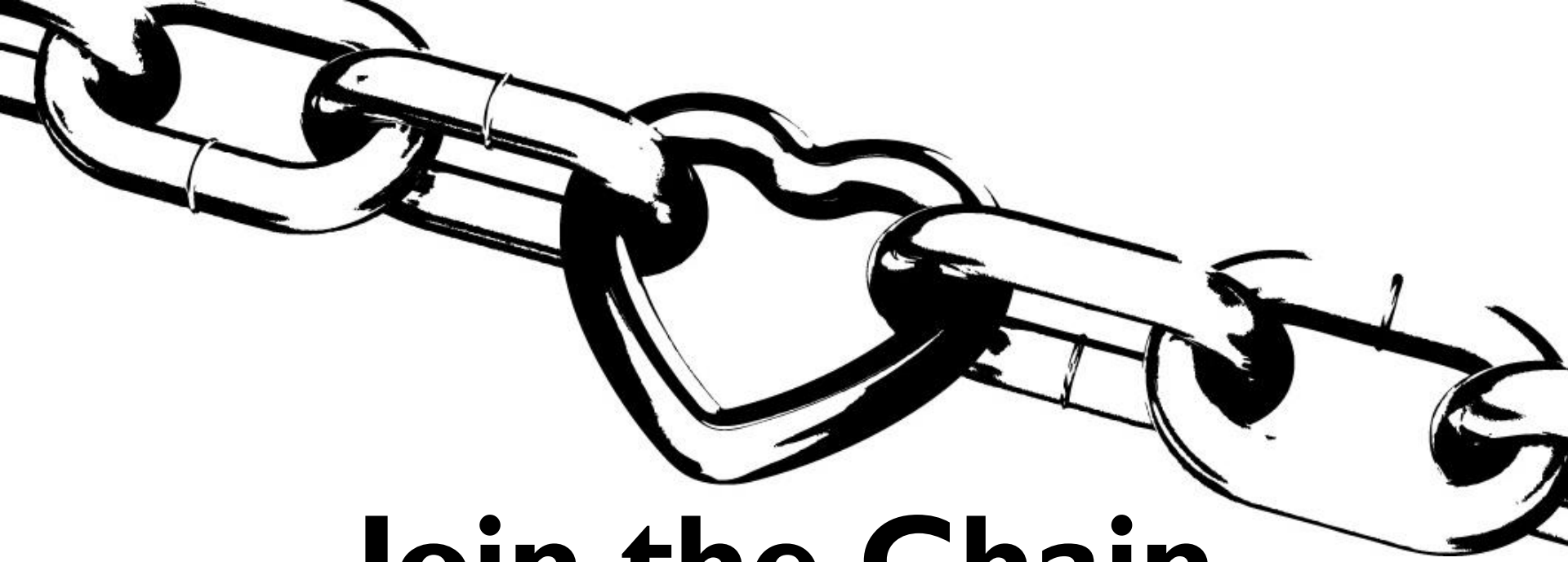

Join the Chain

Stop the Pain of Sickle Cell

Statewide Sickle Cell Conference
April 20, 2012

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Hematopoietic Stem Cell Transplantation for Sickle Cell Disease

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2012 Indiana Statewide Sickle Cell Disease Conference
4/20/2012

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What is hematopoietic stem cell transplantation?

- HSCT: Infusion of adult blood stem cells for correction of genetic, immune, metabolic, or malignant diseases
  - Allogeneic: blood stem cells from someone other than self (sibling, parent, unrelated)
- Other common names:
  - Bone marrow transplantation (BMT)
  - Blood and marrow transplantation (BMT)
  - Hematopoietic cell transplantation (HCT)

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Why HSCT for Sickle Cell Disease?

- Genetic blood disorder (hemoglobinopathy)
  - Median survival ~42-48 yrs
  - Survival ~10 yrs lower in severe disease
- **HSCT provides only available curative therapy**
  - Rationale: replace bone marrow with donor adult blood stem cells that produce normal Hgb A and red cells
- First report of cure in 1984: allogeneic HSCT for 8 y/o girl afflicted with SS disease AND acute myeloid leukemia
  - Johnson FL, et al. *NEJM* 1984

Considerations-HSCT in sickle cell disease

- Diverse spectrum of clinical disease severity
- Identifying the “bad actors” (more severe disease)
- Limited donor availability
  - **<25% with matched related donor (preferred)**
  - **~50% with siblings with Hgb AS (Sickle cell trait)-OK!**
- Weighing risks vs. benefits
  - HSCT-related complications vs. natural history of sickle cell disease
  - Who to transplant and when???

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Who should be considered for HSCT?

Table 4 Indications and contraindications for HCT in sickle cell disease

Recipient characteristics/disease manifestations	*Absolute Indication*	*Relative indication*	*Relative contraindication*	*Absolute contraindication*
Asymptomatic child (<16 years)		X		
Symptomatic child (<16 years)	X			
Symptomatic adolescent (16–19 years)		X		
Symptomatic young adult (20–30 years)			X	
Older adult (>30 years)				X
Overt stroke	X			
Silent stroke		X		
Recurrent ACS/severe VOC/AVN		X		
Poor QOL due to disease		X		
Pulmonary hypertension			X	
Renal failure				X
Hepatic cirrhosis				X

Abbreviations: ACS = acute chest syndrome; AVN = avascular necrosis; HCT = hematopoietic SCT; QOL = quality of life; VOC = vaso-occlusive crisis.

Shenoy S. *BMT* 2007; **40**: 813-821

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HSCT Donor and Preparative Regimen

- Matched related donor (MRD) preferred
  - Bone marrow
    - Overall survival 90-100%, Disease-free survival 85-90%
    - Use of low toxicity chemotherapy or immune suppressive medications to help patients accept donor cells
      - ex.) Alemtuzumab/Fludarabine/Melphalan
    - Low risk of rejection ≤ 5%
      - Only 20-25% donor HSCs needed to make healthy RBCs
    - Risk of infection-1st year due to immune suppression
    - Melphalan: fertility and secondary cancer later (?)
    - GVHD (graft-versus-host disease):
      - 10-15% acute, 10% chronic

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HSCT Donor and Preparative Regimen

- MRD-umbilical cord blood (UCB)
  - Feasible, ongoing area of research
  - Obstacles:
    - Graft rejection/failure: ~4%
      - (Walters, et al. *Ann NY Acad Sci* 2005)
    - Overall survival 89%, Disease-free survival 84%
    - Requires more intensive preparatory therapy for similar success, but with long-term concerns
      - Busulfan- lung, liver, neurotoxicities, ovarian failure
      - Cyclophosphamide: lung, liver, ovarian failure, sterility
      - Risks of secondary cancers later in life (?)

HSCT Donor and Preparative Regimen

- Matched/mis-matched unrelated donor (URD)
  - Requires more intensive therapy
    - similar to related UCB
  - Higher rates of graft failure/rejection
    - Especially a problem for unrelated cord blood
  - Higher rates of GVHD: HSCT-related complications without benefit to Hgb SS patients
    - Associated with prolonged immune suppression and higher rates of infection
  - Progress being made…but more work to be done!

Summary

- MRD HSCT provides a significant opportunity for cure in sickle cell disease
- Ability to use low toxicity preparatory regimens with success in MRD HSCT
  - Benefits > Risks of HSCT>> Morbidity and Morality of Hgb SS disease
- URD HSCT is a consideration and technically feasible, but…careful assessment of risks/benefits
- Consideration for HLA-typing full biological siblings to know what HSCT options exist

Questions?

Riley Hospital for Children
Indiana University Health

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Thank you!