International Sickle Cell Disease Observatory

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London EBMT
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International Sickle Cell Disease Observatory

Objectives

- Sickle cell disease is a severe hereditary hemoglobin disorder leading to death in early childhood or later to various organ failures in the absence of appropriate treatment.
- Most patients are from African or Indian origin but the disease is wildly widespread with a high prevalence in developing countries.
- Our objective is to reduce the barriers to care, burden of pain, organ injury and death.
- For this purpose, we have established an international group which will develop advanced targeted approaches and implementation of new interventions in order to improve patients care and quality of life and transfer innovative practices in countries with limited health care access.
International Sickle Cell Disease Observatory
Workplan

1. Epidemiology
2. Diagnosis
3. Hematopoietic stem cell transplantation and gene therapy
4. Center of bioresources and family cord blood banking
5. Education and dissemination
EPIDEMIOLOGY
• >350,000 children are born each year with a severe inherited Hb disorder

• ~ 80% of affected children are born in low or middle income countries

• 3.4% of deaths in children aged under 5 years

• >9 million carriers become pregnant annually

• 5.2% of the world population carries a significant variant
The Two Worlds of SCD

SCD Babies life expectancy

Poor Countries

- Birth → 6 ms
- 6 ms → 60 ms
- 5 yrs → 15 yrs
- 15 yrs → Adulthood

95%

- SSA and India
- Rest of the World

Wealthy Countries

5%
SCD is recognized as a Public Health issue by UN and several UN Agencies

Resolutions are urging Member States to develop, implement /reinforce comprehensive national programs to manage and prevent SCD

With a paradigmal change: Care then Prevention
50 million heterozygous HbS individuals in the world?

- **Africa**
  - 10-40% HbS mutation carriers in the population
  - 200,000–300,000 SCD newborns/year

- **USA**
  - 1 SCD newborn/600 births in Afro-American population
  - 60,000–70,000 SCD patients

- **France**
  - 405 SCD newborns in 2007
  - 10,000 SCD patients

(de Montalembert M. Br Med J. 2008;337:a1397.)
European Union

Frequency of the Sickle Cell Trait

- 0.60%
- 0.47%
- 0.57%
- 0.47%
- 0.08%
- 0.01%
- 0.02%
- 0.47%
- 0.47%
- 0.60%
- 1.00%
- 0.53%
Sub saharian population in Europe
Breakdown of the annual number of births with the different hemoglobin disorders from data available

<table>
<thead>
<tr>
<th>Major hemoglobin disorder</th>
<th>No. of annual births</th>
</tr>
</thead>
<tbody>
<tr>
<td>β thalassemia major</td>
<td>22,989</td>
</tr>
<tr>
<td>HbE β thalassemia</td>
<td>19,128</td>
</tr>
<tr>
<td>HbH disease</td>
<td>9,568</td>
</tr>
<tr>
<td>Hb Bart hydrops (α°/α°)</td>
<td>5,183</td>
</tr>
<tr>
<td>SS disease</td>
<td>217,331</td>
</tr>
<tr>
<td>S β thalassemia</td>
<td>11,074</td>
</tr>
<tr>
<td>SC disease</td>
<td>54,736</td>
</tr>
</tbody>
</table>

SS indicates sickle cell anemia; SC, sickle cell; and Hb, hemoglobin.

Weatherall et al, Blood, 2010
Establish a registry of newly diagnosed patients

Registry of SCD pregnant women
- High morbidity and mortality
- Absence of prenatal diagnosis
- Collection of blood samples and cord blood

Registry of newly diagnosed newborn with SCD
- Early diagnosis
- Prevention of complications

Work plan
• Establish a common questionnaire and enter information in a common data base
• Analysis of risk factors and long term outcome
Diagnosis

• Compare different methods of diagnosis

• Screen families at risk and establish genetic counseling

• Analyze best methods according to resources of the country (low, medium, high)

• Enter data in the registry to establish traceability and follow up of the patients.
Screened babies in Minas Gerais
(1994 - Jun 2011)

Phenylketonuria
- Started
- 4,344,120

Congenital Hypothyroidism
- Started
- 4,344,120

Sickle Cell Disease
- Started
- 3,471,202

Cystic Fibrosis
- Started
- 1,998,706

Source: UFMG/NUPAD
Sample collection

4th - 5th day
Primary care unit n = 2,483

Collection: 4th-5th day

Post Office

Laboratory

Data base

Treatment Control Sector

Tracking
**Sickle cell disease probability of survival**

**Minas Gerais State**

Table 1 - Estimated probabilities of survival (% ± SE) of 1,396 children diagnosed between March of 1998 and February of 2005, broken down by type of hemoglobinopathy and survival (1, 3 and 5 years)

<table>
<thead>
<tr>
<th>Type of hemoglobinopathy (n diagnosed)</th>
<th>Estimated probability of survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td>SS or Sβ-thalassemia (n = 764)</td>
<td>96.6 (0.7*)</td>
</tr>
<tr>
<td>SC (n = 555)</td>
<td>98.7 (0.5*)</td>
</tr>
<tr>
<td>Sβ+ thalassemia (n = 67)</td>
<td>96.8 (2.2*)</td>
</tr>
<tr>
<td>SD (n = 10)</td>
<td>100.0</td>
</tr>
<tr>
<td>All (n = 1,396)</td>
<td>97.5 (0.4*)</td>
</tr>
</tbody>
</table>

* Standard error of the mean.
Clinical aspects of SCD
Hypothetical mechanisms for complications in SCD
SCD Complications I

- Infection – #1 cause of death in children
- Vaso-Occlusive Crisis
- Splenic Sequestration
- Acute Chest Syndrome - #1 cause of death in adults
- Chronic Lung Disease (pulmonary hypertension)
- Cerebral infarct – 30% of SCD patients (10-12% symptomatic). Recurs in 70-90% if untreated.
SCD Complications II

- Cerebral hemorrhage
- Aplastic crisis
- Priapism
- Renal failure – Progressive glomerular sclerosis
- Avascular necrosis of femoral head (50% of pts)
- Cholelithiasis
- Sickle retinopathy
SCD Complications III

• Growth retardation
• Psychosocial dysfunction and chronic disability
• Neurocognitive/academic difficulties
• Chronic leg ulcers
• Cardiac failure / Pulmonary Hypertension
• Significantly shortened life span (25-30 years less than non-affected persons). 3% Mortality in children
Adolescence is main risk factor in SCD

- 7 of 23 sickle cell-related deaths occurred in patients aged 18–23 years
- 6 of 7 deaths followed recent transition to internist–haematologist...

### Circumstances of death in patients 18 years of age or older and the relationship to transition to adult care

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age at transition (years)</th>
<th>Age at death (years)</th>
<th>Chronic complication of sickle cell disease</th>
<th>Circumstances of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NA</td>
<td>18.8</td>
<td>Renal failure; dialysis</td>
<td>Found dead at home</td>
</tr>
<tr>
<td>2</td>
<td>17.9</td>
<td>19.2</td>
<td>None known</td>
<td>ACS</td>
</tr>
<tr>
<td>3</td>
<td>18.0</td>
<td>18.3</td>
<td>None known</td>
<td>ACS – refused transfusion (Jehovah’s Witness)</td>
</tr>
<tr>
<td>4</td>
<td>18.2</td>
<td>20.6</td>
<td>None known</td>
<td>Fell in hospital while pregnant – cerebral haemorrhage</td>
</tr>
<tr>
<td>5</td>
<td>18.3</td>
<td>19.3</td>
<td>None known</td>
<td>ACS complicated by multi-organ failure syndrome</td>
</tr>
<tr>
<td>6</td>
<td>18.4</td>
<td>23.7</td>
<td>None known</td>
<td>Presumed stroke</td>
</tr>
<tr>
<td>7</td>
<td>18.5</td>
<td>18.7</td>
<td>None known</td>
<td>Multi-organ failure syndrome</td>
</tr>
</tbody>
</table>


Slide created by Bart Biemond for the GIS, March 2012
Mortality Rates for Adults & Children with SCD: 1979-2005

Year
Mortality Rate per 100000 African American Pop
3
2.5
2
1.5
1
0.5

Adult Rate (≥19 yrs)  Child Rate (19 yrs and younger)

Lanzkron S, et al. ASH 2010, abstract 736
Current Therapies For SCD

• Supportive Care
  • Penicillin, Vaccination, Narcotics

• Chronic Transfusions

• Hydroxyurea

• Myeloablative Allogeneic Stem Cell Transplantation remains the only curative therapy for SCD

Freed/Cairo et al, BMT 2011
Chronic RBC Transfusions

Benefits
• Effective in preventing major SCD complications
• Dramatic reduction in stroke– 90% reduction of stroke risk
• Withdrawal of RBC Tx after 30 mo demonstrated increase risk of cerebral infarcts

Risks
• Risk of infection
• Risk of alloimmunization
• Risk of iron overload

Hydroxyurea

Benefits

• Chemotherapeutic agent that increases fetal hemoglobin and improves condition of red cells
• Reduces VOC, ACS, need for transfusions.
• 40% reduction in deaths of adults
• Effective in ~ 2/3 of patients.

Risks

• Effects may take 6 months
• Unknown long-term effects
• Does not reduce the risk of stroke.

Cell Therapy for the Treatment of SCD

Allogeneic Cell Transplantation

- Bone Marrow
- HUCB
- MUD
- Human MSCs

Gene therapy - Autologous transplantation

- Reprogramming
- Donor DNA
- Patient-specific somatic cells
- Transplantation
- Corrected somatic cells
- HR
- Gene addition
- Corrected iPSCs
- Differentiation

Cairo et al
Hematopoietic stem cell transplantation for sickle cell disease
HSCT for SCD
Challenges

• Provide access to transplant in all countries regardless of health resources
• Provide good primary care in order to establish reliable guidelines for indications
• Cost efficiency analyses must be performed in order to adapt to local economic situations
• Develop new protocols for facilitating engraftment and decrease toxicity
• Main goal is to have low mortality, low incidence of GVH and to spare fertility
Hematopoietic stem cell transplantation for sickle cell disease
Why so few patients received HSCT for SCD

- Most patients have no access to HSCT
- Primary care physicians are not aware of this possibility
- Education of families and patients is very important
- An HLA identical sibling is not always available
- Alternative donor transplants are still experimental
- Indications and risks must be explained very carefully

Advantages
- Provides long term survival and cure of the disease with 95% cure with HLA identical sibling donor and myeloablative conditioning
- Avoid major disabilities
## DONOR AVAILABILITY IN CIBMTR DATABASE

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>8/8</th>
<th>7/8</th>
<th>6/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>5%</td>
<td>33%</td>
<td>80%</td>
</tr>
<tr>
<td>South East Asian</td>
<td>7%</td>
<td>33%</td>
<td>75%</td>
</tr>
<tr>
<td>Alaskan Native</td>
<td>11%</td>
<td>42%</td>
<td>83%</td>
</tr>
<tr>
<td>Native American Indian</td>
<td>10%</td>
<td>44%</td>
<td>85%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>36%</td>
<td>81%</td>
<td>98%</td>
</tr>
</tbody>
</table>
Finding a donor

MUD low probability around 25%

Other alternatives

Cord blood 6/8 with >5x10^7/kg

Related haplo identical
CBT for Hemoglobinopathies, n=345

- Related n=257
- Unrelated n=88
Improving results of alternative donors HSCT for SCD

• **Conditioning**
  • reduced toxicity
  • Spare fertility
  • Most popular conditioning
    Thiotepa, Fludarabine, Busulfan, + ATG

• **Source of cells** increase engraftment, decrease GVH
  • Cord blood: double cord, intrabone, ex-vivo expansion, Nicord, MSC, prostaglandin etc...
  • Haplo related: G-CSF bone marrow /PBSC, cyclophosphamide post transplant etc.....
WORLD CORD BLOOD CONGRESS IV
AND
INNOVATIVE THERAPIES FOR SICKLE CELL DISEASE

October 24th – 27th, 2013

Monaco, France
Chairs: E. Gluckman, M. Cavazzana-Calvo, EJ Shpall
Register Now for the FACT Cord Blood Workshop, Rome, October 2011

Organized in conjunction with the World Cord Blood Congress 2011. Register now for:

Cord Blood Inspection & Accreditation Workshop
Wednesday, October 26, 2011
Hotel Nazionale Rome
Rome
Italy

This FACT training workshop will take place in conjunction with the World Cord Blood Congress 2011, in Rome. Register for both events by clicking on 'More Information' below.

The workshop is designed to explain the requirements for FACT-NetCert accreditation of cord blood banks. FACT representatives will be in attendance to clarify the intent of the Cord Blood Standards, provide inspectors tips for conducting inspections, and assist banks in organizing and preparing their banks for the accreditation process.

Practical application of FACT requirements stimulates discussion about effective and ineffective inspection practices and preparation techniques.

More information

Upcoming Events

World Cord Blood Congress III:
Cord Blood Transplantation and Immunobiology of HSCT

Venue: Rome, Italy
Date: 27-30 October, 2011

ESH-Eurocord-Eurocord-Ed
President: E. Clarkman
Eurocord-Ed Local Organizers: W. Arrese, F. Locatelli, P. Rebull
EBMT Immunobiology Working Party: A. Madrigal, A. Toubert, A. Velardi
Netcord: E. Baudoux, C. Navarrete

Registration: http://www.esh.org

ESBB Annual Meeting,
Marseille, 16-19 November 2011

Conference theme: "Identifying the challenges and the opportunities for biorepositories today and in the next five years".