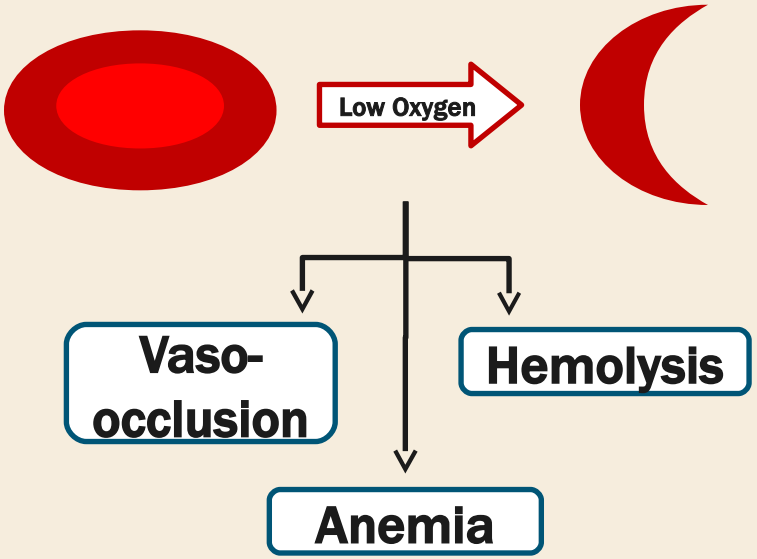
Stem Cell Transplantation to Cure Adults with Sickle Cell Disease

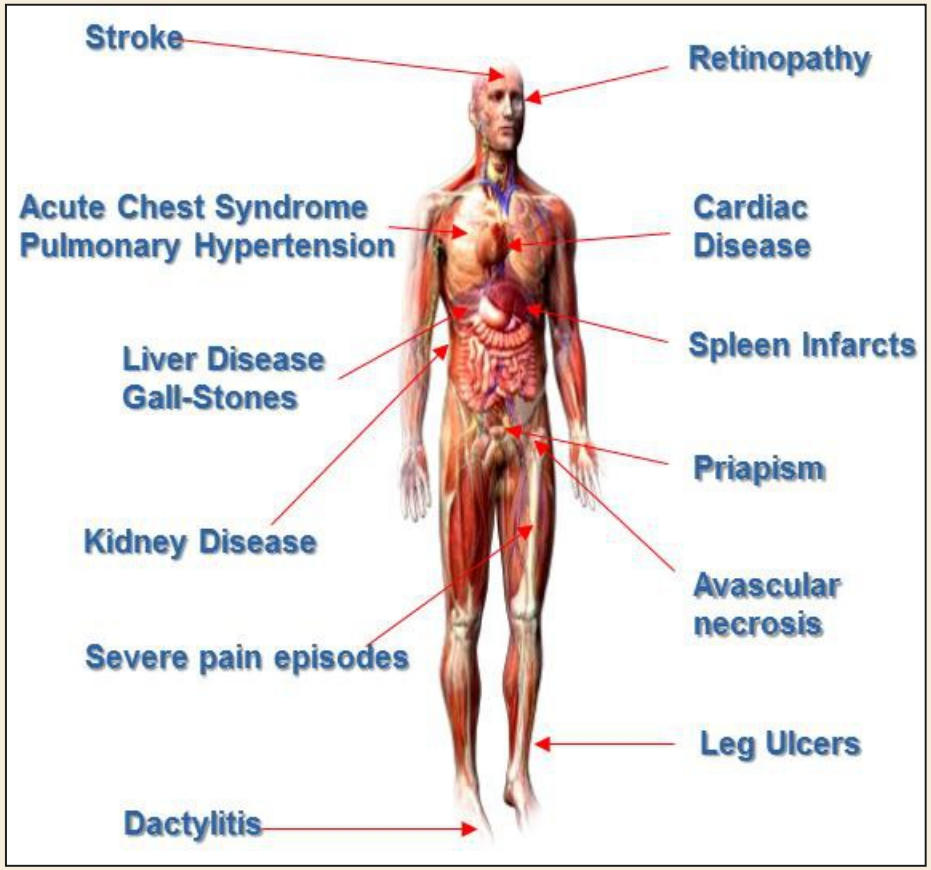
University of Illinois
Hospital & Health Sciences System
Changing medicine. For good.

Disclosure Statement

I have no financial interest or other relationship with any manufacturer/s of any commercial product/s which may be discussed at this activity.

Biology of Sickle cell disease (SCD)





SCD-Related Complications

Vaso-occlusive Crises

- #1 cause for hospitalization and negatively impacts quality of life
- ~50% of SCD patients had ≥3/year acute visits for VOC1

Acute Chest Syndrome

- #2 cause for hospitalization and can become rapidly fatal

Stroke

- Lifetime risk: **30%** overt stroke, **44%** silent infarctions2
- Transfusion therapy: **18%** and **28%** risk of overt or silent infarcts3

1. Lanzkron S et al, Blood Adv 2018
2. WY Wong et al, Hematol Oncol Clin N Am 2005
3. Hulbert ML et al, Blood 2011

Current Therapies for SCD

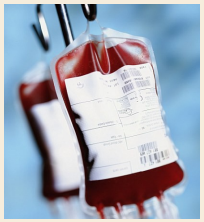
Hydroxyurea

Outcome	HU	Placebo	p-value
Pain crises	1.0/year	2.4/year	< 0.001
Acute Chest Syndrome	25%	51%	< 0.001
Transfusions	336 U	586 U	0.004

L-glutamine

Outcome	L-glutamine	Placebo	p-value
Pain crises	2 events	3 events	0.005
Hospital days	6.5 days	11 days	0.02
Acute chest syndrome	11.9%	26.9%	0.006

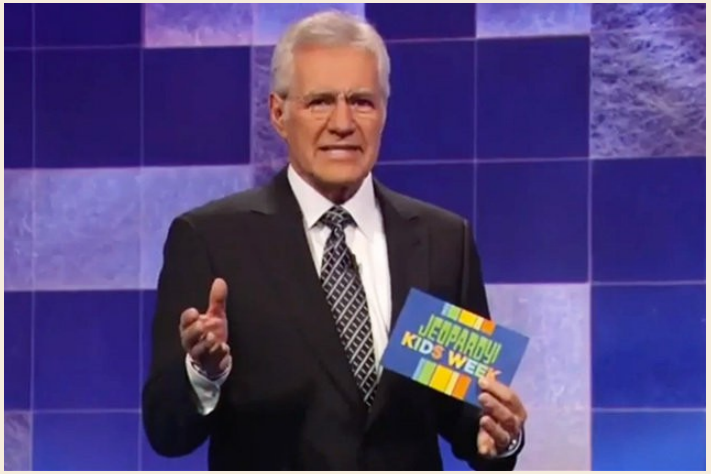
Transfusion

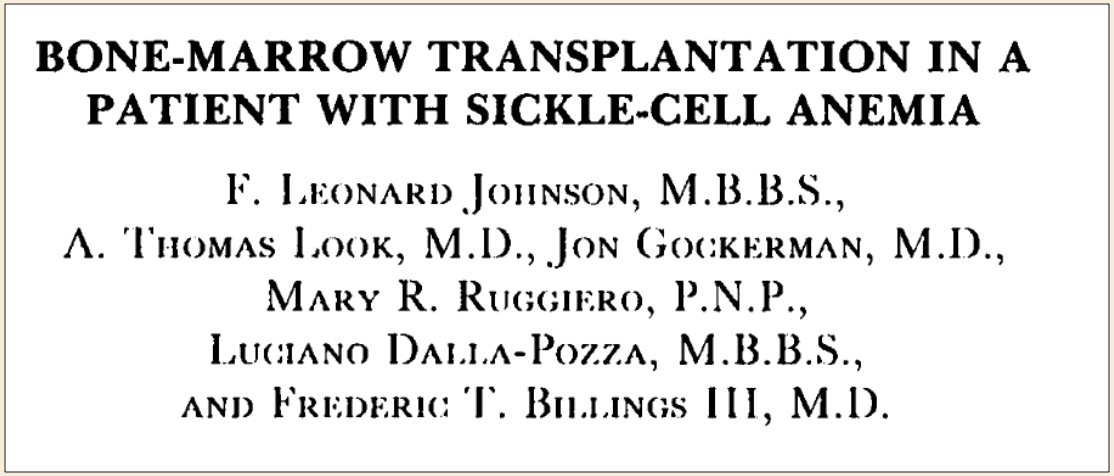


- **Stroke prevention**
- **Acute complications:**
  - acute chest syndrome, intrahepatic cholestasis, splenic sequestration
- **Preoperative management**

Charache S et al, NEJM 1995
Niihara et al., ASH Abstract #1318, 2014
NHLBI Expert Panel Report 2014

What Year did the following take place?





BONE-MARROW TRANSPLANTATION IN A PATIENT WITH SICKLE-CELL ANEMIA

F. Leonard Johnson, M.B.B.S., A. Thomas Look, M.D., Jon Gockerman, M.D., Mary R. Ruggiero, P.N.P., Luciano Dalla-Pozza, M.B.B.S., and Frederic T. Billings III, M.D.

First HSCT performed in an SCD patient in 1984

8 year old girl with Hb SS and AML

- HLA-matched brother with sickle cell trait

Myeloablative conditioning regimen:

- Cyclophosphamide (60mg/kg x 2 days) + TBI (11.5 Gy)

Complications:

- Acute and Chronic GVHD
- Pneumococcal bacteremia

Johnson FI et al, NEJM 1984

Transplant Outcomes:

Myeloablative/intense regimens in Children

Center	N	Rejection	TRM	Cure Rate	Acute GVHD	Chronic GVHD
Belgium	50	10%	7%	83%	20%	20%
US/Europe	59	10%	6%	84%	15%	12%
French	87	7%	7%	86%	20%	14%
Belgium	50	8%	6%	86%	22%	20%
USA	43	2%	7%	91%	23%	13%
	289	8%	7%	86%	20%	16%

Vermylen et al. BMT 2007
Walters et al. BMT 2001
Bernaudin et al. Blood 2007
Dedeken et al. BJH 2014
King et al. AJH 2015

Transplant Outcomes: Improvements with Time

Variable	Before 1/2000 N = 43	After 1/2000 N = 44
Used ATG	**27 (63%)**	**42 (96%)**
Cord Blood	**1 (2%)**	**11 (25%)**
Deaths	**6 (14%)**	**0 (0%)**
Rejection	**5 (12%)**	**2 (5%)**
aGVHD (≥ Grade 2)	**12 (28%)**	**5 (11%)**
cGVHD	**9 (21%)**	**2 (5%)**

Bernaudin et al. Blood 2007

Transplant Outcomes: by Disease Status

Variable	Symptomatic N = 36	Asymptomatic N = 14
Age (median, range)	**8.6 (1.7 – 23)**	**2 (0.9 – 15)**
Deaths	**2 (6%)**	**0 (0%)**
Failed Engraftment/Rejection	**4 (12%)**	**1 (7%)**
aGVHD · **Grade 1 or 2** · **Grade 3 or 4**	 **14 (39%)** **1 (3%)**	 **5 (36%)** **0 (0%)**
cGVHD · **Limited** · **Extensive**	 **5 (14%)** **3 (8%)**	 **2 (14%)** **0 (0%)**

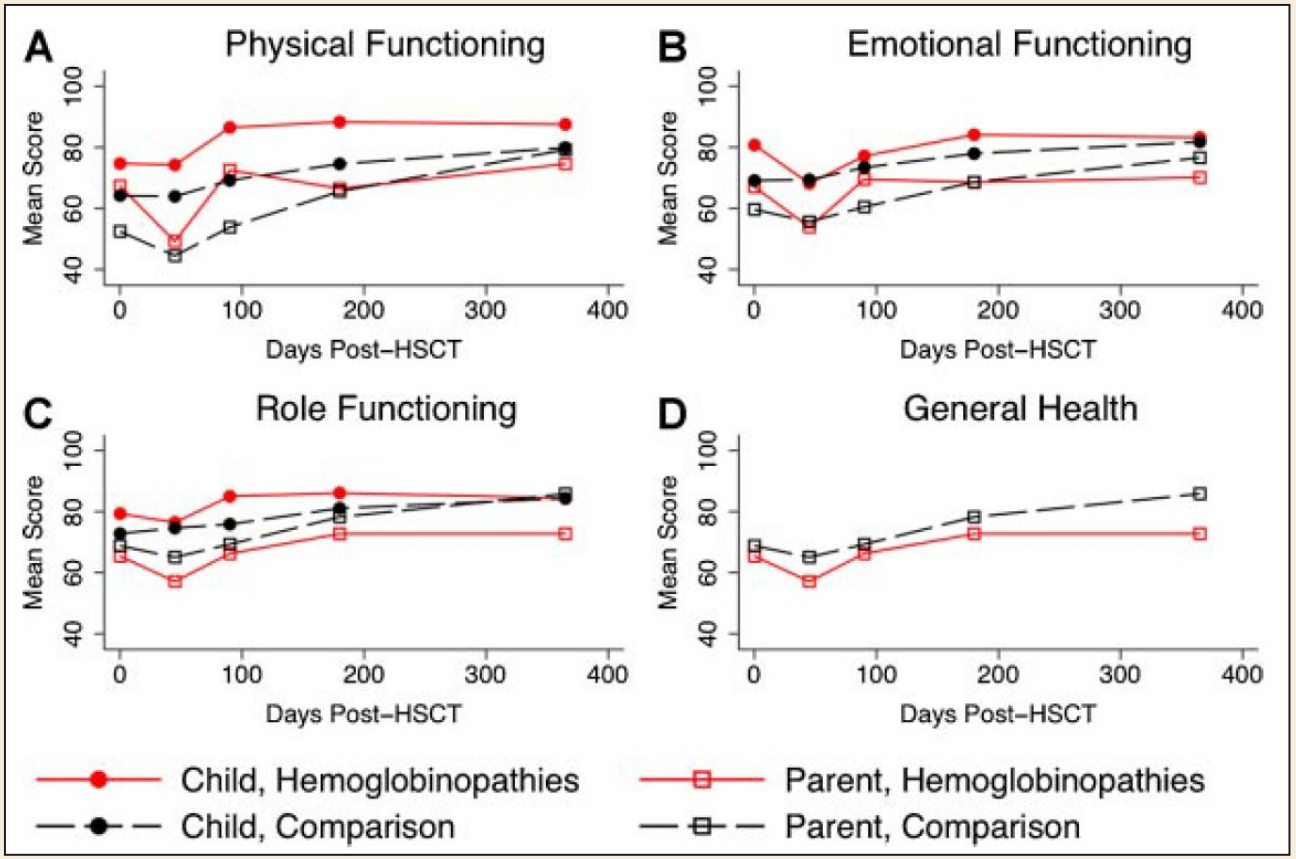
Vermylen et al. BMT 2007

Transplant Outcomes: Long-Term Improvements

Organ System	Outcomes Post-transplant
Brain/CNS	· Stable/Improved MRI/MRA · **No episodes of stroke**
Pulmonary	· Improvement in restrictive pattern 25% of evaluated patients · **No episodes of acute chest syndrome**
Liver	· Resolution of liver changes in 3 of 3 pts

Walters MC et al. BBMT 2010
Dallas MH et al. BBMT 2013
Green NS et al. BBMT 2017

Transplant Outcomes: Improved Quality of life



Kelly MJ et al. Pediatr Blood Cancer 2012

When to consider stem cell transplantation

HLA-Matched
Standard-of-care
• Stroke or silent stroke with cognitive impairment • Pain crises (≥2/year) • Acute chest syndrome (≥2/lifetime) • Recurrent priapisms • Pulmonary hypertension • Osteonecrosis (AVN) of joints • Kidney damage • Multiple red blood cell antibodies

Gluckman E, ASH Education Book 2013

Transplant for SCD
Global Experience (1986-2013)

1000 SCD recipients with HLA-matched sibling donor

- 106 Centers/23 Countries (CIBMTR, EBMT, Eurocord databases)
- Median age 9 years old (range: 1 – 54 years)
- 87% received a myeloablative regimen

At 5 years:

- 91% cure rate
- 15% had acute GVHD
- 14% had chronic GVHD

Transplant for SCD
Global Experience (1986-2013)

	Children (n = 846, median age 8)	Adults (n = 154, median age 19)
Myeloablative regimen	90%	73%
Bone marrow cells	86%	72%
GVHD-free survival	**86%**	**77%**
Overall survival	**95%**	**81%**

For every 1 year increase in age:

- 4% increased risk for acute GVHD
- 9% increased risk for graft failure
- 10% increased risk for death

Transplant for SCD: Experience in adults

Reduced Intensity Conditioning:

Fludarabine 30mg/m2 x 4 days

Melphalan 140mg/m2 x 1 day

ATG 30mg/kg x 4 days

1) Hb SS, Age 40, Frequent VOC, ESRD

Deceased at Day +335 from Lung GVHD complications

2) Hb SC, Age 56, Frequent VOC, AVN, Retinopathy

Deceased at Day +147 from GI GVHD complications

van Besien et al. BMT 2000

Mixed chimerism

Goal of Stem Cell Transplant

- **Therapeutic efficacy → reduce SCD complications**
- **Minimize toxicity → reduce GVHD & mortality**

Is there a **chimerism %** that can:

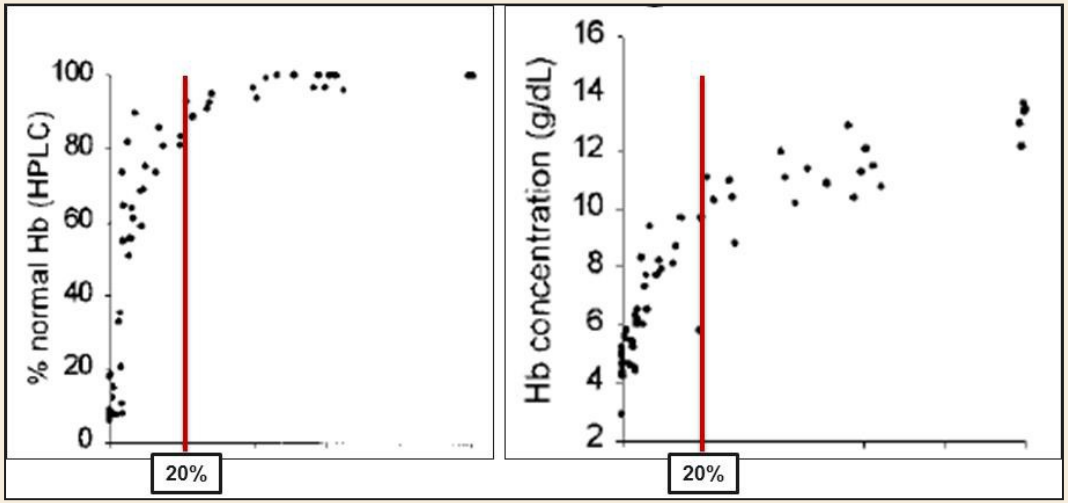
1) Avoid toxicity of intense regimens
2) Reverse SCD phenotype

Mixed chimerism

Mouse Model:

Transplanted varying

Sickle : Normal marrow



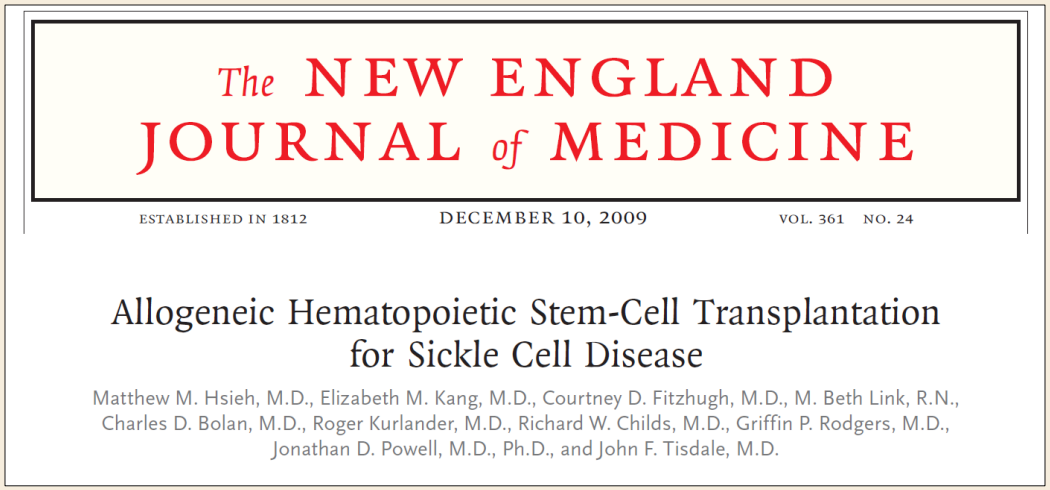
SCD Patients:

Efficacy: No SCD-related complications

Toxicity: No GVHD

Donor	Chimerism	Hb (g/dL)	HbS %
AA	11%	11.3	7
AA	67%	14.2	0
AA	74%	11.3	0
AS	60%	11.3	37
AS	25%	11.8	36

Iannone R et al. Blood 2001
Walters MC et al. BBMT 2001



The NEW ENGLAND JOURNAL of MEDICINE

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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.

- **SCD Adults** (median age 26, range 16 – 45 y.o.)
- **Transplant Regimen:**
  - Alemtuzumab/TBI 300 cGy for conditioning
  - Sirolimus for GVHD prophylaxis/graft rejection
- **90% engraftment**
- **No mortality**
- **No GVHD**

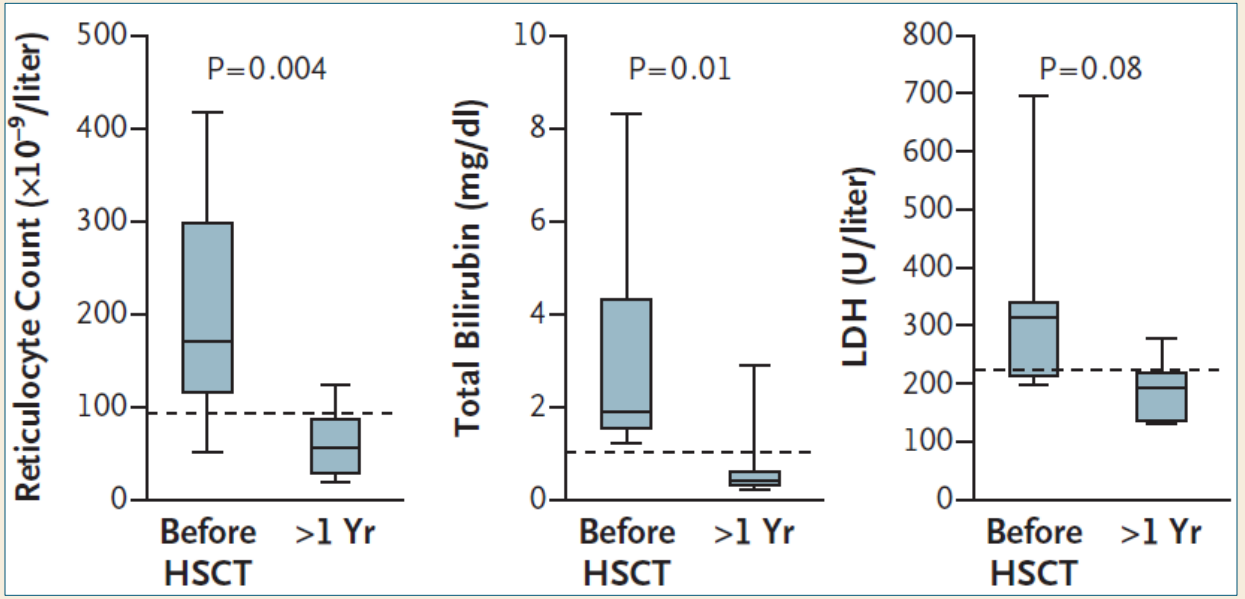
Hsieh M et al. NEJM 2009

Transplant for SCD: NIH Experience

Hemoglobin:

	Pre-HSCT	Post-HSCT
Female	8.8 ± 0.3	12.6 ± 0.6
Male	9.3 ± 0.5	12.7 ± 1.1

Hemolytic Markers:



Hsieh M et al. NEJM 2009

Chemotherapy-Free transplant Regimen

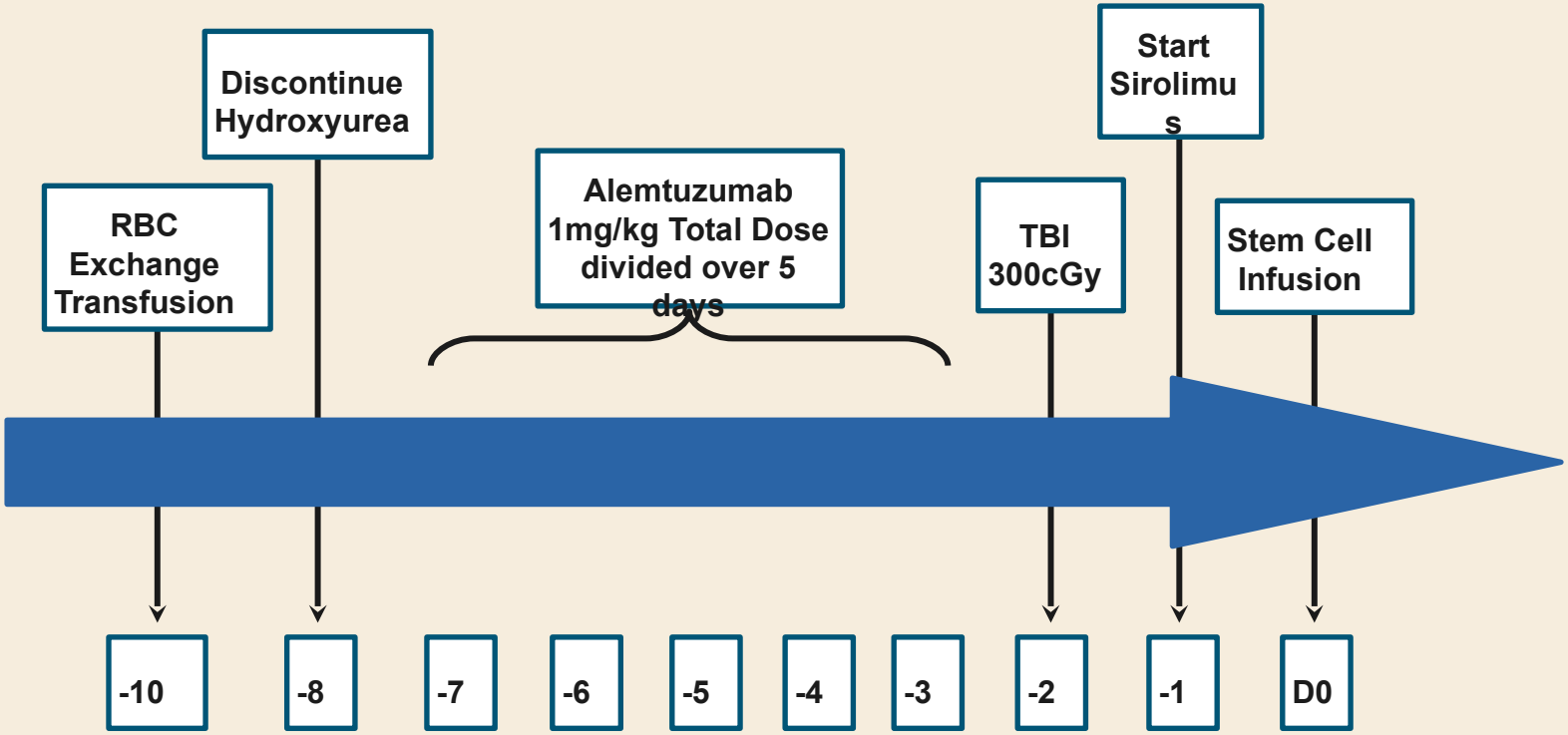
Alemtuzumab

- Antibody targeting CD52
- Depletes T and B immune cells
- Does not affect stem cells
- Major risk is reactivation of a virus, CMV

Sirolimus

- Inhibits T-cell activation and proliferation
- Mouse transplant model: sirolimus vs. cyclosporine
  - Only sirolimus treated mice showed long-term engraftment

Chemotherapy-Free Transplant regimen



Screening process

Time Period: 9/2011 – 12/2017

152 Patients Referred

- 36 lacked full siblings
- 20 declined further evaluation
- 14 denied by insurance

82 SCD Patients with 161 Full Siblings

31 Patients HLA-matched Siblings

- 2 RBC alloimmunized to donor RBC antigen
- 2 declined evaluation

27 (18%) Patients Transplanted

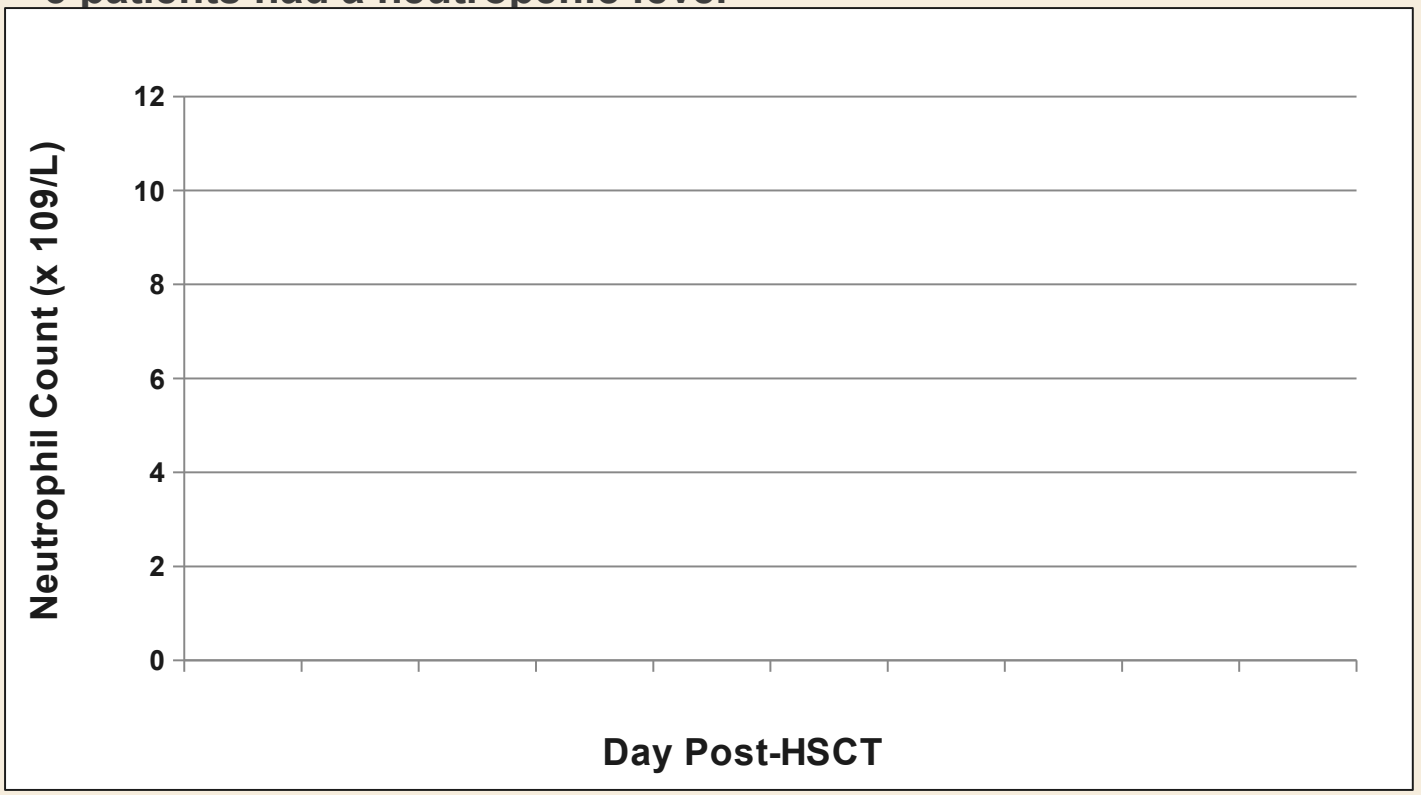
Patient & TRANSPLANT Characteristics

Variable	Result
Age (years)	**33 (17 – 55)**
Gender (Female: Male)	**13 : 14**
SCD Genotype: **Hb SS** **Hb SC** **Hb Sβ+-thalassemia**	 **24** **2** **1**
RBC Alloimmunized	**6**
ABO Major Mismatched	**3**
Donor β-Hemoglobin Status: **Hb AA** **Hb AS**	 **20** **7**
CD34+ Cell Dose (x106 cells/kg)	**8.1 (5.1 – 15.3)**
Duration of Follow-Up (months)	**49 (2 – 79)**

Neutrophil Count

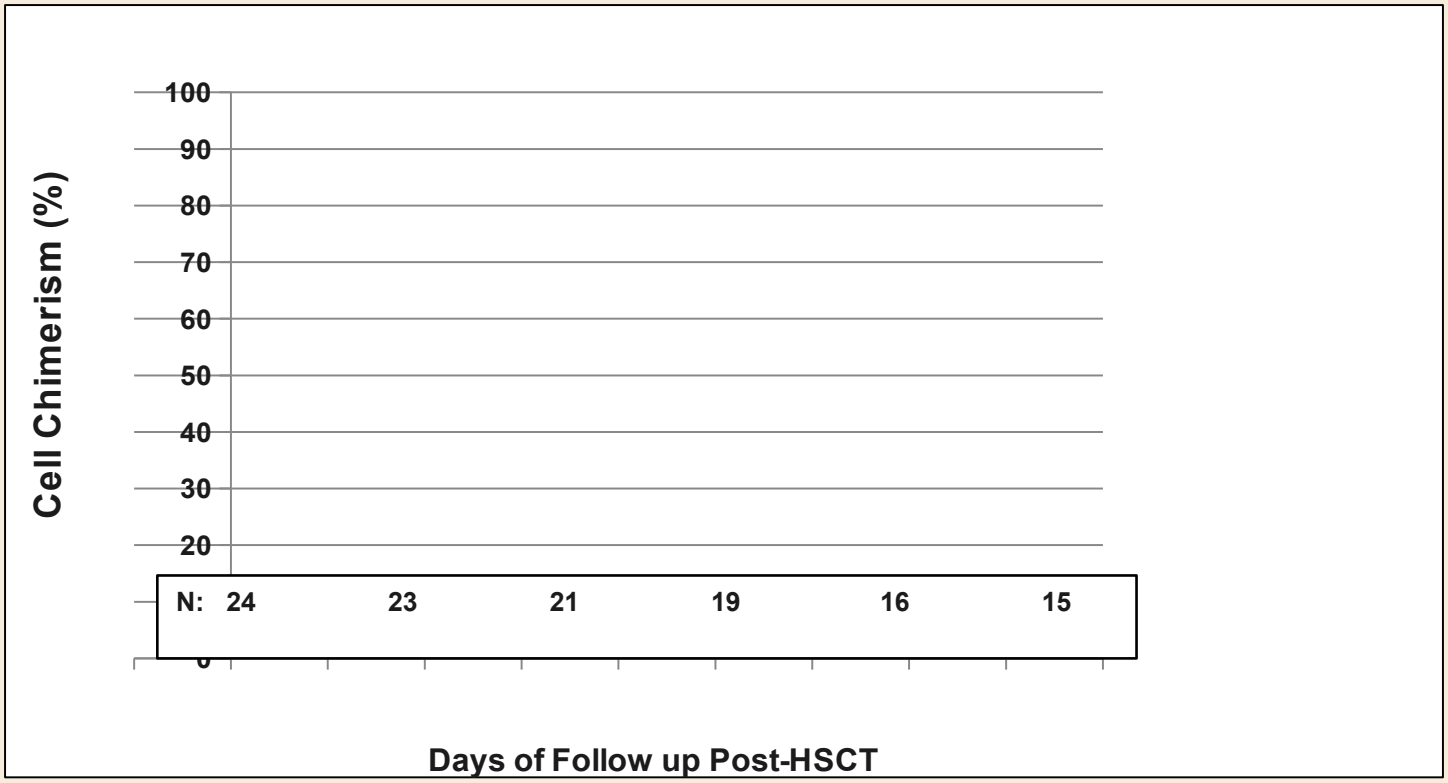
21/27 patients developed ANC < 500

- **Median duration 5 days (range: 1-14)**
- **5 patients had a neutropenic fever**

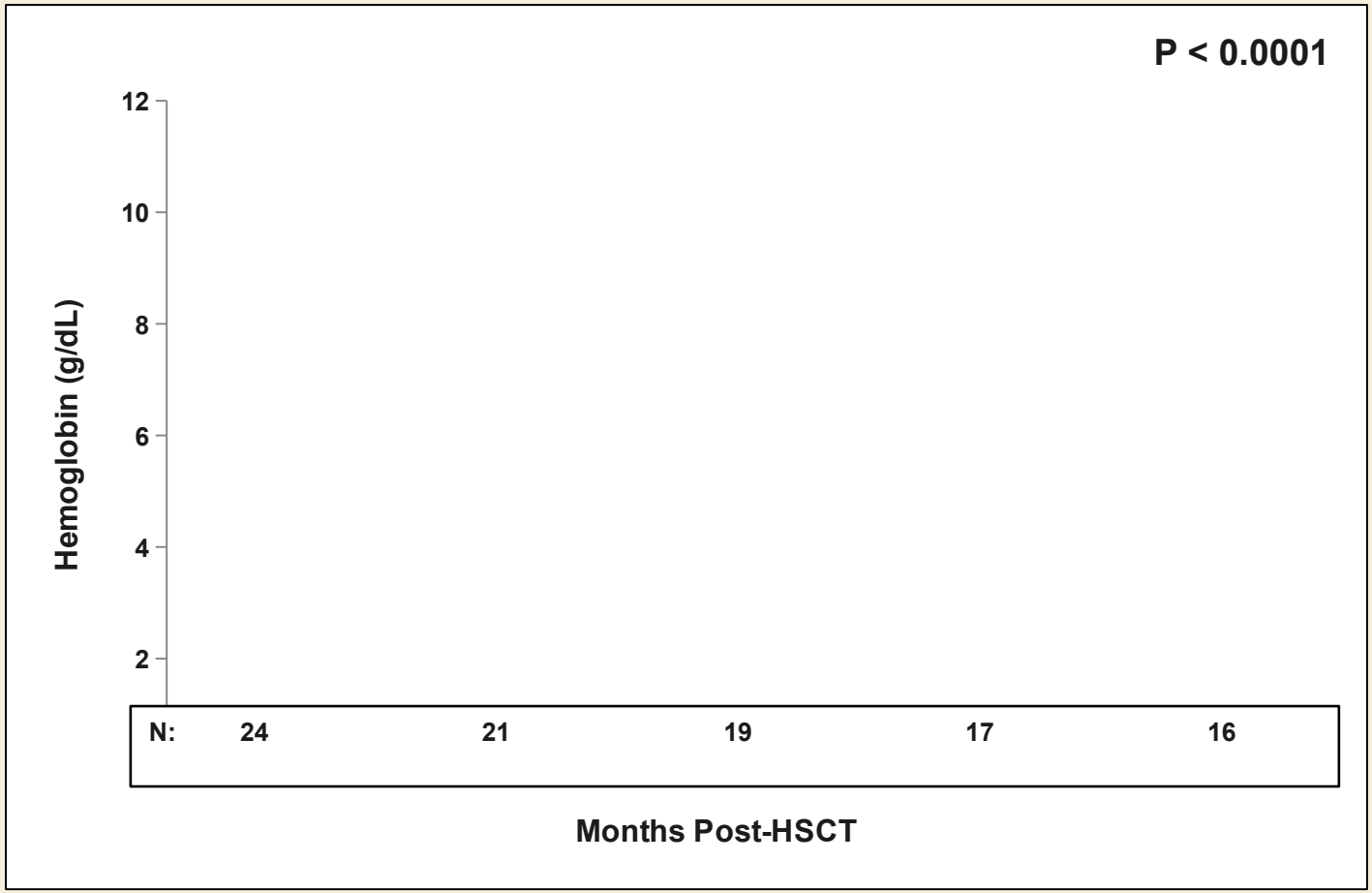


Engraftment

- All 27 patients initially engrafted
- 3 (11%) subsequently rejected (1 noncompliant, 2 intolerant of sirolimus)
- Chimerism in 24 non-rejected patients:

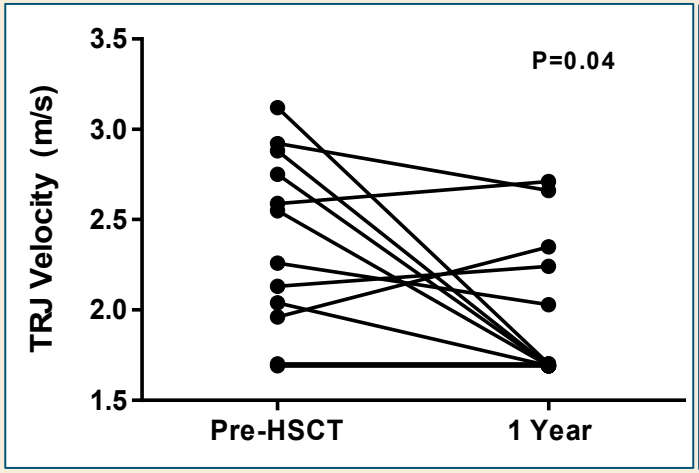


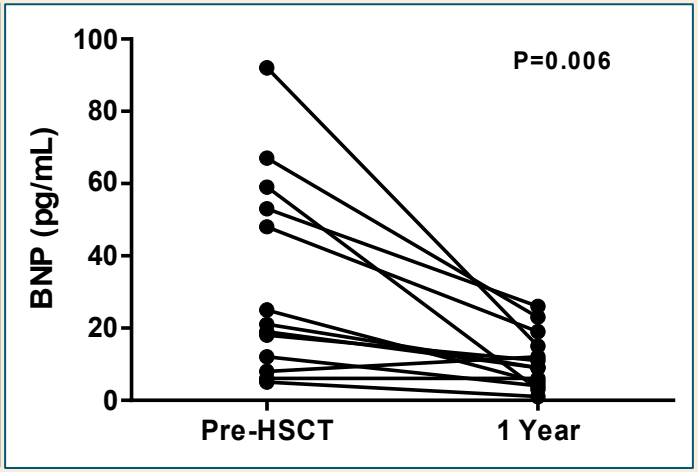
hemoglobin concentration



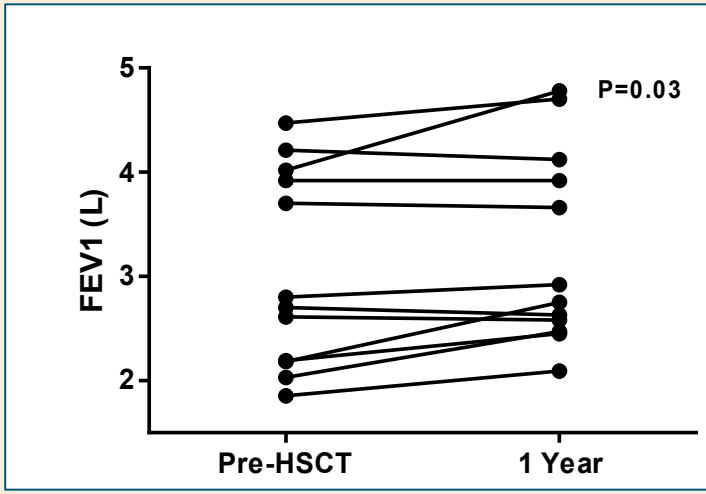
cardiopulmonary Improvements

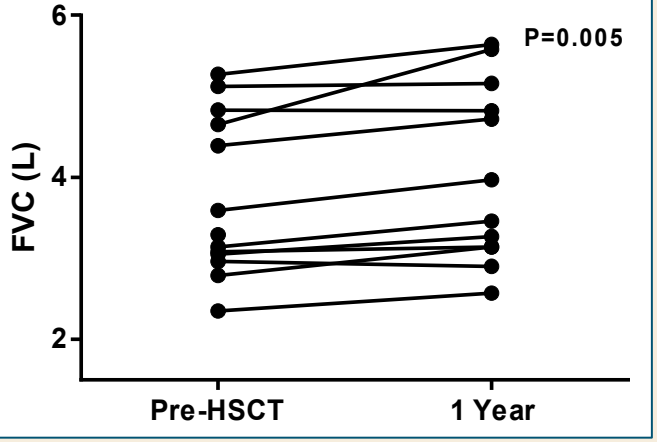
Heart Function:



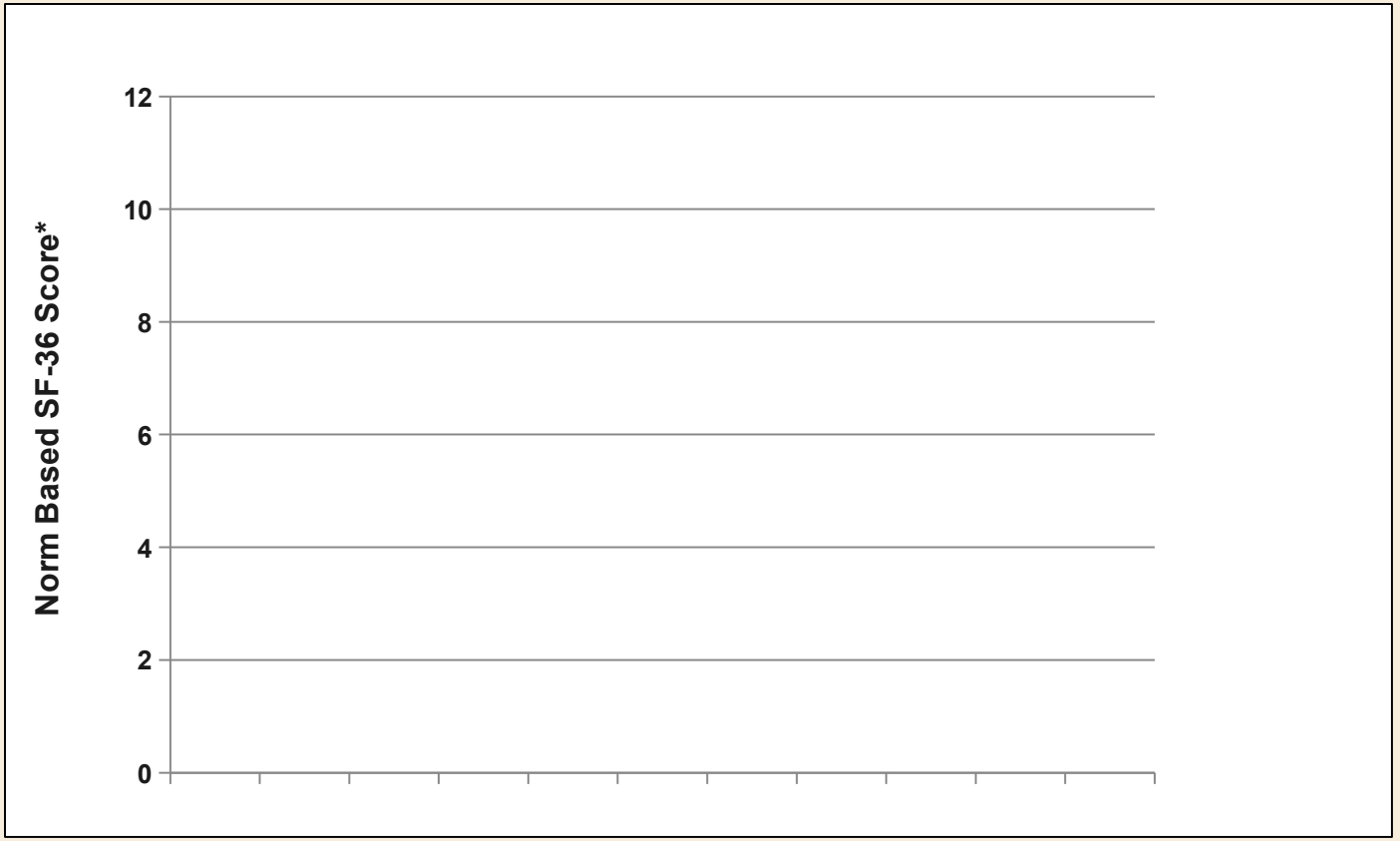


Lung Function:





SF-36 Health Survey



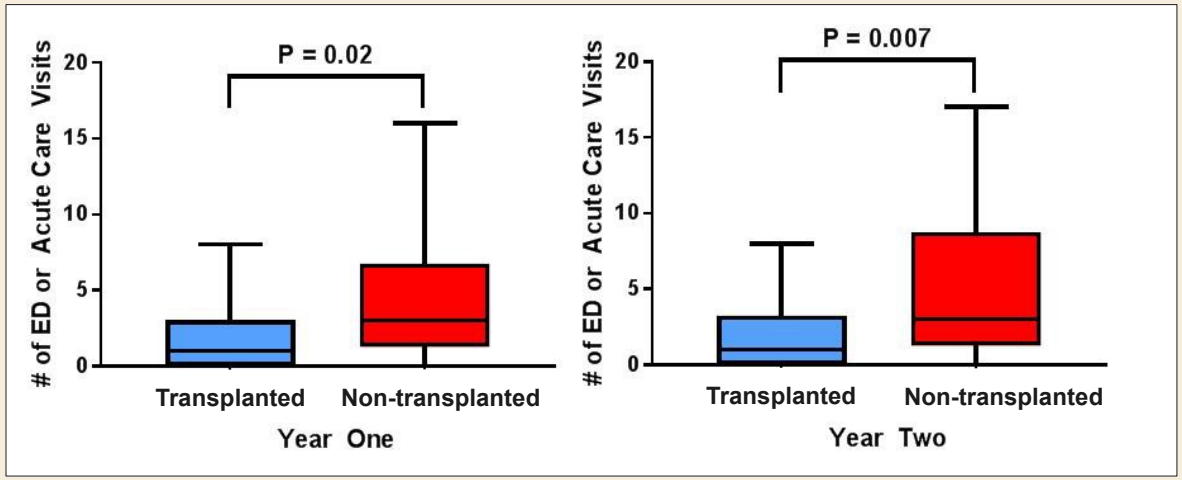
*** 50 is the general US population norm**

TOXICITY

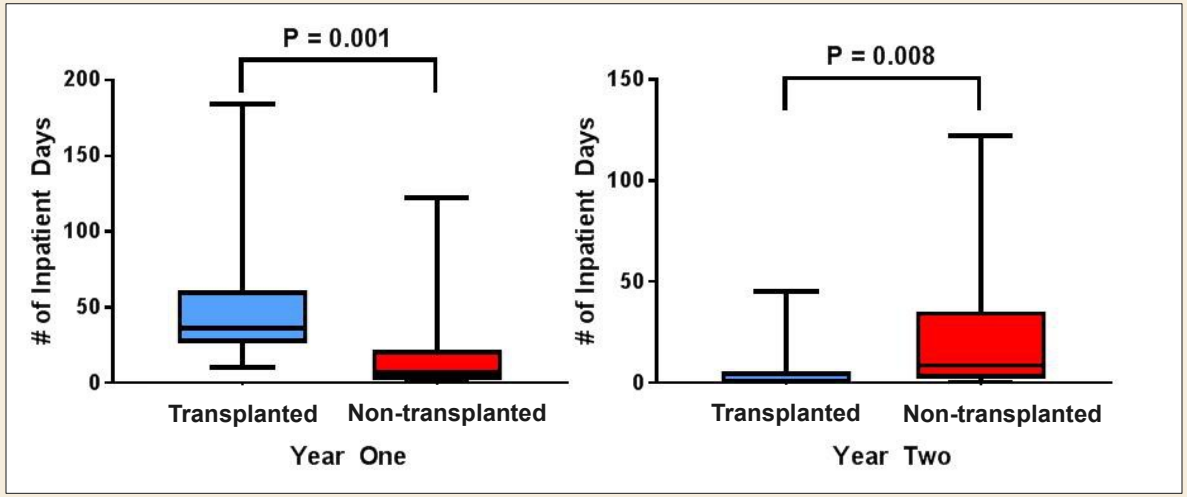
- **GVHD:** 0%
- **Rejection:** 3/27 (11%)
- **Sirolimus:** Lung toxicity 2/27 (7%)
  - Increased urine protein 3/27 (11%)
  - Low blood counts 1/27 (4%)
  - Mouth inflammation 4/26 (15%)
  - Ankle/knee pain 10/26 (38%)

Post-Transplant Health Care Utilization

Emergency Care Use



Inpatient Hospital Days



Transplant for SCD: Chemotherapy-free REgimen

Center	N	Age Range	Rejection	Cure Rate	Acute GVHD	Chronic GVHD
NIH	30	16 – 65	13%	87%	0%	0%
UIC	27	17 – 55	11%	89%	0%	0%
Calgary	8	< 18	0%	100%	0%	0%
			11%	89%	0%	0%

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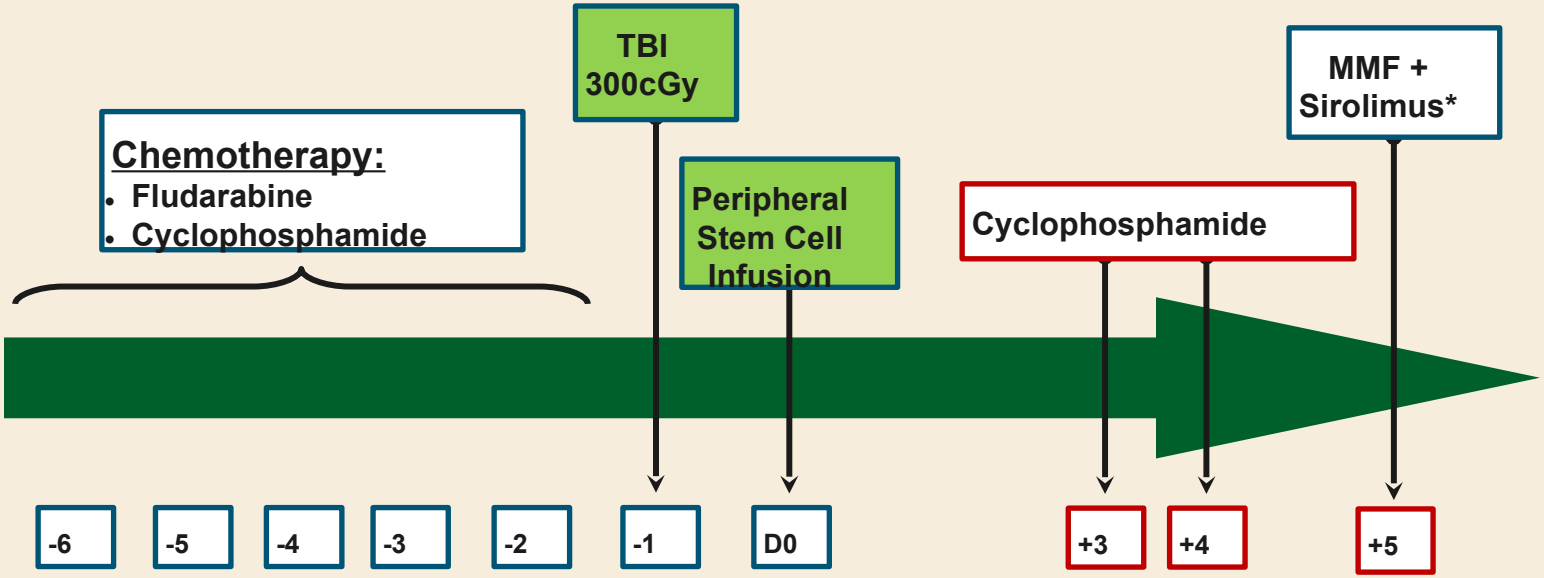
Hsieh et al. JAMA 2014
Saraf et al. BBMT 2016
Guilcher et al. EBMT Abstract # 287 2017

Transplant for SCD: Current Challenges

- **1/3 of SCD patients meet eligibility criteria**
  - **14% have an HLA-matched sibling donor**
- Potentially all SCD patients should have a **haploidentical** related donor
  - **Parents & Children**
  - Siblings (including half-siblings)
  - Aunts/Uncles, Cousins

Haploidentical HSCT: University of illinois



* MMF until day+35
Sirolimus for 1 year

PMID: 29656137

Screening process

Time Period: 1/2016 – 1/2018

50 SCD Patients Referred

- **10 Denied by insurance**

40 SCD Patients & 73 Relatives Screened

~60% had available haplo-donor

- **4 No haploidentical donor identified**
- **12 Donor specific antibodies (DSA) (MFI > 2000)**

24 Eligible SCD Patient-Haploidentical Pairs

- **14 Deferred or declined transplantation**

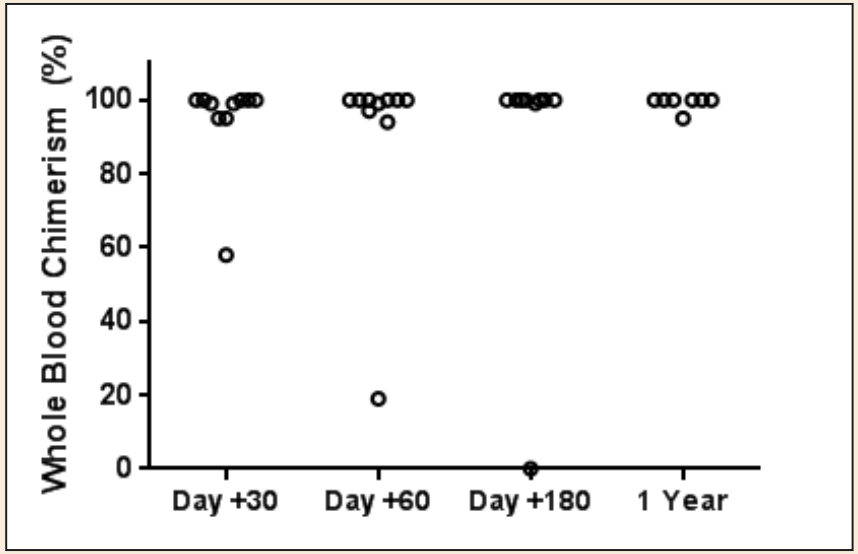
10 (20%) Patients Transplanted

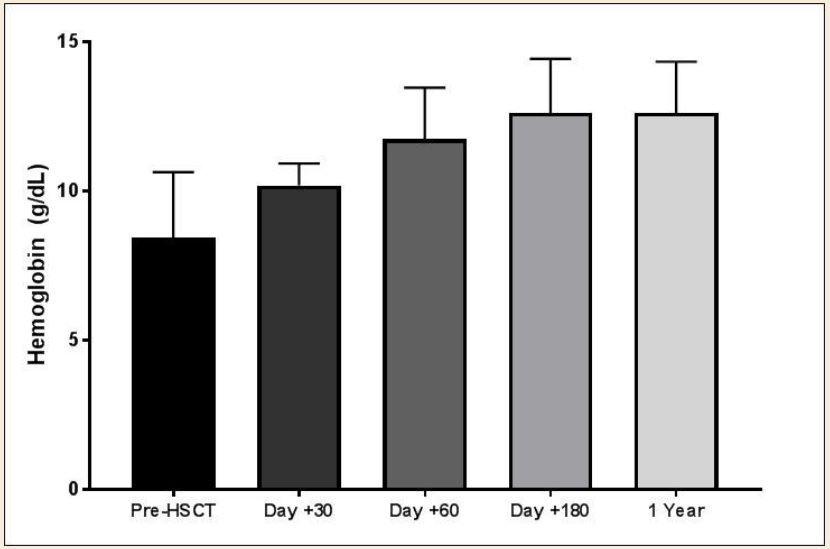
Haploidentical HSCT: University of illinois

Variable	Result
Age (years)	**28 (20 – 37)**
Gender (Female: Male)	**2 : 8**
SCD Genotype: **Hb SS** **Hb Sβ+-thal**	 **9** **1**
Donor β-Hemoglobin Status: **Hb AA** **Hb AS**	 **3** **7**
Donor Source: **Parent** **Sibling** **Child**	 **5** **4** **1**
Follow-Up (months)	**12 (4 – 32)**

Haploidentical HSCT:
University of illinois

Stable engraftment in 9/10 (90%) of SCD patients





Haploidentical HSCT: University of illinois

Transplant-related toxicity

- 2 patients with small brain hemorrhages when platelets low
  - Both had history of strokes
  - Both fully recovered and are working full time

- 2 had acute GVHD
  - 1 noncompliant with sirolimus → acute on chronic GVHD
  - 1 acute Grade 2 gut GVHD
    - Resolved with prednisone therapy

Summary

- Stem cell transplantation should be considered for SCD patients w/ complications + **HLA-matched sibling**
  - >85% cure rate
  - No GVHD observed with alemtuzumab/TBI regimen
- Special circumstances for **Haploidentical** HSCT in SCD
  - Recent regimens demonstrate >80% cure
  - Chemotherapy → more toxicity
  - GVHD risk

Acknowledgements

8 West/BMT Nursing Staff

Sickle Cell Team

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