The Role of Stem Cell Transplantation in Relapsed / Refractory Hodgkin’s Lymphoma

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9th Educational Course on Lymphomas and Stem Cell Transplantation.
Barcelona, October 10th – 11th, 2013
No Doubt that More Intensive 1\textsuperscript{st} Line Treatments Have Improved Long Term Outcome of Advanced Stage HL Patients …..

Engert el al, JCO 2009
There are no Significantly Better Salvage Chemotherapy Regimens to Treat Relapsed Patients with HL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Response Rate (%)</th>
<th>Relapse Rate (%)</th>
<th>TRM (%)</th>
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</thead>
<tbody>
<tr>
<td>DHAP</td>
<td>102</td>
<td>88</td>
<td>92</td>
<td>0</td>
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<tr>
<td>ASHAP</td>
<td>57</td>
<td>70</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>ESHAP</td>
<td>22</td>
<td>73</td>
<td>73</td>
<td>5</td>
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<tr>
<td>ICE</td>
<td>65</td>
<td>88</td>
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<td>GDP</td>
<td>23</td>
<td>70</td>
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<td>Dexa-BEAM</td>
<td>55</td>
<td>60</td>
<td>70</td>
<td>4</td>
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<tr>
<td>Mini-BEAM</td>
<td>44</td>
<td>74</td>
<td>85</td>
<td>0</td>
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<tr>
<td>Cevd</td>
<td>32</td>
<td>58</td>
<td>100</td>
<td>0</td>
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ASCT is the standard therapy for HL Relapsing after 1\textsuperscript{st} Line Chemotherapy

BNLI Trial
Mini-BEAM + ABMT vs Mini-BEAM

<table>
<thead>
<tr>
<th></th>
<th>N. of patients</th>
<th>TRM</th>
<th>EFS (3 yrs)</th>
<th>p value</th>
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</thead>
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<tr>
<td>Mini-BEAM</td>
<td>20</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mini-BEAM + ABMT</td>
<td>20</td>
<td>5</td>
<td>53</td>
<td>0.025</td>
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</table>

*Linch et al, Lancet 1993*
ASCT is the standard therapy for HL Relapsing after 1st Line Chemotherapy. HDR1 Trial (GHSG/EBMT)

Dexa-BEAM + ASCT vs Dexa-BEAM

Early, late and multiple relapse

- 2 x Dexa-BEAM
  - CR or PR
  - 2 x Dexa-BEAM

- 2 x Dexa-BEAM
  - CR or PR
  - BEAM + PBSCT

Schmitz et al, Lancet 2002
Figure 3: Freedom from treatment failure for patients with relapsed chemosensitive Hodgkin’s disease
Not all Relapsing Patients do so Well after an Autologous Stem Cell Transplantation

Predictors of poor response:

- Primary refractory disease
- Early (<12 months) relapse
- Bulky disease
- B-symptoms
- Extranodal involvement
- Advanced stage at relapse
The Impact of the Duration of First Complete Remission in the ASCT Outcome

Schmitz et al, Lancet 2002
The Impact of the Duration of First Complete Remission in the ASCT Outcome

Schmitz et al, Lancet 2002

Number of patients

<table>
<thead>
<tr>
<th></th>
<th>BEAM-HSCT</th>
<th>29</th>
<th>22</th>
<th>19</th>
<th>16</th>
<th>10</th>
<th>5</th>
<th>1</th>
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<td>Dexamethasone</td>
<td>26</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

Late relapse

Freedom from treatment failure (%)

[p=0.0246]
The Impact of the Duration of First Complete Remission in the ASCT Outcome

Schmitz et al, Lancet 2002
The Impact of Disease Status Before Transplantation in the ASCT Outcome

Not All Patients with Relapse HL do Equally Well after an ASCT

**Fig 3.** Kaplan-Meier curves of progression-free survival in four groups of patients differentiated with an adapted prognostic score. Presence of stage IV disease, early or multiple relapse, and anemia summed up to a score ranging from 0 to 3.

Josting et al, JCO 2010
Dose Intensity of Chemotherapy in Patients with Relapsed / Refractory Hodgkin’s Lymphoma

Josting et al, JCO 2010
Is Further Improvement in the ASCT Setting Possible?

- Tandem Transplantation Approaches
- Inclusion of PET/CT evaluation in the ASCT
- Inclusion of new drugs in the ASCT setting:
  - As part of salvage therapy before ASCT
  - Maintenance therapy after ASCT
Is Further Improvement in the ASCT Setting Possible?

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  - As part of salvage therapy before ASCT
  - Maintenance therapy after ASCT
A Tandem Transplantation Approach for Patients with Adverse Prognostic Features. The GELA Experience

- Inclusion criteria for tandem ASCT:
  - Primary refractory patients ($n = 77$)
  - First relapse with $\geq 2$ risk factors ($n = 73$)
    - Time to relapse $< 12$ mo
    - Stage III-IV at relapse
    - Relapse within irradiated areas
- Single ASCT ($n = 95$):
  - Intermediate risk patients ($0 – 1$ risk factors)

1\textsuperscript{st} ASCT:
Cyclophosphamide
Carmustine
Etoposide
Mithoxantrone

2\textsuperscript{nd} ASCT (45 – 90 days after first ASCT):
TBI (or Bu)
Ara-C
Melphalan

\textbf{Morschhauser et al. J Clin Oncol 2008}

\textbf{Fig 1.} (A) Freedom from second failure and (B) overall survival of patients with first-relapse or primary refractory Hodgkin’s lymphoma according to risk group.
Is Further Improvement in the ASCT Setting Possible?

• Tandem Transplantation Approaches
• Inclusion of PET/CT evaluation in the ASCT
• Inclusion of new drugs in the ASCT setting:
  • As part of salvage therapy before ASCT
  • Maintenance therapy after ASCT
PET Scan Can Also Discriminate Those Patients with Worse Outcome after ASCT

Retrospective data, 211 consecutive relapsed/refractory patients, 1993–2004

Progression free survival

Overall survival

Jabbour et al, Cancer 2007
PET Scan Can Also Discriminate Those Patients with Worse Outcome after ASCT

Moskowitz et al. Blood 2010
Is Further Improvement in the ASCT Setting Possible?

- Tandem Transplantation Approaches
- Inclusion of PET/CT evaluation in the ASCT
- Inclusion of new drugs in the ASCT setting:
  - As part of salvage therapy before ASCT
  - Maintenance therapy after ASCT
LBH589 (Panobinostat)

Potent class I/II inhibitor of histones deacetylases. Targeting lysine groups of chromatine, transcription factors and various non-hyston protein such as p53, Rb, tubuline and HSP90.
RAD001: an oral mTOR-inhibitor

- Daily administration results in cont. mTOR inhibition
- Safety data from more than 3,000 cancer patients available
- Numerous phase II und III-studies in RCC, NET, Lymphoma, NSCLC, breast cancer
New Therapeutic Options for Relapsed Patients.

AntiCD30 MoAb

- SGN-35(Brentuximab Vedotin) is a CD30-targeted antibody conjugated to an auristatin E derivative (MMAE)
- MMAE is a potent anti-tubulin agent selectively delivered to CD-30 positive cells via antibody-drug conjugate technology
### HDR3i: Phase II

<table>
<thead>
<tr>
<th>Phase</th>
<th>To do</th>
<th>n</th>
<th>Duration [M]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td><strong>Ever-DHAP:</strong> 3+3 Design, dose levels 2,5; 5; 7,5; and 10 mg, DLT-Definition without hematological tox. (DHAP!)</td>
<td>12-24</td>
<td>6</td>
</tr>
<tr>
<td>Phase II</td>
<td>2x DHAP + PET-CT</td>
<td>50</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>2x Ever-DHAP + PET-CT</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>
HDR3i: Phase II Design

- Screen
- randomization
- Ever-DHAP
- Placebo-DHAP
- Ever-DHAP
- Placebo-DHAP
- PET-CT
- SC-Apheresis
- (SC-Apheresis)

52 (~42-60) Follow up

BEAM

- 28
- 15
- 36
OUTLINE OF THE STUDY

HL ≥18 yr, refractory to first line chemotherapy or first relapse

Registration

2 cycles of BV-DHAP

PET-CT

CT / stem cell harvest

3rd cycle of BV-DHAP

SD/PD

PR/CR

PET-CT

PET-CT

HDT ASCT

Follow up

BV: Brentuximab Vedotin
ASCT: Autologous Stem Cell Transplantation
Treatment Protocol

**ESHAP**

1. **Brentuximav Vedotin**: 1.8 mg/Kg, 1st day of ESHAP and day +21 after 3rd ESHAP (every 21 – 28 days)

2. **ASCT / BEAM**

3. **BV post-ASCT**: from day +28 to +56, 3 doses every 21 days

**PBSC Collection**

**Radiotherapy (Bulky disease)**
A Randomized, Double-Blind Placebo-Controlled Phase 3 Trial of SGN-35 vs Placebo in High-Risk HL Patients Undergoing and ASCT (AETHERA Trial)
Conclusions

• ASCT is the standard of care for the vast majority of patients with HL in first chemosensitive relapse
• Several well defined prognostic factors significantly change the outcome after ASCT in this population of patients
• Results of ASCT can be optimized by:
  • Introduction of functional imaging techniques in the disease re-staging of the patient before ASCT
  • Use of new drugs during salvage therapy before ASCT or as maintenance therapy
• Other treatment strategies have to be developed to treat those patients:
  • With adverse prognostic features at the time of relapse
  • Relapsing after ASCT
OS from relapse after an ASCT.
The experience of the LWP EBMT/GITMO


Median follow-up of survivors 50 months (75% of cases > 34 months)
OS from relapse after an ASCT. The experience of the LWP EBMT/GITMO

- Stage at relapse
- B symptoms at relapse
- Bulky disease at relapse
- Extranodal involvement at relapse
- Poor performance status at relapse
- Early relapse (<6 months) after one ASCT

Allo-SCT vs ASCT. Advantages and Disadvantages

• Advantages:
  – *Infusion of a tumor-free cell product*
  – *Graft-versus-HL effect*

• Disadvantages:
  – *Higher non-relapse mortality*
  – *Availability of a histocompatible donor*
Allo-SCT for Hodgkin lymphoma: 1990-2009

Number of allo-SCT by year

The European Group for Blood and Marrow Transplantation
RIC vs MAC in allo-SCT: 1990-2009

RIC or conventional conditioning by year

- Conventional
- RIC

The European Group for Blood and Marrow Transplantation
HLA identical sibling vs MUD: 1990-2009

HLA identical sibling vs MUD by year

- HLA id-sib
- MUD
We Have Been Able to Reduce NRM with RIC Protocols

Estimate of the NRM and PFS based on a COX model, adjusted by all covariates with impact on the outcomes. RR and p values from multivariate Cox model.

Sureda et al, JCO 2008
We Have Been Able to Demonstrate the Existence of a Beneficial GVL Effect

Impact of cGVHD after allo-SCT in relapse rate and PFS

- Relapse or Progression (%)
  - RR 1.89 (95% CI 1.02-3.49)
  - p=0.04

- Progression free survival (%)
  - RR 1.57 (95% CI 0.91-2.72)
  - p=0.1

Sureda et al, JCO 2008
The donor versus no-donor analysis had the day of relapse after autologous transplantation as the starting point.

Sarina et al, Blood 2010
## RIC-allo in relapsed / refractory HL. Review of the literature

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N. patients</th>
<th>Sensitive vs refractory</th>
<th>Matched sib / MUD / haplo</th>
<th>Condition. regimen</th>
<th>NRM</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>Robinson, 2009</td>
<td>285</td>
<td>213 / 72</td>
<td>172 / 94 / 0</td>
<td>Varied</td>
<td>19.5% (1 yr)</td>
<td>59% (3yr)</td>
<td>25% (3yr)</td>
<td>43% (3yr)</td>
</tr>
<tr>
<td>Anderlini, 2008</td>
<td>58</td>
<td>30 / 28</td>
<td>25 / 33 / 0</td>
<td>Flu-Mel</td>
<td>15% (2 yr)</td>
<td>55% (2 yr)</td>
<td>32% (2yr)</td>
<td>64% (2yr)</td>
</tr>
<tr>
<td>Burroughs, 2008</td>
<td>90</td>
<td>61 / 28</td>
<td>38 / 24 / 28</td>
<td>Flu-TBI</td>
<td>21% / 8% / 9% (2yr)</td>
<td>53% / 63% / 40% (2yr)</td>
<td>23% / 29% / 51% (2yr)</td>
<td>53% / 58% / 58% (2yr)</td>
</tr>
<tr>
<td>Peggs, 2005</td>
<td>49</td>
<td>34 / 16</td>
<td>31 / 18</td>
<td>Flu-Mel-Campath</td>
<td>16.3% (730 days)</td>
<td>NA</td>
<td>32.4% (4yr)</td>
<td>55.7%</td>
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<tr>
<td>Chen, 2011</td>
<td>26</td>
<td>16 / 8</td>
<td>12 / 14</td>
<td>Flu-Mel</td>
<td>13.1% (1yr)</td>
<td>48% (1yr)</td>
<td>27% (2yr)</td>
<td>60% (2yr)</td>
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<tr>
<td>Alvarez, 2006</td>
<td>40</td>
<td>20 / 20</td>
<td>38 / 2</td>
<td>Flu-Mel</td>
<td>25% (1 yr)</td>
<td>NA</td>
<td>32% (2yr)</td>
<td>48% (2yr)</td>
</tr>
</tbody>
</table>
HDR-Allo Protocol

Fludarabine

Melphalan

PBSCs

ATG (URD)

Mtx 10 mg/m²

CsA

Sureda et al. Haematologica 2012
Non-relapse mortality

8% at 100 days 15% at 1 yr 17% at 2 yr 19% at 3 yr

Sureda et al. Haematoloogica 2012
Relapse Incidence in Chemosensitive Patients

Sureda et al. Haematologica 2012
Impact of cGVHD on Relapse Incidence

- No cGVHD (n = 35)
- cGVHD (n = 32)

Sureda et al. Haematologica 2012
PFS and OS after RIC-Allo in Chemosensitive Patients (n = 50)

Sureda et al. Haematologica 2012
DLIs Modulate Relapse Risk in Mixed Chimeras and Induce Durable Responses in Relapsed Patients Treated with a T-Cell Depleted RIC

Peggs et al, JCO 2011
Potential Strategies

- Move forward the allogeneic procedure to earlier phases of the disease
- Modification of the intensity of the conditioning regimen
- Introduction of “new drugs"
Potential Strategies

- Move forward the allogeneic procedure to earlier phases of the disease
- Modification of the intensity of the conditioning regimen
- Introduction of “new drugs"
Response-adjusted transplantation strategy

N = 28
Age [median (range)]: 32 (18 – 66)

Primary refractory disease: 11 pts
Early relapses: 5 pts
Late Relapses: 12 pts

ABVD as initial therapy: 24 pts
ESHAP as first salvage therapy: 24 pts

Survival

Time (years)

ASH 2011: Thomson & Peggs
PAIReD trial: Hodgkin lymphoma: primary resistant or first relapse

- Tissue type patient and siblings. Initiate UD search as appropriate
- 2 cycles of salvage chemotherapy
- PET-CT (centrally reported)

  - CR
  - <CR, non-progressive
  - Progressive disease

  Further line of salvage permissable

  - Non-progressive (incl. CR)
  - Progressive disease

  Not suitable for study

  Suitable donor?

  Yes

  BEAM-C allograft

  No

  Not suitable for study
Protocol for PET2+ patients

PET-2 positive

4 IGEV

Peripheral stem cell harvesting

PET

- BEAM + ASCT

+ High dose melphalan + ASCT

HLA identical donor

no

BEAM + ASCT

yes

RIC allo (Flu-Cy)
Paziente con recidiva/progressione

Chemioterapia di salvataggio

PET negativa

PET positiva

HLA non identico

HLA -identico

BEAM + ASCT

Registrazione del paziente

Tipizzazione HLA

Raccolta CSP

Il tipo di CT è IGEV solo per i pazienti provenienti dallo studio HD0801
Potential Strategies

- Move forward the allogeneic procedure to earlier phases of the disease
- Modification of the intensity of the conditioning regimen
- Introduction of “new drugs"
Allo-SCT in children and adolescents with recurrent HL

The type of conditioning had no impact on NRM. RIC regimens were associated with an increased risk of progression, with a lower PFS.

*Claviez et al. Blood 2009*
Potential Strategies

- Move forward the allogeneic procedure to earlier phases of the disease
- Modification of the intensity of the conditioning regimen
- Introduction of “new drugs"
Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma

Robert Chen,1 Joycelynne M. Palmer,2 Sandra H. Thomas,1 Ni-Chun Tsai,2 Len Farol,3 Auayporn Nademanee,1 Stephen J. Forman,1 and Ajay K. Gopal4

1Department of Hematology/Hematopoietic Cell Transplantation, and 2Division of Biostatistics, City of Hope, Duarte, CA; 3City of Hope—Kaiser Permanente, Los Angeles, CA; and 4Seattle Cancer Care Alliance/Fred Hutchinson Cancer Center/University of Washington, Seattle, WA
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%) or median (range)</th>
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<tr>
<td>No. of patients</td>
<td>18</td>
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<tr>
<td>Age, y</td>
<td>30.5 (range 23-55)</td>
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<td>No. of prior regimens</td>
<td>4.5 (range 3-8)</td>
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<tr>
<td>Prior auto-HCT</td>
<td>17 (94.4)</td>
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<td>Previous XRT</td>
<td>10 (55.6)</td>
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<td>Best response to brentuximab vedotin</td>
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<tr>
<td>CR</td>
<td>7 (39)</td>
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<tr>
<td>PR</td>
<td>8 (44)</td>
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<td>SD</td>
<td>2 (11)</td>
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<td>PD</td>
<td>1 (6)</td>
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<td>No. of cycles of brentuximab vedotin</td>
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<td>Baseline neuropathy before allo-HCT</td>
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<td>Grade 1</td>
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<td>Disease status after brentuximab vedotin</td>
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<td>6 (33)</td>
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<td>5 (28)</td>
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<td>Disease status at allo-HCT</td>
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<tr>
<td>CR</td>
<td>6 (33)</td>
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<tr>
<td>PR</td>
<td>8 (44)</td>
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<td>SD</td>
<td>1 (6)</td>
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<td>PD</td>
<td>3 (17)</td>
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<tr>
<td>Time from brentuximab vedotin to allo-HCT</td>
<td>62 d (range 24-276)</td>
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<td>Flu/Mel</td>
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<td>CSA/MMF</td>
<td>1 (6)</td>
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<tr>
<td>CSA/MTX</td>
<td>2 (11)</td>
</tr>
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</table>

![Graph A](image1.png)  
Survival Probability

![Graph B](image2.png)  
Cumulative Incidence

Chen et al, Blood 2012
Conclusions

- In the absence of prospective clinical trials, allo-SCT is an effective salvage therapy for patients relapsing after an ASCT.
- Non-relapse mortality is not a significant issue nowadays. Major efforts should be dedicated to decrease the relapse rate after allo-SCT.
- The role of allo-SCT in earlier stages of the disease and in the era of “new drugs” needs to be assessed.