Understanding the Complexities of Patient Selection, Enrollment, and the Consent Process: Allogeneic HSCT for Sickle Cell Disease

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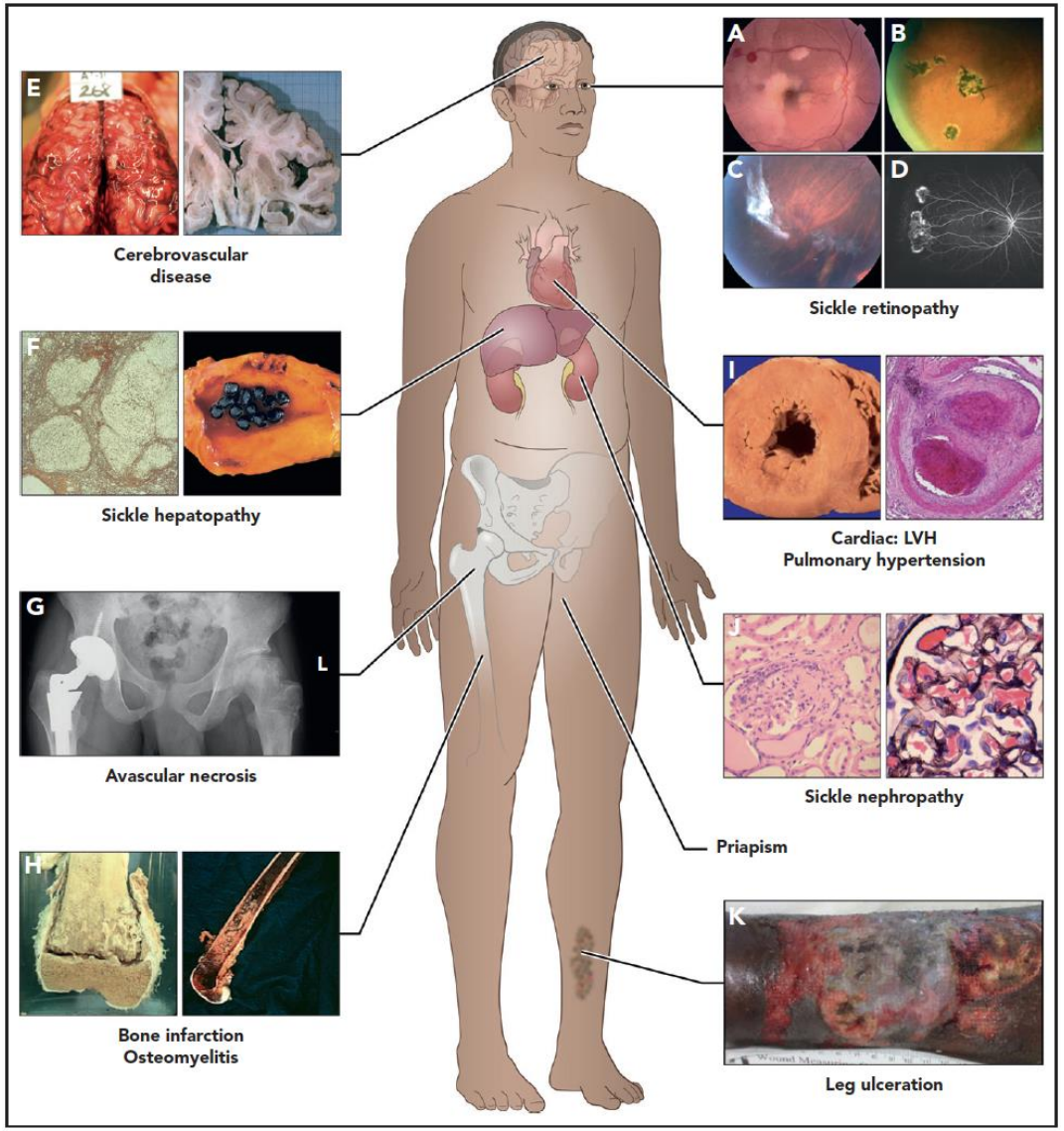
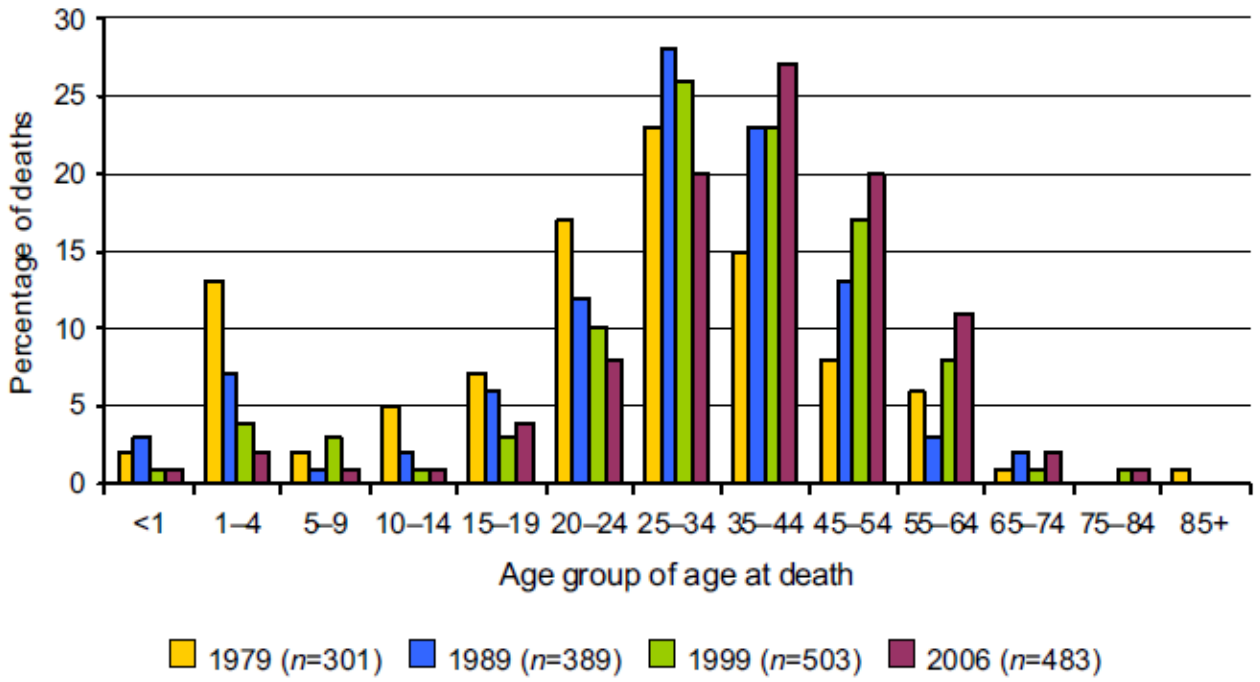
Disclosures

- No financial disclosures

Patients with SCD Experience Extensive Morbidity and Early Mortality



Thein, SL et al. Blood, 2018. 132(17): 1750-1760.



- Median age at death for adults was 39 in 2006[1] and 46 in 2015[2]
- Hematopoietic stem cell transplantation offers a curative option for patients with SCD

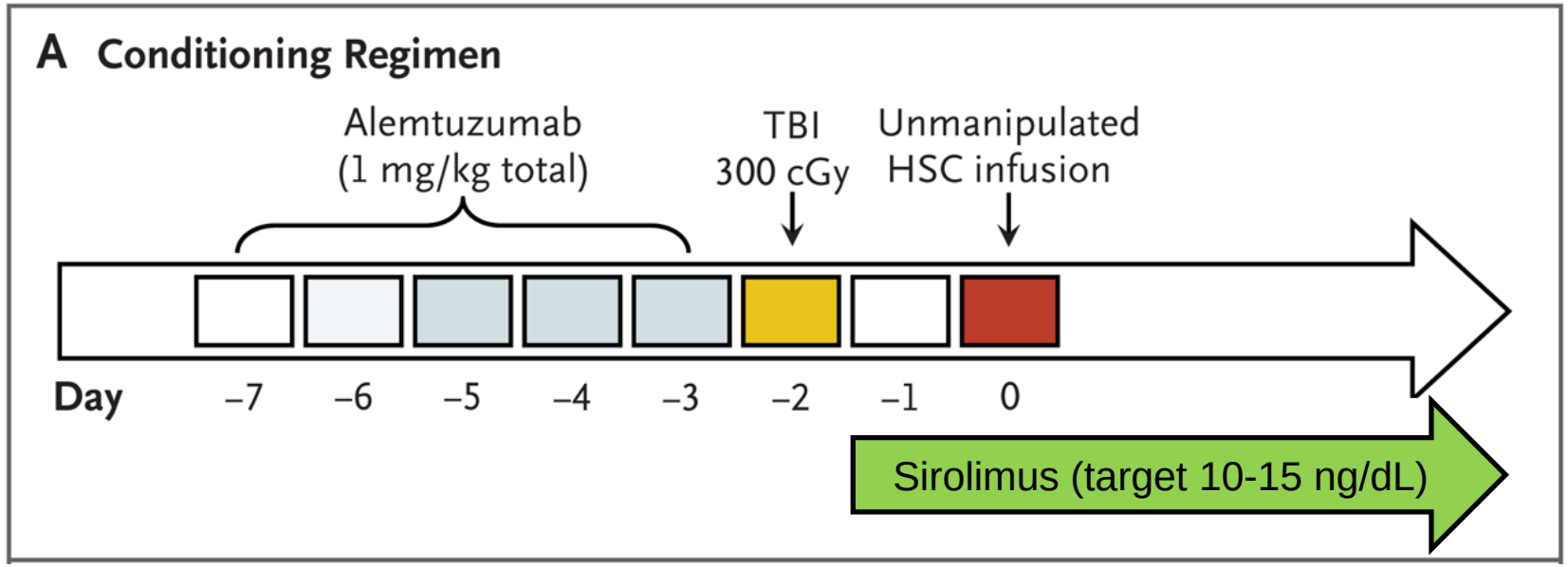
1 Hassell K. American J Preventive Medicine, 2010. 38: S512
2 Fitzhugh CD et al., PLoS One, 2015. 10(11): 1-13.

Myeloablative HLA-Matched Sibling HSCT Offers a Potential Cure for Patients with SCD

- 1000 patients with SCD underwent HLA-matched sibling HSCT from 1986-2013
- Preparative regimen in most includes busulfan, Cytoxan, and ATG
  - 5-year overall survival 92.9%, event-free survival 91.4%
    - 5-year OS was 95% and EFS 93% for patients younger than 16 years of age
  - Cumulative incidence of grade II-IV acute GVHD was 14.8%, chronic GVHD 14.3%

Gluckman E et al. Blood, 2017. 129(11): 1548-1556.

Non-myeloablative HLA-Matched Sibling Peripheral Blood Stem Cell Transplant for SCD

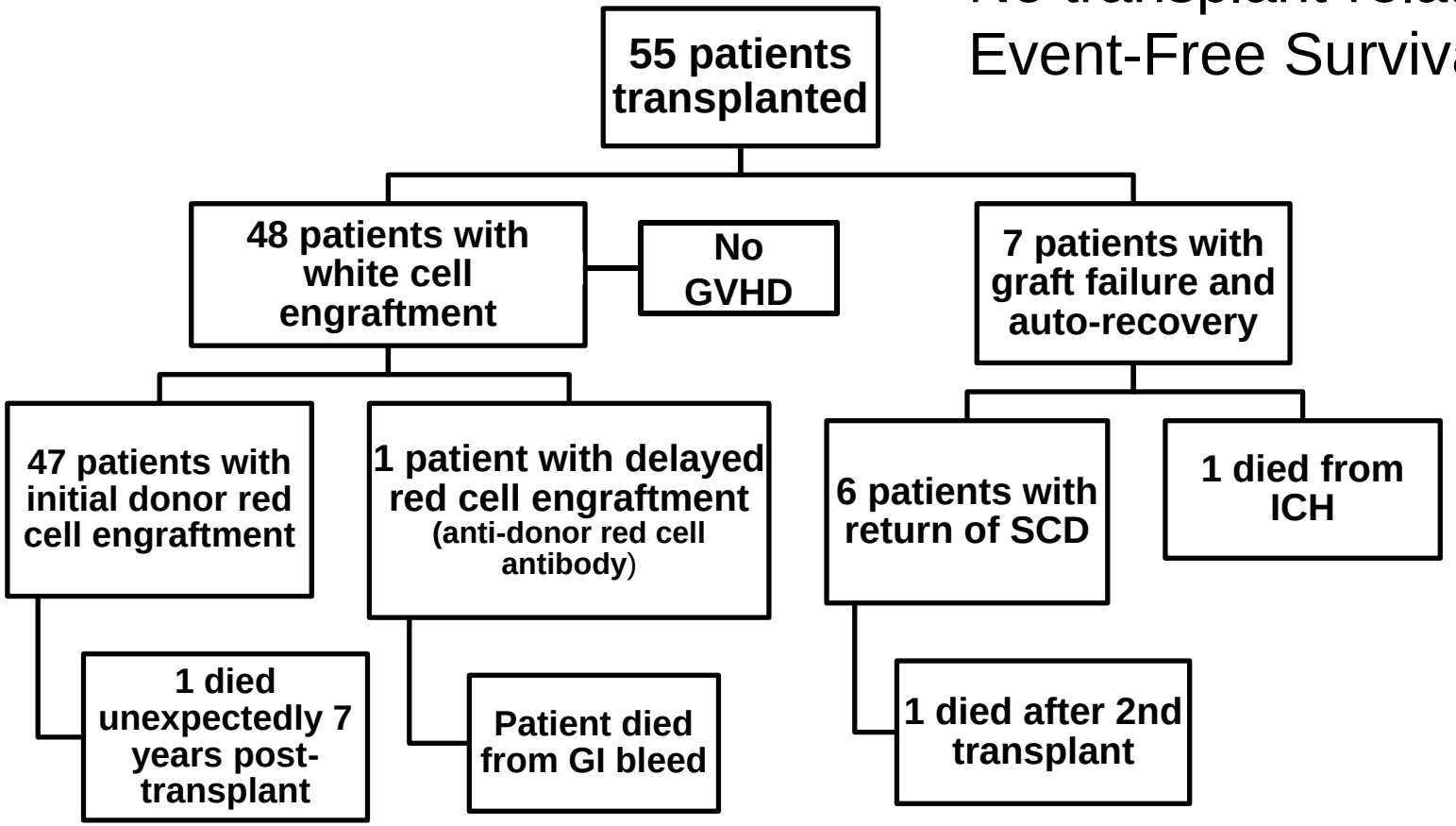


Hsieh MM, Kang E, Fitzhugh CD, et al. NEJM, 2009. 361(24): 2309-2317.

Transplant Outcome

55 patients transplanted, 54 with SCD and 1 with β-thalassemia
Age range: Median 29, range 10-65 years old
Follow-up: 6.4 years (range 0.5-14.4 years)

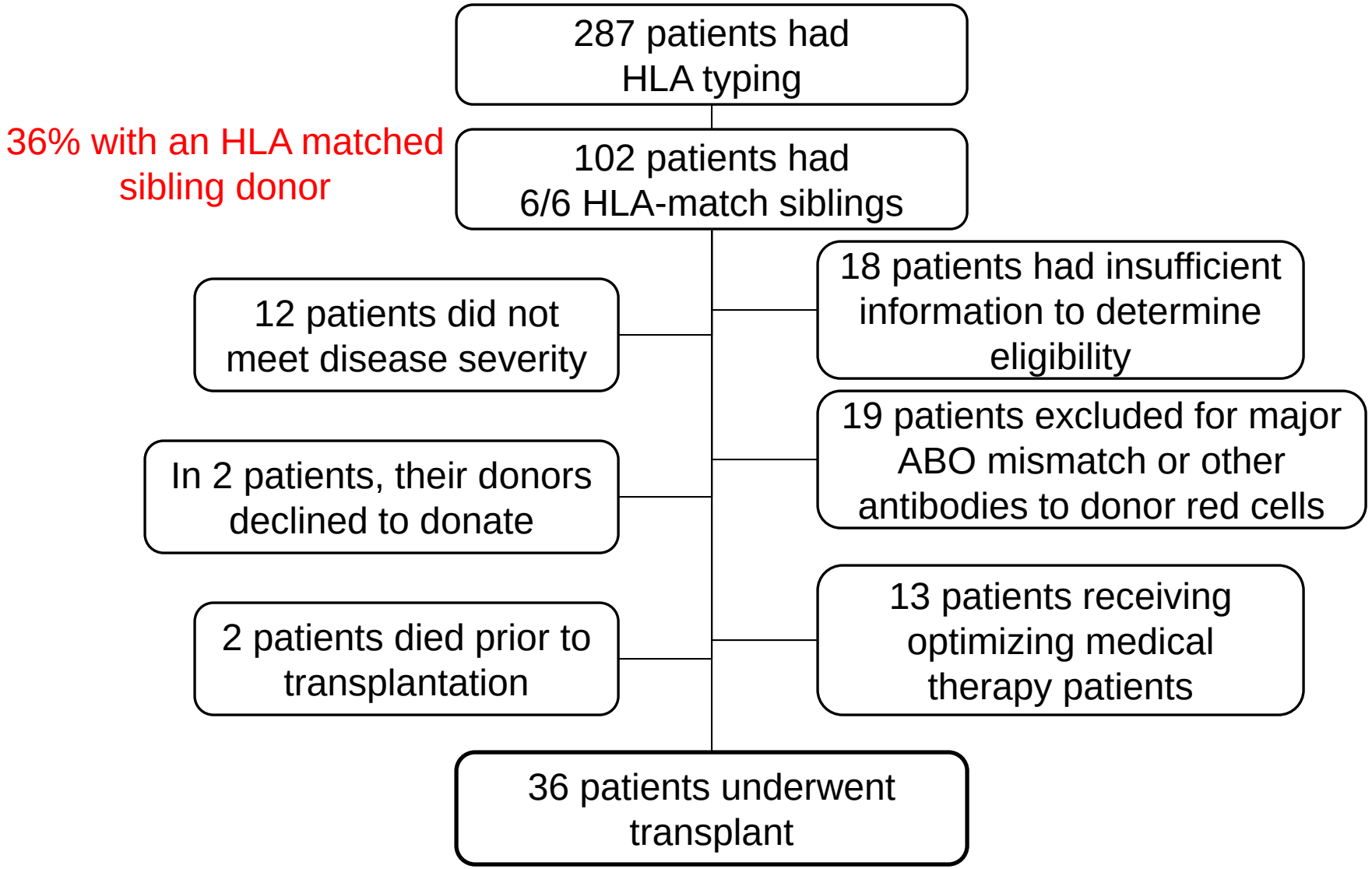
Overall Survival: 93%
No transplant-related mortality
Event-Free Survival: 87%



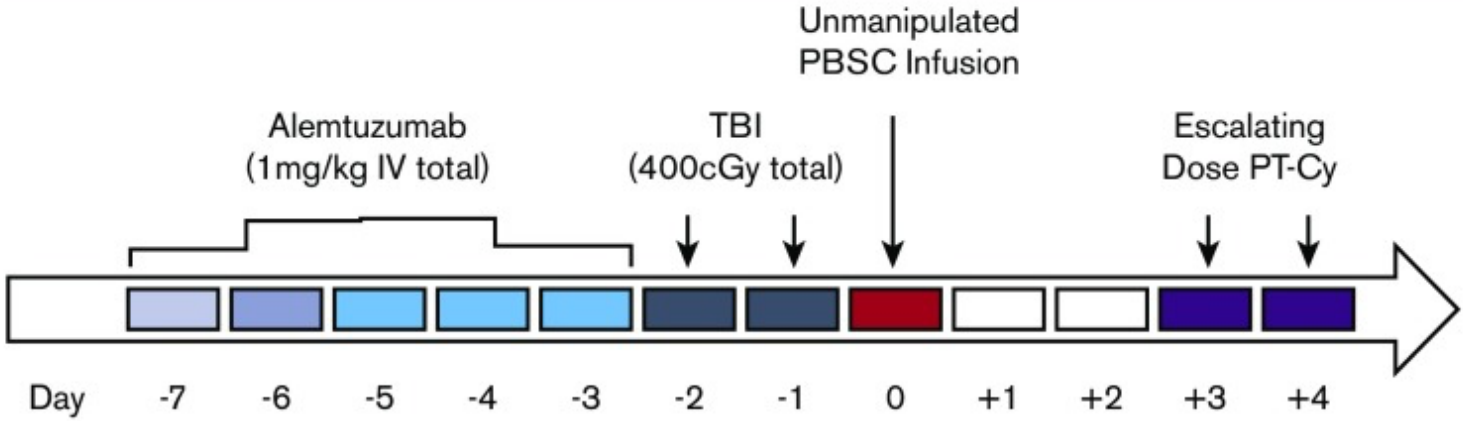
Matthew Hsieh
John Tisdale

8 patients have had 13 healthy babies post-transplant

Vast Majority of Patients do not have an HLA-Matched Sibling



Nonmyeloablative Haploidentical PBSC Transplantation for Adults with Severe Congenital Anemias



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 CD et al. Blood Advances, 2017. 1(11): 652-661.

Engraftment and Success Rates Improve with PT-Cy

Cohort	Cumulative Cytoxan Dose (mg/kg)	Engraftment Rate (Before Day +100)	Event-Free Survival	GVHD
1	**0**	**1/3 (33%)**	**0/3 (0%)**	**0**

- No mortality before day 100 despite very severe disease
- 5 patients who rejected their grafts died 6 months and 3, 5, 7 and 8 years post-transplant, mostly from SCD-related complications (overall survival 78%)

Fitzhugh CD et al. Blood Advances, 2017. 1(11): 652-661.

Gene Transfer for “Gene Addition” Therapies

- Patients serve as their own donor
- Available for all patients
- No need for immunosuppression
- No risk of graft-versus-host disease

- Myeloablative conditioning with busulfan is necessary
- Short and long term success not known

How do patients decide whether to move forward with transplant and which transplant option to choose?

First we help them assess their disease severity

- Mild:
  - Crises are manageable at home
  - About 1 hospitalization or less per year
- Moderate:
  - 2 or more hospitalizations per year with or without 1-2 organs injured
    - High tricuspid regurgitant velocity (at least 2.5m/s)
    - Sickle cell-associated liver disease
    - Avascular necrosis of multiple joints
    - Alloimmunization
- Severe
  - Any permanent organ damage
    - Stroke
    - Kidney failure
    - Cirrhosis
  - 3 or more organs injured

We have to ensure that in each individual patient, the potential benefits outweigh the risks

- The eligibility criteria for our transplant protocols initially included patients at increased risk for early mortality
- The haploidentical protocol only enrolls patients who maintain disease severity with therapeutic doses of hydroxyurea
- Our newer protocols do not include children because the survival for children is so high that any significant mortality cannot be justified
- This can be very difficult for patients because the vast majority of patients who seek transplant believe their disease is severe

Next Steps for Patients with Moderate to Severe Disease

	HLA-matched sibling	**Haploidentical**	**Gene Therapy**
Donors	Sibling	Parent, child, sibling	Self
How many transplants performed?	>1000 worldwide >70 at the NIH	~100 worldwide >20 at the NIH	~20 worldwide >10 at the NIH
Success rate	>90%	50-70%	1st group (~6 pts) all partially worked 2nd group (~6 pts) all with sickle trait
Preparation	~2 months: much testing, titrate up hydroxyurea, red cell exchange	~2 months: much testing, titrate up hydroxyurea, red cell exchange, collect back-up stem cells from self	2-4 months: much testing, stop hydroxyurea, red cell exchange for at least 2 months, collect back-up stem cells from self and for gene therapy

Next Steps for Patients with Moderate to Severe Disease

	HLA-matched sibling	**Haploidentical**	**Gene Therapy**
Conditioning regimen	1. Low dose radiation + antibody (chemo-free) 2. Low dose radiation + antibody + 2 chemo (low dose)	Low dose radiation + antibody + 2 chemo (higher dose)	No radiation 1 chemo at high dose
Time involvement	Inpatient: 1-1.5 months Total: ~4.5 months	Inpatient: 1-1.5 months Total: ~4.5 months	Inpatient: 1-1.5 months Total: ~4-6 months
Fertility potential	Should be able to have kids naturally; younger patients have better chance	Less potential than HLA-matched sibling	Virtually none without help
Testing and storage of sperm/eggs	Optional but recommended	Highly recommended	Strongly recommended

How is the final decision made about haploidentical transplant vs. gene therapy?

- Most commonly determined by eligibility criteria
  - Patients with significant organ damage are currently excluded from gene therapy
- Gene therapy
  - Patients feel they have already inconvenienced family members enough and like that they can be their own donor
    - Do not want to put family members at risk
- Haploidentical
  - Patients no not want to receive full dose chemotherapy
- Both protocols offer ovarian cryopreservation and equivalent stipends

Case Presentation

- 21-year-old African-American gentlemen with homozygous sickle cell disease complicated by stroke requiring chronic transfusion therapy, recurrent painful crises and acute chest syndrome, and history of multi-organ failure
- The patient and his mother were educated multiple times about the potential benefits and risks of haploidentical transplant including graft rejection
  - At the time of consent on 4/27/12, he was the 9th patient to be enrolled, and 5 patients had rejected their grafts
  - While they understood the potential risks that were mentioned, the mother kept saying that she had faith and she knew the transplant would be successful for him
- The patient underwent transplant on 5/10/12, his mother was the donor
- His neutrophil count initially increased to 630/uL 20 days post-transplant with donor chimerism levels up to 84%
  - He never fully engrafted, remaining severely pancytopenic
- On 7/17/12, they were informed that he had rejected the graft
  - They were in shock, as if they had never been told that graft rejection was a possibility

Motivations and Decision-Making of SCD Patients in High Risk Clinical Research

- Our ethics team conducted interviews with patients with SCD who had made a decision about participation in a transplant trial at the NIH
- We sought to evaluate motivations, decision-making process, understanding of research, and retrospective reflections
- 26 patients agreed to be interviewed

Christine Grady MD, Scott Kim MD, Hae-Lin Cho, MD

Baseline Characteristics

Mean age (SD)	**39.7 (11.3)**
Gender	
Male	**10**
Female	**16**
Race	
Black/African American	**23**
White/Caucasian	**1**
Asian/Asian American	**1**
Mixed/Other	**1**
Birthplace†	
U.S.	**14**
Outside the U.S.	**11**
Education†	
Less than high school	**2**
High school	**19**
College or some college	**3**
Graduate school	**1**
Religious Preference	
Protestant/other Christian	**18**
Catholic	**5**
None/not religious	**3**
Income†	
Some money left over	**4**
Just enough money	**7**
Not enough money	**14**
Phase of trial	
Pre-transplant	**7**
Half-match transplant	**4**
Gene therapy	**3**
Post-transplant	**13**
Full-match transplant	**4**
Half-match transplant	**5**
Gene therapy	**4**
Decline	**6**
†Total does not add to up 26 because one patient did not fully respond to demographic information.	

Experiences with SCD

Severe pain, frequent hospitalizations and transfusions	**13**
Functional limitations	**13**
Other SCD complications (e.g., osteoporosis, clots)	**8**
Near death experiences	**4**
When you went to the hospital, what was that experience like?	
Healthcare providers with poor understanding of SCD	**14**
Stigmatization as “drug seeking”	**9**
Long waits/delays in the hospital	**6**
Understanding the attitudes of healthcare providers	**4**
Discrimination due to minority status	**3**
How did you first learn about the NIH?	
Referral from an outside physician	**12**
Friend/family member	**5**
Circumstance (e.g., happening on an advertisement)	**5**
Self-research	**4**

Do Patients Understand the Consent Process?

- 2/3rd of patients clearly described the purpose of research as scientific knowledge and/or benefiting future patients
- All patients expressed awareness that transplant and gene therapy studies carried side effects and risks including death, cancer, GVHD, and HIV
- 22 of 26 acknowledged that the treatment might not work
- Their main worries included unsuccessful response, death, pain, and potential long-term side effects

Decision-Making Process

- Most patients described performing a personal risk-benefit ratio when deciding about participation
- All patients who decided to enroll cited the intolerability of their current SCD symptoms and/or hope for a better future without SCD
  - Wanted to feel like less of a burden on family members, be alive and more present for their children, maintain a job, and finish school
- Those who declined enrollment felt their current status was not bad enough to justify the risks of the trial
- Half of patients referred to altruistic motivations, but none reported altruism as their primary motivation

Role of Family, Faith, and Other Patients

What role, if any, did your family have in your decision making?*	
Providing moral support and reassurance	**21**
Worrying about risk and/or discouraging participation	**8**
Pushing participation	**4**
Not involved	**2**
Did you speak with any other patients who had gone through gene therapy or transplant?*	
No, talked to no one	**7**
Yes, talked to patient(s) who did well	**11**
Yes, talked to both patients who did well and who did not do well	**5**
Would you consider yourself religious and/or spiritual? If so, what role did your faith, if any, have in your decision-making?*	
General support from God and/or faith	**11**
Religious, but no role or influence	**9**
Outcome-related faith in God (e.g., God will protect me from risk)	**5**
Support from church leaders and/or community	**2**
Not religious	**2**
***Total may not add up to 26 because some patients provided multiple responses or did not respond**	

Conclusions

- We must ensure that in each individual patient that the potential benefits outweigh the risks
- We must clearly state the benefits and risks of each transplant process and standard of care to help patients make an informed decision
- Patients rely strongly on their family, other patients, and their faith when making decisions about transplant

Life Without Sickle Cell Anemia

- “Well, my son knows I’m his mother now because I’m not usually in the hospital…I can actually play with him, go to the playground, do normal things…Now, I can keep my promises- when I say I’m going to be somewhere, I can actually be there.”