PET in relapsed and refractory Hodgkin lymphoma

Alison Moskowitz, MD
Assistant Member, Lymphoma Service
Memorial Sloan Kettering Cancer Center
HL pathway

Relapse/Refractory Disease

Second-line chemo

Chemosensitivity

HDT/ASCT

Lesson learned from our first 3 studies 1985-2004

• Intensive RT as part of transplant conditioning is safe and effective

• 3 pre-salvage therapy risk factors predict outcome

• Normalization of functional imaging pre-ASCT is associated with a survival advantage; however to achieve this, tailored salvage therapy may be required
# Prognostic significance of pre-ASCT PET in HL

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>PET neg definition</th>
<th>PFS/EFS PET pos</th>
<th>PFS/EFS PET neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentzler, et al. BJH 2014</td>
<td>32</td>
<td>Deauville 2**</td>
<td>52%</td>
<td>85%</td>
</tr>
<tr>
<td>Akhtar, et al. BMT 2013</td>
<td>141</td>
<td>&lt; Mediastinal blood pool</td>
<td>49%</td>
<td>74%</td>
</tr>
<tr>
<td>Devillier, et al. Haematologica 2012</td>
<td>111</td>
<td>Harmonization</td>
<td>23%</td>
<td>79%</td>
</tr>
<tr>
<td>Smeltzer, et al. BBMT 2011</td>
<td>46</td>
<td>Harmonization</td>
<td>41%</td>
<td>82%</td>
</tr>
<tr>
<td>Mocikova, et al. Leukemia&amp;Lymphoma 2011</td>
<td>76</td>
<td>Harmonization</td>
<td>36%</td>
<td>73%</td>
</tr>
<tr>
<td>Moskowitz, et al. Blood 2010*</td>
<td>153</td>
<td>Harmonization</td>
<td>31%</td>
<td>75%</td>
</tr>
<tr>
<td>Jabbour, et al. Cancer 2007*</td>
<td>211</td>
<td>&lt; Background</td>
<td>27%</td>
<td>69%</td>
</tr>
</tbody>
</table>

*Publications included gallium scans

**Results similar when PET negative defined as Deauville 3

- Risk adapted therapy administered based upon risk factors:
  - B symptoms
  - Extranodal disease
  - Relapse < 1 year

- Pre-transplant functional imaging was the most significant determinant of outcome

HL pathway

Relapse/Refractory Disease

Risk Model

Second-line chemo

Normalization of PET

HDT/ASCT

MSKCC Model
- B symptoms
- Extranodal disease
- Remission duration <1 yr.
MSKCC Protocol 04-047 for relapsed and refractory Hodgkin Lymphoma

Repeat Biopsy, determine risk factors, Staging evaluation: FDG PET, Diagnostic CT CAP, BM BX

ARM A = 0 or 1 Risk Factors
Standard ICE x 1 cycle
Augmented ICE x 1 cycle
PBPC Collection

ARM B = 2 Risk Factors
Augmented ICE x 2 cycles
PBPC Collection

Restaging: FDG PET, CT CAP

PET Negative

PET Positive

GVD x 4

Restaging

Radiotherapy (if Applicable)
HDT / ASCT

CR, PR, MR

POD -- off study

POD on ICE

Memorial Sloan-Kettering Cancer Center
Survival Curves 04-047

**Intent to Treat Cohort**
- Overall Survival: 97 pts; 78 censored
- Event Free Survival: 97 pts; 66 censored

**Transplanted Patients**
- Overall Survival: 85 pts; 75 censored
- Event Free Survival: 85 pts; 66 censored
Pre-ASCT Response

Event Free Survival by Pre-ASCT Response

(1) FDG-PET neg after GVD: 17 pts; 14 censored
(2) FDG-PET neg after ICE: 59 pts; 46 censored
(3) FDG-PET pos after GVD or Ineligible: 21 pts; 6 censored

Log Rank Test
(1) vs (2): p=0.715
(1) vs (3): p=0.001
(2) vs (3): p<0.001
(1) vs (2) vs (3): p<0.001

Cumulative Survival (%) vs Time (years)
FDG-PET and ENS

Event Free Survival by PET and ENS results

(1) PET negative, ENS negative: 46 pts; 40 censored
(2) PET negative, ENS positive: 30 pts; 20 censored
(3) PET positive: 21 pts; 6 censored

Log Rank Test
(1) vs (2): p=0.026
(2) vs (3): p=0.001
(1) vs (3): p<0.001
(1) vs (2) vs (3): p<0.001

Time (years)
Cumulative Survival (%)
Brentuximab vedotin (BV) as salvage therapy in rel/ref HL: Rationale

- Current salvage regimens (i.e ICE, DHAP) are myelosuppressive, toxic
- Brentuximab vedotin is well tolerated and highly active in HL following transplant failure
- Pre-transplant FDG-PET is highly predictive of post-transplant outcome
Weekly Brentuximab vedotin – potential for earlier CRs with increased dose intensity

- Phase I study evaluated weekly schedule for brentuximab vedotin
  - 1.2 mg/kg weekly, 3 weeks on, 1 week off
  - 41 patients; 86% with HL
  - CR rate 34%
    - 12/14 CRs seen at first re-staging (8 weeks)

Weekly BV x 2 cycles

Augmented ICE x2 cycles

PET

Further treatment according to treating physician

HDT/ASCT
FDG-PET assessment
Deauville criteria or 5 point scale

<table>
<thead>
<tr>
<th>Score</th>
<th>FDG-PET/CT scan result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No uptake above background</td>
</tr>
<tr>
<td>2</td>
<td>Uptake $\leq$ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Uptake $&gt;$ mediastinum but $\leq$ liver</td>
</tr>
<tr>
<td>4</td>
<td>Uptake moderately more than liver uptake, at any site</td>
</tr>
<tr>
<td>5</td>
<td>Markedly increased uptake at any site or new sites of disease</td>
</tr>
</tbody>
</table>

- Score of 1 or 2 = PET negative
## Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>25 (56%)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>31 (13-65)</td>
</tr>
<tr>
<td>Initial stage</td>
<td></td>
</tr>
<tr>
<td>I: 1 (2%)</td>
<td></td>
</tr>
<tr>
<td>II: 20 (44%)</td>
<td></td>
</tr>
<tr>
<td>III: 10 (22%)</td>
<td></td>
</tr>
<tr>
<td>IV: 14 (31%)</td>
<td></td>
</tr>
<tr>
<td>Stage at enrollment</td>
<td></td>
</tr>
<tr>
<td>II: 20 (44%)</td>
<td></td>
</tr>
<tr>
<td>III: 6 (13%)</td>
<td></td>
</tr>
<tr>
<td>IV: 19 (42%)</td>
<td></td>
</tr>
<tr>
<td>Prior radiation</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>Relapse &gt; 1 year from initial Rx</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Relapse within 1 year of initial Rx</td>
<td>15 (33%)</td>
</tr>
<tr>
<td>Primary refractory</td>
<td>23 (51%)</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td>19 (44%)</td>
</tr>
<tr>
<td>B symptoms</td>
<td>11 (24%)</td>
</tr>
</tbody>
</table>
**Weekly BV x 2 cycles**

45 evaluable patients

1 pt lost to follow-up

33 pts

Augmented ICE x2 cycles

PET

45 pts

12 pts (27%)

HDT/ASCT

44 pts transplanted

Further treatment according to treating physician

46 enrolled (1 patient misdiagnosed)
## Deauville response to salvage therapy

### BV (n=45)

<table>
<thead>
<tr>
<th>Deauville score</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

### AuglCE (n=32)

<table>
<thead>
<tr>
<th>Deauville score</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
EFS according to treatment and PET status
# Path to ASCT for PET positive patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Deauville Score</th>
<th>Stage at relapse</th>
<th>Post-augICE treatment</th>
<th>Time since ASCT</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After BV</td>
<td>After augICE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>4</td>
<td>IIA</td>
<td>IFRT -&gt; PR BEAM</td>
<td>16 months</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>3</td>
<td>IVA</td>
<td>CBV</td>
<td>23 months</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>4</td>
<td>IIB</td>
<td>IFRT -&gt; CR BEAM</td>
<td>9 months</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4</td>
<td>IIISA</td>
<td>IFRT -&gt; CR BEAM</td>
<td>Relapsed at 9 months</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>4</td>
<td>IIA</td>
<td>IFRT -&gt; PR CBV</td>
<td>Relapsed at 7 months</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>4</td>
<td>IIA</td>
<td>IFRT -&gt; PR BEAM</td>
<td>17 months</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>4</td>
<td>IVA</td>
<td>R-BEAM</td>
<td>Relapsed at 8 months</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>4</td>
<td>IIXA</td>
<td>IFRT -&gt; CR CBV</td>
<td>24 months</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>3</td>
<td>IIA</td>
<td>CBV</td>
<td>Relapsed at 6 months</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>4</td>
<td>IVB</td>
<td>augICE#3-&gt; PR CBV</td>
<td>Progression at 6 weeks</td>
</tr>
</tbody>
</table>
Summary

- 76% CR rate achieved with PET adapted sequential therapy with BV and augmented ICE
- 27% patients avoided ICE salvage therapy
- 44 transplants completed
  - Median time since transplant: 19 months (range 6-29 months)
Additional BV combinations under evaluation in the pre-transplant setting

- Brentuximab vedotin combined with DHAP phase I/II in relapsed/refractory Hodgkin lymphoma (Europe)

- Brentuximab vedotin combined with ICE in relapsed/refractory Hodgkin lymphoma (Washington)
Expansion

Weekly BV x 2 cycles

Augmented ICE x2 cycles

Further treatment according to treating physician

HDT/ASCT

3 cycles 20 pts
Moving forward
Developing novel combinations within the setting of PET-adapted salvage therapy

Novel BV combinations
Weekly BV x 2 cycles

Augmented ICE x2 cycles

PET

Further treatment according to treating physician

HDT/ASCT
Acknowledgements

MSKCC Lymphoma Service

- John Gerecitano
- Paul Hamlin
- Steve Horwitz
- Anita Kumar
- Matt Matasar
- Alison Moskowitz
- Craig Moskowitz
- Ariela Noy
- Lia Palomba
- Carol Portlock
- Heiko Schoder*
- David Straus
- Joachim Yahalom
- Anas Younes
- Andrew Zelenetz