Transplantation - Challenges for the future

Dr Gordon Cook

St James’s Institute of Oncology,

Leeds Teaching Hospitals Trust
Bone Marrow Transplantation Timeline, 1957-2006

- 1955: Initial report on use of BMT as cancer treatment
- 1960: Twin-twin transplantations
- 1965: HLA skin-grafting experiments
- 1970: Successful BMT for radiation accident
- 1975: Cure of lymphoma with autologous BMT
- 1980: Cure of thrombocytopenic purpura with BMT
- 1985: Successful cord-blood transplantation
- 1990: Recognition of human graft-versus-leukemia effect
- 1995: Cure of sickle-cell anemia with BMT
- 2000: Remission with donor lymphocyte infusion
- 2005: Introduction of reduced-intensity transplants
- 2010: Imatinib mesylate for chronic myelogenous leukemia

Autologous
Allogeneic
Indications for Stem Cell Transplantation in North America, 2003

Allogeneic (Total N=7,300)

Autologous (Total N=9,600)
Issues in Stem Cell Transplantation

• Stem cell re-mobilisation in Autologous SCT

• Conditioning Intensity & graft source

• Age – AlloSCT in the older patient

• Alternative donor sourcing
PB Stem Cell Mobilisation & Harvesting

- Minimum required $2 \times 10^6$ CD34$^+$ cells/kg.
- Optimum $4-6 \times 10^6$/kg
- Peripheral counts prior to apheresis correlate with harvest success (>10 cells/μl - optimum >20)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complications</th>
</tr>
</thead>
</table>
| Repeat Mobilization          | - High product volume when combined with previous collection  
|                              | - Higher cost & morbidity                           
|                              | - Associated with high failure rate                 |
| Alternative Cytokines        | - Associated with added toxicity or lack of efficacy |
|     ● Higher dose of G-CSF   |                                                    |
|     ● Combine G-CSF with GM-CSF |                                                   |
| Addition of Chemotherapy     | - Toxicity, neutropenic fever, admission costs      |
| Traditional Bone Marrow Harvest | - Slower engraftment                               |
|                              | - Increased cost, risk (due to anesthesia) and pain for patient |
SDF-1α & CXCR4

- A bicyclam molecule
- SDF-1α (CXCL12) is produced by BM sinus endothelial cells and expressed on BM stromal cells
- Function of SDF-1α depends on expression of the CXCR4 receptor on HSC
- Supports survival and proliferation of hematopoietic progenitor cells
- Distinguished from other chemokines (IL-8, PF4 & MIP-1α) which are inhibitors of hematopoiesis
- SDF-1α is the ONLY known ligand for CXCR4

Plerixafor (AMD3100)

- Reversible inhibitor of SDF-1α/CXCR4 binding
- Initially developed as inhibitor of X4 HIV-1 entry into CD4+ cells
- Caused rapid, transient leukocytosis in patients with HIV infection and healthy volunteers, stimulating interest in capacity to mobilize CD34+ cells

Definitions

• Myeloablative
• Full Intensity
• “Maxi” → “Midi”
• Traditional

• Non-myeloablative
• Reduced Intensity
• “Mini” AlloSCT
Allogeneic Reconstitution

Myeloablative

Reduced Intensity

Recipient
Donor
Pretransplant Disease Status for AML, Registered with the CIBMTR, 1998-2004

- Low Risk – FI
- High Risk – FI
- Low Risk – Reduced Intensity Conditioning
- High Risk – Reduced Intensity Conditioning

Age <50 yrs

Age ≥50 yrs
Spectrum of Intensity

Greater requirement for GvT effect

Toxicity

Intensity

LD-TBI

FluLD-TBI

FluBu

FluBu/Alem

FluMel

BuMel

BuCy/ATG

CyTBI

BuTBI

BuCyTBI
## Mini – Midi – Maxi?

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Mini</th>
<th>Midi</th>
<th>Maxi (=standard conditioning regimen)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>2 Gy TBI ± fludarabine (n = 52)</td>
<td>Busulfan 8mg/kg BW + fludarabine (n = 41)</td>
<td>Melphalan 100-160 mg/m(^2) + fludarabine (n = 111)</td>
</tr>
<tr>
<td></td>
<td>Before 2000 (n = 289)</td>
<td>After 2000 (n = 239)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>27%</td>
<td>24%</td>
<td>32-49%</td>
</tr>
<tr>
<td>TRM</td>
<td>17%</td>
<td>17%</td>
<td>25-32%</td>
</tr>
<tr>
<td>Survival</td>
<td>41% (1.5 years)</td>
<td>62% (2 years)</td>
<td>30-71% (2 years)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; TRM, treatment-related mortality.

\(^a\)Different regimens, mainly total body irradiation/cyclophosphamide or busulfan/cyclophosphamide.
## Tandem ASCT/RICAlloSCT

<table>
<thead>
<tr>
<th>Auto-regimen</th>
<th>n = 109</th>
<th>n = 59</th>
<th>n = 16</th>
<th>n = 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan 200 mg/m²</td>
<td>Melphalan 200 mg/m²</td>
<td>Melphalan 140 mg/m²</td>
<td>Melphalan 200 mg/m²</td>
<td></td>
</tr>
<tr>
<td>2 Gy TBI ± fludarabine</td>
<td>Melphalan 100–150 mg/m²+ fludarabine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 Gy TBI+ fludarabine</td>
<td>Busulfan 4 mg/kg BW+ fludarabine&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>TRM</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto-regimen</td>
<td>52–58%</td>
<td>55–83%</td>
<td>78% (2 years)</td>
</tr>
<tr>
<td>Allo-regimen</td>
<td>16–17% (1 year)</td>
<td>0–17% (1 year)</td>
<td>70–100% (2 years)</td>
</tr>
<tr>
<td>Auto-regimen</td>
<td>62%</td>
<td>16% (1 year)</td>
<td>62% (3 years)</td>
</tr>
<tr>
<td>Allo-regimen</td>
<td>11% (1 year)</td>
<td>57% (2 years)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; OS, overall survival; TRM, treatment-related mortality.

<sup>a</sup>Including also unrelated donors with ATG-Fresenius.

<sup>b</sup>Only high-risk patients with del 13 (FISH) and β₂-microglobulin >3 mg/dl and anti-thymocyte globulin (Thymoglobulin), 12.5 mg/kg BW.
Graft Source by Conditioning Intensity, Registered with the CIBMTR, 2003-2004

- Bone Marrow
- Peripheral Blood
- Cord Blood

Transplants

- FI
- RIC

CIBMTR

Yorkshire
Graft Source – effect on outcome

Incidence of CGvHD by source of stem cells

- BM, N=190
- PBSC, N=130, P=0.60

Non-relapse mortality rate by source of stem cells

- BM, N=190
- PBSC, N=130, P=0.75
Graft Source – effect on outcome

Relapse rate by source of stem cells

Overall survival by source of stem cells
RIC AlloSCT: Issues

• Eligibility & Age – AlloSCT in the unfit or older patient?

• Disease state and RIC AlloSCT

• T-cell depletion

• Complications of RIC AlloSCT
RIC AlloSCT: Issues

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Age

• By 2030, 21% of the USA population will be >65 yrs, equating to 70 million people.

• Cancer is the leading cause of death in the 60-79 year age group.
Age & Treatment

Age: 60 - 85

Number of Comorbidities

GoGo Young Old

Slow Go Elderly / Old

No Go Very Old
Trends in Allogeneic Transplants
Recipient Age* 1987-2004

* Transplants for AML, ALL, CML
Conditioning Intensity by Age for Allogeneic Recipients, - Malignant Disease, 2003-2004

**FI**
- 40-49y (22%)
- 50-59y (18%)
- 60-69y (1%)
- <20y (26%)
- 20-29y (13%)
- 30-39y (16%)
- >70y (<1%)

**RIC**
- 40-49y (18%)
- 50-59y (36%)
- 60-69y (24%)
- <20y (6%)
- 20-29y (5%)
- 30-39y (9%)
- >70y (2%)
Fl AlloSCT in >60 yrs

Wallen et al, J Clin Oncol, 2005, 23, 3439
RIC AlloSCT in AML >60yrs

N=19
Med age: 64 (60-70) yrs
1yr cum survival: 68% (95%CI 48,89)

Bertz et al, J Clin Onc, 2003, 21, 1480-1484
Age-effect in RIC AlloSCT for MCL

Overall survival by age at transplant

Cook et al, Biol BMT, 2010 (in press)
Hematopoietic cell transplantation (HCT)–specific comorbidity index: a new tool for risk assessment before allogeneic HCT

Mohamed L. Sorror, Michael B. Maris, Rainer Storb, Frederic Baron, Brenda M. Sandmaier, David G. Maloney, and Barry Storer

<table>
<thead>
<tr>
<th>Score</th>
<th>Patients, %</th>
<th>HR* (95% CI)</th>
<th>2-year, %</th>
<th>Patients, %</th>
<th>HR* (95% CI)</th>
<th>2-year, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38</td>
<td>1</td>
<td>9</td>
<td>38</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>1.66 (0.9-3.1)</td>
<td>14</td>
<td>18</td>
<td>1.57 (0.7-3.3)</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>3.48 (2.0-6.0)</td>
<td>27</td>
<td>17</td>
<td>1.26 (0.6-2.8)</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>6.09 (3.7-10.1)</td>
<td>41</td>
<td>15</td>
<td>3.95 (2.1-7.5)</td>
<td>41</td>
</tr>
<tr>
<td>4 or more</td>
<td>11</td>
<td>6.93 (4.0-12.0)</td>
<td>43</td>
<td>13</td>
<td>3.05 (1.5-6.2)</td>
<td>40</td>
</tr>
</tbody>
</table>

Sorror et al, Blood, 2005 106, 2912-2919
HCT-CI vs CCI - Outcomes
Sorror et al, Blood, 2005 106, 2912-2919
RIC AlloSCT: Issues

• Eligibility & Age – AlloSCT in the unfit or older patient?

• Disease status and RIC AlloSCT

• T-cell depletion

• Complications of RIC AlloSCT
Disease status at transplant in DLBC

Thomson et al, J Clin Oncology, 2009 27 (3), 426-432
Disease stage & response to AlloSCT in HD

Robinson et al, Hematologica, 2009, 94(2), 230-238
Probability of Survival after HLA-identical RIC MRD for AML (1998-2004) - by Disease Status

P < 0.001
RIC AlloSCT: Issues

- Acute vs Chronic........blurring of definition?
- Eligibility & Age – AlloSCT in the unfit or older patient?
- Disease state and RIC AlloSCT
- T-cell depletion
- Complications of RIC AlloSCT
RIC AlloSCT & MCL - Alemtuzumb

Non relapse mortality by campath use

Overall survival by campath use

Cook et al, Biology Blood & Marrow Transplantation, 2010 (in press)
RIC AlloSCT & Myeloma

RIC AlloSCT: Issues

• Acute vs Chronic........blurring of definition?

• Eligibility & Age – AlloSCT in the unfit or older patient?

• Disease state and RIC AlloSCT

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Umbilical Cord Blood Transplantation (UCBT)

• 1982 UCB might contain sufficient HSC to reconstitute lymphohaematopoiesis
• 1988 First related donor UCBT
• 1993 Public UCB banking programs begin
• 1993 First unrelated donor UCBT
• 1992 ICBTR established
• 1993 Eurocord established
UCB SCT

**Advantages**
- No risk to donor
- No donor attrition
- Speed of acquisition of units
- Infusion date easily rearranged
- Potential for targeting specific ethnic groups
- Low risk of viral transmission
- Reduced incidence of acute and chronic GVHD
- Tolerance of 1-2 HLA mismatch

**Disadvantages**
- Less experience
- Delayed engraftment
- Limited cell dose
- No donor recall
- Potential for transmission of congenital disorders
Haplo-identical HSCT

- Pre-1990s: Prohibitive GvHD + graft rejection
- 1991: T-cell depletion prevented GvHD but graft rejection still a problem in malignancies
- 1994: Stem cell dose escalation could overcome graft rejection
- Currently: Delayed immune reconstitution still a challenge
## Which stem cell source is best?

<table>
<thead>
<tr>
<th></th>
<th>BM</th>
<th>UCB</th>
<th>Haplo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance of donor</td>
<td>10-70%</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Speed of obtaining graft</td>
<td>3-4 months</td>
<td>2-3 weeks</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Cost of obtaining graft</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Risk to donor</td>
<td>Low</td>
<td>None</td>
<td>Low</td>
</tr>
<tr>
<td>Re-access</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Engraftment</td>
<td>Moderate</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Graft rejection</td>
<td>Low</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>GvHD</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>GvL</td>
<td>T cell</td>
<td>T/?NK cell</td>
<td>NK cell</td>
</tr>
<tr>
<td>Immune reconstitution</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Very slow</td>
</tr>
</tbody>
</table>
Conclusions

• With advancing understanding of stem cell biology, conditioning regimens and better patient selection/supportive care, more patients are being considered for AlloSCT, especially older patients.

• RIC AlloSCT allows for wider application of AlloSCT but is not without its complications.

• Alternative donor sourcing will hopefully widen the applicability of AlloSCT.