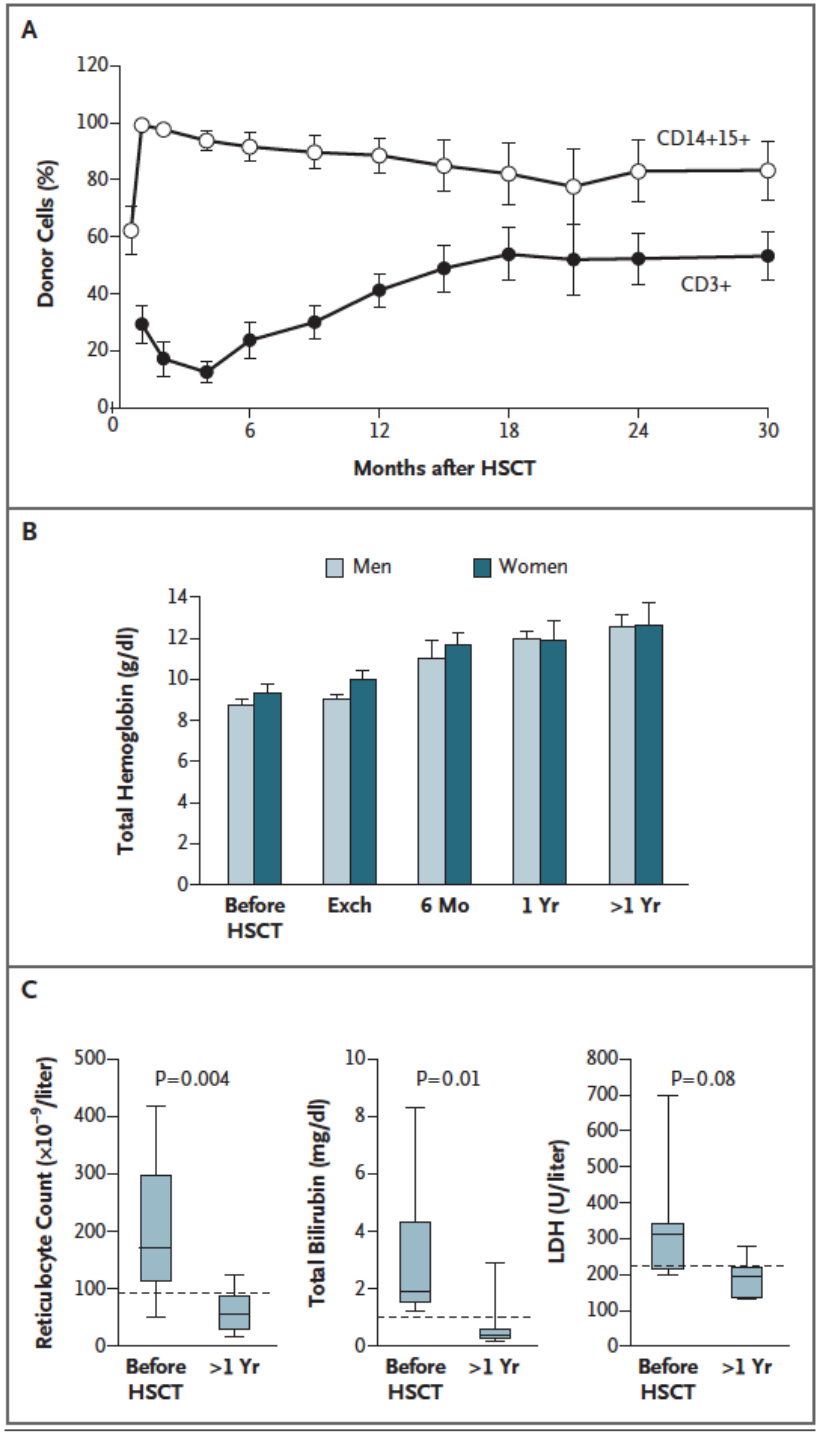
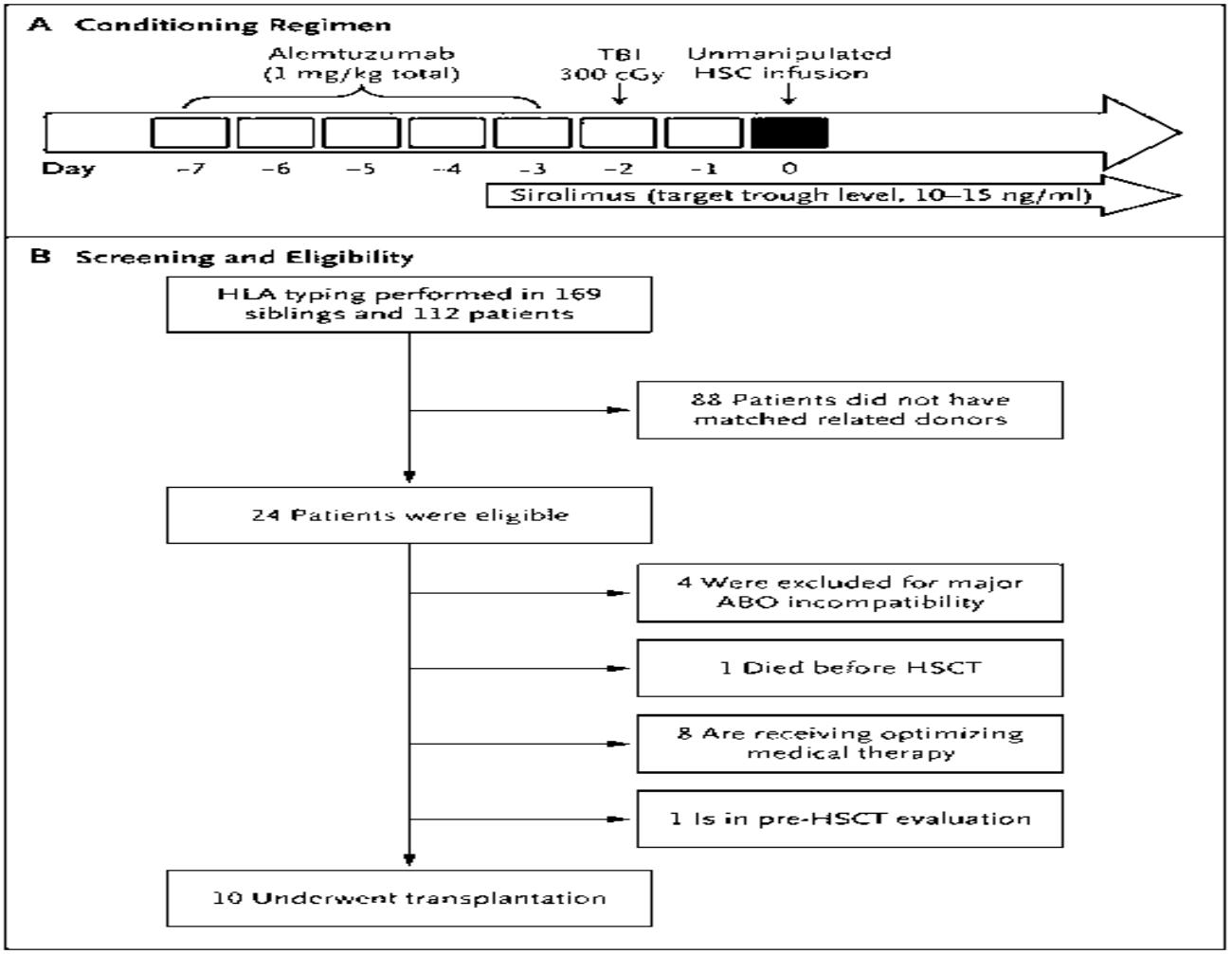


Conditioning Regimen and Screening of Patients.



Hsieh MM et al. N Engl J Med 2009;361:2309-2317.

Results updated JAMA July 2014

Original Investigation

Nonmyeloablative HLA-Matched Sibling Allogeneic Hematopoietic Stem Cell Transplantation for Severe Sickle Cell Phenotype

Matthew M. Hsieh, MD; Courtney D. Fitzhugh, MD; R. Patrick Weitzel, PhD; Mary E. Link, BSN; Wynona A. Coles, MPH; Xiongce Zhao, PhD; Griffin P. Rodgers, MD; Jonathan D. Powell, MD; John F. Tisdale, MD

Patients

Characteristics	No. (%) of Patients
Age at transplant, y	
Median (range)	28.5 (17-65)
No.	
≤20	3 (10)
21-30	14 (47)
31-40	6 (20)
≥41	7 (23)
Men	16 (53)
Women	14 (47)

Indications for HSCT

Vaso-occlusive crisis	23 (77)
Tricuspid regurgitant jet velocity, m/s	13 (43)
2.6 to 2.9	8 (27)
≥3.0	5 (17)
CNS disease	9 (30)
Stroke or silent infarct	5 (17)
Stenotic or irregular arteries	2 (7)
TIA	1 (3)
Moya moya	1 (3)
Acute chest syndrome, No. (%)	7 (23)
Avascular necrosis ≥2 joints	7 (23)
Sickle nephropathy, serum creatinine ≥1.3 mg/dL	4 (13)

Results

- 29 patients alive
  - One patient died from ICH after relapsed SCD (previous stroke and moya moya)
- 87% long-term engraftment
- 4 initial engraftment then rejection with reversion to SCD phenotype
- Stable mixed chimerism
  - Myeloid 86%, lymphoid 43%
- NO GVHD
- G-CSF used in donors with sickle cell trait with no additional consequences

Results

- Hb levels improved
- Markers of haemolysis improved
- TRV improved
- Opiate use decreased
- No further MRI progression
- No progression of renal disease
- Two females and two males have conceived naturally after transplant

But most patients do not have a sibling!

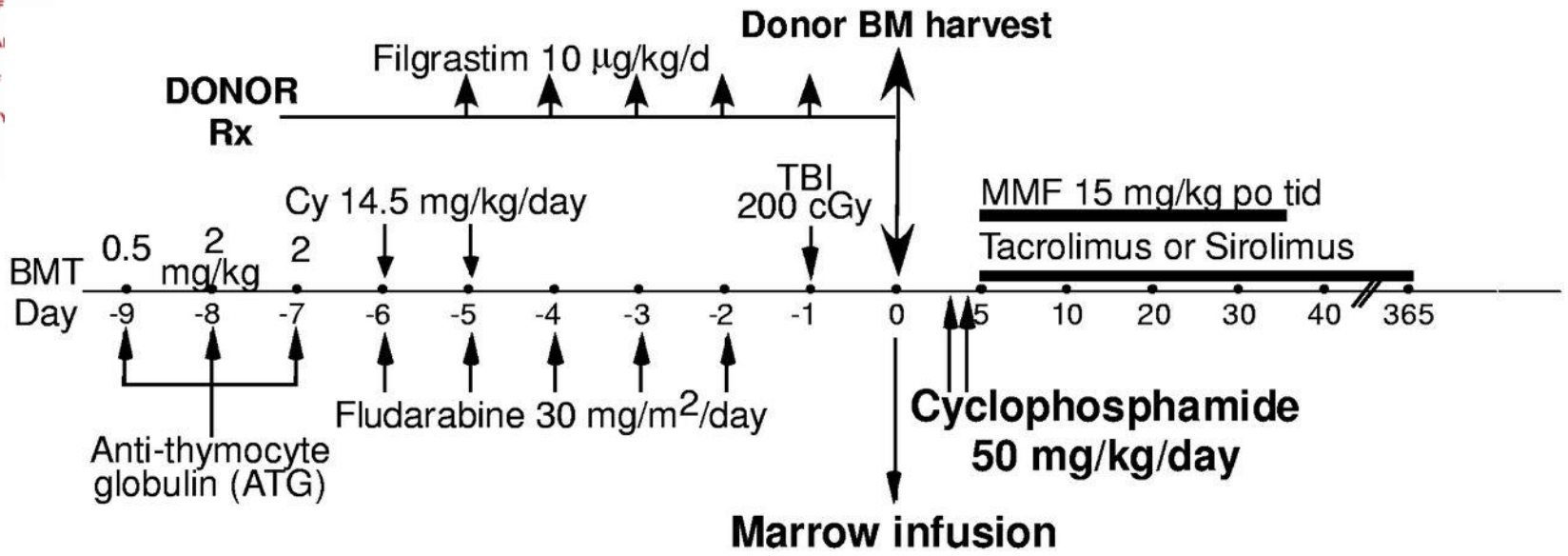
HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease

Javier Bolaños-Meade,[1] Ephraim J. Fuchs,[1] Leo Luznik,[1] Sophie M. Lanzkron,[2] Christopher J. Gamper,[3] Richard J. Jones,[1] and Robert A. Brodsky[1,2]

[1]Hematologic Malignancies and Bone Marrow Transplantation Program, Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and Johns Hopkins University School of Medicine, Baltimore, MD; [2]Division of Hematology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; and [3]Division of Pediatric Oncology, Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and Johns Hopkins University School of Medicine, Baltimore, MD

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

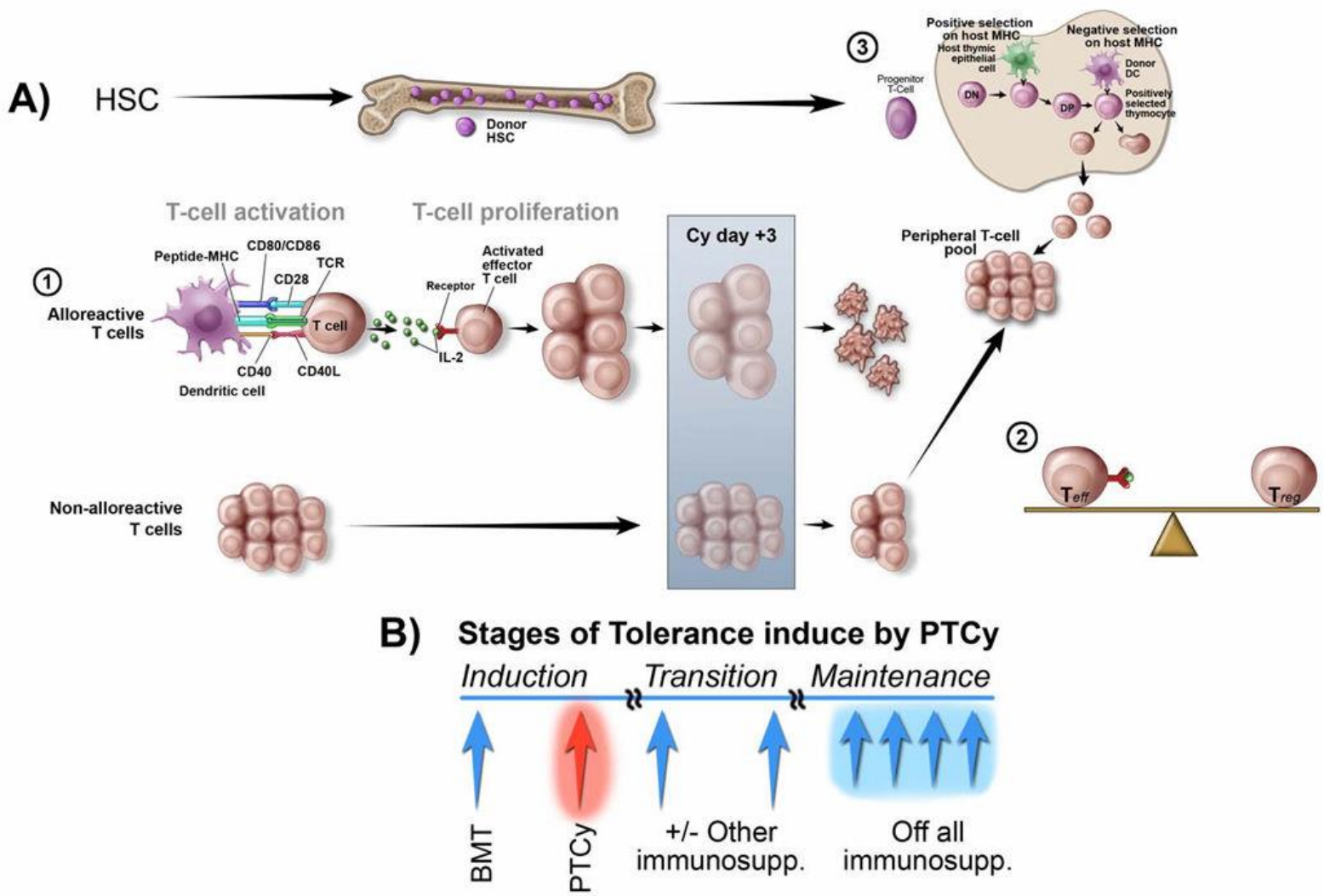
Conditioning protocol



-First 2 pts were transplanted w/o ATG
-Sirolimus replaced tacrolimus w/ 11 pt to reduce the incidence of PRES

Bolaños-Meade J et al. Blood 2012;120:4285-4291

Mechanism of tolerance induction by high dose cytoxan



Leo Luznik, Paul O'Donnell and Ephraim Fuchs, Semin Oncol. 2012

Outcomes data

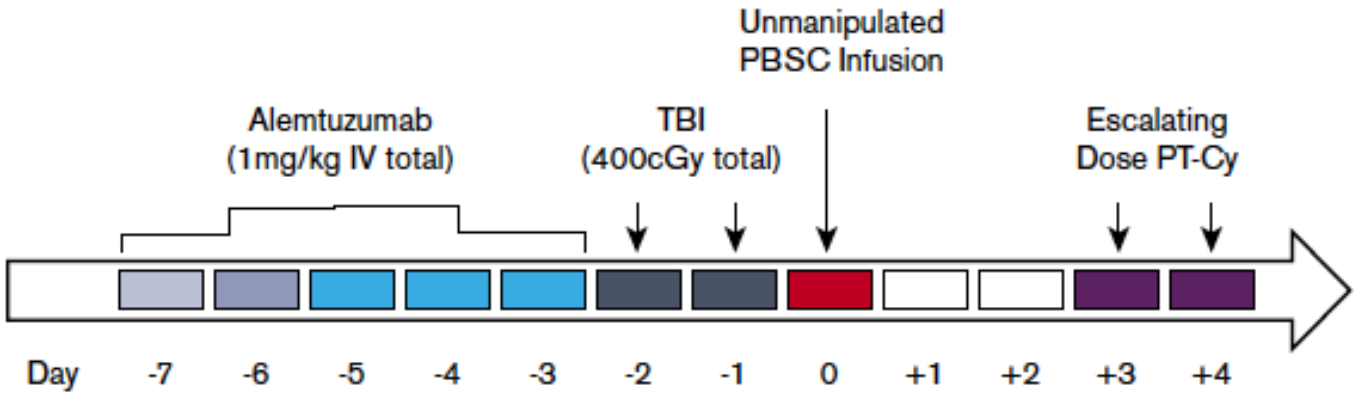
- 19 patients screened, 17/19 were transplanted (89%)
- Eleven patients engrafted durably.
- After median follow-up of 711 days (minimal follow up 224 days), 10 patients are asymptomatic, and 6 patients are off immunosupression.
- Only 1 patient developed skin-only acute GVHD that resolved without any therapy
- No mortality
- **THE PROBLEM → GRAFT FAILURE 43%**

Bolaños-Meade J et al. Blood 2012;120:4285-4291

Protocol updated –ASH 2016

- Thiotepa added to protocol
- Initial engraftment in 100%
- Subsequent graft failure 9.1%
- Overall survival 91%
- TRM around 10%
- Results to be confirmed in BMT CTN study planned for 2017.

The NIH haplo protocol



Cohort Number	Cyclophosphamide Dose (mg/kg/dose)	Day Post-Transplant	Cumulative Cyclophosphamide Dose (mg/kg)	Sirolimus Start Day Post-Transplant
1	0	N/A	0	-1
2	50	+3	50	-1 or +4
3	50 50	+3 +4	100	+5

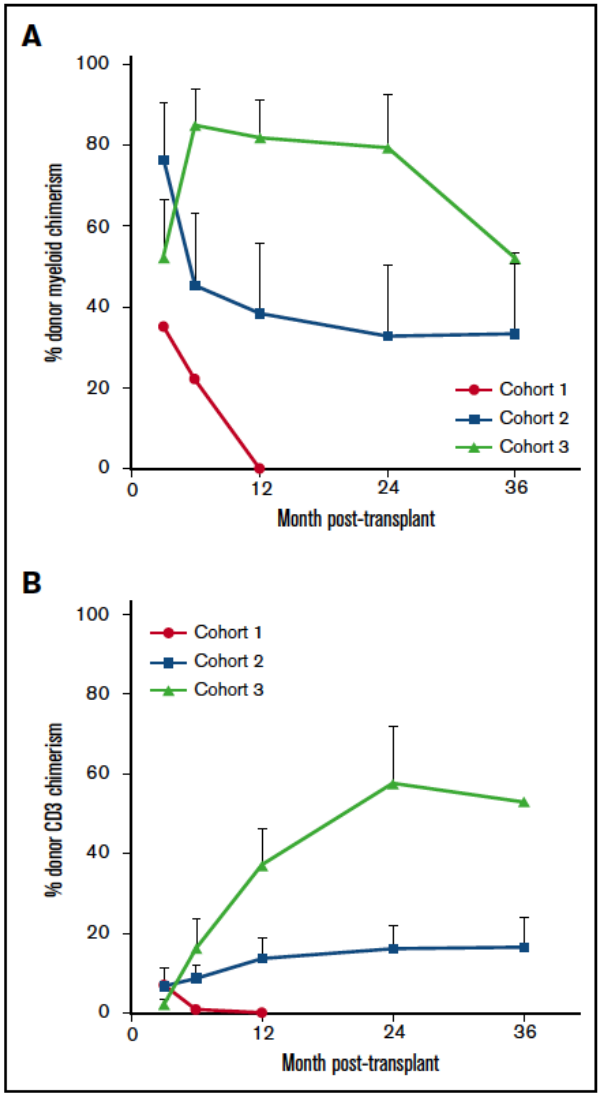
Fitzhugh et al Blood Advances 2017

Engraftment improves with increased dose cyclophosphamide

Cohort	Cumulative cyclophosphamide dose (mg/kg)	Engraftment rate (before day +100)		Disease-free survival	
		No.	%	No.	%
1	0	1/3	33	0/3	0
2	50	5/8	63	2/8	25
3	100	10/12	83	6/12	50

Fitzhugh et al Blood Advances 2017

Chimerism levels and GVHD



GVHD: only two out of 23 patients developed GVHD, 1 grade 1 acute and 1 limited chronic GVHD

Twenty of 23 patients are alive with NO transplant related mortality ➔ OS 87%

Fitzhugh et al Blood Advances 2017

Difference between thalassaemia and sickle cell HSCT

	Thalassemia	Sickle cell disease
Prognostic criteria for disease severity	Homogenous pattern for β thalassemia major	Wide genetic variability; inconsistent development of complications
Currently accepted indication for allogeneic HSCT	Transfusion dependency. For patients with an HLA identical sibling donor or well-matched related or unrelated donor: as soon as possible to avoid transfusion associated complications	Patient with matched sibling donor and complication requiring treatment with hydroxurea or transfusion
Total number of HSCT reported	> 3000 patients transplanted	500-600 patients transplanted
Risk factors for transplant-related complications	Age, organ dysfunction due to iron overload	Age, history of cerebral events
Alternative effective medical therapy	Life-long transfusion with chelation	Hydroxyurea: not curative, but ameliorates some complications. Chronic transfusion and chelation therapy.
Key issue for transplant outcome	Control of iron overload and related tissue damage	Cure from chronic inflammation and prevention of future SCD-related organ damage
Conditioning regimen	Needs to ablate an expanded bone marrow	Reduced intensity regimens seem to induce stable chimerism and full donor erythropoiesis

Angelucci et al 2014 Haematologica. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel

haematologica
the hematology journal

Conclusions

- HSCT is an important therapeutic option for patients with SCD and TM
- Current protocols result in high rates of overall survival
- Newer approaches such as RIC HSCT appear promising in adults with SCT
- State of mixed chimerism indicating tolerance may be desirable