HEMATOPOIETIC STEM CELL TRANSPLANT FOR SICKLE CELL DISEASE: PERSPECTIVES FROM CHILDHOOD TO ADULTHOOD

Karen Swiss, PharmD, BCOP
Clinical Assistant Professor
Clinical Pharmacist in Hematology and Stem Cell Transplant
Department of Pharmacy Practice
University of Illinois College of Pharmacy
Chicago, IL

Disclosures
• I have no actual or potential conflict of interest in relation to this program/presentation.

Objectives
• Define the pathogenesis and clinical sequelae of sickle cell disease (SCD) in pediatric and adult patients
• Identify the indications for allogeneic hematopoietic stem cell transplantation in pediatric and adult patients with SCD
• Explain the immunology underlying the use of allogeneic hematopoietic stem cell transplantation in SCD
• Compare the efficacy and toxicity of the various preparative regimens used in pediatric and adult patients with SCD
Sickle Cell Disease: A Global Burden

- **Incidence**
  - Affects 90,000 to 100,000 Americans
  - Occurs among 1 out of every 500 Black or African-American births
  - In Africa, newborn children born with SCD estimated to be 200,000 to 300,000

- **Mortality**
  - Kills nearly half a million people annually

- **Economic Costs**
  - For adults with SCD the average annual cost of medical care exceeds 35,000 US dollars per year

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SCD: Pathophysiology

SCD: Clinical Sequelae
### SCD Mortality Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>MSH n=559</th>
<th>CSSCD n=9764</th>
<th>CSSCD n=1056</th>
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</thead>
<tbody>
<tr>
<td>Episode of Acute Chest Syndrome (ACS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>≥3 pain crisis annually</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hgb F &lt;0.5 g/dL</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Anemia with low reticulocyte counts</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Seizure History</td>
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<tr>
<td>Elevated WBC</td>
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<tr>
<td>Stroke</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sickle cell lung disease and retinopathy</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Leg Ulcers</td>
<td>X</td>
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<td>X</td>
</tr>
</tbody>
</table>

MSH: Multicenter Study of Hyd Roxylurea in Sickle Cell Anemia, CSSCD: Coop erative Study of Sickle Cell Disease

### SCD Management

- **Supportive**
  - Hydroxyurea
  - Stimulating Agents
  - Blood transfusion
  - Iron Chelation

- **Symptomatic**
  - Analgesics
  - Blood transfusions
  - Antibiotics

- **Prevention**
  - Penicillin/Vaccinations
  - Blood transfusions
  - Hydroxyurea

### Treatment of Adult SCD

- Clinical course worsens in adulthood
- Treatment Challenges
- Mortality sharply increases every decade over 20 years old

Treatment challenges:
- Lack of compliance to long-term medications
- Overuse and dependence of narcotics
- Loss of productivity
- Psychological symptoms in adulthood
What are other treatment options to improve mortality for Adult SCD patients?

Hematopoietic Cell Transplant (HCT)

SCD and Transplant: A historical perspective

As of 2013, there were 1238 BMTs for SCT reported to CIBMTR and EBMT-Eurocord. CIBMTR: Center for International Blood and Marrow Transplant Research. EBMT-European Blood and Marrow Transplant.

Transplantations for SCD

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>HLA-Identical</td>
<td>487</td>
<td>430</td>
</tr>
<tr>
<td>Cord blood related and unrelated</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>Haploidentical donor</td>
<td>34</td>
<td>61</td>
</tr>
<tr>
<td>Other unrelated donor</td>
<td>17</td>
<td>65</td>
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</table>

Overall Survival

<table>
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</thead>
<tbody>
<tr>
<td>1 year</td>
<td>95% ± 1%</td>
<td>96% ± 2%</td>
</tr>
<tr>
<td>2 year</td>
<td>94% ± 1%</td>
<td>94% ± 1%</td>
</tr>
</tbody>
</table>

Gluckman E. ASH educated book 2013: 370-376
**Benefit versus risk in HCT for SCD**

**Benefits**
- Prolonged lifespan
- No clinical vaso-occlusive events
- Improved quality of life
- Cessation of anemia and RBC transfusions
- Fewer hospitalizations

**Risks**
- GVHD
- Infertility
- Delayed immune reconstitution/infection
- Treatment-related malignancy
- Death

**Challenges in SCD patients**
- Patient selection and timing of transplant
  - Still a debate as to who and when transplant should occur
- Limited patient eligibility
  - Disease and age-related comorbidities result in higher morbidity and mortality in older patients
- HCT not available to most patients
  - Socioeconomic setting
  - Absence of matched related donor
- Serious concerns about transplant-related mortality
  - GVHD, infertility, treatment-induced malignancy

**Challenges in SCD patients**
- Donor availability
  - 25% probability of being HLA-matched to sibling
  - 19% chance of finding potential alleleic 8/8 MUD
- Patient perception
  - 62% were willing to accept > 10% TRM
  - 30% willing to accept 30% TRM
  - 50% were willing to accept infertility
  - 20% willing to accept chronic GVHD
**HCT Options for SCD**

- **Matched sibling donor**
  - Majority of transplants performed
  - Preferred due to low GVHD and graft failure
  - Siblings with sickle cell trait acceptable donors

- **Umbilical cord**
  - Related or unrelated UCB transplants have been performed
  - Slower neutrophil recovery and less GVHD

- **Matched unrelated donor**
  - Limited data evaluating MUD for SCD
  - SCURT (Sickle cell unrelated donor transplant) study

- **HLA-haploidentical**
  - Post-transplant cyclophosphamide
  - Low rates of GVHD and graft failure

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**First SCD transplant**

- First successful HCT in an 8-year-old girl with SCD
  - Matched sibling donor (MSD) with sickle cell trait
  - Myeloablative conditioning regimen: CY 120 mg/kg over 2 days and TBI 11.5 Gy
  - GVHD prophylaxis: MTX and methylprednisolone
  - Patient cured of both AML and SCD
  - Proof-of-principle for future platforms to study HCT in SCD

- **Walters et al.** study of 22 patients
  - MSD using Bu/CY/ATG
  - EFS and OS at 4 years 91% and 73%, respectively
  - Graft failure 19%

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**Indications for HCT in Pediatric SCD**

- Age < 16 years old
- HLA-identical sibling
- Symptomatic SCD (1 or more below)
  - Stroke
  - ACS with recurrent hospitalizations or previous exchange transfusions
  - Recurrent non-obstructive or reocclusive retinopathy
  - Abnormal MRI or impaired neurophysiological function
  - Stage 2 or 3 sickle lung disease
  - Moderate or severe proteinuria, GFR 30-50% predicted value
  - Bilateral proliferative retinopathy
  - Osteonecrosis of multiple joints
  - Red cell alloimmunization during long-term transfusion therapy
Indications for HCT in Adult SCD

- Age ≥ 16 years old
- HLA-identical sibling

Symptomatic SCD (1 or more below)

- Irreversible end-organ damage
- Stroke or clinically significant CNS event
- Seizure: TRV ≥ 2.0 m/s
- Sickle-related renal insufficiency (Cr ≥ 1.5 times the UN or biopsy proven)
- Sickle hepatopathy (including iron overload)
- Reversible sickle complication not ameliorated by hydroxyurea
- Two or more VOC requiring hospitalizations for several years
- Any ACS while on hydroxyurea


HCT in pediatric SCD

- Published results are excellent
  - Four large series report outcomes of more than 250 children
  - Median age less than 10 years
- Patients
  - Donors were HLA-identical siblings
  - High-risk patient population
  - Received fully myeloablative conditioning regimens
- Outcomes
  - Graft rejection 7-18%
  - OS 93-100%
  - HCT eliminates vaso-occlusive symptoms and reverses some of the end-organ damage


MSD with MAC regimen in Pediatric SCD

| Conditioning regimen | Complete (in blood) | Partial (in blood) | Complete (in marrow) | Partial (in marrow) | Median follow-up (yrs) | Graft Rejection | 3y OS | 5y OS
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</thead>
<tbody>
<tr>
<td>Bu/CY ± TLI</td>
<td>90%</td>
<td>60%</td>
<td>90%</td>
<td>50%</td>
<td>100%</td>
<td>90%</td>
<td>95%</td>
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<tr>
<td>Bu/CY/ATG</td>
<td>95%</td>
<td>70%</td>
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<td>85%</td>
<td>50%</td>
<td>85%</td>
<td>50%</td>
<td>100%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
</tr>
</tbody>
</table>

*Abbreviations: Bu/CY = Busulfan/Cyclophosphamide; MAC = myeloablative conditioning; MSD = matched sibling donor; MAC = myeloablative conditioning; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; OS = overall survival; EFS = event-free survival; DFS = disease-free survival; TRM = treatment-related mortality; cGVHD = chronic graft-versus-host disease; aGVHD = acute graft-versus-host disease.*
HCT in Pediatric SCD

- **Efficacy**
  - Most centers used MAC regimens
  - Children transplanted earlier in course of SCD had better EFS/OS
  - In patients who engrafted, resolution of sickle cell phenotype observed
  - Amelioration of painful vaso-occlusive crises, ACS, hemolytic anemia, and transfusion dependence

- **Toxicity**
  - Rejection occurred in 7-10% of patients
  - Incidence of seizures high (anticonvulsant therapy instituted)

Clinical Outcomes of HCT

Patients with stable engraftment experienced resolution of SCD complications:

- No episodes of pain, stroke or ACS
- No SCD CNS complications
- Stabilization of CNS disease by cerebral MRI
- Variable reversal of cerebral vasculopathy
- Improvement of osteonecrosis of humeral head
- Correction of splenic reticuloendothelial dysfunction reported

Long term outcomes in children

Multi-center trial of 55 children who had successful engraftment after MD during the 1990s

- **Neurologic**
  - <1 episodes of stroke per year in patients who had experienced stroke before
  - Most males had hypogonadotropic hypogonadism

- **Pulmonary**
  - Stable or improved at median follow up of 7.3 years after HCT
  - 11 patients with PAH, 5 improved, 6 were persistent

- **Genital**
  - Most female had ovarian failure
  - 8 of 13 patients with obstructive changes at baseline, 1 improved and 1 worsened
Nonmyeloablative (NMA) Regimens in Children

- Effort to reduce transplant-related toxicity
- Iannone et al
  - n=7, median age 9 years
  - Fludarabine and TBI 200 cGy
  - 2 patients received horse ATG
  - GVH prophylaxis: MMF + tacrolimus or CSA
- Results
  - ANC < 0.5 x 10^9 for median 5 days and < 0.2 x 10^9 for 0 days
  - 1 patient grade II aGvHD, 6/7 patients had donor chimism
  - All 6 patients had graft failure, autologous hematopoietic recovery and disease recurrence when immunosuppression tapered off

NMA Regimens in Children

- Increase in graft failure attributed to patients being sensitized to minor histocompatibility antigens from prior blood transfusions and to being immunocompetent
- Donor T cell engraftment was not sufficient to establish stable donor chimism
- Note: ATG was not given to all patients and IS was tapered off anytime b/w ~30 to 200 days

AlloHCT in Adult SCD

- Few adults were in pediatric trials
  - ↓ Survival, ↑ acute GVHD
- Contributing Factors:
  - End-organ damage
  - Transfusions = ↑ Risk of graft rejection
  - Increased age = ↑ Risk for GVHD
- MAC regimens are too toxic for adult SCD patients
Selection of conditioning regimen

MAC experience in young adult SCD

MAC in Adult SCD
Reduced-Intensity Conditioning (RIC) in Adult SCD

- 2 adult patients with end-stage SCD with HLA-identical sibling
- Both patients engrafted; however, due to GVHD complications died within 1 year

RIC and MUD in Adult SCD

- SCURT trial: n=29; median age 14 years; median f/u 25.2 months
- Graft rejection before Day 0 (n=6, 17%)
- 1-year EFS 76%; 1-year OS 86%
- Grade II-IV and III-IV aGVHD at Day 180 31% and 17% respectively
- cGVHD at 1-year was 61% (extension 38%)
- 7 deaths (6 from GVHD, 1 from graft rejection after 2nd transplant)
- PRRS in 35% of patients; CMV and EBV in 23% of patients

NMA conditioning

Key Principles

- Stable mixed donor and recipient chimerism
- Classic transplantation regimens used for hematologic malignancies too toxic for SCD adult patients who have accumulated organ failures and comorbidities before transplant
- Less TRM and low rates of acute and chronic GVHD and graft failure
Mixed Donor Chimerism

Mixed donor chimerism

- Use less intense preparative regimens
  - Reduced-intensity (RIC) or nonmyeloablative (NMA)
  - Complete eradication of recipient bone marrow and GVL not necessary
- Red cell compartment replaced with donor red cells
  - Donor erythrocytes (HbAA) have survival and maturation advantage over recipient erythrocytes (HBSS)
  - Results in majority of donor-derived erythropoiesis
  - Resolution of symptomatic SCD over time

Alemtuzumab mechanism of action

- Originally developed for prevention of GVHD and graft rejection
- Recombinant humanized monoclonal antibody which binds to CD52 on the cell surface and triggers cell lysis
  - CD8, CD4, NK cells, monocytes- depleted up to 1 year
  - B-cells transiently depleted
  - Used in conditioning regimens for in vivo T cell depletion (replaces ATG)
### Pharmacy considerations: Alemtuzumab

**Dosing and Administration**
- Test dose: 0.03 mg/kg IV on D-7; 0.1 mg/kg IV D-6; 0.3 mg/kg IV D-5 to D-3
- Infuse IVPB over 2 hours

**Pre-Medications**
- APAP 650-1000 mg PO, diphenhydramine 50 mg PO, hydrocortisone 100 mg IV on cell, atropine 0.4 mg SC on call, meperidine 25-50 mg IV on call

**Monitoring**
- Blood pressure, heart rate, temperature (infusion reaction)
- CMV PCR for CMV reactivation

**Adverse Reactions**
- Infusion reactions (fever, chills, hypotension, rigors, etc)
- Infection (CMV, HSV, PJP)

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### Sirolimus

- Discovered in 1975 in Easter Island (Rapa Nui to native islanders) hence its original name
- Chemical structure: carbocyclic lactone-lactam macrolide antibiotic

**Pharmacokinetics**
- Highly lipophilic drug, highly bound to red blood cells
- Poor bioavailability (~15%)
- Extensive hepatic metabolism (CYP3A4)
- Substrate for P-glycoprotein
- Long half life (~57-62 hours) hence once daily dosing

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### Pharmacy considerations: Sirolimus

**Dosing and Administration**
- Loading: 5 mg PO every 4 hours x 3 doses; Maintenance: 5 mg PO daily

**Therapeutic Drug Monitoring**
- Target trough 8-12 ng/ml

**Drug Interactions**
- CYP3A4 inhibitors (i.e., voriconazole, diltiazem) and inducers (i.e., phenytoin, rifampin)

**Adverse Reactions**
- Cytopenia
- Myalgia/arthritis
- Delayed wound healing
- Interstitial pneumonia
- Stomatitis/pharyngitis/like oral ulcers
- Hypercholesterolemia/hypertriglyceridemia
- Proteinuria
- Peripheral edema
- Hypertension
- Acneiform rash
Sirolimus mechanism of action (MOA)

- Macrolide antibiotic which forms a complex with FKBP-12 that binds to mammalian target of rapamycin (mTOR)
- Halts T cell proliferation by inhibiting progression from G1 to S phase

Sirolimus and mixed chimerism

- Mixed chimerism MOA
  - Sirolimus does not block T-cell activation (signal 1) but binds to mTOR blocking proliferation (signal 2)
  - Signal 1 in absence of signal 2 renders T cell anergy and promotes T cell tolerance

- Murine mouse transplantation models
  - Compared 30 day course of CSA to sirolimus
  - Long-term high level chimerism was attained only in sirolimus-treated mice
  - Mixed lymphocyte reactions demonstrated tolerance to donor cells

Sirolimus stomatitis

- Clinical Presentation
  - Solitary or multiple lesions with rapid onset after initiation
  - Ovoid shape w/ central gray area surrounded by erythematous halo
  - Can be painful and debilitating

- Villa et al reported case series
  - Median time to onset 55 days after allogeneic SCT
  - 92.9% ulcers on non-keratinized mucosa (mostly ventrolateral tongue)
  - 13 patients received topical steroids
  - Clinical improvement in all patients
  - Median time to resolution was 14 days
Nonmyeloablative Conditioning in Adult SCD

- 2 adult patients with end stage SCD and HLA-identical siblings
- 1 - successfully engrafted and SCD complication free at 27 months out
- 1 - Rejected graft 3 months out from transplant

Hsieh et al.

Phase 1-2 Prospective Trial

Inclusion Criteria:
- 16 years or older
- Hemoglobin SS or SC
- HLA identical family member
- Severe SCD

Endpoints:
- Primary: Stem cell survival
  - 88 patients did not have matched donors
  - 112 patients
  - 24 patients
  - 10 patients included

Conditioning Regimen

- Alemtuzumab 1 mg/kg/day
- 300 cGy TBI
- Stem Cell infusion
- Sirolimus

Day: -7, -6, -5, -4, -3, -2, -1, 0
Graft Outcomes

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Time since ASCT (months)</th>
<th>Duration of Neutropenia (days)</th>
<th>Duration of Leukopenia (months)</th>
<th>Hgb (g/dl)</th>
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<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>25</td>
<td>3.5</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>18</td>
<td>2.3</td>
<td>11.5</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>12</td>
<td>6</td>
<td>14.8</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
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<td>15.9</td>
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<td>30</td>
<td>11</td>
<td>1.5</td>
<td>13.5</td>
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<td>9</td>
<td>36</td>
<td>15</td>
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<tr>
<td>10</td>
<td>35</td>
<td>18</td>
<td>6</td>
<td>14.5</td>
</tr>
</tbody>
</table>

- All 10 patients alive, 1 graft rejection
- Mean percentage of donor myeloid cells was 83.3%

Adverse Events

- Acute or chronic GVHD did not occur in any patient

<table>
<thead>
<tr>
<th>Event</th>
<th># of patients</th>
<th>Time after ASCT</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV reactivation</td>
<td>1</td>
<td>14 days</td>
<td>Treated with foscarnet and resolved</td>
</tr>
<tr>
<td>Narcotic withdrawal</td>
<td>3</td>
<td>Varying</td>
<td>Hospital admit to taper narcotics</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2</td>
<td>1 &amp; 12 months</td>
<td>Resolved</td>
</tr>
<tr>
<td>Transfusion-related abdominal pain</td>
<td>1</td>
<td>6 months</td>
<td>Resolved</td>
</tr>
<tr>
<td>Vision-related rhabdomyolish</td>
<td>1</td>
<td>3 months</td>
<td>Switched bacitracin to pentamidine</td>
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<tr>
<td>Ventricular tachycardia</td>
<td>1</td>
<td>Previous to ASCT</td>
<td>Rate controlled</td>
</tr>
<tr>
<td>Clostridium difficile colitis</td>
<td>1</td>
<td>4 months</td>
<td>Resolved</td>
</tr>
<tr>
<td>Cholelithias-induced acute pancreatitis</td>
<td>1</td>
<td>15 months</td>
<td>Resolved</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>1 months</td>
<td>Resolved</td>
</tr>
</tbody>
</table>

Hsieh et al, 2014

- Study
  - High risk SCD patients
  - NMA regimen (extension of previously reported data)

- Outcomes
  - n=30
  - 29 patients survived median 3.4 years, no NRM
  - 1 patient died of intracranial bleed after relapse
  - 87% patients with long-term stable donor engraftment
  - Mean donor T cell level 48% and myeloid 86%
  - No aGVHD or cGVHD
  - 15 patients discontinued IST successfully
  - ↓ annual hospitalization rate, ↓ mean weekly narcotic use
Sirolimus complications

<table>
<thead>
<tr>
<th>Complication</th>
<th># of patients</th>
<th>Time after ASCT</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>1</td>
<td>16 months</td>
<td>Sirolimus switched to cyclosporine</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>1</td>
<td>3 months</td>
<td>Reduction of goal trough</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>1</td>
<td>4 months</td>
<td>Reduction of goal trough and supportive care</td>
</tr>
</tbody>
</table>

- 3 patients being treated for hyperlipidemia

NMA in adult SCD – UIC experience

- Conditioning regimen
  - Alemtuzumab/TBI 300 cGy
  - GVHD prophylaxis with Sirolimus
  - n=13, age 17-40
  - Many patients had high hematopoietic cell transplantation-specific comorbidity index (HCT-CI) ≥ 3

- Outcomes
  - 11 patients had severe neutropenia (ANC <500) for median duration of 6 days
  - Median hospitalization 33 days
  - 1 patient had secondary graft failure (noncompliant with IST)
  - No cases of aGVHD or cGVHD
  - At 1 year, 12/13 patients maintained stable donor chimerism
  - 1 patient had sirolimus pulmonary toxicity
  - 4/13 patients developed infection; 3/13 had CMV reactivation

UIC experience
Transient neutropenia

Hemoglobin concentration

Sirolimus and chimerism
### Hemoglobin fractionation

![Hemoglobin fractionation graph](image)

#### Hemoglobin (%)
- Pre-transplant
- Day + 30
- Day + 90
- Day + 180
- 1 Year
- Hb AA Donor
- Hb AS Donor

### Patient Quality of Life (SF-36 score)

![Patient Quality of Life graph](image)

#### Patient Quality of Life (SF-36 score)
- Pre-HSCT
- Day + 30
- Day + 90
- 1 Year

### HCT–specific Comorbidity Index (HCT-CI)

#### HCT-CI score
- Tool developed by Seattle Fred Hutchinson Cancer Research Center to capture information on 17 different organ-specific co-morbidities
- HCT-CI associated with 30% NRM

#### UIC experience
- HCT-CI assessed baseline in all patients at UIC
- Adult SCD patients have many co-morbidities and this shows that this regimen safe and effective in patients with high HCT-CI

*Figure courtesy of Damiano Rondelli and Pritesh Patel*
UIC experience

- NMA regimen of alemtuzumab and low-dose TBI
  - Normalizes hemoglobin in 92% of patients with clinically aggressive SCD
  - Reduces SCD-related complications
  - Improves cardiopulmonary function
  - Improves quality of life
- Sirolimus trough levels
  - Lower trough levels of sirolimus resulted in chimerism levels equivalent to those observed with higher levels
  - Less toxicity (arthralgias, mucositis, pneumonitis)
- ABO incompatibility
  - 2 patients were ABO mismatched and successfully engrafted (first reported)

ALTERNATIVE DONOR TRANSPLANTATION

UMBILICAL CORD
HLA-HAPLOIDENTICAL

Umbilical cord blood transplant (UCBT)

- CB is an alternative source of hematopoietic stem cells for patients with malignant and nonmalignant diseases
- HLA-identical sibling UCBT
  - ↓ aGVHD and cGVHD
  - Graft failure in 10% of patients\(^1\)
  - Not studied in adults
- Unrelated UCBT much less satisfactory\(^2\)
  - High rate of primary graft failure and TRM
  - DFS only 50\%\(^2\)
BM versus cord in pediatric SCD

- Donor cord and BM
  - Median age: 8.1 years (BM) and 5.5 years (UCBT)
- Thalassemia major or SCD
- CBT versus BM
  - Lower macrophage recovery (19 versus 23 days)
  - Less aGVHD
  - No difference in OS (p=0.22)
  - DFS: 92% (BM) and 90% (CB)
  - 21 patients died of transplant-related causes (14 BM and 3 CB)
- Related UCBT suitable option for patients

<table>
<thead>
<tr>
<th>Stem cell source</th>
<th>Llovet et al. (n=96)</th>
<th>Locate et al. (n=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning regimen</td>
<td>Bu/CY or Bu/Flu/T + ATG</td>
<td>Bu/CY or Bu/Flu/T + ATG</td>
</tr>
<tr>
<td>GVHD prophylaxis</td>
<td>CSA ± MTX (78%)</td>
<td>CSA ± MTX (90%)</td>
</tr>
</tbody>
</table>

- Median follow-up (ms)
  - 72 months

- DFS
  - 94%
  - 89%
- 10-year GVHD free survival
  - n=29 (7.4%)
  - n=10 (10.6%)

- IMR
  - n=18
  - n=5

- aGVHD >2
  - 21%
  - 10%

- cGVHD
  - 35/355 (10%)
  - 8/84 (7%)

RIC and UCBT in Pediatric Adult SCD

- Neupogen 110 mcg/m²
- Methotrexate 140 mg/m²
- Tacrolimus or Cyclosporine M/M
- Alemtuzumab starting D-21

- SCUFT trial: n=8; median age 13.7 years, median follow-up of 1.8 years
- Neutrophil recovery @ median of 22 days, 6 of 8 patients had platelet recovery (>50,000/mm²) by day 100
- 3 patients who engrafted had 100% donor cells by day 100, 5 had autologous recovery
- Conclusion: high incidence of graft failure, SCUFT cord blood arm suspended

Haploidentical SCT

- Rationale
  - HLA-identical matched donors difficult to find
  - MAC prohibited in most adult patients
  - GVT effect not necessary in non-malignant diseases
- Post-transplant cyclophosphamide (PT-CY)
  - Targets proliferating, allo-reactive T cells
  - Spares hematopoietic stem cells because of high levels of aldehyde dehydrogenase
  - Similar GVHD risk and immune reconstitution compared to MSD
Conclusions

- SCD patients need to be completely immunoablated
  - Immunocompetent patients
  - Alloimmunization
- Encouraging data in pediatrics using MAC regimens
  - Bu/Cy/ATG
  - Long term complications (gonadal, neurologic)
- MAC regimens have not been successful in adults
  - High TRM in adults who have more advanced SCD
  - NMA regimens safe and effective in adults
  - Small level chimerism ameliorates SCD symptoms
  - Alternative transplants being explored (haplo-HCT, UBCT)

Overall Survival by Donor Source

The 3-year OS ~90% regardless of the source of HSCs
**Supportive cares considerations**

**ALLOSENSITIZATION**
- RBC exchange prior to HCT
- Goal Hb S < 30%

**INFECTION PROPHYLACS**
- Penicillin VK
- Acyclovir
- Sulfamethoxazole-trimethoprim or pentamidine for PJP prophylaxis
- Fluconazole

**PRECAUTIONS/CONTRAINDICTIONS**
- Maintain platelet count >50K and Hemoglobin >9
- Avoid use of growth factor as it has shown to exacerbate SCD crisis

**PAIN MANAGEMENT**
- These patients are opioid dependent and pain symptoms take time to resolve after HCT

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**Conclusion**

**Growing adult SCD population:**
- ↑ morbidity and mortality
- ↑ hospitalizations and health care costs
- Limited treatments for refractory severe disease

Addition of alemtuzumab and sirolimus to AlloHCT process achieves mixed chimerism and demonstrates a safe and effective option for Adult SCD with severe disease.

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**ARS Question #1**

Myeloablative conditioning regimens are preferred for adult patients over non-myeloablative conditioning regimens due to decrease transplant related mortality and increase chimerism.

A. True  
B. False
Case 1
PT is a 21 year-old female with SCD and is being considered for HCT. She has been admitted several times for pain crisis and acute chest syndrome. She has osteonecrosis in her right knee and had a stroke 1 year ago. She is on chronic partial exchange transfusions.

ARS Question #2
• Based on this patient’s PMH, what is the indication for HCT?
  A. Multiple pain crisis
  B. History of stroke
  C. Osteonecrosis of 1 joint
  D. None of the above. This patient does not have an indication for HCT

ARS Question #3
The most appropriate conditioning regimen for her is?
A. Bu 16 mg/kg, TBI 800 cGy
B. Bu 14 mg/kg, FLU 180 mg/m2, ATG
C. Bu 12 mg/kg, CY 200 mg/kg, alemtuzumab
D. BU 6.4 mg/kg, FLU 180 mg/m2
ARS Question # 4
MA is a 5 year-old male with SCD. He has an HLA identical sibling. His PMH is significant for 2 episodes of ACS, 4 episodes of vaso-occlusive crises, and recurrent priapism. Because of his PMH, he is being considered for HCT.

ARS Question # 4
What is the most appropriate conditioning regimen for this patient?
A. Bu 16 mg/kg, CY 200 mg/kg
B. TBI 200 cGy, FLU 24 mg/m², Cy 500 mg/m²
C. BU 6.4 mg/kg IV, FLU 180 mg/m²
D. TBI 200 cGy, FLU 150 mg/m²

HEMATOPOIETIC STEM CELL TRANSPLANT FOR SICKLE CELL DISEASE: PERSPECTIVES FROM CHILDHOOD TO ADULTHOOD
Karen Swiss, PharmD, BCOP
Clinical Assistant Professor
Clinical Pharmacist in Hematology and Stem Cell Transplant
Department of Pharmacy Practice
University of Illinois College of Pharmacy
Chicago, IL