

# Hematopoietic Stem Cell Transplant for Sickle Cell Anemia: *The changing landscape*

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# Outline of presentation

- Background
  - Improved childhood survival
  - High rate of neurological morbidity in children
  - Continued high mortality in adults
- Hematopoietic stem cell transplant approaches
  - Matched related donor approach
  - Alternative donor HSCT for severe SCD
- Special considerations in low income countries
- Conclusion

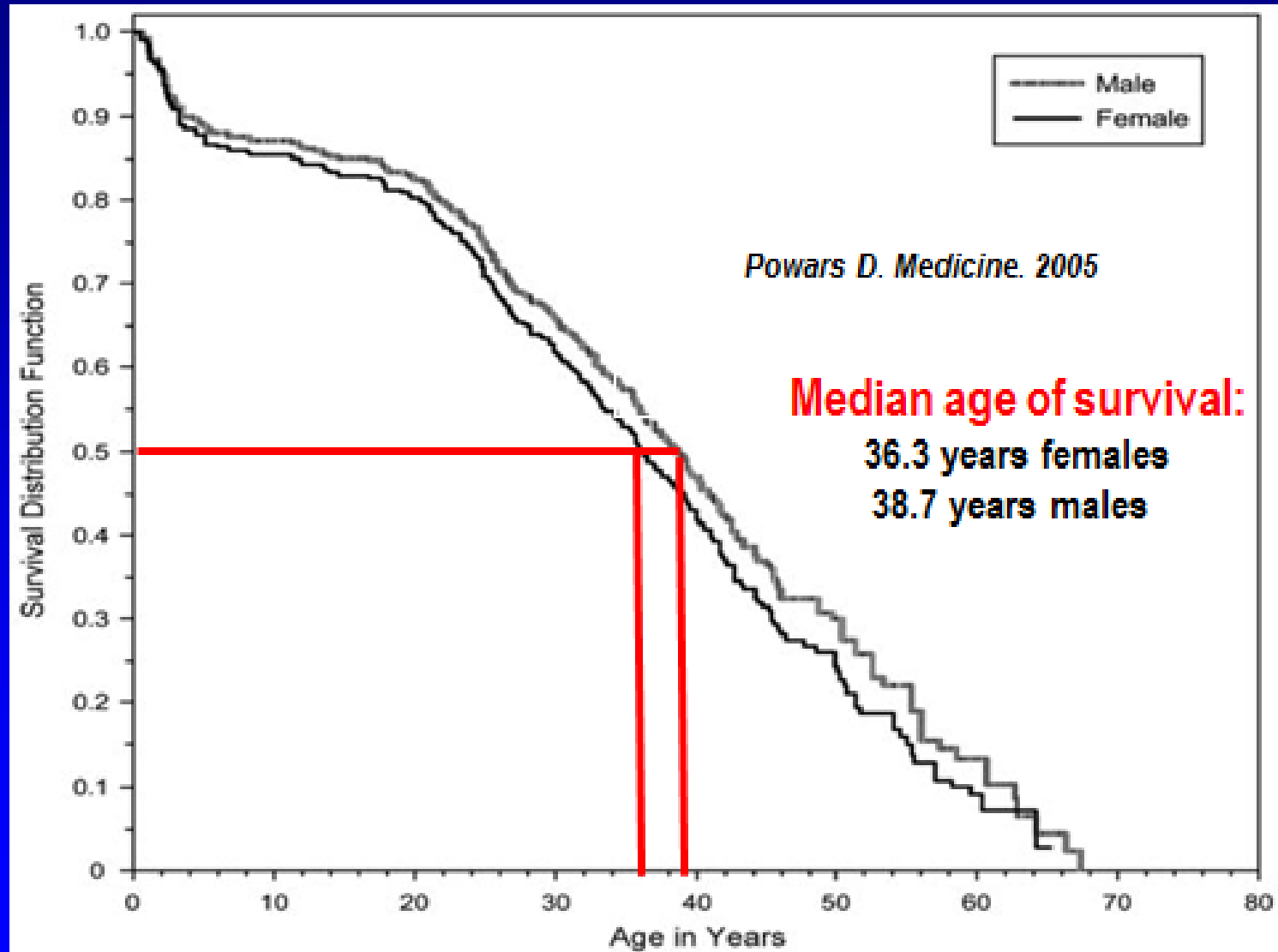
**No disclosures**

# Last 40 years: change in the natural history of sickle cell disease in children

- Paradigm shift from an early life threatening condition to chronic disease with life threatening episodes
- Effective therapies that decreased mortality:
  - Daily penicillin prophylaxis
  - Conjugated PCV 13 and Hib vaccines in childhood
  - Hydroxyurea therapy
  - Chronic blood transfusion therapy
    - >98% living to adulthood
- Presently, most debilitating complications are strokes
  - 2% to 5% of children have overt strokes
  - 35% will have silent strokes

# Still early death in adults

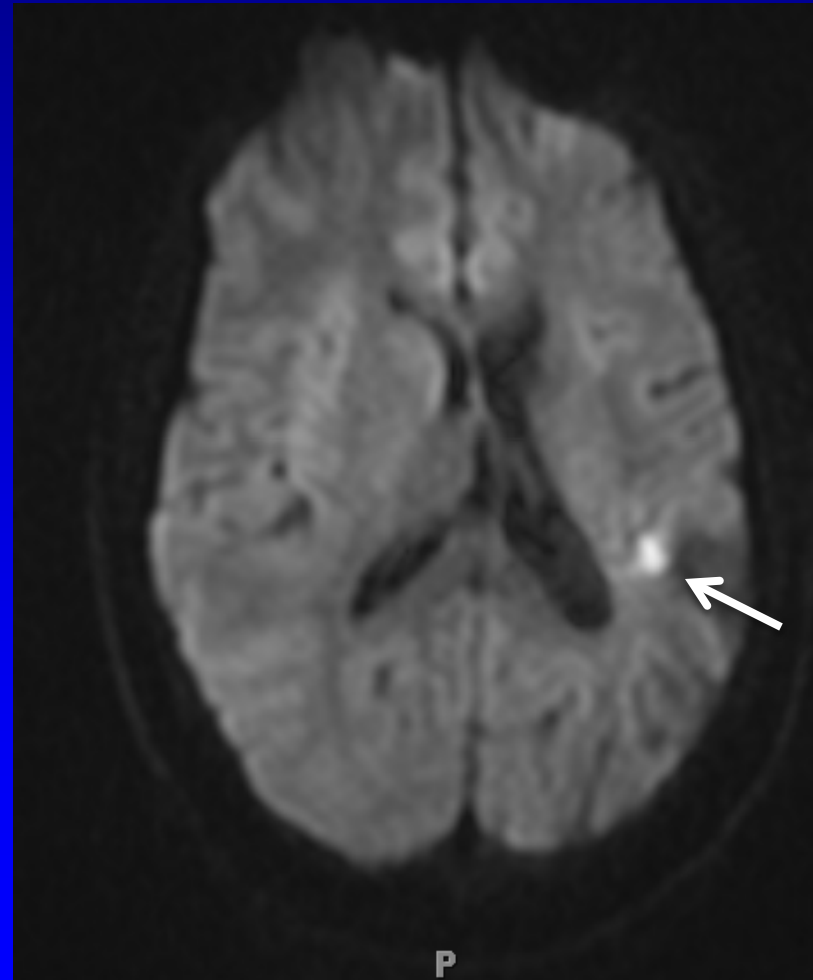
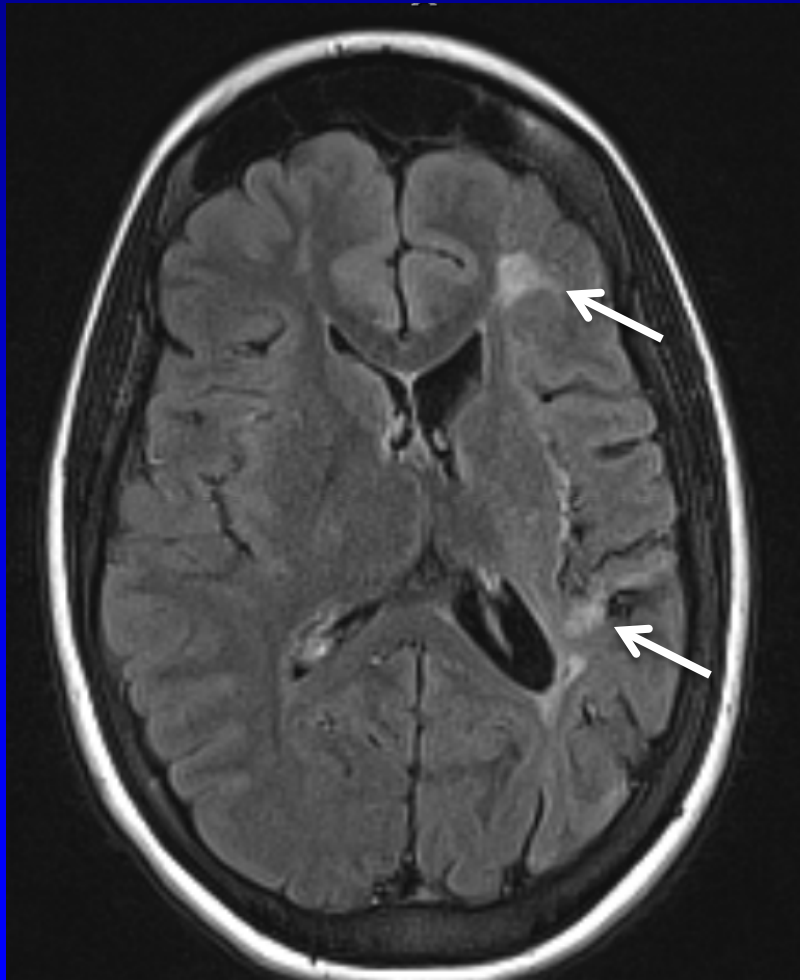
4 decade observational study: 1056 patients at USC, LA



# Case 1

- 15 year old AAF with SCD, HbSS
  - Started on hydroxyurea for recurrent vaso-occlusive pain episodes and acute chest syndrome at age 6
  - Switched to exchange transfusion at age 12 after an overt stroke, with HbS consistently 25-30%.
  - Follow-up MRA showed progressive vasculopathy
  - Presented with right sided weakness and aphasia 2nd to ischemic stroke, one day after transfusion
  - Acute silent cerebral infarct (SCI) on repeat MRI

# FLAIR and DWI MRI in Case 1



# What would be your next management strategy for the case?

- A. Continue current exchange transfusion
- B. Restart hydroxyurea at 15-35 mg/kg/day
- C. Consider for Hematopoietic stem cell transplant to prevent progressive end organ damage

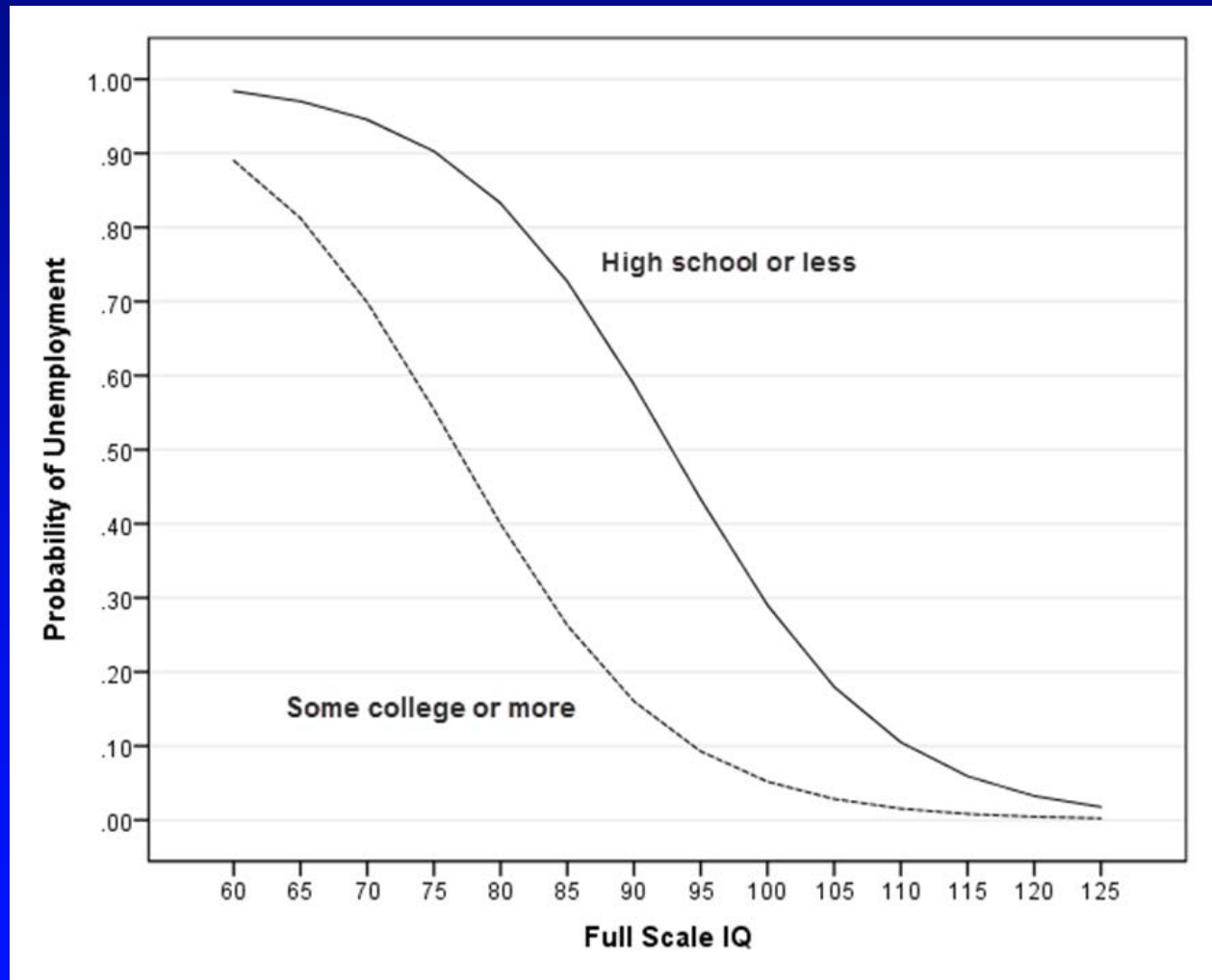
# **Rationale for case 1**



# Consequence of stroke in SCD

- High recurrence rate (progressive)
- Motor, speech, sensory impairment
- Cognitive impairment
- Excessive iron stores secondary to transfusions
  - Burden of chelation due to transfusion therapy
- Death

# Probability of unemployment in unselected adults with SCA given their full scale IQ scores and level of education



# Prospective single arm transfusion trial demonstrates infarct recurrence

- 7 centers, 40 children with strokes
- Mean pre-transfusion Hb S concentration <30%
- Over the course of 5 years, progressive cerebral infarcts occurred in 45% (18 of 40)
  - 7 had second overt strokes with HbS levels of: 10%, 17%, 21%, 28%, 38%, and 48%.
  - 11 had silent cerebral infarcts

# **Blood transfusion therapy decreases, but does not eliminate recurrence of silent cerebral infarcts (SCI)**

- Risk of infarct recurrence and TIA for untreated silent cerebral infarct
  - 5.6 events per 100 patient years
- Risk of infarct recurrence when treated with regular blood transfusion therapy for silent cerebral infarct
  - 2 events per 100 patient years
- Risk of stroke with atrial fibrillation without warfarin treatment
  - 4.4 events per 100 patient years

(JAMA. 2001;285(22):2864-2870)

**Currently, blood transfusion therapy is palliative for secondary prevention of**

–overt strokes

–silent strokes

# Case 2

- 45 year old AAM with SCD, HbS $\beta^0$
- Disease complicated by:
  - Recurrent vaso-occlusive pain episodes
  - Recurrent leg ulcers
  - Disease modifying therapy switched from hydroxyurea to chronic partial exchange transfusion
  - Transfusional iron overload

## Case 2, contd

- Chronic multi-organ system complications
  - CNS disease: old micro infarcts and hemorrhage on MRI
  - Tricuspid regurgitant jet velocity: 3.68-4.51 m/sec  
(6 – min walk test ~62% predicted)
  - Pulmonary function:  
FEV1 65% FEV1/FVC 99% DLCO 45% (moderate restrictive and severe diffusion defect)
  - Chronic renal insufficiency

# What would be your next management strategy for this case?

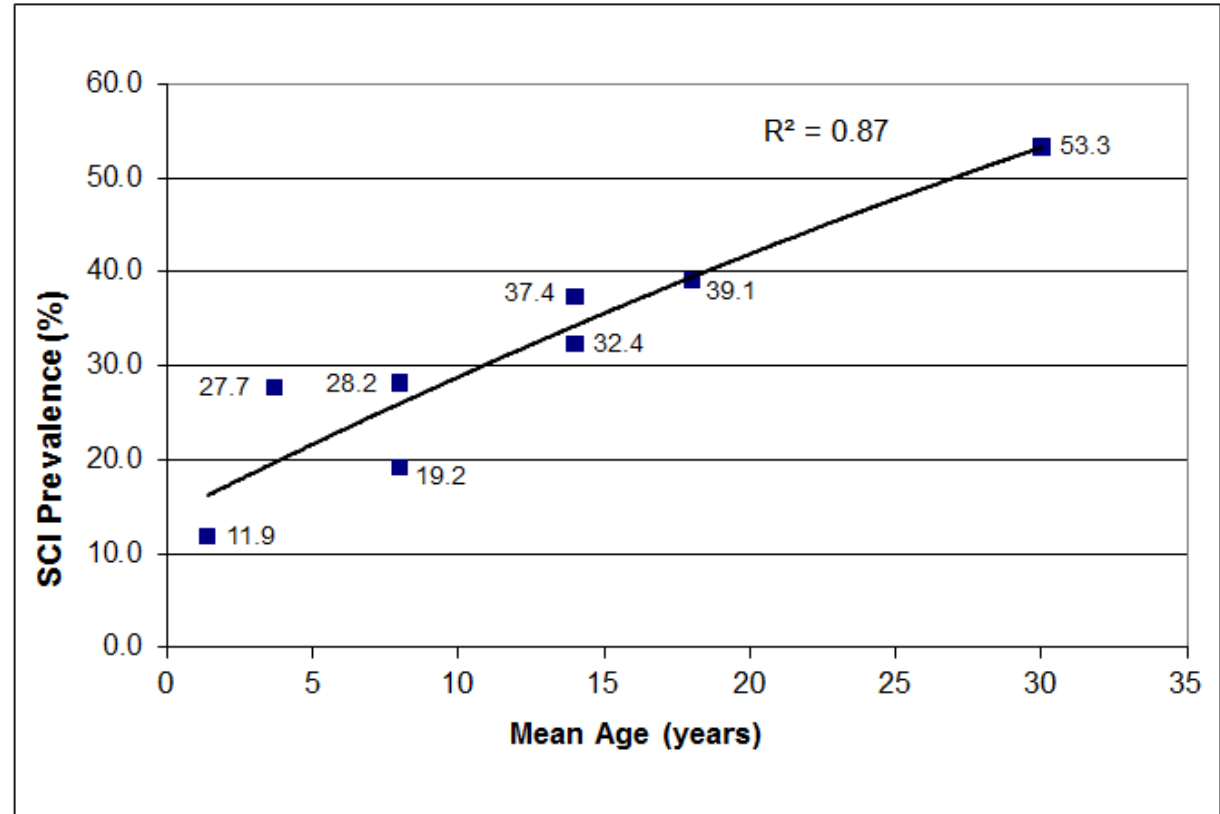
- A. Continue chronic transfusion therapy
- B. Start hydroxyurea at 15-35 mg/kg/day
- C. Consider hematopoietic stem cell transplant to prevent progressive end organ damage



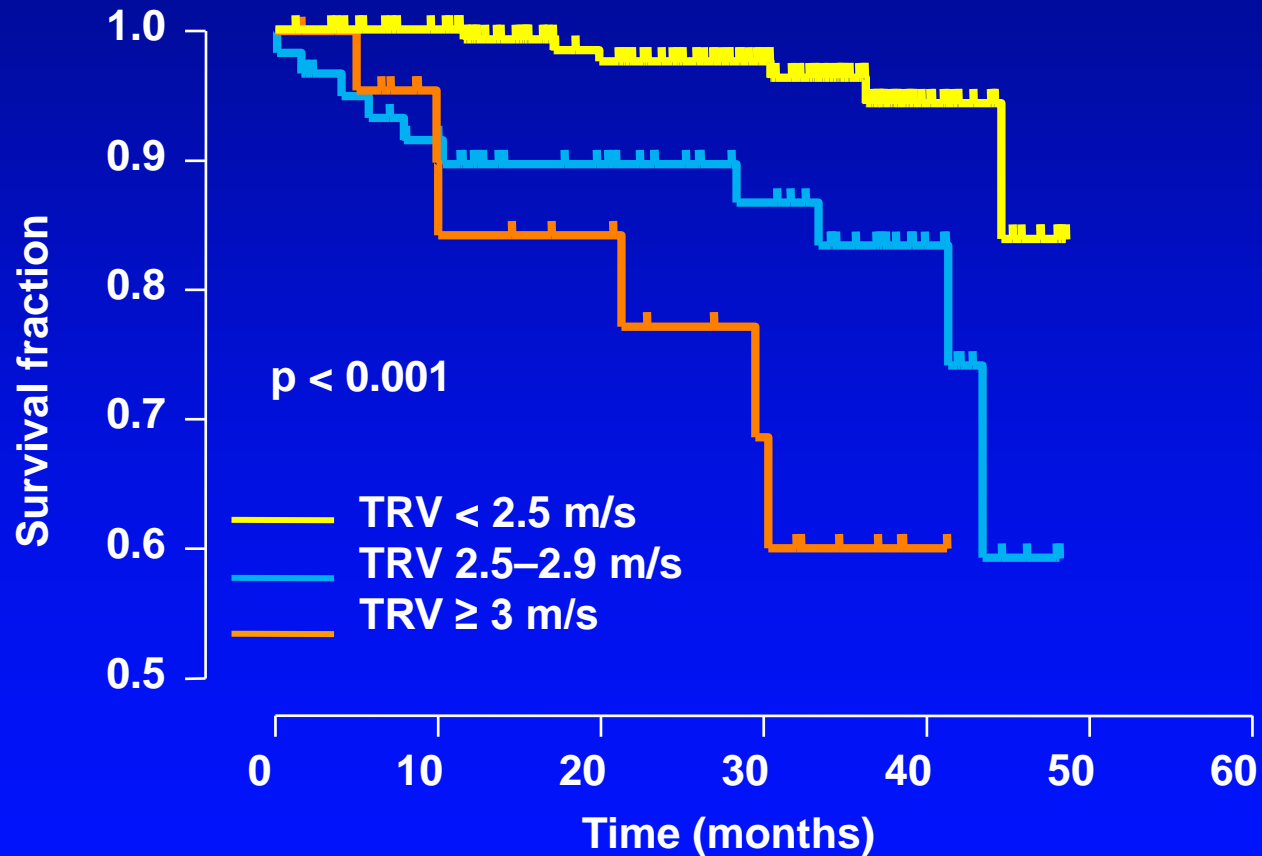
# **Rationale for case 2**

# Over 50% of the adults with sickle cell anemia have silent cerebral infarcts

The cumulative prevalence of SCI suggests that the incidence of SCI does not plateau in young adulthood to at least 30 years of age.

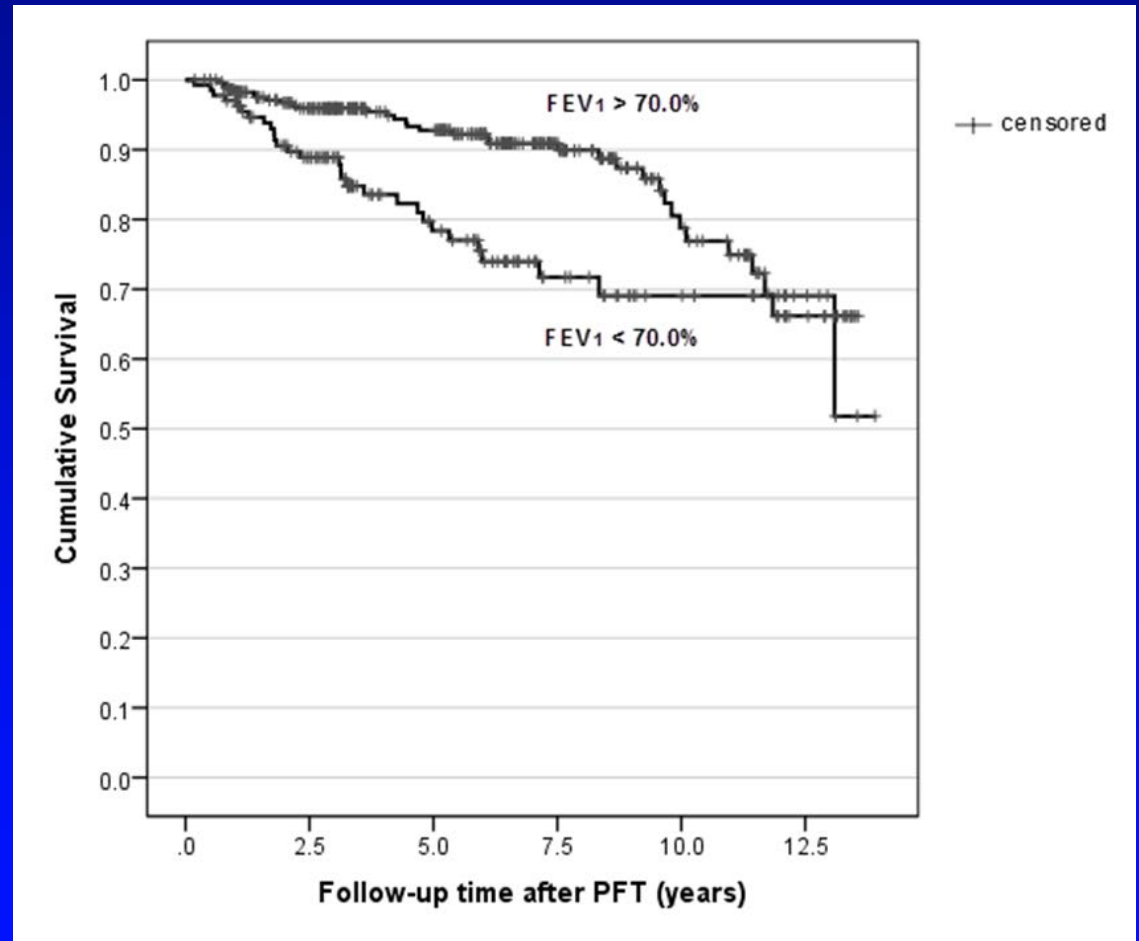


# A tricuspid regurgitant jet velocity of $\geq 2.5$ m/s is associated with an increased risk of death in adults with SCD



# Low forced expiratory volume is associated with earlier death in sickle cell anemia

Kaplan-Meier survival curves stratified by FEV1 above and below 70% predicted in 430 adults with sickle cell anemia followed for a median of 5.5 years ( $p = 0.002$ ; Log rank test).



# Summary of background

- **Sickle Cell Disease causes**
  - Progressive infarct recurrence in children with both overt and silent strokes despite best medical management strategies (RBC tx)
  - Early death in adults
- **Successful HSCT may be an alternative to**
  - Lifelong blood transfusion therapy for children with pre-existing cerebral infarcts
  - Medical management of sickle cell disease in adults with a high mortality rate

# HLA-matched sibling, myeloablative HSCT in children with SCD

Study	Country or registry	N	OS (%)	EFS (%)	Graft rejection (%)	AGVHD (%)	CGVHD (%)	TRM (%)
Panepinto et al	CIBMTR	67	97	85	15	10	22	4.5
Walters et al	USA	22	91	73	18	1	1	6
Bernaudin et al	France	87	93	86	7	13	20	6.9
Locatelli et al	Eurocord Oakland	160	97	92	N/A	N/A	N/A	N/A
Le et al*	Belgium	90	93.8	(85.6)	8	(10)	(20)	5.6

\*Asymptomatic pts. OS 100%; EFS 93%

aGVHD, acute GVHD; cGVHD, chronic GVHD; EFS, event-free survival; TRM, treatment-related mortality.

# Outcome after HSCT for children with SCD among engrafted patients (n = 50)

- No painful crises
- No episodes of ACS
- No episodes of splenic or hepatic sequestration
- No RBC transfusions
- Improved quality of life
- Fertility remains a concern with this approach
- Stroke recurrence 2 events per 100 patient years

# Neurological outcomes among surviving patients (N=55) after BMT

- 28/29 with overt stroke, one recurrence
- 9/25 with 'silent stroke' with improved MRI
- 16 normal at baseline, no stroke
- At 6 years 25 – 40% had mixed chimerism

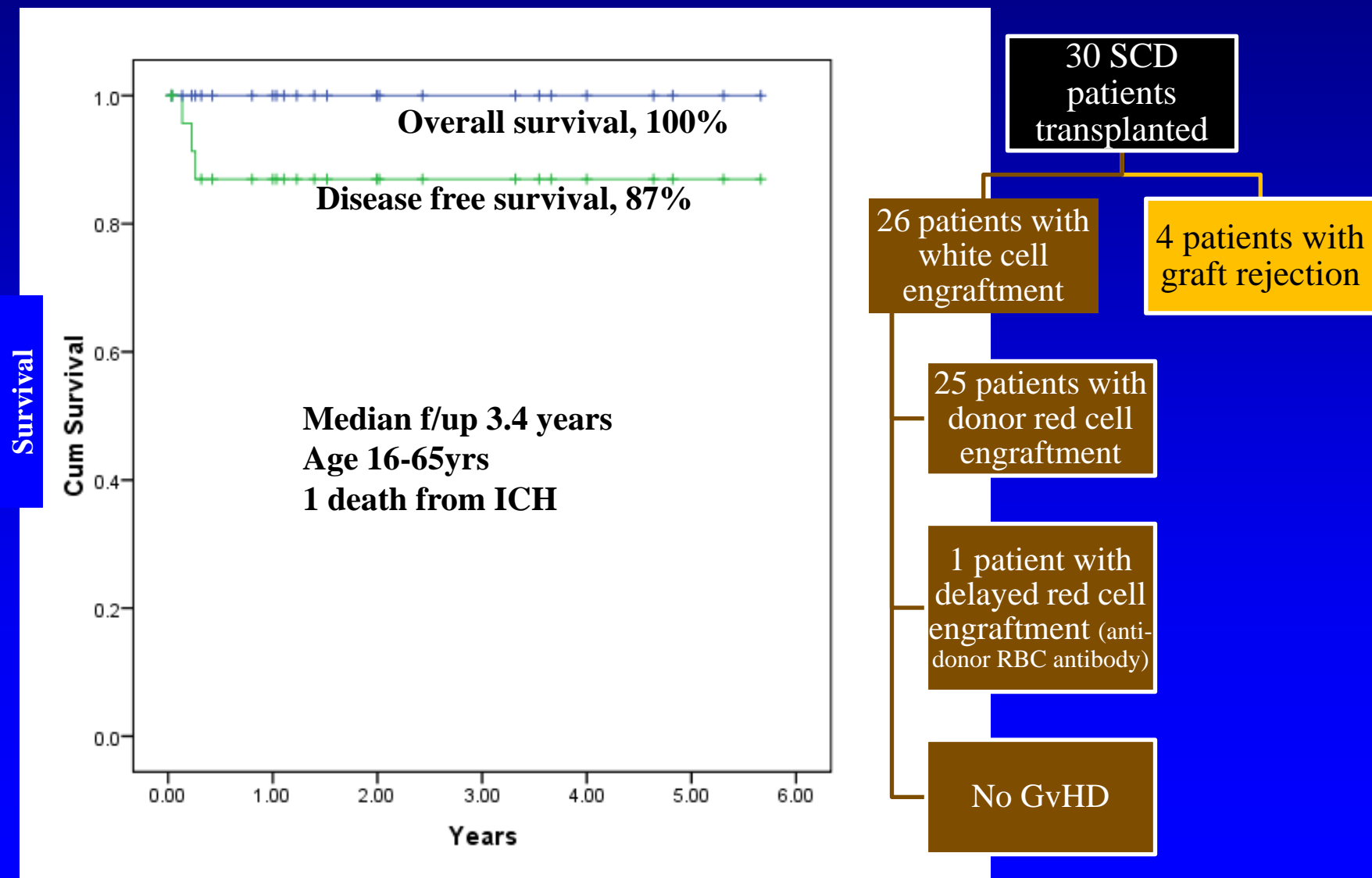


**Are adults with severe SCD  
candidates for this approach?**

# Reducing toxicity of the regimen: Reduced intensity conditioning (RIC)

- Preferred in patients who are ineligible for myeloablative conditioning due to:
  - Age > 55 years
  - Medical contraindications like renal, cardiac or pulmonary insufficiencies
  - Ideal for adult patients with SCD due to age-dependent chronic organ dysfunction

# Improved outcomes of RIC MRDT for adults with severe SCD: NIH



# **RIC MRD transplant is feasible**

- Protocols are still experimental
- No replication of protocol at multiple sites
- Limited number of donors available for adults with severe SCD

# Limitations for HSCT in children (strokes) and adults with severe SCD

- Inadequate pool of donors (<20%)
- Too many open protocols (currently > 30 HSCT open protocols in [clinical trials.gov](http://clinicaltrials.gov))
  - Poorly defined protocol methods with lack of
    - DSMB
    - Futility for enrollment or primary endpoint
    - Multi-center experience

# Alternative donor options for SCD

- Unrelated umbilical cord blood transplant (UCBT)
- Matched-unrelated donor transplant
- Haploidentical related donor transplant

# Poor results of UCBT for SCD

	Unrelated UCBT (BMT / CTN)	Unrelated UCB
	<b>Kamani et al</b>	<b>Ruggeri et al</b>
<b>N</b>	8	15
<b>Age (range)</b>	13.8 yrs (7.4-16.2)	5 yrs
<b>Conditioning</b>	Flu/Mel	Bu/Cy; Bu/Mel; Bu/Flu/TLI
<b>T-cell depletion</b>	Alemtuzumab	ATG
<b>OS (%)</b>	100	<b>75</b>
<b>EFS (%)</b>	38	31
<b>Graft failure (%)</b>	<b>63</b>	<b>53</b>
<b>aGVHD 2-4 (%)</b>	25	23
<b>cGVHD (%)</b>	13	16

\*GVHD- graft-versus-host-disease; UCB –umbilical cord blood

# Challenges with UCBT for SCD

- Relatively low dose of total nucleated cells and CD34<sup>+</sup> cells within an umbilical cord blood unit.
- Delayed hematopoietic recovery contributes to increased morbidity and transplant related mortality.
- Double UCBT in adults increases risk of GVHD
- Primary graft failure is the predominant cause of treatment failure



# Outcomes of matched unrelated donor BMT for severe SCD

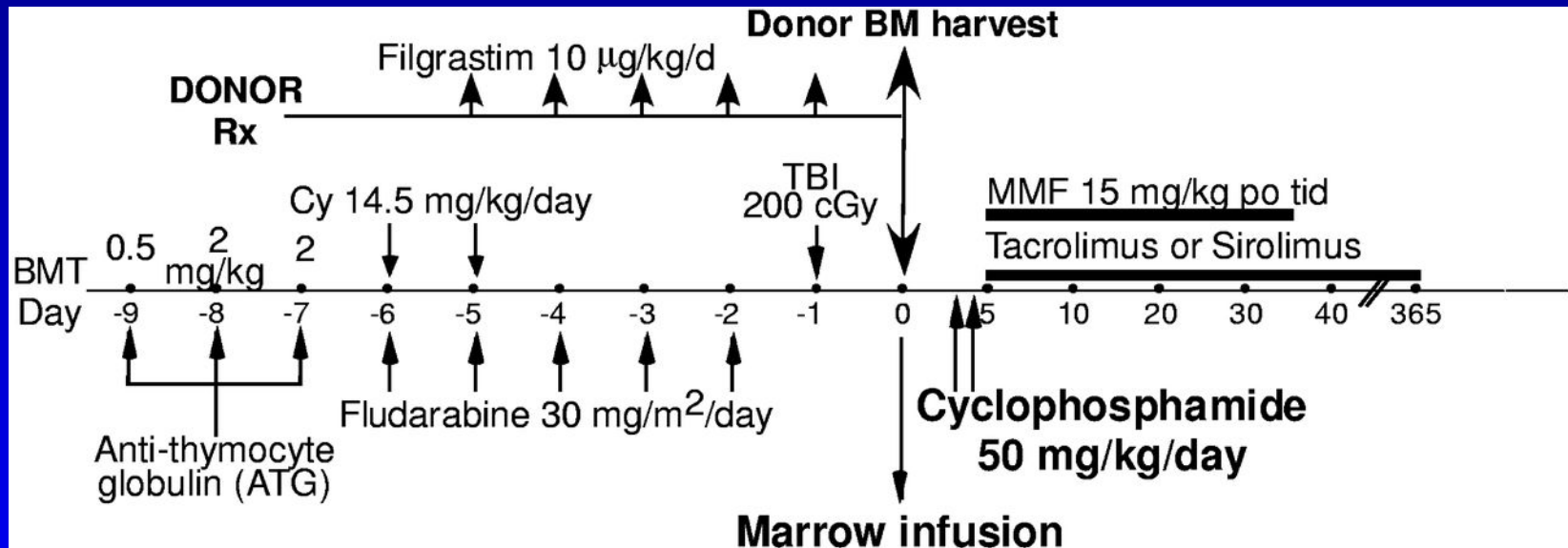
- Multicenter phase II trial, 2008-2014 (BMT/CTN)
- 30 children aged 4-19years; median f/up 26 mths
- Indications: stroke, TCD velocity  $>200$  cm/sec, ACS and recurrent ( $\geq 3$ ) vasocclusive pain crisis/yr
- Graft rejection 10%; 2 year EFS 69%, OS 79%
- Grade II-IV acute GVHD was 28%
- Incidence of chronic GVHD was 62% at 1 year

# Outcomes and conclusion

- There were 7 GVHD-related deaths
- A 34% incidence of posterior reversible encephalopathy syndrome at 6 months
- Regimen considered unsafe for widespread adoption due to RRT and high rate of chronic GVHD

**More than 90% of eligible patients  
with SCD will have a related  
haploidentical donor**

# Novel approach by Johns Hopkins group



Addition of ATG: in 12 patients

G-CSF primed bone marrow in 3 patients

Sirolimus replaced tacrolimus in 5 pts to reduce PRES

# Encouraging initial haplo BMT data

- 14 haploidentical BMT
  - Ages 15 to 42 years
  - Eight patients engrafted durably
  - No patients developed GVHD
  - No patients died
  - Graft failure of 43% remains a major obstacle

**Encouraging initial haplo BMT  
data, but can we do better than a  
~ 60% engraftment rate?**

# Multi-institution International Learning Collaborative

- Objective: to reduce the graft failure rate for Haplo-BMT for SCA based on Hopkins platform
- The critical components of this approach include:
  - monthly team meetings
  - site specific IRB approval
  - common stopping rules
  - consensus on standard care
  - minimizing and accurate data collection
  - importantly, a spirit of collaboration

# Methods

Involved 2 strategies and 3 sites

## Strategy 1

- Initial approach based on the Hopkins platform
- Pre-determined add-on components, if stopping rules are met

## Strategy 2

- Preconditioning therapy with azathioprine, hydroxyurea and hypertransfusion PLUS thiotepa in conditioning regimen

## Common stopping rules

- More > 20% mortality rate, graft rejection or severe GVHD



# Eligibility criteria

- Patients with SCA aged 1-70 years
- Patients with at least one the following complications:
  - Stroke or CNS event lasting more than 24 hours
  - MRA evidence of cerebrovascular disease
  - Recurrent acute chest syndrome
  - Recurrent vaso-occlusive crisis requiring hospitalization (> 2/year for the last 2 years )
  - Stage I or II sickle chronic lung disease
- ECOG 0 or 1; Karnofsky 70-100%
- No HLA-matched related donor

# Results: N=36

Strategy 1: N=13

Johns Hopkins protocol  
only: N=5  
3 graft failure



Stopping rules

DSMC: thiotepa added to  
conditioning regimen: N=8

Strategy 2: N=23

Johns Hopkins protocol  
plus preconditioning  
treatment (hydroxyurea,  
azathioprine,  
hypertransfusion) and  
thiotepa in conditioning  
regimen

# Results of interim analysis:

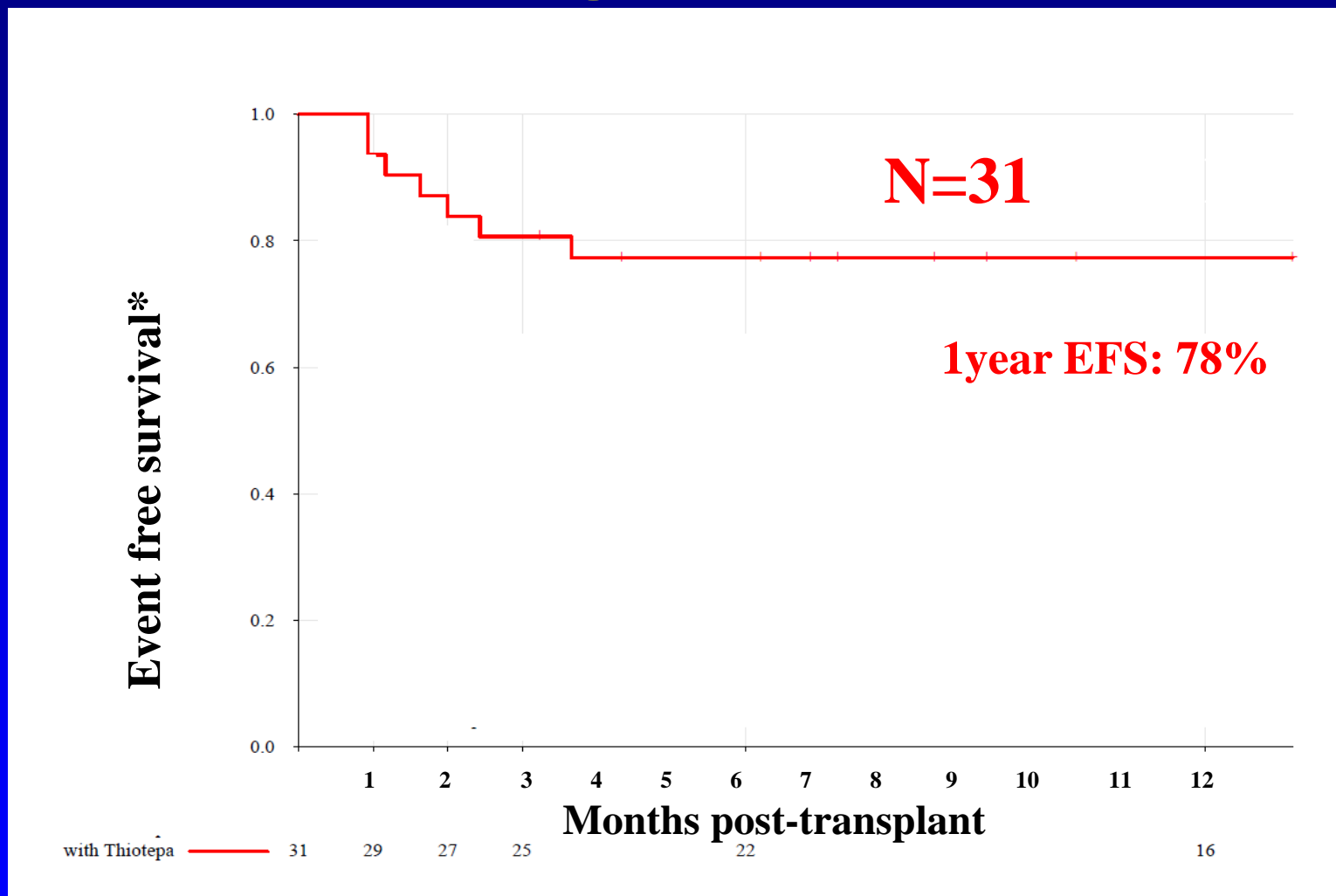
Median follow-up: 15.5 months (0.5-33)

	Strategy 1		Strategy 2
Variables	Group A No Thiotepa N=5	Group B Thiotepa alone N=8	Group C: Thiotepa with Preconditioning N=23
Median ANC >0.5k: days (range)	32 (26-40)	25 (15-35)	17 (15-29)
Median platelet count >20k: days (range)	30.8 (21-59)	33.1 (12-90)	36.5 (20-64)
Graft failure	3 (60%)	1 (12.5%)	2 (8.6%)
Acute GVHD ≥ grade II	0	1 (12.5%)	4 (17%)
Severe chronic GVHD	0	0	0
Deaths	0	0	5 (21%)

# Causes of death (n =5)

- All in pre-conditioning group (azathioprine, HU and hypertransfusion therapy)- strategy 2
- 1 patient, acute GI GVHD, hemorrhagic rectocolitis and sclerosing cholangitis
- 1 patient, with meningoencephalitis
- 3 patients with macrophage activation syndrome
  - idiopathic pulmonary syndrome
  - HHV6 infection with secondary graft failure
- Pretransplant comorbidities :N=3

# One year EFS in patients with thiotepa based regimen ~ 80%



\*EFS = included graft failure or death

# Conclusion

- International multi-center learning collaborative is feasible in HSCT
  - Enrolled 36 patients with SCD in 3 years
- Haplo-BMT with PTCy plus thiotepa
  - Improves donor engraftment to an estimated 90%
  - Not associated with severe chronic GVHD to date
- No benefit for adding preconditioning (azathioprine, hydroxyurea, and hypertransfusion)
- A NIH sponsored BMT CTN phase II trial, of haplo-BMT with PTCy plus thiotepa

**Performing HSCT in children  
and adults with SCD .....**

***“Primum non nocere”***

**(first do no harm)**

# **Standard care in oncology is to reserve HSCT for severe or progressive disease, why not SCD?**

- First chemotherapy (hydroxyurea) or other disease modifying therapy (blood transfusion therapy)
- If progressive disease after therapy then consider HSCT





# Case 2: follow-up

- Patient had no HLA matched sibling
- Underwent a Haplo-BMT from 58yr old sister
- Indication: severe SCD with multiple comorbidities
- Data D+100: RFLP 100% donor; sorted chimerism CD3 / CD 33 100% donor; HPLC: nl hemoglobin
- Presently: >2 years from Haplo-BMT
- Complications: AKI due to sirolimus, and rash (suppurative folliculitis) - resolved

# In his own words...

“ I never thought that this could happen in my lifetime. I still have lingering issues from living with SCD for so long; but no NEW organ damage or bone damage will occur to me because I am cured”.



**Craigie D. Sanders, Esq., AICP**

# Zoo Day

September 6, 2014



## Acknowledgements

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*Thank you!*