Allogeneic Stem Cell Transplantation For DLBCL In The Rituximab Era

Dr Stephen Robinson
University Hospital Bristol
Overview

• Introduction: alloSCT for DLBCL

• Allogeneic SCT For DLBCL Relapsing after autoSCT

• Allogeneic SCT as an alternative to autoSCT
EBMT Registry: SCT for DLBCL 1990-2009

DLBCL: Type of SCT By Year

SCT In DLBCL
- AlloSCT uncommonly used
- Lowest ratio of allo:auto
- 0.3 alloSCT/center/year

PARMA Trial
Problems With Allogeneic SCT In DLBCL

• Toxicity
  - Immunesuppression
  - Graft versus host disease (acute and chronic)

• Limited donor availability?
  - Sibling 25-30%
  - MUD 20-70%
  - Cord or haploidentical donor for >95%

• Cost
  - UK sibling alloSCT £60k
  - UK MUD alloSCT £80-100k
Developments In Transplant Practice

• Improving supportive care
  – Tissue typing
  – CMV monitoring and therapy
  – Antifungal therapy
  – Prevention and treatment of GVHD

• Improving patient selection

• Improving transplantation technique
  – Reduced intensity conditioning
  – Donor lymphocyte infusions
  – Cord blood and haploidentical transplantation
  – Radioimmunotherapy based conditioning
Conditioning Regimens For AlloSCT In DLBCL

### Non-Myeloablative
- Flu+Cyclo+R (Escalon 2004)
- Flu+Melph+CAM (Morris 2004)
- Flu+Cyclo+TT (Corradini 2005)
- 2GyTBI+Flu (Baron 2005)

### Myeloablative
- Cyclo-TBI
- Flu+Cy+Bu (Glass 2009)
- BEAM-CAM (Faulkner 2004)
- LACE-CAM
- 2GyTBI (Baron 2005)
Improving NRM Following Allo-SCT For NHL

NRM (%) by donor type

HLA id siblings

MUD

Excellence in science
European Group for Blood and Marrow Transplantation

Is There A Graft Versus DLBCL Effect?

• Indirect Evidence
  – Relapse rate alloSCT vs autoSCT
  – Impact of GVHD on relapse rate
  – Efficacy of RICalloSCT in autoSCT failures

• Direct Evidence
  – Impact of DLIs for relapse post alloSCT
  – Impact of withdrawal of immunesuppression
Is The Relapse Rate Following AlloSCT Lower Relative To AutoSCT?

Yes (Peniket BMT 2003)

No (Lazarus BBMT 2010)

Jones et al Blood 1991, 77, 649
Ratanatharathorn et al Blood 1994, 84, 1050
Schimmer et al BMT 2000, 26, 859
Impact Of GVHD On Relapse Post AlloSCT (Chopra 2002)

- Retrospective analysis
- 101 patients with NHL
  - Int/HG 38, LBL 55, BL 11, LG 7
- 18 developed cGVHD (all LBL or Int/HG)
  - Relapse Rate 0%
- 30 no cGVH (and survived >3 months)
  - Relapse rate=35%
AlloSCT For Relapse After AutoSCT (van Kampen 2010)

- Overall Survival
- PFS

52% (95% CI, 42% to 63%) at 36 mo

42% (95% CI, 32% to 52%) at 36 mo

Time After Allo-SCT (months)
Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic hematopoietic stem-cell transplantation

M. R. Bishop¹*, R. M. Dean¹,², S. M. Steinberg³, J. Odom¹, S. Z. Pavletic¹, C. Chow⁴, S. Pittaluga⁵, C. Sportes¹, N. M. Hardy¹, J. Gea-Banacloche¹, A. Kolstad⁶, R. E. Gress¹ & D. H. Fowler¹

-Single institution retrospective study
-15 patients with DLBCL
-Persistent/relapsed disease post allogeneic stem cell transplant
-Treatment with withdrawal of immunesuppression+/-DLI+/-chemo
Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic hematopoietic stem-cell transplantation

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Sex</th>
<th>Time from Dx to RIST (months)</th>
<th>Number of prior Tx</th>
<th>Prior auto HSCT</th>
<th>Disease status at study entry</th>
<th>IPI score at study entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>F</td>
<td>10</td>
<td>2</td>
<td>No</td>
<td>Primary refractory</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>F</td>
<td>11</td>
<td>3</td>
<td>No</td>
<td>Primary refractory</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>M</td>
<td>16</td>
<td>3</td>
<td>Yes</td>
<td>Refractory relapse</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>F</td>
<td>9</td>
<td>3</td>
<td>No</td>
<td>Primary refractory</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>F</td>
<td>18</td>
<td>2</td>
<td>No</td>
<td>Sensitive relapse</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>M</td>
<td>18</td>
<td>3</td>
<td>Yes</td>
<td>Refractory relapse</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>F</td>
<td>16</td>
<td>3</td>
<td>Yes</td>
<td>Sensitive relapse</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>F</td>
<td>126</td>
<td>2</td>
<td>No</td>
<td>Sensitive relapse</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>M</td>
<td>14</td>
<td>4</td>
<td>Yes</td>
<td>Primary refractory</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>F</td>
<td>10</td>
<td>6</td>
<td>Yes</td>
<td>Primary refractory</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>M</td>
<td>10</td>
<td>2</td>
<td>No</td>
<td>Primary refractory</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>M</td>
<td>60</td>
<td>6</td>
<td>Yes</td>
<td>Refractory relapse</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>43</td>
<td>M</td>
<td>15</td>
<td>3</td>
<td>Yes</td>
<td>Sensitive relapse</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>49</td>
<td>M</td>
<td>43</td>
<td>5</td>
<td>No</td>
<td>Refractory relapse</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>41</td>
<td>M</td>
<td>71</td>
<td>9</td>
<td>Yes</td>
<td>Refractory relapse</td>
<td>4</td>
</tr>
</tbody>
</table>
Withdrawal Of Immunesuppression
Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic hematopoietic stem-cell transplantation

<table>
<thead>
<tr>
<th>Day +28 response</th>
<th>Day +100 response</th>
<th>Intervention</th>
<th>Response to intervention</th>
<th>GVHDa</th>
<th>Current status (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SD</td>
<td>PD</td>
<td>PD</td>
<td>Y (acute + chronic)</td>
<td>PD/died (4)</td>
</tr>
<tr>
<td>2</td>
<td>SD</td>
<td>PR</td>
<td>CR</td>
<td>Y (acute + chronic)</td>
<td>CR/died sepsis (80)</td>
</tr>
<tr>
<td>3</td>
<td>PR</td>
<td>PD (+40)b</td>
<td>PD</td>
<td>Y (acute)</td>
<td>PD/died (2.5)</td>
</tr>
<tr>
<td>4</td>
<td>PR</td>
<td>PD</td>
<td>PR</td>
<td>Y (acute)</td>
<td>PD/died (6)</td>
</tr>
<tr>
<td>5</td>
<td>CRu</td>
<td>CR → PD (+157)</td>
<td>CR</td>
<td>N</td>
<td>CR/alive (83+)  *</td>
</tr>
<tr>
<td>6</td>
<td>PR</td>
<td>PD</td>
<td>CR</td>
<td>N</td>
<td>CR/alive (76+)  *</td>
</tr>
<tr>
<td>7</td>
<td>CRu</td>
<td>CRu → PD (+169)</td>
<td>CR</td>
<td>Y (chronic)</td>
<td>CR/alive (74+)  *</td>
</tr>
<tr>
<td>8</td>
<td>PR</td>
<td>PR</td>
<td>PD</td>
<td>Y (chronic)</td>
<td>PD/died sepsis (11)</td>
</tr>
<tr>
<td>9</td>
<td>CR</td>
<td>PD</td>
<td>SD</td>
<td>N</td>
<td>PD/died (21)</td>
</tr>
<tr>
<td>10</td>
<td>SD</td>
<td>PD</td>
<td>PD</td>
<td>N</td>
<td>PD/died (5.5)</td>
</tr>
<tr>
<td>11</td>
<td>PR</td>
<td>PD</td>
<td>CR</td>
<td>N</td>
<td>PD/died (26)</td>
</tr>
<tr>
<td>12</td>
<td>PR</td>
<td>PR</td>
<td>CR</td>
<td>N</td>
<td>CR/alive (63+)  *</td>
</tr>
<tr>
<td>13</td>
<td>PR</td>
<td>PR</td>
<td>CR</td>
<td>Y (chronic)</td>
<td>CR/alive (42+)  *</td>
</tr>
<tr>
<td>14</td>
<td>PR</td>
<td>PD</td>
<td>CR</td>
<td>Y (chronic)</td>
<td>CR/alive (44+)  *</td>
</tr>
<tr>
<td>15</td>
<td>SD</td>
<td>PR</td>
<td>SD</td>
<td>Y (acute + chronic)</td>
<td>PD/died (12)</td>
</tr>
</tbody>
</table>

9/15 CR/PR

6/15 Alive
Impact Of DLIs On Relapse Of DLBCL Post AlloSCT (Thomson JCO 2009)

- 4 patients primary DLBCL
  - ¾ developed grade III/IV GVHD
  - All patients died of relapse within 5 months
- 6 patients transformed FL
  - 3 died of relapse within 16/12
  - 3 responded to DLIs alone
Is There A Graft Versus DLBCL Effect?

- Evidence inconsistent
- Difficult to quantify magnitude of effect
- Why?
  - There is no GV DLBCL response
    - Tumour escape mechanisms?
  - There is a GV DLBCL response but.....
    - GVL response inadequate in rapidly growing tumours
    - Available data insufficiently powered to show effect
    - Unidentified bias in retrospective registry studies
Purging vs The GVL Effect (Bierman JCO 2003)
(WF Intermediate Grade NHL, n=1848)

Reduction of relapse rate post alloSCT is due to the provision of a purged graft?

"Purging Effect"
Syngeneic AutoSCT
RR  29%  55%

"GVL Effect"
Syngeneic AlloSCT
RR  29%  25%
What is the role of alloSCT in DLBCL in the Rituximab era?

- Relapse post autoSCT?
- As an alternative to autoSCT in patients failing first line therapy?
Survival Post Relapse After Autologous Stem Cell Transplantation

(Kewalramani et al BMT 2003)
AlloSCT For Relapsed DLBCL After AutoSCT
(van Kampen 2010)

- EBMT retrospective analysis
- 101 patients
- 37 Myeloablative 64 Reduced Intensity
- 1997-2006
- 19 Prior Rituximab
- 72 sibling/29 MUD
AlloSCT For Relapse After AutoSCT (van Kampen 2010)

- Overall Survival: 52% (95% CI, 42% to 63%) at 36 mo
- PFS: 42% (95% CI, 32% to 52%) at 36 mo
AlloSCT For Relapse After AutoSCT (van Kampen 2010)

RIC AllOSCT lower NRM

Outcome better if:-
- chemosensitive
- late relapse
Reduced Intensity AlloSCT For DLBCL (Thomson JCO 2009)

Fludarabine/Melphalan/CAMPATH Conditioning

Prior AutoSCT
n=34
# Results Of RIC AlloSCT In DLBCL

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Prior SCT</th>
<th>NRM % (years)</th>
<th>RR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBMT Registry</td>
<td>64</td>
<td>64/64</td>
<td>20 1yr</td>
<td>3yr</td>
<td>42 3yr</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiotepa/Cyclo/Fludara 2005</td>
<td>61</td>
<td>34/61</td>
<td>15 3yr</td>
<td>15 3yr</td>
<td>54 3yr</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2Gy TBI+/-Flu</td>
<td>33</td>
<td>24/33</td>
<td>25 3yr</td>
<td>25 3yr</td>
<td>35 3yr</td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flu/Mel/CPATH</td>
<td>48</td>
<td>34/48</td>
<td>32 4yr</td>
<td>32 4yr</td>
<td>48 4yr</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Registry</td>
<td>68</td>
<td>54/68</td>
<td>23 1yr</td>
<td>23 1yr</td>
<td>44 2yr</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
AlloSCT For DLBCL Relapse After AutoSCT

• Reduced intensity alloSCT is feasible and effective
• NRM 15-25% with RICalloSCT
• Better outcome if >12 months to relapse after auto and chemosensitive
• Remaining questions
  – Reduced intensity/Intermediate intensity
  – Role of T cell depletion
• Consider sibling, VUD, cord/haploidentical
• Place relative other therapies/novel therapies?
What is the role of alloSCT in DLBCL in the current era?

- Relapse post autoSCT?

- As an alternative to autoSCT in patients failing first line therapy?
Allogeneic Stem Cell Transplant As An Alternative To Autologous Stem Cell Transplant?

ALLOGENEIC SCT
Conditioning Therapy
The GVL Effect
Purged marrow
No Late MDS

AUTOLOGOUS SCT
Conditioning Therapy
Lower toxicity
Lower cost
Allogeneic Stem Cell Transplantation in Relapsed and Refractory Aggressive Non-Hodgkin Lymphoma: Results of the DSHNHL R3 Study

- n = 86 (n = 84 randomized patients)
- Relapsed / refractory DLBCL (55% refractory to last treatment)
- Donor:
  - HLA id sib: 23 patients
  - MUD: 34 patients
  - Mm UD: 26 patients
  - Mm Related donor: 1 patient
- Conditioning regimen: iv Flu (25 mg/m2 iv from -8 to -4) + po BU (4 mg/kg/day from -6 to -4) + iv Cy (60 mg/kg/day from -3 to -2)
- aGVHD prophylaxis: FK-506 + MMF
  - Rituximab randomization
  - From the first 60 evaluable pts, ATG from -3 to -1 in MUD or mm SCT
- Median FU: 4 yrs

(Glass B, et al. Lancet Oncol 2014)
AlloSCT For DLBCL Failing First Line Therapy
DSNHL (n=86)

OS, 50 events, n= 84...49...43...41...35...28...26...23...18...16...14...9...6...2...0
PFS, 51 events, n= 84...52...37...36...32...26...25...22...17...15...13...9...6...2...0

(Glass B, et al. Lancet Oncol 2014)
BEAM-CAMPATH AlloSCT For DLBCL and PTCL

- **n**: 46
- **Median age**: 43 (17-59)
- **DLBCL**: 31
- **TCL**: 15
- **Prior auto**: 5
- **Median Prior Lines**: 2.5 (1-5)
- **Chemosensitive**: 34
- **Chemrefractory**: 11
- **Sib/UD**: 32/14

**Probability of non-relapse mortality**

- **NRM 11% at 3yrs**
- **NRM Sibling**: 3% at 3yrs
- **NRM VUD**: 30% at 3yrs

*(Truelove BBMT 2015)*
BEAM-CAMPATH AlloSCT
For DLBCL and PTCL

PFS 36% at 5 years

OS 42% at 5 years

(Truelove BBMT 2015)
The Outcome Of Autologous SCT and Allogeneic SCT When Performed As A First Transplant For Chemosensitive Relapsed DLBCL

<table>
<thead>
<tr>
<th></th>
<th>AutoSCT</th>
<th>MAC AlloSCT</th>
<th>RIC AlloSCT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2652</td>
<td>54</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Age, median (Q3-Q4)</td>
<td>52 (43-59)</td>
<td>44 (36-51)</td>
<td>54 (46-57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male/Female</td>
<td>58/42</td>
<td>53/47</td>
<td>62/38</td>
<td>0.66</td>
</tr>
<tr>
<td>Diagnosis-SCT, median (Q3-Q4)</td>
<td>23.3 (43-59)</td>
<td>18.5 (36-51)</td>
<td>23.7 (46-57)</td>
<td>0.097</td>
</tr>
<tr>
<td>Diagnosis-SCT &lt; 1 year %</td>
<td>21.9</td>
<td>31.5</td>
<td>32.8</td>
<td>0.033</td>
</tr>
</tbody>
</table>

(Robinson Submitted)
Chemosensitive Relapse: Disease Free Survival

Adverse Risk Factors For DFS:
- Male Sex
- Diag-SCT<1yr
- MACallo SCT

DFS Auto 46% 4yrs
DFS MACallo 37% 4yrs
DFS RICallo 37% 4yrs
Chemosensitive Relapse: Overall Survival

Adverse Risk Factors For OS:
- Age>50
- Diag-SCT<1yr
- MACallo SCT

OS Auto  55% 4yrs
OS MACallo  42% 4yrs
OS RICallo  57% 4yrs

(Robinson Submitted)
Conclusions From This Study

- Retrospective study
- Why were patients selected for an alloSCT in place of an autoSCT?
- PFS and OS in RICalloSCT and autoSCT cohorts were similar
Is there any role for allogeneic SCT in place of autoSCT?

• Failure to collect autologous stem cells

• In patients predicted to be at high risk of failing an autoSCT?
Identifying Patients At Risk Of Failing AutoSCT

Gisselbrecht C et al. JCO 2010;28:4184
Guglielmi et al. JCO 1998, 16:3264
# CORAL: Prognostic factors for maintenance post-ASCT – multivariate Cox Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EFS</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment with rituximab: no</td>
<td>0.1979 0.748</td>
<td>0.3509 0.808</td>
<td>0.2874 0.760</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>0.4658 1.179</td>
<td>0.4536 1.188</td>
<td>0.5665 1.159</td>
</tr>
<tr>
<td>Age-adjusted IPI 2–3</td>
<td>0.0030 1.846</td>
<td>0.0007 2.028</td>
<td>0.0004 2.252</td>
</tr>
<tr>
<td>Response after complete induction: PR</td>
<td>0.2050 1.295</td>
<td>0.4286 1.180</td>
<td>0.4638 1.186</td>
</tr>
<tr>
<td>Arm of treatment: R-ICE</td>
<td>0.0853 1.417</td>
<td>0.0676 1.457</td>
<td>0.0716 1.511</td>
</tr>
<tr>
<td>Arm of second randomisation: Rituximab</td>
<td>0.9208 1.020</td>
<td>0.6104 1.111</td>
<td>0.4822 1.175</td>
</tr>
</tbody>
</table>

Prognostic Factors Predicting Outcome Of Autologous Stem Cell Transplantation

150 patients with chemosensitive DLBCL

Second line age adjusted IPI (sAAIPI)

Factors: High LDH, Stage 3 or 4, Poor performance status

Low risk: 0 factors
Int. risk: 1 factor
High risk: 2 or 3 factors

Prognostic Factors Predicting Outcome Of Autologous Stem Cell Transplantation

Low Risk (n = 18)
Intermediate Risk (n = 34)
High Risk (n = 56)

P = 0.005

Prognostic value of PET status pre-auto transplant for aggressive lymphoma: PFS

Who Should Be Considered For An AlloSCT Rather Than An Auto Transplant?

- DLBCL Failing R-Chemo AutoSCT **REMAINS** the standard therapy

- However high risk of failure in some patients:-
  - High sAAIPI Score
  - Time to relapse <12 Months
  - PET+ve post salvage
  - Myc+?
  - ABC subtype?
  - “Double Hit” lymphomas?

- Clinical studies required to assess efficacy of alloSCT in this setting
AlloSCT As Alternative To AutoSCT For Salvage

- Conditioning Regimen
  - Myeloablative?
  - Intermediate Intensity?
  - Reduced intensity?

- Donor
  - Sib/MUD/Cord/haploidentical

- T Cell Depletion?
Summary

Relapsed/Refractory DLBCL

Salvage Candidate?

- Yes
  - Salvage Induction I
    - CR/PR
    - <CR/PR
  - Salvage Induction II
- No
  - Palliation Novel Agent
  - Novel Agents
    - High risk patients? (Clinical Trial)
  - AlloSCT
    - High risk patients? (Clinical Trial)
  - AutoSCT
    - All low risk patients

Risk Assessment
- PET post salvage
- Time to relapse
- SaaIPI
- MYC status?
- ABC?

Tissue Type

Palliation Novel Agent RGDP?
Acknowledgements

• EBMT LWP
  – Peter Dreger
  – Anna Sureda
  – Herve Finel
  – Ariane Boumendil
  – Norbert Schmitz

• BSBMT
  – Christopher Fox
  – Bronwen Shaw