Hematopoietic Stem Cell Transplantation for Thalassemia Major

Alok Srivastava
Department of Haematology
Christian Medical College
Vellore, India
Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine

Figure 2. Kaplan-Meier survival curves, after the first decade of life, by birth cohort (A) and by sex (B).

Table 2. Distribution of complications affecting 720 patients born after 1970.

<table>
<thead>
<tr>
<th>Complication</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>49</td>
<td>6.8</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>41</td>
<td>5.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>46</td>
<td>6.4</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>12</td>
<td>1.7</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>8</td>
<td>1.1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>78</td>
<td>10.8</td>
</tr>
<tr>
<td>Hypogonadism*</td>
<td>273</td>
<td>54.7</td>
</tr>
</tbody>
</table>

*Only 499 patients were old enough to be assessed for hypogonadism.
Medical management of Thalassemia Major in Developing countries

• Transfusion
  – Packed red cells to maintain Hb>9gm%
  – Use leucodepletion filters

• Chelation
  – Initiate when ferritin is ~1000ng/ml
  – Desferrioxamine 50mg/Kg SC CI / Deferasirox 20-40mg/kg PO / Deferiprone 75-100mg/kg PO
  – Monitor ferritin

Challenges: Access / Compliance / Cost / Safety
Marrow Transplantation for Patients With Thalassemia: Results in Class 3 Patients

~First BMT for thalassemia major done in 1981
Stem Cell Transplantation for Thalassemia – Causes of failure

- Infections – Microbial exposure
- Immunological complications – GVHD / Rejection
- Disease related factors – [Organ dysfunction / Disease relapse]
- Regimen related toxicities – Conditioning

*HIGH INCIDENCE OF GRAFT REJECTION IN CLASS III PATIENTS (~35%)
(42% rejection in the first 17 patients from India transplanted in Pesaro)

*HIGH INCIDENCE OF RRT - VOD / SOS (~30-40%)
BMT for Thalassemia Major - CMC Vellore

- Between October 1991 to December 2011
- Total No of Patients: 355
  - Median age 7 years (range: 2 – 24)
  - Males 221 (62.3%)
  - BM graft 317 (89.3%)

Risk stratification:

<table>
<thead>
<tr>
<th>Class</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>16</td>
<td>4.5</td>
</tr>
<tr>
<td>Class II</td>
<td>144</td>
<td>40.6</td>
</tr>
<tr>
<td>Class III</td>
<td>195</td>
<td>54.9</td>
</tr>
</tbody>
</table>

Liver size > 2cms 236 (66.5%)
Inadequate chelation 319 (89.9%)
Liver fibrosis 247 (69.6%)
Survival:
Mean follow up 171 months
5 year KM estimate of overall survival 73.2 ± 2.5%
5 year KM estimate of event free survival 66.8±2.6%

Class I : n=14 : 87.5±8.3%
Class II : n=144 : 81.4±3.3%
Class III : n=195 : 65.4±3.7%

P-value = 0.004
Conditioning regimens

Randomized trial of two different conditioning regimens for bone marrow transplantation in thalassemia – the role of busulfan pharmacokinetics in determining outcome

M Chandy¹, P Balasubramanian¹, SV Ramachandran¹, V Mathews¹, B George¹, D Dennison², R Krishnamoorthy³ and A Srivastava¹

¹Department of Hematology, Christian Medical College, Vellore, India; ²Sultan Qaboos University Hospital, Muscat, Oman; and ³INSERM, U458, Hospital Robert Debre, Paris, France

1. REGIMEN A [Bu600] – busulfan 600mg/m² given as four divided doses over 4 days and cyclophosphamide 200mg/kg given over 4 days (50mg/kg/day i.v over 1 h).

2. REGIMEN B [Bu16] – busulfan 16mg/kg as 1mg/kg/dose four times daily × 4 days, cyclophosphamide 200mg/kg given over 4 days (50mg/kg/day i.v over 1 h) and ALG (Pasteur Merieux) 30mg/kg/day for 3 days.

*EVALUATE Bu KINETICS – CORRELATE WITH OUTCOME
*REGULATORS OF Bu METABOLISM – GST/GSH LEVELS (HEPATIC / PLASMA) & GST POLYMORPHISM
Randomized trial of two different conditioning regimens for bone marrow transplantation in thalassemia – the role of busulfan pharmacokinetics in determining outcome

Table 3  Analysis of outcome in relation to busulfan dose

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bu 600/Cy 200</th>
<th>Bu 16/Cy 200/ALG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td>Overall survival</td>
<td>32</td>
<td>(68)</td>
<td>34</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>32</td>
<td>(68)</td>
<td>30</td>
</tr>
</tbody>
</table>

Follow-up (months) median
- Overall survival: 63 months (1–124), 52 months (1–124), P = 0.376
- Disease-free survival: 2 months (4), 4 months (9), P = 0.677*
- Mortality: 15 months (32), 13 months (28), P = 0.652*

Outcome by class

<table>
<thead>
<tr>
<th>Class</th>
<th>n = 21</th>
<th>n = 22</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>17 (81)</td>
<td>19 (86)</td>
<td>0.698</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>17 (81)</td>
<td>19 (86)</td>
<td>0.698</td>
</tr>
<tr>
<td>Rejection</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (19)</td>
<td>3 (14)</td>
<td>0.631</td>
</tr>
</tbody>
</table>

Class III

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n = 26</th>
<th>n = 25</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>15 (58)</td>
<td>15 (60)</td>
<td>1.000</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>15 (58)</td>
<td>11 (44)</td>
<td>0.406</td>
</tr>
<tr>
<td>Rejection</td>
<td>2 (10)</td>
<td>4 (22)</td>
<td>0.302</td>
</tr>
<tr>
<td>Mortality</td>
<td>9 (35)</td>
<td>10 (40)</td>
<td>0.691</td>
</tr>
</tbody>
</table>

95% CI: *0.08, 0.16; **0.17, 0.07.

Figure 1  Probability of graft rejection depending on busulfan C_{min}.

Bone Marrow Transplantation (2005) 36, 839–845
Glutathione S-transferase M1 polymorphism: a risk factor for hepatic venoocclusive disease in bone marrow transplantation

Alok Srivastava, Balasubramanian Poonkuzhali, Ramachandran V. Shaji, Biju George, Vikram Mathews, Mammen Chandy and Rajagopal Krishnamoorthy

Table 2. Frequency of GSTM1 and GSTT1 genotypes in patients with and without HVOD

<table>
<thead>
<tr>
<th></th>
<th>GSTM1 null, n (%)</th>
<th>GSTM1 positive, n (%)</th>
<th>GSTT1 null, n (%)</th>
<th>GSTT1 positive, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVOD⁻</td>
<td>23 (53.5)</td>
<td>58 (81.7)</td>
<td>28 (82)</td>
<td>53 (66.5)</td>
</tr>
<tr>
<td>HVOD⁺</td>
<td>20 (46.5)*</td>
<td>13 (18.3)*</td>
<td>6 (18) †</td>
<td>27 (33.5) †</td>
</tr>
</tbody>
</table>

Table 4. Busulfan pharmacokinetic parameters with reference to GSTM1 genotype

<table>
<thead>
<tr>
<th></th>
<th>Css-1, ng/mL</th>
<th>CI/F-1, L/h/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTM1 null</td>
<td>544 ± 184</td>
<td>0.40 ± 0.064</td>
</tr>
<tr>
<td>GSTM1 positive</td>
<td>667 ± 256</td>
<td>0.333 ± 0.071</td>
</tr>
<tr>
<td>P*</td>
<td>.001</td>
<td>.000001</td>
</tr>
</tbody>
</table>

*Css-1 indicates steady-state concentration after the first dose of busulfan; and CI/F-1, clearance after the first dose of busulfan. *P value calculated by 2-tailed t test.
Unpredictability of Intravenous Busulfan Pharmacokinetics in Children Undergoing Hematopoietic Stem Cell Transplantation for Advanced Beta Thalassemia: Limited Toxicity with a Dose-Adjustment Policy

Figure 2. Kaplan-Meier probabilities of OS, DFS, current thalassemia-free survival, rejection, and TRM in 25 patients with class III thalassemia.
Busulfan PK in Thalassemia Major – Oral vs IV

<table>
<thead>
<tr>
<th>Age</th>
<th>2-7 yrs</th>
<th>2-7 yrs</th>
<th>2-7 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=100</td>
<td>n=41</td>
<td>n=16</td>
</tr>
<tr>
<td>Bu Dose</td>
<td>16 mg/kg oral</td>
<td>600mg/m2 oral</td>
<td>0.8 mg/kg IV</td>
</tr>
<tr>
<td>AUC1 (mg*h/L)</td>
<td>5.02 +1.38</td>
<td>5.88 +1.42</td>
<td>2.96 + 1.34</td>
</tr>
<tr>
<td>Cl (ml/min/kg)</td>
<td>3.58 +1.08</td>
<td>4.6 +1.16</td>
<td>6.62 +5.01</td>
</tr>
</tbody>
</table>

The oral Busulfan PK data is calculated using NONMEM software by population PK analysis (Carl Panetta, St Jude)

IV Bu PK data is calculated using trapezoidal rule

B Poonkuzhali, CMC Vellore (2010, unpublished)
17-114% IIV and 12-103% IOV in CY and HCY PK parameters were observed.

*Body Wt and age were the main covariates

*CYP2C9*2 explained a significant portion of the IIV in the clearance
Population pharmacokinetics of cyclophosphamide in patients with thalassemia major undergoing HSCT

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cases</th>
<th>Disease</th>
<th>Age (years) Median (range)</th>
<th>CY CL (L/h/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qiu et al.³⁰ᵃ</td>
<td>8</td>
<td>Leukemia</td>
<td>11.2 (2.8–15.9)</td>
<td>2.56 (1.69–3.95)</td>
</tr>
<tr>
<td>Chinnaswamy et al.¹¹</td>
<td>11</td>
<td>Rhabdomyosarcoma</td>
<td>12.8 (5.4–21)</td>
<td>3.02 (2.3–4.0)</td>
</tr>
<tr>
<td>Yule et al.⁴³</td>
<td>38</td>
<td>Cancer</td>
<td>2.9 (1.2–10.6)</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>55</td>
<td>Thalassemia</td>
<td>7.3 (2–14)</td>
<td>0.55 (0.12–1.43)</td>
</tr>
</tbody>
</table>

*CY PK data from pediatric patients included in the study were requested from investigators and obtained.

Table 4. Comparison of CY and HCY pharmacokinetic parameters between this study and previous studies using BU/CY-conditioning regimen for HSCT

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cases</th>
<th>Disease</th>
<th>Age (years) median (range)</th>
<th>BU dose (mg/kg)</th>
<th>Total CY dose (mg/kg)</th>
<th>CY Cₘₐₓ (µg/mL)</th>
<th>CY t₁/₂ (h)</th>
<th>CY AUC (µg·h/mL)</th>
<th>HCY Cₘₐₓ (µg/mL)</th>
<th>HCY t₁/₂ (h)</th>
<th>HCY AUC (µg·h/mL)</th>
<th>Ratio HCY/CY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassan et al.²⁰</td>
<td>12</td>
<td>CML/AML</td>
<td>37 (5–51)</td>
<td>16</td>
<td>100 - 120</td>
<td>390 ± 223</td>
<td>10.9 ± 2.9</td>
<td>1913 ± 1019</td>
<td>1.14 ± 0.54</td>
<td>8.14 ± 0.25</td>
<td>8.34 ± 2.13</td>
<td>0.0053 ± 0.002</td>
</tr>
<tr>
<td>Slattery et al.¹⁹</td>
<td>7</td>
<td>BrCa/AML</td>
<td>42 (12–52)</td>
<td>Variable</td>
<td>120 - 200</td>
<td>227 ± 56</td>
<td>2.36 ± 0.37</td>
<td>861 ± 172</td>
<td>–</td>
<td>2.19 ± 0.74</td>
<td>–</td>
<td>0.123 ± 0.036</td>
</tr>
<tr>
<td>McCune et al.¹⁷</td>
<td>75</td>
<td>MDS/AML/MCL</td>
<td>47 (20–66)</td>
<td>Variable²</td>
<td>120</td>
<td>87.1 ± 48</td>
<td>–</td>
<td>715 ± 332</td>
<td>10.2 ± 5.3</td>
<td>8.5 ± 2.9</td>
<td>–</td>
<td>0.011</td>
</tr>
<tr>
<td>Present study</td>
<td>55</td>
<td>Thalassemia major</td>
<td>7.3 (2–14)</td>
<td>16</td>
<td>200</td>
<td>723 ± 375</td>
<td>1.73 ± 0.5</td>
<td>2276 ± 1585</td>
<td>1.98 ± 1.1</td>
<td>0.13 ± 0.024</td>
<td>6.04 ± 3.3</td>
<td>0.0037 ± 0.0037</td>
</tr>
</tbody>
</table>

Abbreviations: AUC = area under the concentration curve; BrCa = breast cancer; HCY = hydroxy CY. *P*-values generated using two-tailed t-test. ²These patients received targeted BU doses.

Bone Marrow Transplantation (2012) 47, 1178–1185
HSCT for Thalassemia Major

*Extensive PK and PG evaluation of Busulfan and Cyclophosphamide.

*Elaborate assessment of immunological aspects of graft composition and post-engraftment recovery

*Not a major impact on outcome of high risk patients
BMT for Thal Major - CMC Vellore
Risk Stratification - Limitations

- Class III a heterogeneous group (in the setting of sub optimal medical therapy prior to transplant)

<table>
<thead>
<tr>
<th></th>
<th>Patient I</th>
<th>Patient II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver size</td>
<td>3 cms</td>
<td>7 cms</td>
</tr>
<tr>
<td>Inadequate chelation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Age</td>
<td>6 years</td>
<td>14 years</td>
</tr>
<tr>
<td>Spleen size</td>
<td>NP</td>
<td>5 cms</td>
</tr>
</tbody>
</table>
A New Stratification Strategy That Identifies a Subset of Class III Patients with an Adverse Prognosis among Children with \( \beta \) Thalassemia Major Undergoing a Matched Related Allogeneic Stem Cell Transplantation


- **Age**: \( \geq 7 \) years
- **Liver size**: \( \geq 5 \) cms
- **Class III HR**: 40%

Comparison of 5-year EFS of Class III transplants in the high-risk group (n = 41) and rest of transplants in Class III (n = 64).
HLA-matched sibling bone marrow transplantation for \( \beta \)-thalassemia major

- Age < 7 years without hepatomegaly (n=49)
- Age ≥ 7 years without hepatomegaly (n=29)
- Age < 7 years with hepatomegaly (n=37)
- Age ≥ 7 years with hepatomegaly (n=46)

\( P < .0001 \)
Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan

Figure 1. Outcomes of the study population. (A) Cumulative incidence of transplantation-related mortality (TRM) and graft rejection (Reject). (B) Five-year Kaplan-Meier estimate of overall survival (OS) and TFS for the whole cohort of patients. (C) Five-year Kaplan-Meier estimate of TFS according to the type of donor used (MFD indicates matched family donor, and MUD, matched unrelated donor). (D) Five-year Kaplan-Meier estimate of TFS according to the patient’s class of risk.
Improved Clinical Outcomes of High Risk β Thalassemia
Major Patients Undergoing a HLA Matched Related
Allogeneic Stem Cell Transplant with a Treosulfan Based
Conditioning Regimen and Peripheral Blood Stem Cell
Grafts

Vikram Mathews¹, Biju George, Auro Viswabandya, Aby Abraham, Rayaz Ahmed, Abhijeet Ganapule,
Eunice Sindhuvi, Kavitha M. Lakshmi, Alok Srivastava

**Figure B**
- Treo n=50
  - Overall Survival
  - Treo: 87.4±4.8%

**Figure C**
- Treo n=50
  - Event-free Survival
  - Treo: 78.8±6%

**Figure D**
- Treo n=24
  - Overall Survival
  - Treo: 86.6±7.3%

**Figure E**
- Treo n=24
  - Event-free Survival
  - Treo: 77.8±8.8%

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**Figure Details**
- **P = 0.011**
- **P = 0.041**
- **P = 0.002**
- **P = 0.003**
Treosulfan based conditioning for Thalassemia Major

* Better toxicity profile – Larger therapeutic window

* Higher incidence of mixed chimerism requiring manipulation of post HSCT immunosuppression / DLI

* Major impact on outcome of high risk patients

* Limited data on PK so far

* Cost a major limitation

* Generic Treosulfan – received conditional approval from DCGI

* Subject to PK data being submitted – Study being initiated to be completed over the next 4-6 months
Cyclophos: 55mg/kg/day days -10, -9
Busulfan: 2.8-4.4mg/kg/day days -8 to -6
Thiotepa: 10mg/kg/day day -5
Fludarabine: 40mg/m²/day days -8 to -4

Table 1. NF-index of categorization of NF-08-TM

<table>
<thead>
<tr>
<th>Group</th>
<th>Ferritin</th>
<th>Hepatomegaly</th>
<th>Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt; 3000 µg/L</td>
<td>&lt; 2.5 cm under the costal margin</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>II</td>
<td>Nor group I or group III</td>
<td>&gt; 4 cm</td>
<td>&gt; 8</td>
</tr>
</tbody>
</table>

Table 4. Clinical outcome according to transplant groups

<table>
<thead>
<tr>
<th></th>
<th>MSD-HSCT (range)</th>
<th>UD-PBSCT (range)</th>
<th>Total (range)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Engraftment, median day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC &gt; 500/mm³</td>
<td>17.5 (12-30)</td>
<td>19 (11-26)</td>
<td>19 (11-30)</td>
<td>.230</td>
</tr>
<tr>
<td>PLT &gt; 20 x 10³/mm³</td>
<td>17 (9-58)</td>
<td>15.5 (8-42)</td>
<td>16 (8-56)</td>
<td>.344</td>
</tr>
<tr>
<td>Hgb &gt; 8.0 g/dL</td>
<td>13 (2-42)</td>
<td>13 (6-28)</td>
<td>13 (2-42)</td>
<td>.073</td>
</tr>
<tr>
<td>Duration of ANC &lt; 500/mm³</td>
<td>18 (1-33)</td>
<td>22 (13-32)</td>
<td>21 (1-33)</td>
<td>.010</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade III-IV (%)</td>
<td>1 (3.6)</td>
<td>5 (9.6)</td>
<td>6 (7.5)</td>
<td>.328</td>
</tr>
<tr>
<td>Transplantation-related complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC (%)</td>
<td>3 (10.7)</td>
<td>9 (17.3)</td>
<td>12 (15.0)</td>
<td>.431</td>
</tr>
<tr>
<td>CMV reactivation (%)</td>
<td>9 (32.1)</td>
<td>22 (42.3)</td>
<td>31 (38.8)</td>
<td>.373</td>
</tr>
<tr>
<td>VOD (%)</td>
<td>3 (10.7)</td>
<td>2 (3.8)</td>
<td>5 (6.3)</td>
<td>.226</td>
</tr>
<tr>
<td>Mucositis (%)</td>
<td>10 (35.7)</td>
<td>33 (63.5)</td>
<td>43 (53.8)</td>
<td>.019</td>
</tr>
<tr>
<td>IFD (%)</td>
<td>1 (3.6)</td>
<td>5 (9.6)</td>
<td>6 (7.5)</td>
<td>.328</td>
</tr>
<tr>
<td>Results of transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS (at 3 y)</td>
<td>.900</td>
<td>.923</td>
<td>.915</td>
<td>.678</td>
</tr>
<tr>
<td>TFS (at 3 y)</td>
<td>.893</td>
<td>.904</td>
<td>.878</td>
<td>.309</td>
</tr>
<tr>
<td>TRM (at 3 y)</td>
<td>.100</td>
<td>.077</td>
<td>.085</td>
<td>.678</td>
</tr>
<tr>
<td>GR (at 3 y)</td>
<td>.069</td>
<td>.019</td>
<td>.037</td>
<td>.259</td>
</tr>
</tbody>
</table>

All patients received Azathioprine / Hydroxyurea from day -45
Stem cell transplant for thalassemia major:

1. Only curative treatment for thalassemia major that is standard of care

2. Results have improved over last 10-15 years
   - Low risk patients: 85-95% survival
   - High risk patients: 70-80% survival (?)
   \(\Rightarrow\) These are the best results – not universal experience

3. Many challenges
   - Risk stratification
   - Conditioning regimen and RRT
   - Suitable donor – Matched / mismatched
   - Immunological complications – GVHD / Rejection
   - Geographic variabilities

4. Impact of co-existing morbidities
APBMT Registry - HSCT for Thalassemia Major

Number of transplants

Year


0 3 5 11 5 12 30 36 34 40 39 43 37 31 56 77 88 75 75 69 75 108 214 241 268 292 313

Courtesy: APBMT Registry, 2014
INDIAN STEM CELL TRANSPLANT REGISTRY

Number of Transplants – India (N=7242)

~150 HSCT for Thalassemia Major in India / year
~10,000 children with Thalassemia Major / year

Total centers – 37 centers
Data submitted - 33 centers
What is gene therapy?

• **Gene Therapy** - technique that uses genes as a means of treatment and/or prevention of a particular disease caused by genetic defects

• **Includes:**
  - Replacing a mutated gene with a healthy copy,
  - Inactivating a mutated gene
  - Introducing a new gene into the body

• **Technology of molecular genetics /cellular biology** made this possible from the 1980’s - insert a gene into the cell

• **First gene therapy** done at NIH, USA in 1990 for SCID
Transfusion independence and **HMGA2** activation after gene therapy of human β-thalassaemia

2-4 gm% rise in Hb over 12-24 months
Cure for Major Hemoglobin Disorders

*Increasing number of HSCT → With good results
*Continued thrust on enhancing access

*The focus should also be on reducing long term complications (LTC)

*For best results several steps needed:
  - Good transfusion chelation before HSCT
  - Early HSCT (2-5 years of age), before 7 years
  - Reduce HSCT related LTC: Safer conditioning
  - Early and planned attention to post HSCT iron chelation / immunization / growth monitoring

*Initiate an effective control program
*Work towards successful gene therapy!
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