Stem cell transplantation for haemoglobinopathies

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Birmingham Childrens Hospital
Survival by Cohort of Birth (N=977)

Survival Probability

Age (Yr)

0.00 0.25 0.50 1.00

60 - 64
65 - 69
70 - 74
75 - 79
80 - 84
85 - 97

P<0.00005

Borgna-Pignatti et al. Haematologica, 2004
Probability of death due to heart disease after age 10 yrs


Born <1980

Born 1980-89

Cumulative incidence (%)
Figure 2. Results of a recent survival study in Torino, Northern Italy, showing the effect of strict compliance with desferrioxamine therapy on survival.
Effects of Iron Chelators on Liver Iron Concentration (LIC)

LIC: Good control with desferrioxamine or deferasirox; inconsistent effects with deferiprone

Deferasirox shown to maintain and reduce LIC in phase 2/3 clinical trials in adult and paediatric patients (12-month efficacy—LIC)

![Graph showing mean change in LIC (mg Fe/g dw) with different doses of deferasirox for β-thalassaemia, SCD, β-thalassaemia, MDS, other rare anaemias.](image)
Role of BMT for Thalassaemia major

PREDICTED SURVIVAL IN THALASSAEMIA MAJOR

% SURVIVAL

SURVIVAL FOR 10, 20 OR 30 YEARS
Figure 6. Total affected thalassaemia conceptions and outcomes since thalassaemia appeared in the UK in the late 1950s, by 5-year intervals.
### Management of $\beta$-thalassaemia: the role of BMT

<table>
<thead>
<tr>
<th>Patient choice:</th>
<th>quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician choice:</td>
<td>poor compliance</td>
</tr>
<tr>
<td></td>
<td>failure of medical Rx</td>
</tr>
<tr>
<td>Political choice:</td>
<td>unavailability of good quality medical care</td>
</tr>
</tbody>
</table>
Principles of stem cell transplantation for haemoglobinopathies

Multipotent stem cell

- BFU-e (burst-forming unit-erythroid)
  - Red cells
- CFU-GM (colony-forming unit-granulocyte-macrophage)
  - White blood cells
  - Platelets

Platelets
SCT in Haemoglobinopathies
CCLG

**β Thalassaemia Major**

- Offered to all children ≤ 16 years with transfusion-dependent thalassaemia
  PLUS
- HLA-identical family donor

**Sickle Cell Disease**

- Stroke
- Recurrent Chest Syndrome*
- Recurrent VOC*
  * if hydroxycarbamide fails

Emerging indication:
- CNS disease
- Risk of CNS disease

**Consider carefully:**
- patients >16 years
- previous failed SCT
SCT for haemoglobinopathies: conditioning

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulphan</td>
<td>14 mg/kg</td>
<td>day -9 to -6</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>200 mg/kg</td>
<td>day -5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campath 1H</td>
<td>0.1 mg/kg</td>
<td>day -9 to -7</td>
</tr>
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</table>
## SCT for haemoglobinopathies: conditioning

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine</td>
<td>125 mg m²</td>
<td>day -12 to -7</td>
</tr>
<tr>
<td>Busulphan</td>
<td>14 mg/kg</td>
<td>day -9 to -6</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>200 mg/kg</td>
<td>day -5 to -2</td>
</tr>
</tbody>
</table>
BCH Conditioning Protocol

- **D-9**: Busulfan 14 mg/kg
- **D-8**: Cyclophosphamide 200 mg/kg
- **D-6**: Udarabine 25 mg/m2
- **D-5**
- **D-4**
- **D-2**
- **D-1**
- **D0**: Ciclosporin
- **Stem Cells**: 4 – 6 x $10^8$/kg
- **Hypertransfusion**
Imperial College Healthcare Conditioning Protocol

D-9     D-8       D-6    D-5    D-4         D-2    D-1 D0
Busulfan 14 mg/kg

D-9

Hypertransfusion

D-8

Alemtuzumab 0.3 mg/kg

D-6

Cyclophosphamide 200 mg/kg

D-5

Ciclosporin

D-4

Stem Cells 4 – 6 x 10^8/kg

D-2

MTX

D-1

D0
<table>
<thead>
<tr>
<th>DONOR CHARACTERISTICS</th>
<th>No of Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA-IDENTICAL:</strong></td>
<td></td>
</tr>
<tr>
<td>Brother</td>
<td>26</td>
</tr>
<tr>
<td>Sister</td>
<td>25</td>
</tr>
<tr>
<td>Parent</td>
<td>3</td>
</tr>
<tr>
<td><strong>AGE (years):</strong></td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>(1.4 to 32)</td>
</tr>
<tr>
<td><strong>THALASSAEMIA TRAIT:</strong></td>
<td>34</td>
</tr>
</tbody>
</table>

Lawson et al, 2003
# BMT for thalassaemia: the Birmingham and Hammersmith experience

<table>
<thead>
<tr>
<th>No of Children</th>
<th>54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>6.6 (2 - 16)</td>
</tr>
</tbody>
</table>

**Ethnic origin:**

- Pakistani / Indian: 39
- Mediterranean: 10
- Arabic: 5

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BMT for Children with Thalassaemia at BCH/HH

Fig 1. The probability of survival, EFS and rejection post-HLA-matched related BMT in the UK.

Lawson et al, 2003
FIGURE 2. Kaplan-Meier probabilities of survival, event-free survival, rejection, and non-rejection mortality for 121 thalassaemic patients aged less than 17 years, transplanted from HLA-identical donors after preparation with busulfan (14mg/kg), cyclophosphamide (200 mg/kg), and cyclosporine alone from January 2, 1986 through April 10, 1997 and calculated on May 15, 1997.
FIGURE 3. Kaplan-Meier probabilities of survival, event-free survival, rejection, and non-rejection mortality for 272 Class 2 thalassaemic patients aged less than 17 years, transplanted from HLA-identical donors after preparation with busulfan (14mg/kg), cyclophosphamide (200 mg/kg), and cyclosporine alone from June 6, 1985 through April 10, 1997 and calculated on May 15, 1997.
FIGURE 4. Kaplan-Meier probabilities of survival, event-free survival, rejection, and non-rejection mortality for 125 Class 3 thalassaemic patients aged less than 17 years, transplanted from HLA-identical siblings after preparation with busulfan (14mg/kg), cyclophosphamide (120-160 mg/kg), and cyclosporine plus “short” methotrexate from March 1989 through April 10, 1997 and calculated on May 15, 1997.
SCT for thalassaemia major: Class 3


Figure 1. Kaplan-Meier probabilities of survival, thalassemia-free survival, and cumulative incidences of rejection and nonrejection mortality in 33 thalassemic patients aged younger than 17 years, prepared for transplantation with protocol 26.
BMT for Thalassaemia major:
Long-term effects

**GROWTH**
Usually normal or improved

**SEXUAL DEVELOPMENT**
Delayed in 50%

**FERTILITY**
Gonadal failure common, esp girls

**OTHER**
Iron overload
Malignancy (0.9%)
Follow up

- Must include venesection
- 34% women  67 % of men went through puberty normally
- Spontaneous pregnancy very rare after Bu/Cy conditioning
- New in vitro techniques may benefit some men
Follow up

- Second malignancy rare mostly EBV and GVH related less than 1%
- One case of mouth SCC in Birmingham
- No real studies of quality of life but reasonable assumption that life without DFO better than life with infusions
- No one asked the patients!
Limitations of SCT

• Lack of donors
• Length of Treatment:
  – 2 months as an inpatient
  – 4 months as outpatient
• Transplant Related Mortality
• Long Term Effects:
  – Infertility
  – Pubertal failure
  – Chronic GvHD
  – Organ toxicity
  – Secondary malignancy
### SCT for thalassaemia: mismatched related donors

<table>
<thead>
<tr>
<th>No of patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplanted</td>
<td>29</td>
</tr>
<tr>
<td>m/m sibling donors</td>
<td>13</td>
</tr>
<tr>
<td>m/m parental donors</td>
<td>8</td>
</tr>
<tr>
<td>other relatives</td>
<td>8</td>
</tr>
<tr>
<td>Event-free survival</td>
<td>21%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>65%</td>
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</table>

Gaziev et al, 2000
Unrelated donor BMT for thalassaemia

<table>
<thead>
<tr>
<th>No of patients</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Transplanted</td>
<td>32</td>
</tr>
<tr>
<td>Class 1 or 2:</td>
<td>15</td>
</tr>
<tr>
<td>Class 3:</td>
<td>17</td>
</tr>
<tr>
<td>Survived</td>
<td>26</td>
</tr>
<tr>
<td>Cured</td>
<td>22</td>
</tr>
</tbody>
</table>

La Nasa et al, Blood 99: 4350-6, 2002
Unrelated donor BMT for thalassaemia

<table>
<thead>
<tr>
<th>No of patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplanted</td>
<td>32</td>
</tr>
<tr>
<td>Extended haplo match</td>
<td>22</td>
</tr>
<tr>
<td>Survived</td>
<td>19 / 22 (86%)</td>
</tr>
<tr>
<td>Cured</td>
<td>17 / 22 (77%)</td>
</tr>
</tbody>
</table>

La Nasa et al, Blood 99: 4350-6, 2002
Unrelated cord blood transplants for thalassaemia major

- 5 children aged 2-11 years
- Conditioning: Bu 14/Cy 200 + ATG
- 1-2 antigen mismatched CB mononuclear cells
- Engraftment: 5/5
- Acute GVHD > grade II: 1
- Survival with 100% donor cells: 5/5 (follow up 6-15m)

BMT for Adults with Thalassaemia Major: Outcome 1988-1996

<table>
<thead>
<tr>
<th></th>
<th>No of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplanted</td>
<td>107</td>
<td>-</td>
</tr>
<tr>
<td>Survival</td>
<td>69</td>
<td>64</td>
</tr>
<tr>
<td>Event-free survival</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td>Recurrence</td>
<td>4</td>
<td>4</td>
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</table>

Lucarelli et al, Blood 93:1164, 1999
Eurocord Study: thalassaemia

• Largest series, multicentre study: 33 patients with β-thalassaemia major and 11 patients with SCD.
• The median age for the whole group was 5 years (range 1-20 years).
• Pesaro staging (hepatomegaly, portal fibrosis and a history of irregular iron chelation therapy):
  – Class I: 20/33
  – Class II: 13/33
  – Class III: 0/33
• Donor cells:
  – All were transplanted with family donors: 32/33 were fully matched, one being A locus mismatch.
  – median number of TNC infused: $4.0 \times 10^7$/kg (range 1.2-13)
• Conditioning regimens:
  – Bu/Cy: 26 patients (10 with added ATG)
  – Added thiotepa: 16 patients
• GvHD prophylaxis: 12 methotrexate

Locatelli, Blood 2003
• **Engraftment:**
  - 7/33 patients experienced graft failure including the patient who received the class I mismatched CBT.
  - TNC doses given to the patients who experienced graft failure varied from 1.2 to 10 x 10^{7}/kg (median 5.0).
  - They were subsequently rescued with either re-injection of autologous back-up marrow or BMT at a later date when the matched sibling donors could donate marrow cells.
  - Neutrophil and platelet recovery kinetics occurred as standard.
  - Persistent mixed chimerism: 3/33, but transfusion-independent.

• **Transplant-related complications:**
  - OS: 100%
  - EFS at 2 years:
    • Pesaro class I: 89%
    • Pesaro class II: 62%
  - No cases of life-threatening infection
  - GvHD:
    • Acute: 11%
    • Chronic: 6%
• Early transplant related mortality (TRM) has been reported to be higher following CBT in some series (possibly because of slower engraftment rates and an increased risk of infection) (Rocha, et al 2001).

• Results vary according to the population studied and prognostic factors for these observations are not clear.

• By contrast, it is now widely established that overall survival (OS) and event-free survival (EFS) rates after CBT = unrelated donor marrow transplant.

• CB contains sufficient haemopoietic stem cells to transplant most patients lacking an HLA-matched sibling marrow donor, especially when double cord transplants are considered.
Sickle cell disease

Thalassemia

EFS

0  500  1000  1500  2000  2500

Days

n  events

Thalassemia  33  7

Sickle cell disease  11  1

P = .05
Engraftment

- Engraftment of neutrophils and platelets following CBT tends to be delayed compared to that following BMT or PBSCT.
- Long-term results are similar, especially in terms of immune reconstitution (Inoue, et al. 2003).
- Higher total nucleated cell (TNC) doses (> 2.5 to 3.7 x 10^5/Kg recipient) yield shorter recovery times and better outcomes (Gluckman, et al. 1997).
- Major concerns with CBT in adolescents and adults, where the cell doses given tend to be lower.
Directed Sibling CB in the NBS

• 10 year experience
• Based at NBS Stem Cell Services in Oxford
• 44 units collected from newborn siblings from families with major haemoglobinopathies:
  – Thalassaemia: 36
  – SCD: 8
• Usage:
  – Thalassaemia: 7 (20%).
    • SCD: 0/8

Smyth, Stem Cells 2007
Sibling Donor Cord Blood Program

- National CB bank for medically indicated banking of sibling CB in the US
- More than 1600 CB collections over a period of 6 years since 1998:
  - Thalassaemia: 6%
  - SCD: 28%
- 32/96 (33%) donor-recipient pairs with β-thalassaemia were HLA identical and 14 of them (44%) received a CBT
  - Eleven survived free of disease with a median follow up of 12.4 months.
  - Fewer than 1 in 6 have so far been used, mainly because of HLA-incompatibility.
- Number of cords banked for SCD is much greater and the usage even lower:
  - 163 CB units collected and stored
  - 4 (2%) used. Median age at the time of transplant was 8.3 years (range 2 to 13.6 years) and median cell dose $4.4 \times 10^7$ TNC/kg (range 1.67 to 9.15).
  - All 4 patients engrafted and 3/4 survived, all disease-free, median follow-up of 22.3 months (range 5.2 to 25.4 months).
  - 2005 report: total number of CB banked from SCD families had risen to more than 450 but the number used for CBT (8) remained low (2%).

Walters, Blood 2005
Conclusion

- The outcome of CBT from related donors is increasingly approaching the results for bone marrow transplants.
- Main complication is graft rejection, which may be reduced by increasing pre-transplant immune suppression and modifying existing GvHD prophylaxis.
- Combination CB and BM is extremely useful when there is a large weight and size difference between donor and patient.
- Unrelated donor CBT have resulted in successful outcomes in a very small number of patients, albeit with a higher mortality and morbidity than conventional transplantation.
Future developments

Reduced intensity grafts

Ability to utilise either VUDs or unrelated Cords

Will HSCT still be a useful procedure in 10 years time?
Limitations of stem cell transplantation for thalassaemia major

• Transplant-related mortality

• Lack of donors for the majority of children

• Long-term effects (concerns about fertility)

• Role of SCT in treatment of adults
CB Graft Characteristics

- Much smaller in volume (50-200mL) and cellularity.
- Lower numbers of CB cells can effectively restore a full haematopoietic repertoire after transplant.
- Lower numbers of CD4+, CD8+ and CD3+ T-cells, with a higher CD4/CD8 ratio and a higher proportion of naïve CD45RA+ T-cells (producing lower amounts of Th1-type cytokines) and NK-cells with higher cytotoxic activity.
- Together these immunological differences are likely to be responsible for the lower rates of GVHD and preserved GVL responses (Gardiner, *et al* 1998, Harris, Nomura, *et al* 2001).
GvHD

- Incidence and severity of acute and chronic GVHD with both related and unrelated CBT is reduced when compared with unmanipulated marrow or PB, even where donor/recipient are not fully HLA-matched.

- HLA-matching:
  - Low resolution A, B and high resolution DR instead of high resolution A, B, C, DR, DQ
  - More disparity is tolerated: 1-2 mismatches (Gluckman, et al 2004)

- For non-malignant haematological diseases, where a GVL effect is not required, the criteria for finding the optimal unrelated donor should include both a higher cell dose and as few HLA disparities as possible.

- This is particularly the case in haemoglobinopathies for which unrelated CBT remains an experimental procedure.
Incidence and severity of acute and chronic GVHD with both related and unrelated CBT is reduced when compared with unmanipulated marrow or PB, even where donor/recipient are not fully HLA-matched.

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## CB and BM

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>4</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Donor with β-thal trait</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Major ABO incompatibility</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CD34+/kg</td>
<td>0.6 x 10^5</td>
<td>1.7 x 10^5</td>
<td>0.5 x 10^5</td>
</tr>
<tr>
<td>Number of BM TNC/kg</td>
<td>0.7 x 10^8</td>
<td>1.6 x 10^8</td>
<td>1.7 x 10^8</td>
</tr>
</tbody>
</table>

Goussetis, Pediat Hemat Onc 2000
Reality of obtaining CB

• Human Tissue Authority regulations:
  – Procurement
  – Collection and Processing

• Who should be collected from? – how to balance the economic cost and resources, the needs of the donor and cell dose requirements
  – Thalassaemia: all siblings of affected patients
  – SCD: if on transfusions or HU

• Pre-implantation diagnosis and HLA typing
Thalassaemia major: rationale for transplantation

- morbidity
- mortality
- quality of life
“Mini-allografting” in thalassaemia

Hongeng et al, BMT 30: 409-410, 2002

• Girl aged 10 years received PBSC from 4 yr old sib
• Conditioning: busulphan 8 mg/kg
  fludarabine 175 mg/m²
  ALG
  TLI (500cGy)
• GVHD prophylaxis: CSA (d+100), MMF (d+35)
• Outcome: Alive & well with full donor engraftment at 1yr