The Role of Stem Cell Transplantation in Relapsed / Refractory Aggressive Lymphoma

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ESH/EBMT Training Course
Haematopoietic Stem Cell Transplantation
Viena, May 8-10, 2014
Institut Català d’Oncologia

Frequency of Lymphomas Subtypes

- Follicular Lymphoma: 22%
- Other subtypes: 17%
- T-cell lymphoma: 7%
- Small lymphocytic lymphoma: 6%
- Mantle Cell Lymphoma: 6%
- Malt Lymphomas: 8%
- Diffuse large B-cell lymphoma: 34%
- Other subtypes: 17%

Incidence of NHL: ~ 14 / 100,000
Incidence of HL: ~ 3 / 100,000
EBMT indications for SCT in DLBCL

<table>
<thead>
<tr>
<th>Disease risk</th>
<th>SIB</th>
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<tbody>
<tr>
<td>First remission</td>
<td>GNR</td>
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</tr>
<tr>
<td>CR/PR &gt;1</td>
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<td>Sens. auto failure</td>
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</tr>
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<td>Refractory</td>
<td>CO</td>
<td>CO</td>
<td>D</td>
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</tr>
</tbody>
</table>

Sureda et al, in preparation
TTP and OS in DLBCL. (A) TTP for all patients with DLBCL treated with R-CHOP with curative intent in BC between 2001 and 2011 (N = 1366).

Sehn L H Hematology 2012;2012:402-409

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EBMT indications for SCT in DLBCL

**Disease risk**

- First remission
- CR/PR >1
- Sens. auto failure
- Refractory

**auto**

- CO
- S
- GNR
- GNR

*Sureda et al, in preparation*
Rationale for HDT in DLBCL

The PARMA trial for relapsed/resistant DLBCL

- 5-yr EFS: 46% vs 12%
- 5-yr OS: 53% vs 32%

Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Devinder Singh Gill, David C. Linch, Marek Trneny, Andre Bosly, Nicolas Ketterer, Ofer Shpilberg, Hans Hagberg, David Ma, Josette Brière, Craig H. Moskowitz, and Norbert Schmitz

Gisselbrecht et al, JCO 2010
ASCT in DLBCL in First Relapse. Information from the Rituximab Era. The Coral Trial

<table>
<thead>
<tr>
<th>Response</th>
<th>R-ICE (n = 197)</th>
<th>R-DHAP (n = 191)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>48</td>
<td>53</td>
<td>24</td>
</tr>
<tr>
<td>Unconfirmed complete response</td>
<td>24</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Partial response</td>
<td>53</td>
<td>45</td>
<td>27</td>
</tr>
<tr>
<td>Stable disease</td>
<td>23</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>38</td>
<td>35</td>
<td>19</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Premature withdrawal, not evaluated</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

**Autologous transplantation**
- Median CD34⁺ cells collected, million/kg: 4.5, 4.9
- Collection failure < 2,000,000 CD34⁺ cells: 20, 10, 15, 8
- Mobilization-adjusted response: 103, 52.3, 104, 54.5
- Consolidation with BEAM performed per protocol: 101, 51, 105, 55

Abbreviations: R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; BEAM, carmustine, etoposide, cytarabine, and melphalan.

Gisselbrecht et al, JCO 2010
ASCT in DLBCL in First Relapse. Information from the Rituximab Era. The Coral Trial

Fig 4. (A) Progression-free survival (PFS) of patients undergoing autologous stem-cell transplantation (intent to treat; n = 206). (B) PFS according to response after salvage regimen (including death) for all patients: complete response (CR) plus unconfirmed complete response (CRu; n = 147) and partial response (PR; n = 98).

Gisselbrecht et al, JCO 2010
Fig 3. (A) Overall survival according to the first random assignment (intent to treat). (B) Progression-free survival according to treatment arm. (C) Event-free survival (EFS) according to prior rituximab treatment and relapse less than 12 months after diagnosis. (D) EFS according to prior rituximab treatment and relapse more than 12 months after diagnosis. R-ICE, rituximab, ifosfamide, carboplatin, etoposide; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin.

Gisselbrecht et al, JCO 2010
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<td>D</td>
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</table>

*Sureda et al, in preparation*
ASCT vs Allo-SCT in DLBCL
RIC vs MAC

![Column chart showing RIC vs MAC for years 2000 to 2012. The chart indicates the percentage of MAC and RIC each year.](chart.png)
### Allo-SCT in aggressive B cell NHL. Review of the literature

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>De novo/Transformed</th>
<th>N. Lines of tx</th>
<th>Prior ASCT (%)</th>
<th>CS/CR</th>
<th>NRM</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson, 2009</td>
<td>48</td>
<td>30/18</td>
<td>5 (2-7)</td>
<td>34 (71)</td>
<td>40/8</td>
<td>32% (4y)</td>
<td>33% (4y)</td>
<td>48% (4y)</td>
<td>47% (4y)</td>
</tr>
<tr>
<td>Sirvent, 2010</td>
<td>68</td>
<td>54/14</td>
<td>25 (37) &gt; 2 lines</td>
<td>54 (79)</td>
<td>55/13</td>
<td>30% (2y)</td>
<td>45% (2y)</td>
<td>43% (82y)</td>
<td>50% (2y)</td>
</tr>
<tr>
<td>Van Campen, 2010</td>
<td>101</td>
<td>101/0</td>
<td>3 (2-6)</td>
<td>101 (100)</td>
<td>75/26</td>
<td>28% (3y)</td>
<td>30% (3y)</td>
<td>42% (3y)</td>
<td>52% (3y)</td>
</tr>
</tbody>
</table>
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
  - R randomization
  - From the first 60 evaluable pts, ATG from -3 to -1 in MUD or mm SCT
- Median FU: 4 yrs

Probability of NRM according to donor type and use of ATG

PFS and OS of all eligible patients (n=86)

OS, 50 events, n= 84
62 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

OS according to donor type and use of ATG

Distribution of 1,314 cases by consensus diagnosis.

- Peripheral T-cell Lymphoma: 25.9%
- Angioimmunoblastic: 12.2%
- Natural killer/T-cell lymphoma: 10.4%
- Adult T-cell leukemia/lymphoma: 9.6%
- Anaplastic large cell lymphoma, ALK+: 6.6%
- Anaplastic large cell lymphoma, ALK-: 5.5%
- Enteropathy-type T-cell: 4.7%
- Primary cutaneous ALCL: 1.7%
- Hepatosplenic T-cell: 1.4%
- Subcutaneous panniculitis-like: 0.9%
- Unclassifiable PTCL: 0.9%
- Other disorders: 2.5%

International T-Cell Lymphoma Project JCO 2008;26:4124-4130
©2008 by American Society of Clinical Oncology
EBMT indications for SCT in PTCL

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<td>CO</td>
<td>CO</td>
<td>GNR</td>
</tr>
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</table>

Sureda et al, in preparation
(A) Overall survival of patients with the common subtypes of peripheral T-cell lymphoma (PTCL).

International T-Cell Lymphoma Project JCO 2008;26:4124-4130

©2008 by American Society of Clinical Oncology

Institut Català d’Oncologia
Adding Etoposide to CHOP: German High-Grade NHL Study Group Analysis

PTCL Subtype | n
---|---
ALCL, ALK+ | 78
ALCL, ALK- | 113
PTCL-NOS | 70
AITL | 28
Other | 31
Total | 320

EFS, aged < 60 yrs

- Etoposide (n = 34) | EFS, ALCL, ALK+ YES
- Non-etoposide (n = 12) | EFS, other subtypes Probably NO
- p = 0.003

EFS, aged ≥ 60 yrs

- Etoposide (n = 69) | EFS, other subtypes
- Non-etoposide (n = 34) | EFS, other subtypes
- p = 0.057

PTCL, anaplastic large cell lymphoma; LCL, anaplastic large cell lymphoma; EFS, event-free survival; CHOEP, CHOP + etoposide

## EBMT indications for SCT in PTCL

### Disease risk

<table>
<thead>
<tr>
<th>Category</th>
<th>Auto</th>
<th>CO</th>
<th>D</th>
<th>GNR</th>
</tr>
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<tr>
<td>First remission</td>
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</tbody>
</table>

*Sureda et al, in preparation*
## Autologous SCT in First Remission: Prospective Studies

<table>
<thead>
<tr>
<th>Study Author (Yr)</th>
<th>n</th>
<th>Regimen</th>
<th>Transplanted, %</th>
<th>Outcomes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corradini (2006)</td>
<td>62</td>
<td>Mitoxantrone/melphalan or BEAM</td>
<td>74</td>
<td>12-yr EFS: 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12-yr OS: 34</td>
</tr>
<tr>
<td>Rodriguez (2007)</td>
<td>26</td>
<td>MegaCHOP ± IFE</td>
<td>73</td>
<td>3-yr PFS: 56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-yr OS: 84</td>
</tr>
<tr>
<td>Mercadal (2008)</td>
<td>41</td>
<td>High-dose CHOP/ESHAP</td>
<td>41</td>
<td>4-yr PFS: 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4-yr OS: 39</td>
</tr>
<tr>
<td>Reimer (2009)</td>
<td>83</td>
<td>dexaBEAM or ESHAP ± TBI</td>
<td>66</td>
<td>3-yr PFS: 36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-yr OS: 48</td>
</tr>
<tr>
<td>d’Amore (2011)</td>
<td>160</td>
<td>CHO(E)P-14 x 6 ± BEAM/BEAC</td>
<td>71</td>
<td>5-yr OS: 51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-yr PFS: 44</td>
</tr>
</tbody>
</table>

BEAC, BiCNU, etoposide, Ara-C, cyclophosphamide; BEAM, BiCNU, etoposide, ara-C, melphalan; ESHAP, etoposide, methylprednisolone, ara-C and cisplatin; IFE, ifosfamide, etoposide; TBI, total body irradiation

German Prospective Study: OS After ASCT in First Remission

Nontransplanted patients did poorly

- PIT group 1: 0 risk factors
- PIT group 2: 1 risk factor
- PIT group 3: 2 risk factors
- PIT group 4: 3-4 risk factors

Transplanted (n = 55)

Nontransplanted (n = 28)

N = 83
- CHOP x 4-6
- If ≥ PR, dexaBEAM or ESHAP
- Cyclo + TBI
- Median follow-up: 33 mos

Poor-risk patients did poorly

- PIT group 1 (n = 25)
- PIT group 2 (n = 34)
- PIT group 3 (n = 21)
- PIT group 4 (n = 3)

p = .0414

p < .001

PIT, Prognostic Index for PTCL

**NLG-T-01: Flow chart**

<table>
<thead>
<tr>
<th>ORR pre-Tx</th>
<th>131 (82%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>82 (51%)</td>
</tr>
<tr>
<td>PR</td>
<td>49 (31%)</td>
</tr>
<tr>
<td>% Tx</td>
<td>115 (72%)</td>
</tr>
<tr>
<td>CR/CRu 100d post-Tx</td>
<td>90 (56%)</td>
</tr>
</tbody>
</table>

OS and PFS in NLG-T-01 Trial

The novel gold standard?

EATL, enteropathy-associated T cell lymphoma.

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<td>CO</td>
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</table>

*Sureda et al, in preparation*
## Studies of alloSCT in relapsed T-cell NHL

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>N pts</th>
<th>CT lines</th>
<th>OS</th>
<th>NRM</th>
<th>RIC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corradini P et al (2004)</td>
<td>17</td>
<td>2</td>
<td>81% (3y)</td>
<td>6% (2y)</td>
<td>100</td>
</tr>
<tr>
<td>Feyler S et al (2007)</td>
<td>18</td>
<td>2</td>
<td>33% (3y)</td>
<td>38% (1y)</td>
<td>NA</td>
</tr>
<tr>
<td>Jacobsen ED et al (2011)</td>
<td>52</td>
<td>2</td>
<td>41% (3y)</td>
<td>27% (3y)</td>
<td>40</td>
</tr>
<tr>
<td>Le Gouill S et al (2008)</td>
<td>77</td>
<td>2</td>
<td>57% (5y)</td>
<td>33% (5y)</td>
<td>26</td>
</tr>
<tr>
<td>Shustov AR et al (2010)</td>
<td>17</td>
<td>3</td>
<td>59% (3y)</td>
<td>19% (3y)</td>
<td>100</td>
</tr>
<tr>
<td>Delioukina M et al (2011)</td>
<td>27</td>
<td>4</td>
<td>55% (2y)</td>
<td>22% (2y)</td>
<td>100</td>
</tr>
<tr>
<td>Dodero A et al (2011)</td>
<td>52</td>
<td>2</td>
<td>50% (5y)</td>
<td>12% (5y)</td>
<td>100</td>
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</table>
Survival and transplant-related mortality (TRM) curves

17 patients
(15 chemosensitive)
Estimated OS 80%,
PFS: 60% at 3 yrs
NRM: 6% at 2 yrs

Graft versus lymphoma effect for aggressive T-cell lymphomas
(Le Gouill et al. JCO 2008)

- 77 aggressive T cell lymphoma
- 57 (75%) myeloablative,
- 20 (25%) RIC
- Median age: 36

Results:
- 5-year OS 57%
- 5-year EFS 53%
- 23 patients in PR at transplant
  → 17 CR (74%)
- 23 patients in SD/PD/refractory
  → 13 CR (56%)
- TRM → 34%
Allogeneic SCT in Angioimmunoblastic T Cell Lymphoma

• EBMT retrospective study; 45 pts, median, age 48 yrs
• Before allo-SCT: 60% chemosensitive disease
• 56% myeloablative, 44% RIC.
• NRM 25% 1 year

Kyriakou et al. J Clin Oncol 2009
DSHNHL 2006-1A: Study design

first-line treatment of mature (peripheral) T-cell lymphoma (PTCL) for patients \( \leq \) 60 years

**Inclusion criteria**
- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK negative
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy type T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis type T-cell lymphoma
- All stages and IPI except stage I with IPI 0

**Diagram Description**
- Days: 1, 15, 29, 43, 54, 4-8 weeks
- Patients are randomized to allogeneic or autologous transplantation (tx). Donor search (family or unrelated) will be initiated only in patients randomized to allogeneic transplantation. Patients randomized to allogeneic tx but without a donor will receive autologous tx. Peripheral blood stem cells are harvested after DHAP in patients who are to receive autologous tx (randomized or crossed over [dotted line *** in the diagram] from the allogeneic transplant arm because no donor is available).

**Abbreviations**
- ASCT = autologous stem cell transplantation
- SCT = allogeneic stem cell transplantation
Take home messages

• In patients with diffuse large B cell lymphoma:
  – ASCT is the standard of care for patients with relapsed chemosensitive diffuse large B cell lymphoma.
    • Results of ASCT in patients relapsing after a short first CR are sub-optimal
  – Allo-SCT is an effective salvage therapy for patients relapsing after an ASCT
    • Should be explored earlier on in patients with bad prognostic features at relapse

• In patients with T-cell lymphoma:
  – ASCT is the standard of care for patients in 1st CR and allo-SCT in relapsed disease
  – The role of allo-SCT as first line consolidation therapy is currently explored in prospective clinical trials