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Sickle Cell Disease and What the Future Holds

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1

Speaker Disclosure

- No financial disclosures to note

2

Learning Objectives

Review	• Review the pathophysiology of sickle cell disease and common complications
Summarize	• Summarize the standard of care treatment and allogenic bone marrow transplant for sickle cell disease
Discuss	• Discuss gene therapy and the two recently FDA approved gene therapies
Compare	• Compare allogenic bone marrow transplant to gene therapy

3

Sickle Cell Overview

4

Demographics & Incidence

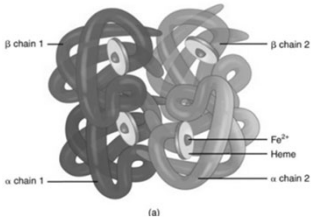
- Globally, most common in Africa, Middle East, and India
  - ~300,000 new cases per year
  - Anticipated to surpass 400,000 cases by 2050
- In the United States
  - Affects approximately 100,000 people
  - Occurs among 1:356 Black or African American births
  - Idenfified by newborn screening

(CDC, 2023; Novartis, 2023)5

5

Hematology 101

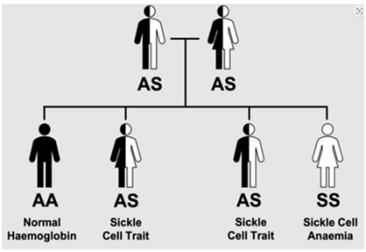
- Erythrocytes mature in the bone marrow
- Lifespan of ~120 days
- Hgb comprised of 2 alpha and 2 beta chains
  - Contain iron, which binds to oxygen
- Rd blood cell shape suits function
  - Biconcave and spectrin allow entry into small capillaries



(Quinn, 2013) 6

6

Sickle Cell Inheritance



- Autosomal recessive
- Inherited through single amino acid substation in beta globin chain
- Sickle cell trait vs sickle cell disease

(CDC, 2023) 7

7

Sickle Cell Disease vs Trait

Sickle Cell Anemia

- HbSS - inherited two abnormal Hgb genes, typically most severe form of disease
- HbSC – less severe form of sickle cell

Sickle Cell Trait

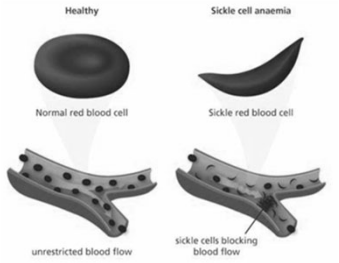
- HbAS – one abnormal Hgb gene and one normal gene
  - Typically no signs of the disease

(CDC, 2023) 8

8

Sickled Hemoglobin

- Amino acid substitution affects shape
  - Elongated, sickled shape when blood is deoxygenated
- Red blood cell membrane becomes dehydrated, rigid, and abnormally adherant to blood vssles
- Reduction in sickled cell survival time
- Blockages to small vessles and tissue distruction



(Vinod et al., 2016) 9

9

Diagnosing Sickle Cell Disease

- Blood test
  - Hemoglobin electrophoresis
  - Genetic testing
- Prenatal Screening
  - Amniocentesis
- Newborn Screening
  - Heel prick at birth
- Symptomatic onset
  - Sickled cells begin production at ~6mo

(Andrews, 2014) 10

10

Symptoms

Anemia	• Lifespan of sickled cell is 10-20 days • High reticulocyte count
Episodes of pain	• Sickled cells block flow through tiny vessels • Lasts hours to days
Swelling of hands/feet	• Sickled cells block blood circulation in periphery

(Mayo Clinic, 2023) 11

11

Symptoms

Frequent infections	• Sickled cells damave the spleen • Prophyltic Penicillin
Delayed growth/puberty	• Shortage of healthy red blood cells can slow growth
Vision problems	• Sickled cells can obstruct vessels to the eyes

(Mayo Clinic, 2023) 12

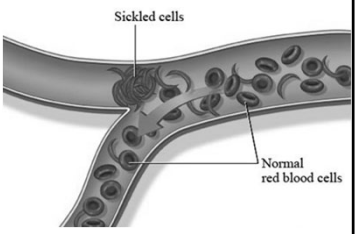
12

Complications

13

Acute Pain Crisis

- Pain is the most common complication of Sickle Cell Disease
- Pain Crisis (Vaso-occlusive episode)
  - Starts suddenly
  - Mild-to-severe
  - Can last for any length of time
  - Typically in hands, feet, chest, and back
  - Fever can occur concurrently
- Often requires hospitalization
- Simple or exchange transfusion may be warranted

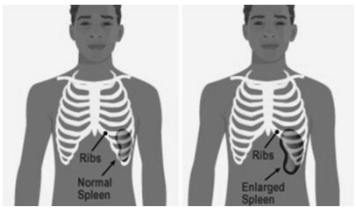


(Borhade et al., 2022; CDC, 2023)

14

Splenic Sequestration

- Most commonly occurs between 6mo to 5yr old
- Occurs when an excessive amount of blood becomes trapped in the spleen
- Causes dangerous drop in circulating blood volume
- Diagnosed through clinical exam
- Magement includes
  - Red blood cell transfusion
  - Splenectomy in extreme case



(Kane et al., 2023)

15

Stroke

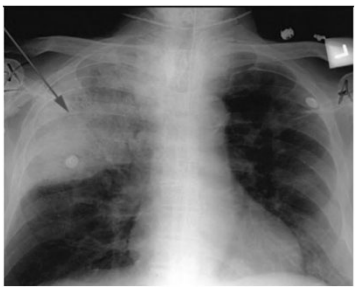
- Occurs if sickled cells get stuck in blood vessels of the brain
- Approximately 10% of children with sickle cell will have a symptomatic stroke
  - Silent cerebral infarct occurs in 17%
- Transcranial doppler ultrasound recommend every 2 years until 16 years of age

(CDC, 2023)

16

Acute Chest Syndrome

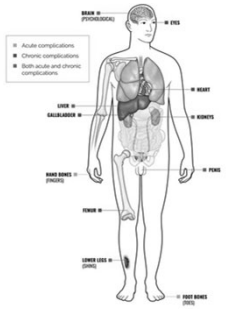
- Life threatening complication
- Occurs when sickled cells block blood and oxygen from reaching lungs
- Causes
  - Infection – viral vs bacterial
- Symptoms are similar to pneumonia
  - Chest pain
  - Coughing
  - Difficulty breathing
  - Fever
- Treatment
  - Supportive care



17

Long Term Effects

- Average lifespan reduced by 20 years
- Vision loss
- Cardiac chamber dilatation
- Chronic transfusions cause liver/gallbladder damage
  - Iron overload
  - Cholelithiasis
- Priapism
- Leg ulcers



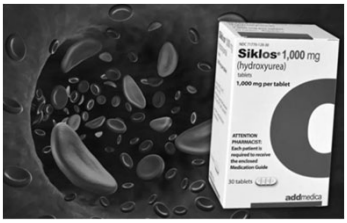
18

Treatment Options

19

First Line Therapy

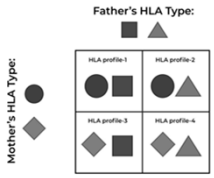
- Hydroxyurea
- First line therapy
- Increases fetal Hgb and decreases the deoxygenazation-induced polymerization of sickled Hgb
- Decreases hemolysis and vaso-occlusion but does not provide a cure
- Side effects: bone marrow suppression, increased risk for infection, skin ulcers, secondary leukemia



20

Curative Matched Sibling Allogenic Bone Marrow Transplant

- First BMT in SCD was in 1984 in a child who developed AML who was cured of both disorders
- Cure rate using HLA-matched sibling donor >90%
- 25% chance of a sibling being a match
- Okay if sibling has sickle cell trait
- Only ~10% of patients with SCD have an HLA-MSD



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(Fitzhugh, 2014) 21

21

Alternative Donors

- Matched unrelated donor is associated with increased risk of GVHD and limited donor pool
- Umbilical cord is limited due to lower cell dose and not all institutions being cord blood institutions
- Haploidentical donors are more accessible and becoming more popular in patients with SCD
  - T-cell depletion using post-transplant cyclophosphamide has improved engraftment rates and reduced GVHD
- Increasingly being used to treat older SCD patients, <3,000 patients globally have undergone allogenic BMT

National Association of Pediatric Nurse Practitioners

(Brandow & Liem, 2022) 22

22

Downsides to Allogenic Bone Marrow Transplant

- Lack of available donor
- Only available for patients with severe sickle cell
- Chronic complications are not reversed with BMT
- Risk of morbidity and mortality
- Risk for post-transplant complications including GVHD and graft failure
- Several months of IST to prevent GVHD
- Better to come to transplant at a younger age

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(Brandow & Liem, 2022) 23

23

Gene Therapy

24

24

What's Next? The Future is Here

- SCD results from a single point mutation making gene therapy an attractive treatment option
- The Cure Sickle Cell Initiative was developed in 2018 and is a NHLBI-led collaborative effort that will accelerate the development of gene therapy
- Visit curesickle.org for more information

25

Gene Therapy

Gene Addition

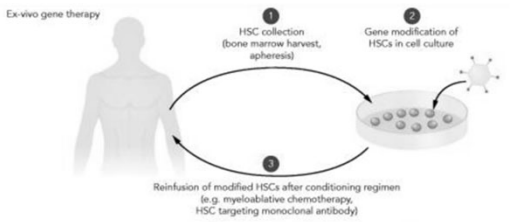
- Addition of a new gene using a viral vector to deliver a non-sickling globin gene

Gene Editing

- CRISPR technology adds/deletes genes to increase gamma globin production

26

Autologous – Ex Vivo



27

Mobilization for Stem Cell Collection

- Discontinuation of disease modifying therapies >60 days prior to mobilization
- Monthly red cell exchanges until transplant to keep HbS ≤30%
- GCSF is contraindicated in SCD so patients will receive plerixafor to mobilize CD34+ stem cells
- Will undergo 1 to 3 leukapheresis cycles to collect cell goal for manufacture
- **A challenge is collection requires specialized expertise that not every center has**

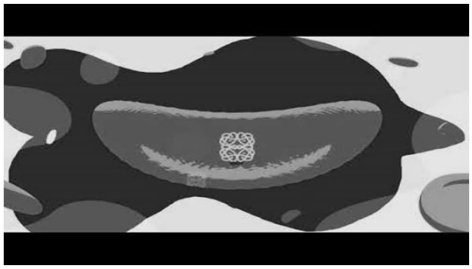
28

Conditioning Regimen & Stem Cell Infusion

- Single agent use of busulfan - it is myeloablative but not immunosuppressive
- Manufactured product will be infused on Day 0
- Since single agent use will take longer to nadir and count recover
- No risk of GVHD or graft rejection

29

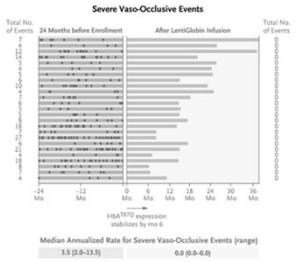
For Visual Learners



30

Lyfgenia - Bluebird Bio

- **Design:** HGB-206 phase 1/2 trial
- **Intervention:** Lentiviral gene addition resulting in anti-sickling HbA_{T87Q}
- **Results:** sustained production of HbA_{T87Q} leading to reduced hemolysis and resolution of severe vaso-occlusive events
- FDA approved 12/8/23



31

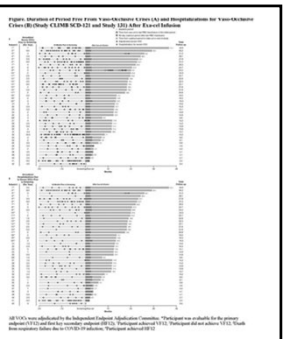
Qualified Treatment Centers

- Majority are Children's Hospitals
- This list is evolving as more centers become qualified centers
- Visit www.lyfgenia.com for up-to-date list

32

Casgevy – Vertex

- **Design:** CLIMB SCD-121 phase 3 trial
- **Intervention:** CRISPR gene editing of BCL11A to reactivate fetal hemoglobin
- **Results:** sustained increase in HbF leading to elimination of vaso-occlusive events in 95% of pts
- FDA approved 12/8/23



(Frangoul et. al., 2023)

33

Qualified Treatment Centers

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(Vertex, 2023)

34

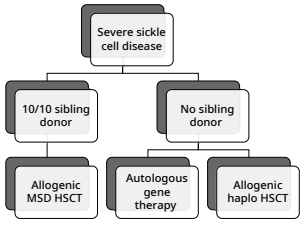
Allogenic BMT vs Gene Therapy

	ALLOGENIC HSCT	GENE THERAPY
Myeloablation Risks	Present	Present
Speed of Engraftment	Faster	Slower, particularly plts
Autoimmunity Risk	Present	None
Infection Risk	Higher	Lower
Medication Burden	Higher	Lower
IST/GVHD	Yes	No
Degree of Phenotype Correction	Typically complete, if full chimerism	Partial, but okay for SCD
Time When Efficacy Can be Determined	Early	Late (6-9 months post)

35

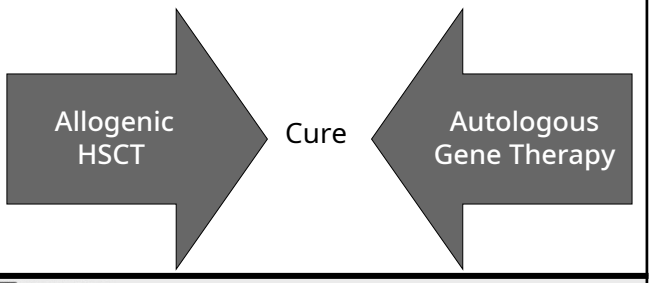
How to Decide?

- HLA matched sibling still preferred
- Gene therapy is just becoming FDA approved and long-term outcomes are still being studied
- Future research comparing outcomes



36

What would you do?



37

Current and Future Challenges for Gene Therapy

Availability
- Current: limited qualified treatment centers
- Future: limited manufacturing capacity?
- $$$

Exportability
- Conditioning/infusion straightforward
- Collection requires specialized expertise
- Long Term Follow-Up
- 15+ years, coordinating networks of centers likely needed

In the Future…
- Comparison to HLA-MSD allogenic BMT
- Elimination of alkylating agent conditioning?

38

Case Study

- 27yo with SCD self-referred himself from Arkansas to CHCO when he heard we had an investigational gene therapy available
  - Did not have his 1st VOE until 4yo
  - Had intermittent VOE growing up which were usually treated outpatient
  - Started hydroxyurea at 20yo
  - Over the past 2 years has had increasing frequency of VOE requiring hospital admissions (11x) and 6 ED visits requiring IV analgesia but not admission
  - Baseline: essential HTN and persistent proteinuria/CKD d/t underlying SCD
- Screening visit completed and consented to study
- Discontinued hydroxyurea and started on monthly exchange transfusions

39

Case Study

- Mobilized w/ plerixafor and underwent 3 leukapheresis cycles to collect cell goal that was sent out for manufacturing
- Received an exchange transfusion prior to each collection cycle
- He continued to come to CO monthly for exchange transfusions and had to be admitted several times for VOE
- In February 2023 he was admitted to start his conditioning regimen with busulfan on day –7 through –4
- Received his autologous gene edited stem cells on 2/28/23
- Transplant course complicated by mucositis, F/N, CINV, AKI but no SAEs
- Engrafted on day +24, central line removed and discharged on day +26
- A year post transplant he has had no VOE and reports he feels like a new man!

40

Acknowledgments

- Mentorship
  - Dr. Verneris
  - Dr. Fabrizio
  - Dr. McKinney
  - Ali Keasler, RN
- BMT APP Team
- BMT MD Team
- Patients & Families of CHCO
- Our emotional support
  - Jaxon, Billie & Zola

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41

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42

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43