Mantle cell lymphoma

Allo stem cell transplantation in relapsed and refractory patients

Olivier Hermine MD, PhD
Department of Hematology
INSERM and CNRS, Imagine Institute
Necker Hospital
Paris, France
European MCL Network MCL Younger Trial

Hazard Ratio 0.68

p=0.0382 (one sided sequential test)

When is an alloSCT justified for MCL?

R-DHAP + AutoSCT

R-CHOP + AutoSCT

CHT alone

numbers at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-DHAP</td>
<td></td>
<td>208</td>
<td>147</td>
<td>99</td>
<td>67</td>
<td>29</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>R-CHOP</td>
<td></td>
<td>212</td>
<td>134</td>
<td>95</td>
<td>66</td>
<td>36</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>
Outcome after autoSCT failure

360 patients with relapse after autoSCT

Median observation time 40 months
Median OS after relapse: 19 months (range: 0.4 to 117)
Prognostic factors after autoSCT failure
OS by remission duration after autoSCT

< 12 months  120 (33%)
> 12 months   240 (67%)

P < 0.0001 HR 0.25

EBMT Registry Analysis, Ann. Onc. 2014, S. Dietrich
Prognostic factors after autoSCT failure OS by remission duration after autoSCT

- < 12 months: 120 (33%)
- > 12 months: 240 (67%)

* Low sMIPI >5y / in high sMIPI (>>1/2 cases) 0.9y

EBMT Registry Analysis, Ann. Onc. 2014, S. Dietrich
Relapses and Allo SCT

• In relapse, allo SCT is the only curative procedure
• However, allo SCT is associated to a significant NRM and new targeted therapies may improve prognosis and may induce long term response/cure
• Allo SCT in relapse
  – Which patients ?
  – Which treatment to bridge to AlloSCT ?
  – Which conditionning regimen ?
  – Which type of graft ?
  – Which follow up ?
Allo vs Auto at relapse

Mature results of MDACC MCL transplants: OS

MCL: AlloSCT for autoSCT failure HD/KI/HH 1994-2008 (52 REL after 119 autotransplants)

Overall survival

\[
p = 0.059 \text{ HR } 0.49 \text{ 95\% CI } 0.24 \text{ to } 1.02
\]

No allo (32)

allo (20)

Dietrich et al, Cancer May 1, 2011
Lymphoma Registry: Allo-SCT adults 18-50 yo

NRM (%) by period

100d NRM
6 m NRM
12 m NRM

- 1994-1998
- 1999-2003
- 2004-2008
- 2009-2013
Lymphoma Registry: Allo-SCT adults 51-70 yo

NRM (%) by period

- 100d NRM
- 6 m NRM
- 12 m NRM

1999-2003
2004-2008
2009-2013
Mantle Cell Lymphoma: Relapse

Eligible for clinical trial?

Yes | No

Clinical trial

Allogeneic transplant candidate?

Yes | No

Non-cross-resistant salvage therapy

Ibrutinib available and not contraindicated?

Yes | No

SD/PD

CR/PR

Second-line salvage therapy

Ibrutinib

Fit for conventional dose therapy?

Yes | No

R-BAC, BR
R-lenalidomide bortezomib

Supportive care

Donor stem cell source available?

Yes | No

Reduced intensity allogeneic stem cell transplantation

Maintenance rituximab?

Michael L. Wang, JCO 2016
OS by response to 1st salvage therapy

EBMT Registry Analysis; ASH 2012, S. Dietrich
Chemotherapy salvage strategies

- No standard/ participation in clinical trials

- The salvage regimen used depends upon:
  - patient comorbidities
  - side effect profile of the selected regimen
  - prior therapies
  - clinical situation
Response to salvage chemotherapy

Before 1st autoSCT

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>48%</td>
</tr>
<tr>
<td>PR</td>
<td>44%</td>
</tr>
<tr>
<td>Refractory</td>
<td>8%</td>
</tr>
</tbody>
</table>

Salvage after autoSCT-relapse

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>31%</td>
</tr>
<tr>
<td>PR</td>
<td>27%</td>
</tr>
<tr>
<td>Refractory</td>
<td>42%</td>
</tr>
</tbody>
</table>
Treatment options for relapsed MCL

✓ Chemotherapy
  - Aracytine
  - Bendamustine combination
  - Anthracyclins/alkylating agents

✓ Novel drugs alone or in combinations
  - PI3K inhibitors
  - Temsirolimus
  - Ibrutinib
  - Lenalidomide
  - Bortezomib
  - Venetoclax
# Mantle cell lymphoma

## R-BAC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 40)</th>
<th>Previously Untreated Patients (n = 20)</th>
<th>R/R Patients (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Response rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>36</td>
<td>90</td>
<td>20</td>
</tr>
<tr>
<td>CR</td>
<td>33</td>
<td>83</td>
<td>19</td>
</tr>
<tr>
<td>PR</td>
<td>3</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>NR</td>
<td>3</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

![Graph](Visco, JCO 2013)
BTK inhibitor Ibrutinib
Duration of response

Wang, NEJM 2013, ASH 2014
BTK inhibitor Ibrutinib

Duration of response

Allo SCT or long term responders?

Wang, NEJM 2013, ASH 2014
Mantle Cell Lymphoma: Relapse

Eligible for clinical trial?

- Yes
  - Clinical trial
  - Non-cross-resistant salvage therapy
    - CR/PR
      - Second-line salvage therapy
        - SD/PD
        - Donor stem cell source available?
          - Yes
            - Reduced intensity allogeneic stem cell transplantation
          - No
            - Maintenance rituximab?
              - Yes
                - R-BAC, BR
              - No
                - Supportive care
        - Ibrutinib
      - Ibrutinib available and not contraindicated?
        - Yes
          - Fit for conventional dose therapy?
            - Yes
              - R-BAC, BR
            - No
              - Supportive care
        - No

- No
  - Allogeneic transplant candidate?
    - Yes
    - Ibrutinib
    - Fit for conventional dose therapy?
      - Yes
        - Supportive care
      - No
        - Ibrutinib
Donors for alloSCT in Lymphoma

Adjusted for year of SCT, remission, performance status

Dietrich et al, Leukemia 2016
Donor Choice

(A pooled analysis of MCL, DLBCL, FL, TCL)
Mantle Cell Lymphoma: Relapse

- Eligible for clinical trial?
  - Yes: Clinical trial
  - No: Allogeneic transplant candidate?
    - Yes: Non-cross-resistant salvage therapy
      - SD/PD: Second-line salvage therapy
      - CR/PR: Donor stem cell source available?
        - Yes: Reduced intensity allogeneic stem cell transplantation
        - No: Maintenance rituximab?
    - No: Ibrutinib available and not contraindicated?
      - Yes: Ibrutinib
      - No: Fit for conventional dose therapy?
        - Yes: R-BAC, BR, R-lenalidomide, bortezomib
        - No: Supportive care

Michael L. Wang, JCO 2016
## MAC vs. RIC alloSCT in MCL

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Conditioning</th>
<th>2y-NRM</th>
<th>2y-DFS</th>
<th>2y-OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khouri</td>
<td>phase-II;</td>
<td>16</td>
<td>TBI/Cy</td>
<td>6 of 16</td>
<td>55% (3y)</td>
<td>55% (3y)</td>
</tr>
<tr>
<td>Laudi</td>
<td>phase-II</td>
<td>17</td>
<td>TBI/Cy</td>
<td>29%</td>
<td>50%</td>
<td>49%</td>
</tr>
<tr>
<td>Ganti</td>
<td>retrospective</td>
<td>17</td>
<td>TBI/Cy</td>
<td>19% (3m)</td>
<td>53%</td>
<td>58%</td>
</tr>
<tr>
<td>Maris</td>
<td>phase-II;</td>
<td>33</td>
<td>TBI2/F</td>
<td>24%</td>
<td>60%</td>
<td>65%</td>
</tr>
<tr>
<td>Khouri</td>
<td>phase-II</td>
<td>35</td>
<td>FC-R +/- CD52</td>
<td>9%</td>
<td>50% (4y)</td>
<td>54% (4y)</td>
</tr>
<tr>
<td>Morris</td>
<td>phase-II</td>
<td>10</td>
<td>F/Mel/CD52</td>
<td>20%</td>
<td>50% (3y)</td>
<td>60% (3y)</td>
</tr>
</tbody>
</table>
THE IMPACT OF GRAFT VERSUS HOST DISEASE ON RELAPSE RATE IN PATIENTS WITH LYMPHOMA DEPENDS ON THE HISTOLOGICAL SUB-TYPE AND THE INTENSITY OF THE CONDITIONING REGIMEN

\[ P_{\text{Log-Rank}} = 0.002 \]
THE IMPACT OF GRAFT VERSUS HOST DISEASE ON RELAPSE RATE IN PATIENTS WITH LYMPHOMA DEPENDS ON THE HISTOLOGICAL SUB-TYPE AND THE INTENSITY OF THE CONDITIONING REGIMEN

**Mantle Cell**
- AG-N/CG-N (n=94)
- AG-Y/CG-N (n=29)
- AG-N/CG-Y (n=48)
- AG-Y/CG-Y (n=37)

**Follicular**
- AG-N/CG-N (n=209)
- AG-Y/CG-N (n=42)
- AG-N/CG-Y (n=62)
- AG-Y/CG-Y (n=54)

*Biol Blood Marrow Transplant. 2015*
Is there a Graft versus MCL (GV-MCL)?

T-Cells

- Cumulative Incidence of relapse
  - CAMPATH
  - No CAMPATH

Immun-Effect

- Chronic GVHD
  - CAMPATH
  - No Chronic GVHD

S. Robinson, EBMT Registry

2) Which benefit provides an alloSCT?
Non-myeloablative Allogeneic Hematopoietic Stem Cell Transplantation for Adults with Relapsed and Refractory Mantle Cell Lymphoma: A Single Center Analysis in the Rituximab Era

![Graphs showing survival probability over months post allo-SCT for patients with and without alemtuzumab.](image-url)

Response prior to RIC-Allo and role of cGvH

**PFS**

<table>
<thead>
<tr>
<th>Survival rate</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>100</td>
</tr>
<tr>
<td>PD</td>
<td>90</td>
</tr>
<tr>
<td>PR</td>
<td>80</td>
</tr>
</tbody>
</table>

\[ p = 0.006 \]

**OS**

<table>
<thead>
<tr>
<th>Survival rate</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>100</td>
</tr>
<tr>
<td>PD</td>
<td>90</td>
</tr>
<tr>
<td>PR</td>
<td>80</td>
</tr>
</tbody>
</table>

\[ p = 0.001 \]
MCL_{BV}: relapse after alloSCT
⇒ Rituximab + DLI

Molecular remission

![Graph showing lymphoma cells per 100,000 PBMCN over months after diagnosis with specific events such as 6x R-CHOP, allogeneic PBSCT, GvHD IV°, and Rituximab treatment.]
Failure after ASCT

- 366 EBMT pts with MCL relapsed after ASCT (first line 64%; prior rituximab 68%; prior HD-ARAC 49%; 12% refractory to autoSCT).
- Salvage therapy: alloSCT in 23% and 2\textsuperscript{nd} ASCT in 2%.
- Median f-up: 37 months.

- OS for patients who received a 2nd ASCT was very poor.
- AlloSCT performed for late relapse (>12 mo after ASCT) was associated with superior OS.
- Donor source, T-cell depletion or conditioning intensity did not affect OS.

How to improve these results?

Reduce TRM vs early relapses
Monitor Response and apply pre-emptive therapies (Ritux, Ibrutinib, mTOR ?)

DLI++

Long term survivors
Maintenance therapy ?
How to improve these results?

New drugs to bridge or after Allo SCT?
Haploidentical early relapses?
Lymphoma Registry: SCT 2005-2014

Allo-SCT: Proportion of Haploidentical SCT

<table>
<thead>
<tr>
<th>Year</th>
<th>Haploidentical SCT</th>
<th>Allo SCT (including haplo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>2</td>
<td>1012</td>
</tr>
<tr>
<td>2006</td>
<td>7</td>
<td>1126</td>
</tr>
<tr>
<td>2007</td>
<td>21</td>
<td>1178</td>
</tr>
<tr>
<td>2008</td>
<td>31</td>
<td>1244</td>
</tr>
<tr>
<td>2009</td>
<td>37</td>
<td>1414</td>
</tr>
<tr>
<td>2010</td>
<td>57</td>
<td>1480</td>
</tr>
<tr>
<td>2011</td>
<td>81</td>
<td>1537</td>
</tr>
<tr>
<td>2012</td>
<td>121</td>
<td>1510</td>
</tr>
<tr>
<td>2013</td>
<td>156</td>
<td>1709</td>
</tr>
<tr>
<td>2014</td>
<td>205</td>
<td>1577</td>
</tr>
</tbody>
</table>
Haplo-identical transplantation for MCL

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>HCl</th>
<th>Disease</th>
<th>Prior therapies</th>
<th>prior auto-SCT</th>
<th>Disease status pre allo-HSCT</th>
<th>Graft Source</th>
<th>Donor</th>
<th>CMV donor</th>
<th>CMV recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>24</td>
<td>1</td>
<td>AILT</td>
<td>4</td>
<td>Yes</td>
<td>refractory</td>
<td>BM</td>
<td>brother</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td>M</td>
<td>53</td>
<td>6</td>
<td>AILT</td>
<td>6</td>
<td>No</td>
<td>PR</td>
<td>BM</td>
<td>sister</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>M</td>
<td>51</td>
<td>3</td>
<td>MCL</td>
<td>5</td>
<td>Yes</td>
<td>PR</td>
<td>BM</td>
<td>sister</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>F</td>
<td>66</td>
<td>5</td>
<td>MCL</td>
<td>4</td>
<td>Yes</td>
<td>PD</td>
<td>BM</td>
<td>son</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>M</td>
<td>55</td>
<td>3</td>
<td>MCL</td>
<td>6</td>
<td>Yes</td>
<td>PD</td>
<td>PBSC</td>
<td>son</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>M</td>
<td>66</td>
<td>3</td>
<td>MCL</td>
<td>3</td>
<td>No</td>
<td>PD</td>
<td>BM</td>
<td>daughter</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>M</td>
<td>61</td>
<td>1</td>
<td>MCL</td>
<td>7</td>
<td>Yes</td>
<td>PD</td>
<td>BM</td>
<td>daughter</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>M</td>
<td>46</td>
<td>1</td>
<td>MCL</td>
<td>1</td>
<td>No</td>
<td>PR</td>
<td>BM</td>
<td>half brother</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td>M</td>
<td>62</td>
<td>4</td>
<td>MCL</td>
<td>6</td>
<td>No</td>
<td>PD</td>
<td>BM</td>
<td>son</td>
<td>neg</td>
<td>pos</td>
</tr>
<tr>
<td>F</td>
<td>52</td>
<td>5</td>
<td>DLBCL</td>
<td>4</td>
<td>Yes</td>
<td>PR</td>
<td>BM</td>
<td>daughter</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>M</td>
<td>49</td>
<td>2</td>
<td>DLBCL</td>
<td>4</td>
<td>Yes</td>
<td>PD</td>
<td>BM</td>
<td>cousin</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>F</td>
<td>58</td>
<td>2</td>
<td>sDLBCL</td>
<td>3</td>
<td>Yes</td>
<td>PD</td>
<td>BM</td>
<td>son</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td>M</td>
<td>46</td>
<td>2</td>
<td>sDLBCL</td>
<td>5</td>
<td>No</td>
<td>PR</td>
<td>BM</td>
<td>daughter</td>
<td>neg</td>
<td>pos</td>
</tr>
<tr>
<td>M</td>
<td>61</td>
<td>8</td>
<td>CLL</td>
<td>5</td>
<td>No</td>
<td>PR</td>
<td>BM</td>
<td>son</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td>F</td>
<td>46</td>
<td>0</td>
<td>follicular lymphoma</td>
<td>3</td>
<td>No</td>
<td>PR</td>
<td>PBSC</td>
<td>mother</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td>F</td>
<td>23</td>
<td>1</td>
<td>B-LBL</td>
<td>3</td>
<td>No</td>
<td>PD</td>
<td>BM</td>
<td>mother</td>
<td>pos</td>
<td>pos</td>
</tr>
</tbody>
</table>
Haplo-identical transplantation for MCL

<table>
<thead>
<tr>
<th>Patient</th>
<th>Day 30 Response</th>
<th>Full Donor Chimerism</th>
<th>Day 100 response</th>
<th>Full Donor Chimerism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CR</td>
<td>Y</td>
<td>CR</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>CR</td>
<td>Y</td>
<td>PD</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>PR</td>
<td>Y</td>
<td>PR</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>PR</td>
<td>Y</td>
<td>PR</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>PR</td>
<td>Y</td>
<td>CR</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>PR</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>PR</td>
<td>Y</td>
<td>CR</td>
<td>Y</td>
</tr>
<tr>
<td>8</td>
<td>PR</td>
<td>Y</td>
<td>CR</td>
<td>Y</td>
</tr>
<tr>
<td>9</td>
<td>PR</td>
<td>Y</td>
<td>CR</td>
<td>Y</td>
</tr>
<tr>
<td>10</td>
<td>PR</td>
<td>Y</td>
<td>CR</td>
<td>Y</td>
</tr>
<tr>
<td>11</td>
<td>PR</td>
<td>Y</td>
<td>PR</td>
<td>Y</td>
</tr>
<tr>
<td>12</td>
<td>PD</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>CR</td>
<td>Y</td>
<td>PD</td>
<td>Y</td>
</tr>
<tr>
<td>14</td>
<td>PR</td>
<td>Y</td>
<td>PR</td>
<td>Y</td>
</tr>
<tr>
<td>15</td>
<td>CR</td>
<td>Y</td>
<td>CR</td>
<td>Y</td>
</tr>
<tr>
<td>16</td>
<td>PR</td>
<td>Y</td>
<td>CR</td>
<td>Y</td>
</tr>
</tbody>
</table>
Product-limit survival estimates
With number of subjects at risk

Survival probability

OS
PFS

Time (months)

Outcome OS PFS

+ Censored

1616 15 12 12 11 10 8 6 5 5 4 4 4 0
1616 15 11 9 9 8 6 6 5 5 4 4 4 1
Allogeneous Stem Transplantation in MCL

- GVL effect occurs (DLI)
- Curative procedure
- In relapsing setting in responding patients (CR or PR)
- Role of a new targeted therapies remains to be define (before to bridge and after) ?
- Haploidentical (sequential ?) in R/R pts ?
- CAR-T cells ?
ORIGINIAL ARTICLE

The EBMT/EMCL consensus project on the role of autologous and allogeneic stem cell transplantation in mantle cell lymphoma

S Robinson¹, P Dreger², D Caballero³, P Corradini⁴, C Geisler⁵, M Ghielmini⁶, S Le Gougil⁷, E Kimby⁸, S Rule⁹, U Vitolo¹⁰, M Dreyling¹¹ and O Hermine¹² on behalf of the European MCL Network and the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation
Relapse Therapy For MCL

Patients relapsing after an autoSCT should be considered for an allogeneic stem cell transplant following reinduction therapy.

Patients undergoing an allogeneic SCT should receive reduced intensity conditioning regimens.

Patients with evidence of MRD should, in the absence of graft versus host disease, be considered for rapid withdrawal of immunesuppression and DLI.