Current issues in bone marrow transplantation for aplastic anaemia

Judith Marsh
Diagnosis of constitutional AA
Graft rejection and chronic GVHD
Poor outcomes of BMT in older patients
No suitable BM donor - role of UCBT
The Bone Marrow Failure Syndromes

RBDS – Ribosomal Dysgenesis syndromes
DC – Dyskeratosis congenita
FA – Fanconi Anaemia
AA – Aplastic Anaemia
PNH – Paroxysmal Nocturnal Haemoglobinuria
LGL – Large Granular Lymphocytosis

5q- MDS/MPD
Low Risk
High Risk
AML

Adapted from N. Young, G. Mufti
Fanconi anaemia

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>6.6yr (0-49)</td>
</tr>
<tr>
<td>% diagnosed ≥ 16 yr</td>
<td>9%</td>
</tr>
<tr>
<td>Age at cancer</td>
<td>15yr (0.1-48)</td>
</tr>
<tr>
<td>Cumulative probability</td>
<td>85%</td>
</tr>
<tr>
<td>of cancer* by 45-50 yr</td>
<td></td>
</tr>
<tr>
<td>Absent physical</td>
<td>25%</td>
</tr>
<tr>
<td>anomalies</td>
<td></td>
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</table>

Alter, Hematology 2007; 29
Classical mucocutaneous features of Dyskeratosis congenita

<table>
<thead>
<tr>
<th>Other clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Premature greying</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Abnormal dentition</td>
</tr>
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90% develop bone marrow failure by the age of 30yr

Walne and Dokal, BJH 2009; 145: 164
'Atypical/cryptic DC' in apparent acquired AA

- Inherited TERC, TERT, TINF2 mutations
- Milder disease and later onset than DKC1 mutations
- Muco-cutaneous features mild/absent
- Bone marrow failure, pulmonary fibrosis, cirrhosis, AVN, osteoporosis
- Late deaths from pulmonary fibrosis after BMT
Alternative to BMT: Immunosuppressive therapy

Events after ATG:
- Non-response
- Treatment related death
- Relapse
- Clonal evolution

Passweg & Tichelli, Haematologica 2009; 94: 310

Frickhofen N et al. Blood 2003; 101:1236
Treatment of acquired severe aplastic anaemia
(BCSH*, 2009)

Age of patient

≤ 40yr

HLA identical sibling

Yes

NO response

HLA id sib BMT

> 40 yr

No response

ATG + CSA

UDBMT if < 50yr (or 50-60* and good performance status)

2nd ATG + CSA if no UD or > 50-60yr

*British Committee for Standards in Haematology
www.bcshguidelines.com

Other options?
 Conditioning regimen

- Cyclophosphamide 200mg/kg +ATG
- CSA + MTX
- Non-myeloablative
- No irradiation
- Fertility usually well preserved
Factors for graft rejection in aplastic anaemia (5-15% MRD; 10-30% MUD)

- Allosensitisation from multiple blood transfusions
- Reduced intensity conditioning
- Low marrow cell dose < 3 x 10^8 nucleated cells/kg
- T-cell depletion of donor marrow
- Donor-recipient sex mis-matching (M→F)*
- Progressive mixed chimerism

*Stern, Transplantation 2006;82:218
Chronic GVHD (30-40%)

Factors:
- Acute GVHD
- Older age
- Donor chimerism
- Use of PBSC
- Alemtuzumab
## Incidence of mixed chimerism (MC) after allogeneic sibling BMT for SAA

PCR for STR on whole blood or BM DNA

<table>
<thead>
<tr>
<th>Chimerism Type</th>
<th>All patients</th>
<th>Graft failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC (&gt;99.9% donor cells)</td>
<td>23 (51%)</td>
<td>0</td>
</tr>
<tr>
<td>Transient MC (MC &gt; 0.1% recipient cells, changing to DC by 6mo)</td>
<td>11 (24%)</td>
<td>0</td>
</tr>
<tr>
<td>DC+TMC</td>
<td>34 (75%)</td>
<td>0</td>
</tr>
<tr>
<td>Stable MC (&lt;5% fluctuation in recipient cells)</td>
<td>5 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive MC (&gt;10% initial recipient cells or &gt; 15% increase over 3mo period)</td>
<td>6 (13%)</td>
<td>50%</td>
</tr>
</tbody>
</table>

McCann, S et al, BMT 2007; 39: 109
Mixed chimerism after HLA id sib BMT
Combined CIBMTR/EBMT study
Retrospective
134 PBSCT, 558 BMT
1995-2003
HLA identical siblings

Results
1. Neutrophils > 0.5 - 13 v 18d, PB v BM
2. Platelets >20 - 19 v 25 d, PB v BM
3. Similar recovery at day +28 (89 v 85%) and at day +100 (80 v 85%)
4. Graft failure
   - primary: 9% v 9%
   - secondary: 6% v 7%
5. Probability grade II-IV aGVHD
   - 10% v 14% if age < 20y
   - 20% v 19% if age > 20y

Worse outcome and more chronic GVHD with PBSC in younger patients

Campath-based Allogeneic Transplantation In Acquired Aplastic Anaemia: HLA id sib (37), MUD (17)
Poor outcome in older patients: impact of Fludarabine-based regimen

Sibling BMT - effect of age

Sibling BMT in patients > 30yr age

Flu+Cy+/-ATG (n=30)
Cy+/-ATG (n=206)

p=0.1 (log-rank)

S Maury for EBMT SAA WP, 2007
Impact of older age after HLA matched sibling BMT (Gupta et al, ASH 2008)

Retrospective study, n = 1563, 1991-2004
<20y  n = 818
20-40y n = 618
>40y   n = 127 (>50y n=55)

Patients >40yr, more likely:

- Received > 50 BTs
- Received IST pre-BMT (65 v 50%)
- Poor performance status
- Longer time (>6mo) Dx to BMT
- Received PBSCT (27 v 11%)
Impact of older age after HLA matched sibling BMT

Neutrophil recovery

Platelet recovery

Survival

Acute GVHD

Chronic GVHD
Unrelated donor HSCT
Unrelated stem cell transplantation for severe acquired aplastic anemia: improved outcome in the era of high-resolution HLA matching between donor and recipient

Sébastien Maury, Marie-Lorraine Balère-Appert, Zina Chir, Jean-Michel Boiron, Claire Galambrun, Karima Yakouben, Pierre Bordigoni, Aude Marie-Cardine, Noel Milpied, Judith Kanold, Natacha Maillard, Gérard Socié on behalf of the French Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC)

Figure 1. Probability of survival after HSCT from unrelated donors for SAA according to the period of transplantation: 1989-1998 (n=37) or 1999-2004 (n=52).
Changes to conditioning regime
- two approaches

• Low dose TBI 2Gy (Deeg et al)

• Fludarabine-based regimen (Bacigalupo et al)
Flud 30mg/m² x 4
CY 300mg/m² x 4
ATG 3.75mg/kg x 4
Cyclosporin + MTX

n = 38 (32 MUD)
A,B,DRB1 matched

Graft failure/rejection: 18%
- 5% (<14 yr age)
- 32% (>14 yr age)

Acute GVHD 11%
(grade II, 2; III-IV, 2)

Chronic GVHD 27%
(limited 7, extensive 2)
Fludarabine, Cyclo, ATG +/- low dose TBI for alternative donor BMT in acquired SAA

<table>
<thead>
<tr>
<th></th>
<th>FLU-CY- ATG 15</th>
<th>FLU-CY- ATG 7.5-TBI 2Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>45</td>
<td>25</td>
</tr>
<tr>
<td>Median age</td>
<td>13 (1-51)</td>
<td>29 (17-46)</td>
</tr>
<tr>
<td>Median year Tx</td>
<td>2003</td>
<td>2005</td>
</tr>
<tr>
<td>UD</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>Family m/m</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Interval Dx-TX</td>
<td>595 days</td>
<td>572 days</td>
</tr>
<tr>
<td>GvHD III-IV</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rejection</td>
<td>6 (13%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Surviving</td>
<td>36 (80%)</td>
<td>20 (80%)</td>
</tr>
</tbody>
</table>

Bacigalupo et al, EBMT SAAWP, BBMT 2009a
Alternative donor transplant for acquired SAA

![Graph showing survival rates over days from transplant for two different groups: FLU, Cy, ATG; n=45; med. age 13y with 79% survival and FLU, Cy, ATG, TBI; n=25; med. age 29y with 77% survival.]

Bacigalupo et al., EBMT SAAWP, BBMT 2009a
Options for non-responders to ATG who have no matched BM donor
Possible options

- Second course of ATG
- Novel IST eg Alemtuzumab?
- Novel transplant procedure – haploidentical transplant, umbilical core blood transplant

- n=9
- Failed one course IST
- Diag→UCBT: 4mo (1.5-10)
- CTX 60mg/kg + ATG
- CSA + MTX
- Median age: 25yr (15-37)
- Median wt: 57Kg (52-60)
- Single cord (3), double (6)
- Median FU: 32mo

<table>
<thead>
<tr>
<th></th>
<th>N&gt;0.5</th>
<th>Plts&gt; 20</th>
<th>FU (mo)</th>
<th>Chimerism*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>26</td>
<td>69(A)</td>
<td>Mixed</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>82</td>
<td>53(A)</td>
<td>Mixed</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>21</td>
<td>3(D)</td>
<td>Mixed</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>15</td>
<td>41(A)</td>
<td>Mixed</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>49</td>
<td>41(A)</td>
<td>Mixed</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>NA</td>
<td>2(D)</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>0</td>
<td>11(A)</td>
<td>Mixed</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>36</td>
<td>6(A)</td>
<td>Mixed</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>20</td>
<td>4(A)</td>
<td>100% Donor</td>
</tr>
</tbody>
</table>

* Microsatellite DNA for multiple STR; Mixed chimerism: 30-40%, stable
Unrelated Cord Blood Transplantation for Severe Aplastic Anaemia
Yoshimi A et al
BBMT 2008; 14: 1057

Japan Cord Blood Bank Network
1998-2006
31 patients
Age 27.9yr (0.8-72.7)
8 patients > 50yr

<table>
<thead>
<tr>
<th>Conditioning Regimen</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI (4-5 Gy) + MEL + FLU</td>
<td>12</td>
</tr>
<tr>
<td>TBI (2-4 Gy) + CY + FLU</td>
<td>5</td>
</tr>
<tr>
<td>TBI (10-12 Gy) + CY + ATG</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
</tr>
<tr>
<td>TBI/TAI</td>
<td>25/1</td>
</tr>
<tr>
<td>No radiation</td>
<td>7</td>
</tr>
<tr>
<td>ATG</td>
<td></td>
</tr>
<tr>
<td>Yes/No</td>
<td>7/24</td>
</tr>
<tr>
<td>GVHD prophylaxis</td>
<td></td>
</tr>
<tr>
<td>CSA</td>
<td>6</td>
</tr>
<tr>
<td>CSA + others (MTX/steroid/MMF)</td>
<td>10</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>7</td>
</tr>
<tr>
<td>Tacrolimus + others (MTX/steroid)</td>
<td>8</td>
</tr>
</tbody>
</table>
Sustained engraftment (17): chimerism done in 8, all complete donor
Primary graft failure (5)
Failure sustained engraftment (7)
Autologous recovery (1); one graft failure D+176

Factors: single agent CSA/tacrolimus. No effect of cell dose or HLA matching

**Neutrophil engraftment > 0.5**

![Graph A](image)

- 54.8%; med. 19 (12-35 days)

**Platelet engraftment > 50**

![Graph B](image)

- 72.2%; med. 59 (39-145 days)
GVHD and Survival

- Acute GVHD $\geq$ Gd II 17%; chronic GVHD 19%
- OS at 2yr = 41%; 20% for age > 40yr
- COD: graft failure (7), bacterial/fungal inf (3), VOD (3)
- CMV reactivation (9), disease (1), EBV reactivation (1)
  Adenovirus cystitis (1)
Outcomes of unrelated UCBT in severe acquired AA and PNH: EUROCORD & EBMT AA WP

Ruggieri, BMT 2009; 43: S1, 0298a

Patients
• n = 68, 31 centres, 1996-2008
• Age 12yr (1-68), 27 adults. Wt 46Kg (9-100)
• SAA (59), AA/PNH (9)
• Conditioning: myeloablative (24), RIC (43). + ATG (83%)

Results
• Neutrophil recovery: 37/68: 55% at 25d (6-59)
  78% if > 3.2 x 10^7 TNC/kg
  45% < “ “ “
• Platelet recovery: 26/38: 38% at 45d (15-127)
• Acute GVHD: 24%
• Chronic GVHD: 32%
• Survival at 2yr: 39% (45% if > 3.2 x 10^7 TNC)
Conclusions

• Improved outcomes after HSCT
• Change timing of UD HSCT
• But, poor outcomes in older patients: new approaches needed
• Further evaluation of novel transplant procedures indicated for those lacking BM donor
• Ensure careful assessment at diagnosis for constitutional AA
The End
12. 24/M, MUD, Flu-30, Mel, Campath. 100% donor chimerism, no GVHD. Died, 15 months: Obliterative fibro-alveolitis, GI ulceration, nodular hyperplasia of liver, portal hypertension, oesophageal varices. FH pulmonary fibrosis, TERC mutation (Amarasinghe et al. BMT 2007; 110: 1397)