Donor Lymphocyte Infusions

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Stimulating the body’s immune system against cancer: T-cells can kill tumor cells
T Lymphocytes are essential in the Graft vs Tumour effect.

T cell depletion decreases GVHD incidence, but increases risk of relapse.

“Old” Concept: Myeloablative SCT
Regimen Compromises

Minimise toxicity and TRM

Maximise anti-tumour effect

RIC

MAC

Relapse
Early DLI

High TRM
Non-myeloablative hematopoietic cell transplant

Preparative regimen

Recipient

Donor

Mixed chimera

Complete chimera

A Host

B Donor

HSCT

± DLI
Chimerism

The chimera of Greek mythology was said to possess the head of a lion, the body of a goat and the hind part of a dragon. Despite these disparate components, the chimera was functional, able to spit fire and terrorize Asia Minor until its demise.
How do we measure chimerism?

- **Patient pre SCT**
- **Donor**
- **Patient post SCT**
- **Neutrophils post SCT**
- **Lymphocytes post SCT**
Mixed chimerism
What is a DLI?
DLI may have modified cells

Cytokines
- Interleukin-2
- GM-CSF
- Interferon

T Helper
Cytotoxic T Lymphocyte

Tumor Cell
DLI may have more than one type of cell
What is a DLI?

- **UNMANIPULATED Lymphocytes**
  - Harvested and infused fresh
  - Harvested and cryopreserved
  - Harvested, selected and infused fresh
  - Harvested, selected and cryopreserved

- To prevent or treat relapse of the disease
- To treat mixed or decreasing chimerism
- To treat Infections
- Prophylaxis or pre-emptive therapy
  - Relapse
  - Chimerism
  - Infections
What is also a DLI?

- **MANIPULATED Lymphocytes**
  - Primed and expanded with cytokines
  - Cultured with antigens, viruses, etc
  - Gene modified with suicide genes
  - Depleted of “unwanted” lymphocytes

- To enhance immune reconstitution
- To improve engraftment
- To prevent or modulate GvHD
- In combination with other cells
  - Mesenchimal stem cells
  - Dendritic cells

They may be also considered as cellular therapy
Relapse of CML: current practice in Europe

Type of Relapse

- Molecular
- Cytogenetic
- Haematologic

- DLI
- No therapy
- Other
- Imatinib
DLI: current practice in Europe

Type of Schedule

- Escalating
- Bulk
- Other
### Graft-versus-tumour effect

<table>
<thead>
<tr>
<th>Responders</th>
<th>15%</th>
<th>20%</th>
<th>40%</th>
<th>&gt;70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Response to DLI**
<table>
<thead>
<tr>
<th>Disease</th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>18/81</td>
<td>(22%)</td>
</tr>
<tr>
<td>Acute Lymphocytic Leukemia</td>
<td>3/37</td>
<td>(8%)</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>5/14</td>
<td>(36%)</td>
</tr>
</tbody>
</table>

Luznik and Fuchs. Cancer Control 9(2):123-137
Survival After Donor Lymphocyte Infusion (DLI) For Acute Myeloid leukaemia

Survival After Donor Lymphocyte Infusion (DLI) For Acute Myeloid leukaemia

- 56±10% DLI in remission and/or favorable cytogenetics (n = 29)
- 21±8% no remission at DLI, but female and <35% blasts at relapse (n = 24)
- 9±3% all other patients (n = 75)

Quantitative PCR Analysis After Allogeneic BMT and DLI for Low Grade Lymphoma
Treatment of CML relapse after SCT

Months post relapse

Probability of survival

DLI (n=91)
2nd BMT (n=27)
other (n=47)
## Results of DLI in CML

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>271</td>
<td>188</td>
<td>83</td>
</tr>
<tr>
<td>GvHD</td>
<td>45</td>
<td>47</td>
<td>40</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>19</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Cytogenetic Response</td>
<td>69</td>
<td>80</td>
<td>43</td>
</tr>
<tr>
<td>Survival at 3y</td>
<td>67</td>
<td>80</td>
<td>38</td>
</tr>
<tr>
<td>Failure free survival</td>
<td>53</td>
<td>66</td>
<td>25</td>
</tr>
<tr>
<td>DLI-related mortality</td>
<td>15</td>
<td>12</td>
<td>21</td>
</tr>
</tbody>
</table>
Detection of Relapse

Haematological Relapse

Cytogenetic Relapse

Molecular Relapse

RT-PCR positive using 'optimized' PCR

RT-PCR positive

RT-PCR negative

Sensitivity of PCR

Leukaemic cells

BMT

Healthy donors

10^{-2}

10^{-6}

10^{-8}

10^0

10^4

10^6

10^8

10^{10}

10^{12}
Molecular response to DLI

- **Molecular/Cytogenetic relapse**
  - 87%

- **Overall**
  - 61%

- **Haematological relapse**
  - 47%

- **Molecular remission (%)**
  - **p = 0.004**

- **Months post DLI**
  - 0 6 12 18 24 30
Response after Relapse

- Haem Remission
  - RT-PCR positive
  - RT-PCR negative

- Cytogenetic Remission
  - Cytogenetics positive
  - RT-PCR positive
  - RT-PCR negative

- Molecular Remission
  - FBC positive

- No response

Imatinib vs DLI

Sensitivity of PCR

Leukaemic cells
Probability of molecular remission

Cytogenetic remission (%)

- BDR (n=28)
  - 91%
- EDR (n=20)
  - 67%

Months post first DLI

Probability of molecular remission
Molecular relapse after remission with DLI
Survival post-DLI in CML relapse (n=66)

Achievers of molecular remission (n=44)

Non responders (n=22)
## Escalating dose schedule at HH

<table>
<thead>
<tr>
<th></th>
<th>SIB (CD3 cells/Kg)</th>
<th>VUD (CD3 cells /Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose</td>
<td>$10^7$</td>
<td>$10^6$</td>
</tr>
<tr>
<td>Second dose</td>
<td>$5 \times 10^7$</td>
<td>$10^7$</td>
</tr>
<tr>
<td>Third dose</td>
<td>$10^8$</td>
<td>$5 \times 10^7$</td>
</tr>
<tr>
<td>Fourth dose</td>
<td>Optional</td>
<td>$10^8$</td>
</tr>
</tbody>
</table>

Interval between infusions = 3 - 4 months
Donor lymphocyte infusions: EDR vs BDR

<table>
<thead>
<tr>
<th></th>
<th>BDR (n=28)</th>
<th>EDR (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytogenetic remission</strong></td>
<td>67% (49-83)</td>
<td>91% (63-98)</td>
</tr>
<tr>
<td><strong>GVHD:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>10 (37%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Grade I-II</td>
<td>10 (36%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Grade III-IV</td>
<td>7 (27%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/limited</td>
<td>15 (59%)</td>
<td>17 (89%)</td>
</tr>
<tr>
<td>Extensive</td>
<td>11 (41%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>
## Donor lymphocyte infusions: EDR vs BDR

### Initial Cell Dose

<table>
<thead>
<tr>
<th>ICD groups groups (10^8/kg)</th>
<th>&lt;0.2</th>
<th>0.2-3.0</th>
<th>&gt;3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>GvHD</td>
<td>26</td>
<td>53</td>
<td>62</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>10</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Response</td>
<td>78</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Survival (at 3 years)</td>
<td>84</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>DFS (at 3 years)</td>
<td>66</td>
<td>57</td>
<td>45</td>
</tr>
<tr>
<td>DLI- RM (at 3 years)</td>
<td>5</td>
<td>20</td>
<td>22</td>
</tr>
</tbody>
</table>
Acute GVHD Post-DLI
Influence of BMT-DLI interval (n=60)

< 365 days post transplant
- Grade 0 - I: 57%
- Grade II - IV: 43%

> 365 days post transplant
- Grade 0 - I: 85%
- Grade II - IV: 15%

p = 0.028
## Factors influencing GHVD after DLI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate p-value</th>
<th>Multivariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient &gt;40y at DLI</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>unrelated donor</td>
<td>&lt;0.001</td>
<td>ns</td>
</tr>
<tr>
<td>female donor</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>D/R sex mismatch</td>
<td>&lt;0.001</td>
<td>ns</td>
</tr>
<tr>
<td>SCT &gt;CP1</td>
<td>&lt;0.001</td>
<td>ns</td>
</tr>
<tr>
<td>stem cell source</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>T-depletion</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>TBI</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>prior acute GvHD</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>prior chronic GvHD</td>
<td>&lt;0.001</td>
<td>1.5 (1.2-1.9) &lt;0.001</td>
</tr>
<tr>
<td>SCT-DLI &lt;1 year</td>
<td>&lt;0.001</td>
<td>1.7 (1.2-2.2) &lt;0.001</td>
</tr>
<tr>
<td>Haematological relapse</td>
<td>&lt;0.001</td>
<td>1.6 (1.2-2.0) &lt;0.001</td>
</tr>
</tbody>
</table>
## CONCLUSIONS

<table>
<thead>
<tr>
<th>Response</th>
<th>Disease stage</th>
<th>Donor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Dose for Response</th>
<th>Disease stage</th>
<th>Donor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>GVHD</th>
<th>Disease stage</th>
<th>Donor type</th>
</tr>
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<tbody>
<tr>
<td>YES</td>
<td>YES</td>
<td>YES</td>
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<thead>
<tr>
<th>Dose for GVHD</th>
<th>Disease stage</th>
<th>Donor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>YES</td>
<td>YES</td>
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</table>
Double Edge Sword
Incidence of GHVD after DLI
(n=500)

<table>
<thead>
<tr>
<th>Response*</th>
<th>GvHD post DLI</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>32%</td>
<td>36%</td>
</tr>
</tbody>
</table>

*Molecular and/or cytogenetic remission*
Imatinib after DLI: overall survival

- CP (n=51)
- AP (n=31)
- BC (n=46)

Probability of Survival

p = 0.0001

Months

CP (n=51)
AP (n=31)
BC (n=46)
Combination of DLI and other therapies

- **CML**
  - Imatinib, Dasatinib, Nilotinib, Interferon
- **AML / MDS**
  - Mylotarg, 5-Azacytidine
- **ALL**
  - Campath, Rituximab, other MoAb
- **Myeloma**
  - Lenalidomide, Bortezomib
- **Lymphoma**
  - Rituximab, Lenalidomide, Bortezomib, other MoAb