Haematopoietic Stem cell transplantation in Haemoglobinopathies

ESH-EBMT training course
Eliane Gluckman
800,000 - 500,000 children are born with Hb disorders annually:

~80% of affected children are born in developing countries

50,000 - 100,000 children with thalassemia major die each year in low and middle income countries

3% OF ALL DEATHS OCCUR IN CHILDREN UNDER 5 YEARS OF AGE

These diseases are: Preventable, Treatable, Curable.

Approximately 250 million people, 4.5% of the world population, are heterozygous for a defective globin gene and at least 300,000 lethally affected homozygotes are born annually, approximately equally divided between thalassemias and sickle cell disorders.

B Thalassemia

- Decreased production of red cells and hemoglobin

  A genetic defect in $\beta$ globin gene causes decreased production of $\beta$ protein

Ref: $\beta$-Thalassemia D. Rund and E. Rachmilewitz New Engl J of Med 353:1135, 2005
HUMAN HEMOGLOBIN SYNTHESIS

GENES

mRNA

GLOBINS

HEMOGLOBINS

\[ A - \alpha_2 \beta_2 \]

\[ A_2 - \alpha_2 \delta_2 \]

\[ F - \alpha_2 \gamma_2 \]

+ hemin
Genetics of β thalassemia

- **Thalassemia trait**: benign
  - One thalassemia gene excess α genes
- **Thalassemia major**: severe disease
  - Two thalassemia genes
- **Thalassemia intermedia**: mild to severe
  - 2 mutations one is mild with excess α globin genes
- **Hemoglobin E Thalassemia**: mild to severe
  - One β gene carrying a thalassemia mutation with a β globin gene carrying the point mutation encoding hemoglobin E
Globin synthesis in $\beta$ thalassemia (% of normal)

- $\beta^+\text{thal} - 30\% \beta \ 100\% \alpha$
- $\beta^0\text{thal} - 0 \% \beta \ 100\% \alpha$

- Anemia due to:
  - Decreased $\beta$ globin synthesis
  - Sustained normal $\alpha$ globin synthesis
  - Uncompensated $\gamma$ globin synthesis

- Leading to excess $\alpha$ globin precipitation - hemolysis
Treatment for β Thalassemia

- **Blood transfusions**: usually monthly
- **Iron chelating agents**
  - Subcutaneous Desferal
  - Oral Deferoxamine, Deferiprone, Deferasirox
- **Endocrine support**
- **Osteoporosis** Osteoclast replacement, VitaminD
- **Bone marrow transplantation**
- **Experimental approaches**
  - Increase fetal hemoglobin: hydroxyurea
  - Gene therapy
Survival by Availability of Chelation Therapy

Transfusion-Dependent Patients With Thalassemia Major

Survival probability

Age (y)


(N=1073) P<0.00005

Prevention of Haemoglobinopathies

- Prenatal Screening
- Genetic counseling
- Antenatal diagnosis:
  - Chorionic villous biopsy
  - Amniocentesis
- PGD/IVF
Indications of HSCT in Thalassemia

- **Definite indication**
  - Transfusion-dependent α or β thal; transfusion-dependent HbE/β-thal
  - Age ≤ 16 years
  - HLA identical family donor

- **Candidates who may be considered for HSCT**
  - Transfusion-dependent thal major in adults 17-35 years
  - Thal relapsing after previous HSCT
  - Transfusion-dependent S-β° thal
  - Thal intermedia
Factors affecting the decision to transplant patients with hemoglobinopathies

1. The expected results of SCT: cure, TRM and the risk of chronic GVHD
2. The long-term effects of SCT
3. The age of the patient
4. The availability of the donor
5. The expected long term survival without SCT based on transfusion and compliance history and the impact of current treatment on quality of life
6. Prospects for improved management in the future
## Risk Classes for BMT in Thalassemia


<table>
<thead>
<tr>
<th>Class</th>
<th>Chelation</th>
<th>Hepatomegaly</th>
<th>Hepatic Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>Regular</td>
<td>NO</td>
<td>Absent</td>
</tr>
<tr>
<td>Class 2</td>
<td>Reg/ Irr</td>
<td>NO/YES</td>
<td>NO/YES</td>
</tr>
<tr>
<td>Class 3</td>
<td>Irregular</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>
Class 1 Thalassemia (age < 17 years) (n=126)

Busulfan 14 mg/kg Cyclophosphamide 200 mg/kg

Survival

Thalassemia-Free Survival

Non-Rejection Mortality

Rejection

Years

Probability

92%

90%

8%

3%
Class 2: Thalassemia – age <17 years (n=292)

Busulfan 14 mg/kg  Cyclophosphamide 200 mg/kg

Probability

Survival

Thalassemia-Free Survival

Non-Rejection Mortality

Rejection

Years

Survival

Thalassemia-Free Survival

Non-Rejection Mortality

Rejection

Years

Survival

Thalassemia-Free Survival

Non-Rejection Mortality

Rejection

Years

87%

84%

14%

4%

YEARS
Class 3 Thalassemia ( <17 years) n = 35

Busulfan 14 – Cyclophosphamide 200

- Probability of Survival
- Probability of Thalassemia-Free Survival
- Probability of Non-Rejection Mortality
- Probability of Rejection
Class 3 Thalassemia (<17 years) (n=122)

BU 14 – Cyclophosphamide 120/160

SURVIVAL

THALASSEMIA-FREE SURVIVAL

REJECTION

NON-REJECTION MORTALITY

Pesaro May 2000
ADULT THALASSEmia (n=109)

- Survival: 66%
- Thalassemia-free survival: 62%
- Non-rejection mortality: 36%
- Rejection: 4%

Years range from 0 to 14 on the x-axis.
Probability values range from 0 to 1 on the y-axis.
BMT IN THALASSEMI A
FUTURE DIRECTIONS

- Specific conditioning regimen for patients with advanced disease
- Reduced intensity or non myeloablative preparative regimen: encouraging results??
- Induction of persistent chimerism
- Alternative source of Stem cells (cord blood)
- Alternative donors (matched unrelated donors 10/10)
- Expansion of BMT Donors’ Registries on regional basis
  Preimplantation diagnosis
HSCT for sickle cell disease

- Severe recessive genetic disorder resulting from a single nucleotide substitution in codon 6 of the β globin: gene β6 Glu → Val
- In the homozygous state, it produces abnormal hemoglobin that is prone to polymer formation under deoxygenated conditions.
- The polymerized haemoglobin leads to decreased RBC deformability and sickling in end arterioles resulting in vasoocclusion and pain.
- It is associated with severe complications: stroke, acute chest syndrome and recurrent pain.
The median age of survival for female patients was 36.3 years and for males, 38.7 years.

Fifty percent of children born with sickle cell anemia during the 21st century can expect to survive into the fifth decade of life.

This longer life span is accompanied by an increasing number of complications that negatively impact their quality of life.

Powers et al. Medicine (Baltimore) 2005;84:363-376
Sickle Cell Disease Morbidity

- Overt and incomplete (silent) cerebral infarction.
- Silent cerebral infarcts result in impaired cognitive functioning.
- Children with SCD are at risk educationally because of cognitive and intellectual impairment as compared with siblings or non-affected peers.
- Nearly half of all patients with sickle cell anemia suffer brain injury.

Opposing Attitudes Regarding Transplantation in Sickle Cell Disease

- Since disease severity cannot be predicted, transplant only those patients who have developed severe complications of the disease are transplanted because some patients will die as a result of transplantation.
- Early transplantation would prevent irreversible morbidity and decrease transplanted related complications.
- Will 50% of patients transplanted at an early age be dead by age 50?
SCD Palliative treatment

- Pneumococcal vaccines and prevention of infections
- Pain management
- Hydroxyurea
- Exchange transfusion
Indications of HSCT in SCD

- Young patients with HLA identical donors
- 1 or more of the following complications
  - Stroke without severe cognitive disabilities
  - Stenosis or occlusions on cerebral magnetic resonance angiography
  - Ischaemic lesions demonstrated by cerebral MRI
  - Recurrent vaso-occlusive crisis and/or acute chest syndrome and/or priapism despite hydroxyurea
  - Osteonecrosis in multiple joints
  - Red cell immunisation with 2 or more antibodies
- Or with 1 or more severe risk factors
  - Abnormal high velocities on transcranial Doppler
  - Severe chronic anaemia Hb<7g/dl
  - Tricuspid jet regurgitation >2.5 m/sec on cardiac Doppler
worldwide experience of HSCT in SCD

<table>
<thead>
<tr>
<th></th>
<th>Belgium Vermylen</th>
<th>USA Walters</th>
<th>France Bernaudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n</td>
<td>50</td>
<td>50</td>
<td>87</td>
</tr>
<tr>
<td>Median age</td>
<td>7.5</td>
<td>9.4</td>
<td>8.8</td>
</tr>
<tr>
<td>Strokes</td>
<td>8%</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Rejection</td>
<td>10%</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>TRM</td>
<td>7%</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>EFS</td>
<td>82%</td>
<td>84%</td>
<td>86%</td>
</tr>
<tr>
<td>A.GVH</td>
<td>20%</td>
<td>15%</td>
<td>86%</td>
</tr>
<tr>
<td>C.GVH</td>
<td>20%</td>
<td>12%</td>
<td>13%</td>
</tr>
</tbody>
</table>
HSCT in Sickle Cell Disease

- 67 patients from 30 centers transplanted between 1989 and 2002 with matched sibling donors.
- Median age = 10 years; 67% had >10 transfusions before HSCT.
- Stroke, n= 24; nephropathy, n= 7, acute chest syndrome, n=6.
- Acute GVHD = 10% (grade 3-4 in 2 patients); chronic GVHD = 22% (limited in 75%).
- 5-year probability: OS = 97%; DFS = 85%

Panipinto et al., (CIBMTR)
British J Haematol
2007;1327:479-485
Clinical results and perspectives of allo stem cell transplants for patients with sickle cell disease

F Bernaudin and E Gluckman

Société Française de Greffe de Moelle et Thérapie Cellulaire

French experience 60 Patients (11/1988 to 03/2002)

- Multicentric study
- Genoidentical (n=58), mismatch related (n=2)
- Source of cells:
  - Bone Marrow (n=51),
  - cord blood (n=7),
  - Bone marrow+ cord blood (n=1),
  - Peripheral Blood (n=1)
- Median Age : 8.8 years (2.2 to 22)
  - 3 cases >16 y
Indications (60 patients)

- Cerebral Vasculopathies  n = 26
  - Strokes  n = 22
  - Transit. Ischemia  n = 1
  - Stenosis  n = 3
- Vaso-occlusive crisis +/- arterial stenosis  n = 25
- Severe anemia ± stroke  n = 9
- Osteonecrosis, non responders to Hydrea  n= 5
- Poly-erythro-allo-immunization  n = 1
## Conditioning

- BU + EDX  \( n = 17 \)
- BU + TLI  \( n = 1 \)
- BU + EDX + ATG  \( n = 42 \)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( BU ) 485 mg/m(^2) ( (&gt;16 \text{ mg/kg}) ) +</th>
<th>EDX 200 mg/kg +</th>
<th>ATG rabbit 20 mg/kg</th>
</tr>
</thead>
</table>

## Prevention of GVH

- CSA  \( n = 13 \)
- CSA + MTX  \( n = 47 \)
Engraftment

- **59/60 engraftment**
  - Median days of neutrophil recovery (PN>500):
    - 20 days in bone marrow transplants
    - 28 days in cord blood transplants

- **1 non-engraftment**

  cord blood (first transplant): non engraftment at day 34, bone marrow (second transplant) with autologous reconstitution
Chimerism and rejection

- **Before association with ATG**
  - 4/12 mixed chimera
  - 3 rejection
    - autologous reconstitution (5m, 28m, 100m)
  - 1 aplasia (2nd transplant)

- **After association with ATG**
  - 1 non-engraftment
Survival: 90% (Kaplan-Meier, median 52 months)
60 patients (02/2002)
Rejection according to use of ATG in the conditioning

Follow-Up (mois)

P (log rank)=0.06
DFS patients transplanted with ATG, genoidentical and < 15 years: 88% (n=33)
Causes of death (n = 60)

- Median Follow-up: 52 months (1-159 months)
- 6 deaths
  - Severe GVH (n=4)
    - 2 m: adenovirus
    - 4 m: CMV, pneumocystis, aspergillosis
    - 12 m: bronchiolitis obliterans
    - 12 m: sepsis
  - Intracerebral Hemor. (n=1) (Moya-moya)
  - Non engraftement (n=1): sepsis, ARDS
## Long Term F/U after BMT: CNS (N=55 surviving pts.)

<table>
<thead>
<tr>
<th>BASELINE</th>
<th>&gt; 2 YEARS FOLLOW/UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 stroke</td>
<td>One stroke</td>
</tr>
<tr>
<td></td>
<td>29 stable or improved MRI</td>
</tr>
<tr>
<td>9/25 ‘silent’ stroke</td>
<td>No stroke</td>
</tr>
<tr>
<td></td>
<td>7/9 studied had stable or improved MRI</td>
</tr>
<tr>
<td>16 normal (12 not studied)</td>
<td>No stroke</td>
</tr>
<tr>
<td></td>
<td>4 studied had normal MRI</td>
</tr>
</tbody>
</table>
Conclusion 1

- HLA identical allotransplant can cure:
  - 88% of severe SCD in patients <15 years
  - With a risk of 10% of mortality (mainly GVH)

- Addition of ATG decreased the risk of rejection from 25% to 2.4%
Related Cord Blood Transplant in Patients with Thalassemia and Sickle Cell disease

F. Locatelli, V. Rocha, W. Reed, F. Bernaudin, M Ertem, S Grafakos, B Brichard, X Li, G. Giorgiani, A Nagler, Lubin BH, Gluckman E.
on behalf of Eurocord - Cord Blood Transplant Group
Related CBT for Hemoglobinopathies

44 patients transplanted from 06/94 to 06/2001 in 10 countries and 22 transplant centers

- Median age: 5 y (1-20); 1 patient > 15 years
- Median weight: 18 kg (9-45)
- 19 male; 25 female
- Median follow-up time: 24 months (3-76)
Related CBT for Hemoglobinopathies

<table>
<thead>
<tr>
<th>Conditioning</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BU + CY:</td>
<td>26</td>
</tr>
<tr>
<td>(associated to ATG/ALG: 18)</td>
<td></td>
</tr>
<tr>
<td>BU + CY + Thiotepa</td>
<td>10</td>
</tr>
<tr>
<td>BU + Thiotepa + Fludarabine</td>
<td>8</td>
</tr>
<tr>
<td>BU + CY + Fludarabine</td>
<td>1</td>
</tr>
</tbody>
</table>
Related CBT for Hemoglobinopathies

Donors

- HLA identical siblings: 41
- HLA mismatched donors: 3 (1 HLA-A difference)
Related CBT for Hemoglobinopathies

**Engraftment during the first 60 days: n=38**

- KM estimate for neutrophil recovery (≥500): 89%
  
  **Median days**: 23 (12-60)

- KM estimate for platelet recovery (≥20000): 90%
  
  **Median**: 39 (19-92)

Non-engraftment at day 60: **6 patients**

**Late graft failure**: n=2 at day +150 and +165
Related CBT for hemoglobinopathies

Neutrophil recovery

Neutrophil engraftment
44 38

89%
Related CBT for Hemoglobinopathies

**Acute GVHD**

- KM estimate of aGVHD for patients with neutrophil recovery = 11%

**Chronic GVHD**

- 2/36 patients at risk
- KM estimate: 6%
Related CBT for hemoglobinopathies
Event free survival according to diagnosis

- Sickle cell disease: 90%
- Thalassemia: 79%

Event free survival

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

P=0.5
Related CBT for hemoglobinopathies

Event free survival according to conditioning

BuCy: n=26, events=7
Other: n=18, events=1

P=0.07
Related CBT for Thalassemia

Event free survival according to Pesaro classification

Pesaro Class I (89%)
Pesaro Class II (62%)

EFS

Days

0 500 1000 1500 2000 2500

0.0 0.2 0.4 0.6 0.8 1.0

Class I
Class II

20 2
13 5

p=0.06

n events

89%
62%
Conclusions

- Related CBT for hemoglobinopathies offers a probability of success comparable to that offered by BMT and is associated with lower risk of both TRM and cGVHD.

- Optimization of transplant strategies could further improve these results.

- In particular, in view of the lower rate of engraftment associated with use of MTX and of the low risk of GVHD in patients given transplantation of placental blood, prophylaxis of GVHD including this drug is contra-indicated.

- A preparative regimen consisting of either BU, TT and CY or BU, TT and FLU should be preferred in thalassemia patients.
A MULTICENTRIC COMPARATIVE ANALYSIS OF OUTCOMES OF HLA IDENTICAL RELATED CORD BLOOD AND BONE MARROW TRANSPLANTATION IN PATIENTS WITH BETA-THALASSEMI A OR SICKLE CELL DISEASE


ASBMT meeting February 15 2008
OBJECTIVES & INCLUSION CRITERIA

- Compare outcomes of CBT & BMT from HLA identical sibling in hemoglobinopathy.

- Transplant centers: both type of transplantations have been performed.

- Eurocord data base: (1994-2005) 76 patients had either thalassemia major or Sickle cell disease.

- 13 of 17 centers agreed to participate in the study.
## Patients & Methods

<table>
<thead>
<tr>
<th>Patients and Disease</th>
<th>BM N=389</th>
<th>CB N=70</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (years)</strong></td>
<td>8.1 (0.7-24)</td>
<td>6.1 (2-20)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Donor age, median (years)</strong></td>
<td>9 (0.2-30)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalassemia</td>
<td>259 (67%)</td>
<td>44 (63%)</td>
<td>0.55</td>
</tr>
<tr>
<td>SCD</td>
<td>130 (33%)</td>
<td>26 (37%)</td>
<td></td>
</tr>
<tr>
<td><strong>Indications for Thalassemia</strong></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pesaro I</td>
<td>86 (33%)</td>
<td>26 (61%)</td>
<td></td>
</tr>
<tr>
<td>Pesaro II</td>
<td>122 (47%)</td>
<td>15 (35%)</td>
<td></td>
</tr>
<tr>
<td>Pesaro III</td>
<td>51 (20%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Indications for SCD</strong></td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>CNS+</td>
<td>57 (56%)</td>
<td>14 (54%)</td>
<td></td>
</tr>
<tr>
<td>CNS -</td>
<td>73 (44%)</td>
<td>12 (46%)</td>
<td></td>
</tr>
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</table>
### Patients & Methods

<table>
<thead>
<tr>
<th>Transplant characteristics</th>
<th>BM N=389</th>
<th>CB N=70</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median year of transplantation</td>
<td>1999 (94-05)</td>
<td>2001 (94-05)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditioning regimens (myeloablative)</th>
<th></th>
<th></th>
<th>&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan-Cytoxan</td>
<td>345 (89% )</td>
<td>44 (63% )</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Busulfan-Cytoxan-Fluda</td>
<td>16 (4% )</td>
<td>4 (6% )</td>
<td></td>
</tr>
<tr>
<td>Busulfan-Thiotepa-Fluda</td>
<td>27 (7% )</td>
<td>14 (20% )</td>
<td></td>
</tr>
<tr>
<td>Busulfan-Fludarabine</td>
<td>0</td>
<td>3 (4% )</td>
<td></td>
</tr>
<tr>
<td>Busulfan-Cytoxan-Thiotepa</td>
<td>0</td>
<td>5 (7% )</td>
<td></td>
</tr>
</tbody>
</table>

| ATG/ ALG/ MonoAb | 259 (67% ) | 33 (44% ) | 0.002 |

| Number of cells infused | 4.1 (0.1-46) | 0.39 (0.1-1.4) | <0.01 |

<table>
<thead>
<tr>
<th>GvHD prophylaxis</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate based</td>
<td>297 (76% )</td>
<td>18 (26% )</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CsA alone</td>
<td>82 (21% )</td>
<td>43 (61% )</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CsA +/- other IS</td>
<td>385 (99% )</td>
<td>68 (97% )</td>
<td></td>
</tr>
<tr>
<td>MMF</td>
<td>0</td>
<td>6 (8.6% )</td>
<td></td>
</tr>
</tbody>
</table>
Acute GvHD (II-IV) & cGvHD by graft type

<table>
<thead>
<tr>
<th>Grade</th>
<th>BM</th>
<th>CB</th>
<th>cGvHD BM: 41/355 (12+-2%)</th>
<th>cGvHD CB: 3/58 (5+-3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>46  (12%)</td>
<td>3   (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>29  (7%)</td>
<td>4   (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>8   (2%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BM: n=83, 20±2%
CB: n=7, 10±4%

Days
## Overall Survival by graft type

<table>
<thead>
<tr>
<th>Graft Type</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB (n=70)</td>
<td>96±3%</td>
</tr>
<tr>
<td>BM (n=389)</td>
<td>95±1%</td>
</tr>
</tbody>
</table>

### Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>CB (n=70)</th>
<th>BM (n=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GvHD</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Toxicities (VOD, ARDS, Seizures)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
In multivariate analysis

Disease
Age at Tx
Year at Tx

(Ev= death or autologous reconstitution or transfusion dependency)
Event free Survival by disease

SCD (n=156, ev=13) 92±2%

Thalassemia (n=303, ev=47) 84±2%

p<0.04

ASBMT meeting February 15 2008
Conclusion

- Patients with Thal. or SCD have excellent outcome.

- Results were not statistically different according to the source of stem cell used.

- Cord blood is associated with less acute GvHD, but delayed neutrophil engraftment.

- Sibling cord blood banking for Hemoglobinopathies should be encouraged to avoid discomfort and risks of BM harvest
These data argue for early referral and HCT in sickle cell disease patients so that HCT may be performed in younger patients with minimal exposure to red blood cell transfusions.

Finding a matched adult donor for a patient with sickle cell disease is very difficult.

Therefore, the only hope of satisfying the needs of sickle cell disease patients is the use of BM or CB from unrelated donors.

- 34% of patients with sickle cell disease were willing to accept the risk of a 20% short-term mortality in exchange for cure.
- There was no agreement between the recommendations of health care providers and the risk accepted by patients.
- If the parents of a child with sickle cell anemia want the child to be transplanted, should access to transplantation be denied?
- At present, the option of transplantation is usually not even presented to families who have a child with sickle cell disease.
HSCT from unrelated donors

in patients with Thalassemia

Results of the GITMO study
<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>50</td>
</tr>
<tr>
<td>Sex (M / F)</td>
<td>28 / 22</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>8</td>
</tr>
<tr>
<td>Pesaro classification:</td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>23</td>
</tr>
<tr>
<td>Class 2</td>
<td>27</td>
</tr>
<tr>
<td>Iron chelation:</td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>44</td>
</tr>
<tr>
<td>Irregular</td>
<td>6</td>
</tr>
<tr>
<td>Portal fibrosis:</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>29</td>
</tr>
<tr>
<td>Mild</td>
<td>15</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>HCV-RNA:</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>44</td>
</tr>
<tr>
<td>Positive</td>
<td>6</td>
</tr>
<tr>
<td>ALT - AST &gt; 2-fold increase:</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
</tr>
</tbody>
</table>
## Donor-Recipient HLA compatibility

- **HLA Class I:**
  - Matched: 42 (84%)
  - Mismatched: 8 (16%)

- **HLA Class II:**
  - Matched: 50 (100%)

- **HLA DPB1:**
  - Matched: 13 (26%)
  - Mismatched: 34 (68%)
  - Unknown: 3 (6%)
Grade III-IV acute GVHD

Cumulative incidence

15% (8-30%)
Primary Graft Failure

8% (3-20%)
Chronic GVHD - extensive

Cumulative incidence

Years

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 1 2 3 4 5 6 7 8 9 10 11 12

7% (0-15%)
Transplant-Related Mortality

Cumulative incidence

6% (2-19%)
Overall Survival

Years

Probability

94% (87-100%)
Thalassemia-free survival

82% (71-94%)
MUD THAL

AGE >15 (n=27)

SURV 70%  EFS 70%

TRM 28%

REJECTION 4%

PROBABILITY

YEARS

0 1 2 3 4 5 6 7 8 9 10 11 12
Conclusions

- HSCT from unrelated volunteers is able to cure a proportion of patients with thalassemia comparable to that cured with an allograft from a compatible sibling, provided that an accurate selection of the donor is employed;
- Results are mainly dependent on patient’s clinical conditions and age;
- It remains to be established who are the optimal candidates for this innovative procedure.
High Graft Failure Rates after Unrelated Cord Blood Transplantation for Thalassemia Major and Sickle Cell Disease.

Vanderson Rocha, Mary Eapen, Eliane Gluckman, Wagnara Chaves, Mary M. Horowitz, Joanne Kurtzberg, John Wingard and John E. Wagner

for the Eurocord Registry, Paris, France and the Center for International Blood and Marrow Transplant Research, Milwaukee, U.S.A
Patients

- First UCB transplants
  - N=25 patients
  - 1998 to 2006
  - Centres=17
  - Diseases
    - Thal major (N=16)
    - SCD (N=9)

- Median age at Tx: 5 years (0.2-15)

- Median follow-up: 29 months (4-98)
# Disease Characteristics

## Indications for UCBT

<table>
<thead>
<tr>
<th></th>
<th>THAL N=16</th>
<th>SCD N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td><strong>Acute Chest Syndrome</strong></td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Pesaro I</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Pesaro II</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td><strong>Time from diag to UCBT (years)</strong></td>
<td>3.7 (0.1-15)</td>
<td>5.14 (0.6-8)</td>
</tr>
</tbody>
</table>
## Transplant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>THAL N=16</th>
<th>SCD N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>*HLA Matched (6/6)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1-locus MM</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>2-loci MM</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Median number of NC infused/kg $\times 10^7$</td>
<td>5.3 (2.5-39)</td>
<td>5.7 (2.9-9.3)</td>
</tr>
</tbody>
</table>

*HLA definition: HLA-A and-B by low resolution typing and DRB1 by high resolution typing.

1 patient with Thal major received 2 UCB units.
## Transplant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>THAL N=16</th>
<th>SCD N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GVHD prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CsA alone</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>CsA+ steroid</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>CsA+ MMF</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>FK506 (± MMF± steroid)</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td><strong>Conditioning regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloablative</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>BU+CY+ATG</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>BU+other</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Reduced Intensity</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>BU+TLI+FLU+ATG</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Melphalan+FLU+ATG</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>FLU+TBI 2Gy</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>FLU+CY+TLI 2Gy+ATG</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td><strong>Use of ATG/Campath</strong></td>
<td>10/0</td>
<td>8/1</td>
</tr>
</tbody>
</table>
## Hematopoietic Recovery

### Graft versus Host Disease

<table>
<thead>
<tr>
<th></th>
<th>THAL N=16</th>
<th>SCD N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC500 @d28</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Full chimerism</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Second transplants (after 1(^{st}) Tx)</td>
<td>3 (0.3; 9 &amp;10 months)</td>
<td>2 (1 &amp; 8 months)</td>
</tr>
<tr>
<td>Grade 2-4 acute GVHD @d100</td>
<td>6 grade II n=4 grade III n=2</td>
<td>0</td>
</tr>
<tr>
<td>Chronic GVHD @2 yrs</td>
<td>2 of 9</td>
<td>0 of 3</td>
</tr>
</tbody>
</table>
## Mortality and Event free survival

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>THAL N=16</th>
<th>SCD N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOD</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Organ failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Marijuana</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

| Event Free Survival      | 5         | 3       |

<table>
<thead>
<tr>
<th>EFS by Conditioning regimen</th>
<th>THAL N=16</th>
<th>SCD N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloablative</td>
<td>5/13</td>
<td>3/7</td>
</tr>
<tr>
<td>Reduced intensity</td>
<td>0/3</td>
<td>0/2</td>
</tr>
</tbody>
</table>
Conclusion

- Graft failure is a challenge in these patients

- All 5 recipients of reduced intensity conditioning regimen had graft failure

- Exploration of novel approaches in prospective clinical trials is needed.
Sibling cord blood banking
Family and physician contact staff and enroll following informed consent. Maternal and patient medical history obtained. Maternal testing for infectious disease.

Collection kit sent to family

CB collected at time of delivery by the obstetrician/midwife and shipped to the lab for processing

Samples processed and cryopreserved within 48 hours of collection
Diseases N=107

- Thalassemia: 24%
- Sickle Cell Disease: 21%
- Rare: 22%
- Oncology: 33%
Sibling Cord Blood Banking
Fraction of CBUs released for UCBT

2531 total

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant diseases</td>
<td>35</td>
</tr>
<tr>
<td>Sickle Cell</td>
<td>22</td>
</tr>
<tr>
<td>Other/ Rare</td>
<td>24</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>26</td>
</tr>
</tbody>
</table>

- Collected: 96%
- Released for transplant: 4%
### SDCB Units Collected, HLA matched, Number Released for Transplant

<table>
<thead>
<tr>
<th>Categories</th>
<th>No. Collected (HLA Matched)</th>
<th>No. Released</th>
<th>% Released (HLA Matched)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Diseases</td>
<td>1,096 (250)</td>
<td>35</td>
<td>3% (14%)</td>
</tr>
<tr>
<td>Sickle Cell</td>
<td>673 (170)</td>
<td>20</td>
<td>3% (11%)</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>131 (33)</td>
<td>23</td>
<td>18% (70%)</td>
</tr>
<tr>
<td>Other</td>
<td>329 (80)</td>
<td>24</td>
<td>7% (30%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,229 (557)</strong></td>
<td><strong>102</strong></td>
<td><strong>5% (18)</strong></td>
</tr>
</tbody>
</table>
Why do these differences between thalassemia and SCD exist?

Criteria for transplantation differ (disease severity for SCA, transfusion and chelation for thalassemia)

Transplant considered to risky by parents or by treating physician

Sickle cell disease is clinically variable compared to thalassemia

Centers where patients are treated do not perform transplantation

Parents are not explained risks/ options for transplantation by treating physicians without bias
Decision making issues regarding CB transplantation for SCD

Role of Physician
- Bias against transplantation
- Don’t perform transplantation
- Risk/benefit considerations

Psychosocial Factors
- Family not explained options
- Considered to risky
- Child doing well at the time
- Family empowerment?

Cultural

Economics
- Economics of family and impact of transplant
- Insurance
Challenges to overcome for worldwide sibling CB banking for Hb disorders

Public Health Issues
Collection staff
Informed consent
Transportation to laboratory
Laboratory procedures
Transplantation facilities
Cost