Allogeneic Transplantation for Hodgkin Lymphoma (past, present and future)

Dr Karl Peggs
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**Allogeneic HSCT for HL**

More is less … NRM 40-65%

- 100 HLA identical sibling allografts
- median age 28 yr
- TRM 61%
- Relapse 65%
- DFS 15%

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*Gajewski et al. JCO 1996;14:572*
Allogeneic HSCT for HL

More is less …

- Matched pair study - 45 pts in each group
  - sex, age, status at Tx, time D - Tx ± TBI
  - TRM
    - Allo 12% 65%
    - Chemosensitive OS 64% 30%
  - Acute GVHD ≥ II lower risk of relapse
  - Lower overall survival

“allogeneic HSCT not recommended”

Milpied et al. *JCO* 1996;14:1291
Immunosuppression
Tumour Control / Myelosuppression
Flu~TBI 2Gy
Flu~Cy
Flu~Mel~Alemtuzumab
Flu~Bu~ATG
BEAM~Alemtuzumab
FLAG~Ida
TBI 2Gy
Cy~TBI
Flu+Mel 34%
Flu+Bu 10%
Flu+Cyclo 8%
Flu+Cyclo+Thio 4%
Other Chemo 27%
TBI+/-Chemo 17%

Present: 2000s ‘Reduced intensity’ transplants
Practice across Europe: 2007
### Summary of early RIC experience

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>TRM</th>
<th>Relapse</th>
<th>PFS Refractory</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBMT</td>
<td>401</td>
<td>22% (2yr)</td>
<td>53% (3yr)</td>
<td>26% (3yr)</td>
<td>7% (3yr)</td>
<td>41% (3yr)</td>
</tr>
<tr>
<td>UK (MF-A)</td>
<td>49</td>
<td>16% (2yr)</td>
<td>45% (3yr)</td>
<td>39% (4yr)</td>
<td>22% (4yr)</td>
<td>56% (4yr)</td>
</tr>
<tr>
<td>Spain (MF)</td>
<td>40</td>
<td>25% (1yr)</td>
<td>44% (3yr)</td>
<td>32% (2yr)</td>
<td>10% (2yr)</td>
<td>48% (2yr)</td>
</tr>
<tr>
<td>FHCRC (F-TBI)</td>
<td>35</td>
<td>??</td>
<td>&gt;70% (3yr)</td>
<td>8% (3yr)</td>
<td>??</td>
<td>35% (3yr)</td>
</tr>
<tr>
<td>UMN (F-TBI-Bu/C)</td>
<td>21</td>
<td>25% (6m)</td>
<td>??</td>
<td>20% (2yr)</td>
<td>??</td>
<td>48% (2yr)</td>
</tr>
<tr>
<td>GITMO (CFT)</td>
<td>32</td>
<td>3% (3yr)</td>
<td>81% (3yr)</td>
<td>16% (3yr)</td>
<td>??</td>
<td>32% (3yr)</td>
</tr>
<tr>
<td>MDACC (MF)</td>
<td>58</td>
<td>15% (2yr)</td>
<td>55% (2yr)</td>
<td>32% (2yr)</td>
<td>12% (3yr)</td>
<td>64% (2yr)</td>
</tr>
<tr>
<td>DFCI (F-Bu)</td>
<td>36</td>
<td>15% (3yr)</td>
<td>63% (3yr)</td>
<td>22% (3yr)</td>
<td>??</td>
<td>56% (3yr)</td>
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</tbody>
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<tr>
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<th>PFS</th>
<th>PFS Refractory</th>
<th>OS</th>
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Relapse has become the commonest cause for treatment failure

- TRM: Treatment-related mortality
- PFS: Progression-free survival
- OS: Overall survival
- 30-60% for TRM, 10-40% for Relapse, 45-80% for PFS, 30-60% for OS
RIC compared with conventional allogeneic SCT in relapsed or refractory Hodgkin Lymphoma

Non-relapse mortality (n=168)

Progression free survival (n=168)

RR 2.85 (95% CI, 1.62 to 5.02); \( P < 0.001 \)

RR 1.53 (95% CI, 0.97 to 2.4); \( P = 0.07 \)

52% failed ASCT

Allogeneic HSCT in children and adolescents with recurrent Hodgkin Lymphoma

- n=151 (1987-2005); failed ASCT: 55%
- Median age at diagnosis: 15 yrs (2-18); at SCT: 17 yrs (4-21)

Relapse or Progression

Same NRM, but increased RR following RIC, with a trend to lower PFS

Defining prognostic factors: EBMT

Adverse Fc for NRM:  
• age ≥ 45 years  
• poor performance  
• chemorefractory

Risk of progression after 9 months of RIC according to cGVHD (Landmark analysis)

Prior Transplant, Donor Relation and TCD: ns  
TCD no significant impact

Sureda et al. JCO 2008; 26:455-62
RIC to salvage autograft failure

Outcome for relapsed HL post-autologous transplant is poor: median survival <24 months

- **RIT group:** 1998-2004, 7 UK centres (n=38)
  - all autograft failures
  - 34% chemorefractory
  - related 63%, unrelated 37%

- **Control group:** autograft 1990-1997 (n=34)
  - all autograft failures
  - all chemosensitive at relapse
  - survival >12m from relapse

Thomson et al. *BMT* 2008;41(9):365-70
Overall survival from autograft

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RIT</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS at 10yrs from diagnosis</td>
<td>48%</td>
<td>15%</td>
<td>0.001</td>
</tr>
<tr>
<td>OS at 5yrs from autograft</td>
<td>65%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Thomson et al. *BMT* 2008;41(9):365-70
Overall survival from autograft

Sarina et al. *Blood* 2010;115:3671-7
• DLI are used to enhance alloreactivity in an attempt to enhance GvT
• Allo- and GvT-reactivity are closely aligned using current strategies
• Tumour-specific responses may occur

3 general strategies:
– Therapeutic
– Pre-emptive: targeted to e.g. mixed chimerism or MRD
– Prophylactic
## ‘Therapeutic’ Donor Lymphocyte Infusions

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Preceding chemotherapy</th>
<th>CR/PR</th>
<th>Response rate</th>
<th>Response rate (DLI only)</th>
<th>Response at latest follow-up: time from last DLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. American survey (1999)</td>
<td>6</td>
<td>unknown</td>
<td>0/2</td>
<td>29%</td>
<td>unknown</td>
<td>2 PR 6+ and 18+ months</td>
</tr>
<tr>
<td>UK</td>
<td>24</td>
<td>10</td>
<td>14/5</td>
<td>79%</td>
<td>93%</td>
<td>9 CR, 2 PR median 4.6 yrs for CR</td>
</tr>
<tr>
<td>Spain</td>
<td>11</td>
<td>3</td>
<td>3/3</td>
<td>55%</td>
<td>N/A</td>
<td>None ongoing</td>
</tr>
<tr>
<td>UMN</td>
<td>2</td>
<td>unknown</td>
<td>0/2</td>
<td>100%</td>
<td>unknown</td>
<td>None ongoing</td>
</tr>
<tr>
<td>GITMO</td>
<td>9</td>
<td>0</td>
<td>3</td>
<td>33%</td>
<td>33%</td>
<td>unknown</td>
</tr>
<tr>
<td>MDACC</td>
<td>27</td>
<td>10</td>
<td>6/4</td>
<td>37%</td>
<td>29%</td>
<td>2 CR 8+ months</td>
</tr>
<tr>
<td>DFCI</td>
<td>13</td>
<td>unknown</td>
<td>2/0</td>
<td>15%</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>EBMT Registry</td>
<td>41</td>
<td>23</td>
<td>13</td>
<td>32%</td>
<td>44%</td>
<td>unknown</td>
</tr>
<tr>
<td>EBMT Registry (adolescent)</td>
<td>6</td>
<td>unknown</td>
<td>1/0</td>
<td>17%</td>
<td>unknown</td>
<td>1 CR 1 year</td>
</tr>
</tbody>
</table>

- Overall response rates variable 30-80% ($44/92 = 48\%$)
- A significant minority have durable responses ($16/40 = 40\%$)
If the major aim of HSCT is to foster GvT, modulation of the locally immunosuppressive microenvironment may be key to success, allowing access of effectors to the target population.
Minimally intensive regimens may fail to allow full benefit of alloreactivity (cf. Seattle and GITMO - highest relapse rates) i.e. dose intensity may be important for indirect immunological as well direct anti-tumour effects

Furthermore, intervention at a state of minimal disease may be particularly important for ‘therapeutic’ DLIs when the tumour microenvironment is so critical to immunity
Donor Lymphocytes - Basic concepts

• **Pre-emptive** DLI for mixed chimerism remains controversial

• Based on the argument that MC = bidirectional tolerance, which can be broken using DLI: this may be the case in TCD but not T-replete protocols i.e. relevance of MC likely contextual

• In TCD setting MC potentially allows titration of alloreactivity with a readout that might allow dissociation of Gv-LymphoHaematopoietic system vs ‘other GvHD’ (lessons from CML)

• Potential impact on HL relapse may only be unmasked when the tumour environment is permissive to effector responses i.e. even if the relevance of MC were equivalent in TCD vs TCR, the outcome of DLI may not be
Donor Lymphocytes - Predictions

- **Pre-emptive** DLI for mixed chimerism will reduce relapse risk
- Monitoring the shift to full donor chimerism will allow titration of DLI dose to dissociate alloreactive GvHL effect from GvHD
- **Therapeutic** DLI will be more effective if intervention is directed earlier by functional imaging studies
**RIC for Hodgkin Lymphoma: UCL experience**

- n = 76 HL patients transplanted Oct ’97 - July ’09 at UCL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31 (13-59) yrs</td>
</tr>
<tr>
<td>Sex</td>
<td>M 42, F 34</td>
</tr>
<tr>
<td>Primary resistant</td>
<td>50 (66%)</td>
</tr>
<tr>
<td>Failed autograft</td>
<td>45 (59%)</td>
</tr>
<tr>
<td>Prior lines</td>
<td>5 (2-10)</td>
</tr>
<tr>
<td>Status at Tx</td>
<td>CR 17 (22%), PR 33 (43%), Ref. 26 (34%)</td>
</tr>
<tr>
<td>Donor</td>
<td>MRD 42, MUD 29, MMUD 5 (8-9/10)</td>
</tr>
<tr>
<td>Follow-up (med, range)</td>
<td>2yrs (0.5-12.1)</td>
</tr>
</tbody>
</table>

**Non relapse mortality**

- Peggs et al. *JCO* 2011;41;29(8):971-8
RIC for Hodgkin Lymphoma: Relapse

- aGvHD Gd II-III
  - MRD n=3/0, 7%
  - MUD n=8/2, 29%
- 31 relapses:
  - CR 5/17
  - PR 17/33
  - Refractory 9/26

![Cumulative Incidence](image)
DLI indications and schedule

- DLI given for either mixed chimerism (from 6m) or relapse
- Relapse defined by recurrence or progression of FDG-avid lesions in sites of prior disease, with or without new sites
- If FDG-avid lesions only in new sites relapse confirmed by biopsy if accessible (n=12), otherwise an interval scan was performed at 6-8 weeks to confirm progression in the absence of other potentially causative pathology

- Dose escalation:
  - 1x10^6 CD3^+ /kg
  - 3x10^6 CD3^+ /kg
  - 1x10^7 CD3^+ /kg
  - 3x10^7 CD3^+ /kg
  - 1x10^8 CD3^+ /kg
  - 3x10^8 CD3^+ /kg

Relapse: MUD/MMUD
Mixed Chimerism: MRD
• 22 patients received DLI for mixed chimerism (18 MRD, 4 UD):
  – 20 converted to full donor
  – 2 stable at 5% following reduction from 30-40%

• Median time to 1\textsuperscript{st} DLI: 287 days (9 months)

• GvHD:
  – acute: 1 Gd IV, 2 hepatitic
  – chronic: 4 limited, 1 extensive
Outcomes post relapse: n=31

- 7 not given DLI:
  - 2 early progression (refractory)
  - 3 GvHD
  - 1 radiotherapy
  - 1 PR following CsA withdrawal, coincident with GvHD

- 24 received DLI
  - 13 MRD, 11 UD
  - 10 received cytoreduction prior to/between DLIs
    - gemcitabine, radiotherapy, ABVD, ESHAP, miniBEAM, IVE

All dead at 45-494 days
14 CR, 5 PR (79% response rate)
- MRD: 77% (9CR, 1PR, 3NR); UD: 82% (5CR, 4PR, 2NR)
- 13 responders (11CR) had no prior salvage

Relapse

Post DLI > post HSCT (n=12)

Post HSCT > post DLI (n=4)
DLI for relapsed disease

Jan 03 - Aug 04  Nov 06 - Feb 08
Survival outcomes from transplant

Progression free survival (May 2011)
(n=93)

Survival

Time post transplant (years)

- Therapeutic donor lymphocytes
- Pre-emptive donor lymphocytes?
What next?
Autologous transplantation in primary refractory HL

IBMTR (n=122)

Overall survival

PFS: 5yr 38%

EBMT (n=175)

Overall survival

PFS: 5yr 32%

Lazarus B et al. JCO 1999;17:534

Sweetenham J et al. JCO 1999;17:3101
Functional imaging predicts outcome post autograft

Moskowitz AJ. Blood 2010;116:4934

Jabbour E. Cancer 2007;109:2481
Tandem autografts

- Generally 2 ASCT within 1-3 months
  - OS 54-78%, PFS 49-59%

- GELA/SFGM H96 risk adapted strategy:
  - time to relapse <12 months
  - stage III-IV at relapse
  - relapse in previously irradiated site

- 0-1 = intermediate risk (n=95) 2-3 or PRHL = poor risk (n=150)
  - IR single ASCT: 5yr OS 85%, PFS 73%
  - HR tandem ASCT: 5yr OS 57%, PFS 46% (PRHL PFS 46%), TRM 6%

Tandem ASCT superior in poor risk patients with anything <CR to initial salvage? Single ASCT for intermediate risk patients, or poor risk attaining CR?
A role for allografting?

- Alemtuzumab reduces long term GvHD-related morbidity and may modulate the tumour environment
- Aggressive treatment of MC may reduce relapse risk following TCD allogeneic HSCT
- Unrelated donors mismatched at up to 2/10 HLA-loci are a viable graft source following alemtuzumab-based conditioning
- FDG-PET may identify a group of patients with poor predicted outcome following autologous HSCT (PFS ~ 30% at 3-5 yrs)
- Transplant earlier in the disease pathway may be better tolerated allowing further reductions in NRM
- This may also allow consideration of escalating dose intensity
All series include significant nos. of refractory cases (33-50%)

PFS rates: 10-22% at 2-4 years in smaller series
7% at 3 years in the EBMT analysis

PFS rates: Flu-Melph > less intensive Flu-Cy
(MDACC, Anderlini et al, 2005)

Some regimens are essentially devoid of anti-tumour activity
- particularly high relapse rates in GITMO and FHCRC
Conclusions

- Encouraging outcomes following BEAM-alemtuzumab allogeneic transplantation in a cohort predicted to have a relatively poor prognosis according to response to salvage.
- Results require confirmation in a prospective multi-centre setting.
- An appropriate subsequent comparison could be with a strategy of autologous transplantation (+/- brentuximab), with salvage consolidated by allogeneic transplantation in relapsing patients.