Mantle Cell Lymphoma

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Oncology Institute of Southern Switzerland
Ospedale San Giovanni - 6500 Bellinzona, Switzerland
Summary of the talk

- The disease
- Treatment of the young/fit
- Treatment of the elderly/unfit
- Relapse and new drugs
- Indolent MCL
MCL, a bad luck disease: the worse of FL and DLBCL

Centrocytic lymphoma

IOSI Database
NHL frequency at the IOSI

- Diffuse Large B-cell Lymphoma: 37%
- Follicular Lymphoma: 20%
- Mantle Cell Lymphoma: 6.5%
- CLL/SLL: 15%
- MALT lymphoma: 7%
Clinical prognostic factors: MIPI

N = 455

Adverse factors:
- Age
- ECOG PS
- LDH
- WBC

Score calculated with a rather complex formula

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MCL: ESMO guidelines 2013

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Rituximab + Chemo meta-analysis (Overall Survival)

Schulz et al., JNCI 2007

FIG. 3B - p. 711

Schulz et al, JNCI 2007: 99
European MCL Network

4-6x CHOP-like induction

2x CHOP-like consolidation

PR, CR

Dexa-BEAM mobilization

IFN- \( \rightarrow \) maintenance

Cyclo-TBI

ASCT

RECURRENT

RELAPSE

Progression Free Survival
N=122

Median PFS, 39 mos. (ASCT) vs. 17 mos (IFN)

Dreyling et al. Blood 2005
Analysis of 3 pooled trials: ASCT vs. IFN Overall survival

Dreyling et al, ASCO 2009

![Graph showing survival probability over time for ASCT and IFN]

- **ASCT, median = 90**
- **IFN, median = 65**
- **p = 0.0377**

<table>
<thead>
<tr>
<th>months after end of induction therapy</th>
<th>numbers of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASCT</td>
</tr>
<tr>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>73</td>
</tr>
<tr>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td>36</td>
<td>63</td>
</tr>
<tr>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>60</td>
<td>42</td>
</tr>
<tr>
<td>72</td>
<td>25</td>
</tr>
<tr>
<td>84</td>
<td>19</td>
</tr>
<tr>
<td>96</td>
<td>13</td>
</tr>
<tr>
<td>108</td>
<td>9</td>
</tr>
<tr>
<td>120</td>
<td>5</td>
</tr>
<tr>
<td>132</td>
<td>1</td>
</tr>
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HyperCVAD

- R-Hyper CVAD as per MDACC protocol (first-line)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CR</th>
<th>RR</th>
<th>2y PFS</th>
</tr>
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<tbody>
<tr>
<td>MDACC</td>
<td>97</td>
<td>87%</td>
<td>97%</td>
<td>90%</td>
</tr>
<tr>
<td>SWOG</td>
<td>49</td>
<td>58%</td>
<td>88%</td>
<td>63%</td>
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Epner, abstr. 387, ASH 2007
MCL European Network Study

R-CHOP vs R-CHOP alt. R-DHAP in young MCL, first line

**Time to treatment failure**

- **R-DHAP**
  - median follow-up = 56 months
  - median = 88
  - \( p = 0.0382 \)

- **R-CHOP**
  - median = 46

**Overall Survival**

- **R-DHAP**
  - median follow-up = 59 months
  - median not reached
  - \( p = 0.092 \)

- **R-CHOP**
  - median not reached

Hermine at al, Abstr 86, 12-ICML, Lugano 2013

P value:
- ICML 2011: NS
- ASH 2012: 0.048
- ICML 2013: NS
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Bendamustine in MCL: At least as good as CHOP


MCL: PFS

Median (IQR; months)
B-R: 35.4 (28.8–54.9)
R-CHOP: 22.1 (15.1–33.8)

HR 0.49
(95% CI 0.28–0.79)
p=0.0044
R-benda vs R-CHOP (CVP): BRIGHT

Study design

- n = 447
- FL = 83%
- MCL = 17%

BRIGHT study: results

R-maintenance in MCL

559 MCL aged > 60 years

2 RANDOMISATIONS

R

R-CHOP

R-FC

R

R-maintenance

IFN-maintenance

R-CHOP better than R-FC

The effect of R-maintenance depends on the induction regimen

After R-CHOP

OS

After R-FC

What about maintenance after R-bendamustine?

Superior PFS but not OS with VR-CAP vs R-CHOP

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<th>VR-CAP</th>
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<tbody>
<tr>
<td>Median PFS, months</td>
<td>14.4</td>
<td>24.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63</td>
<td>(0.50, 0.79)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Median OS, months</td>
<td>56.3</td>
<td>Not reached</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.80</td>
<td>(0.59, 1.10)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.173</td>
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F. Cavalli, ASCO 2014
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<td></td>
<td>Lenalidomide</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ibrutinib</strong></td>
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Published series of allo-transplant in relapsed MCL

<table>
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<th>Study Type</th>
<th>N</th>
<th>3-5 y PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 studies (myeloablative)</td>
<td>10-18</td>
<td>42-55%</td>
</tr>
<tr>
<td>4 studies (RIC)</td>
<td>35-180</td>
<td>14-46%</td>
</tr>
<tr>
<td>CIBMTR registry (2011)</td>
<td>105</td>
<td>20%</td>
</tr>
<tr>
<td>EBMT registry (2011)</td>
<td>325</td>
<td>32%</td>
</tr>
</tbody>
</table>

Conclusions: Allo-BMT cures 1/3 of transplant eligible relapsed MCL
Promising targeted drugs

<table>
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<th>Drug</th>
<th>RR in relapse</th>
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<tr>
<td>Bortezomib</td>
<td>30%</td>
</tr>
<tr>
<td>Everolimus / Temsirolimus</td>
<td>20%</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>50%</td>
</tr>
<tr>
<td>Ibrutinib (PCI 32765)</td>
<td>60%</td>
</tr>
<tr>
<td>Idelalisib (CAL 101)</td>
<td>50%</td>
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</table>
Small molecules

Modified from Wiestner, JCO 2013.
Ibrutinib in Relapsed MCL

111 cases
Median 3 previous regimens

68% RR (22% CR)
Over time: 75% (35% CR)
Median PFS 1 year

Side effects mild:
Diarrhea, fatigue, nausea

Ibrutinib + rituximab in 50 R/R MCL Best Response

Wang et al, ASH 2014, abstr. 627

** Ki67 N/A for 4 patients **
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Weill-Cornell experience

97 MCL over 10 years
66 Immediate treatment
31 Observed (median TTT = 1 y)

The observation group had a less aggressive MCL

Deferring treatment did not compromise efficacy

OS from diagnosis

OS from start of treatment

Martin P et al. JCO 2009
Weill-Cornell: MIPI is not predictive of indolent course!

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66 Immediate treatment
31 Observed (median TTT = 1 y)

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Deferring treatment did not compromise efficacy

OS from diagnosis

OS from start of treatment

Martin P et al. JCO 2009
## Nodal vs non-nodal leukemic MCL

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<th>Nodal (n=43)</th>
<th>Non-nodal (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenomegaly</td>
<td>58</td>
<td>76</td>
</tr>
<tr>
<td>GI tract</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>CD38+</td>
<td>94</td>
<td>48</td>
</tr>
<tr>
<td>IgVH unmutated</td>
<td>90</td>
<td>44</td>
</tr>
<tr>
<td>Complex caryotype</td>
<td>100</td>
<td>53</td>
</tr>
<tr>
<td>Immediate treatment</td>
<td>95</td>
<td>49</td>
</tr>
<tr>
<td>Median OS</td>
<td>30m</td>
<td>79m</td>
</tr>
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Orchard et al, Blood 2003
Negative SOX11 associated with indolent MCL?

GEP identifies 13 genes expressed in cMCL and not in iMCL. For one of these, SOX11, the protein can be stained in IHC.

112 MCL cases

iMCL cases were:

- Non-nodal
- Hypermutated IGVH
- No genomic complexity
- SOX11 neg

Fernàndez et al., Cancer Res. 2010
Indolent mantle cell leukemia: a clinicopathological variant

Cleveland Clinic, 2000-2010: 8 cases

- morphology and immunophenotype of MCL
- no symptoms
- lymphocytosis
- Kappa light-chain restriction
- low-level BM involvement
- SOX-11 neg

Equivalent of MBL (monoclonal B-lymphocytosis)?
In the majority of MCL you can **consider watch and wait.**

<table>
<thead>
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<th>Useful for decision</th>
<th>Not useful for decision</th>
</tr>
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<tbody>
<tr>
<td>GELF/BNLI criteria as</td>
<td>Ki 67</td>
</tr>
<tr>
<td>- absence of symptoms</td>
<td>IGHV mutation</td>
</tr>
<tr>
<td>- no rapidly progressive LN</td>
<td>SOX11</td>
</tr>
<tr>
<td>- no altered blood counts</td>
<td>Genetic abnormalities</td>
</tr>
<tr>
<td>- ...</td>
<td></td>
</tr>
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(MIPI ?)
Conclusions

- MCL is neither an indolent nor a curable disease
- Few randomized trials give clear hint on the best treatment strategy
- Several studies suggest that
  - Bendamustine is superior to CHOP
  - Rituximab improves the effect of chemo
  - HD-AraC and HDCT improve OS
  - Rituximab maintenance is good after R-CHOP
- Ibrutinib and lenalidomide offer new perspectives
- Consider W+W in very selected cases