Is there such thing as an “indolent” Mantle Cell Lymphoma?

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Summary of the talk

- «Typical» mantle cell lymphoma
- Clinically indolent MCL exist
- Identifying iMCL: clinical presentation
- Identifying iMCL: biological parameters
- Nodal vs non-nodal MCL and the SOX-11 issue
- Model of genetic progression
- Conclusions
MCL: Clinical presentation

- Median age ~ 60 years
- Male predominance (~3:1)
- Advanced disease (>80%)
- Generalised adenopathy (90%)
- Bone marrow and spleen involvement (50-80%)
- Peripheral blood involvement (20-80%)
- PB ~100% involved by FACS
## GI involvement

<table>
<thead>
<tr>
<th></th>
<th>Upper GI</th>
<th>Lower GI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>(dyspepsia)</td>
<td>(diarrhea)</td>
</tr>
<tr>
<td><strong>Macro alterations</strong></td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>(gastritis)</td>
<td>(polyps)</td>
</tr>
<tr>
<td><strong>Microsc. MCL</strong></td>
<td>60%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Overall, 90% have upper and/or lower GI-tract involvement

Romaguera et al., ASH 2000
Salar et al., Am. J. Surg Path 2006

Lymphomatous polyposis
MCL, a bad luck disease: the worse of FL and DLBCL

Centrocytic lymphoma

IOSI Database
# MCL: ESMO guidelines 2013

## First line

<table>
<thead>
<tr>
<th>≤ 65 y</th>
<th>&gt; 65 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-chemo Containing HD-Ara C + HDT</td>
<td>R-benda or R-CHOP + R-maintenance (after R-CHOP)</td>
</tr>
</tbody>
</table>

## Relapse

<table>
<thead>
<tr>
<th>1st relapse</th>
<th>(R) – chemo</th>
<th>(consider Allo transplant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd relapse</td>
<td>Temsirolimus Bortezomib Lenalidomide Ibrutinib</td>
<td></td>
</tr>
</tbody>
</table>

Dreyling M et al, Ann. Oncol. 2013
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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
Plymouth experience

52 MCL over 14 years
   33 immediate treatment
   16 observed (median TTT = 1y)

Deferring treatment did not compromise OS

OS from diagnosis

Eve H E et al. JCO 2009
Nordic experience

1389 MCL over 11 years, cancer registries

Abrahamsson et al. Blood 2014

1317 immediate systemic treatment
43 immediate RT
29 observation
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Clinical prognostic factors: MIPI

N = 455

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

Score calculated with a rather complex formula

## Simplified MIPI

<table>
<thead>
<tr>
<th>Points</th>
<th>Age (years)</th>
<th>ECOG PS</th>
<th>LDH/ULN</th>
<th>WBC, $10^9$/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 50</td>
<td>0-1</td>
<td>&lt; 0.67</td>
<td>&lt; 6.7</td>
</tr>
<tr>
<td>1</td>
<td>50-59</td>
<td>-</td>
<td>0.67 - 0.99</td>
<td>6.7 - 9.99</td>
</tr>
<tr>
<td>2</td>
<td>60-69</td>
<td>2-4</td>
<td>1 - 1.49</td>
<td>10 - 14.99</td>
</tr>
<tr>
<td>3</td>
<td>≥ 70</td>
<td>-</td>
<td>≥ 1.5</td>
<td>≥ 15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Nr. of adverse factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0-3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4-5</td>
</tr>
<tr>
<td>High risk</td>
<td>6-11</td>
</tr>
</tbody>
</table>

MIPI validation: The Netherlands

178 MCL from registry

Modified MIPI added
  • PS in 4 groups
  • Sex
  • B-symptoms

van de Schans et al. Haematologica 2010
MIPI in transplanted patients: Nordic

MCL treated intensively (HD-AraC + HDCT)

Intensive treatment cannot overcome MIPI

Geisler et al. Blood 2010
MIPI in transplanted patients: USA

118 MCL consolidated with HDCT

Intensive treatment can not overcome MIPI

Budde et al. JCO 2011
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5-gene model to predict OS

33 genes studied in MCL from 73 pts

5 genes

- RAN
- MYC
- TNFRSF 10B
- POLE 2
- SLC 29 A2

Problem: Needs Fresh frozen samples and expensive techniques

Hartmann et al. JCO 2008
Ki67 is an important predictor

249 advanced MCL

CHOP

R-CHOP

Problem: interobserver variability in scoring. Which is the cut-off?

Determann et al., Blood 2008
P53 expression is prognostic

MCL treated intensively

Nordström et al., BJH 2014
PET:
High SUV could mean blastoid variant

Problem: good predictor of tumor proliferation, but does not add to LDH or Ki67

Brepoels et al., Leuk Lymphoma 2008
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# Nodal vs non-nodal leukemic MCL

<table>
<thead>
<tr>
<th></th>
<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>
</tbody>
</table>

Orchard et al, Blood 2003
Negative SOX11 defines 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.

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)?

Ondrejka et al., Haematologica 2011
Mutated IGHV, SOX11 neg, non-nodal are indolent MCL

Multicenter study, 177 MCL
Multivariate analysis: IGHV gene status and SOX11 expression are independent risk factors

Navarro et al., Cancer Res. 2012
A different view from Stockholm

186 MCL, 17 had clinical indolent course

<table>
<thead>
<tr>
<th>%</th>
<th>Indolent</th>
<th>Non-indolent</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-symptoms</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td>Nodal</td>
<td>35</td>
<td>66</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>31</td>
<td>53</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>MIPI High</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>Ki67 high</td>
<td>21</td>
<td>62</td>
</tr>
<tr>
<td>Blastoid</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Median OS</td>
<td>5.9 y</td>
<td>2.8 y</td>
</tr>
<tr>
<td>SOX11 +</td>
<td>88</td>
<td>93</td>
</tr>
</tbody>
</table>

Nygren et al., Blood 2012
Model of genetic progression in MCL

SOX11 as a marker of non-nodal pathway rather than an independent prognostic marker

Conclusions 1

A predictable indolent course is uncommon

1) "in situ" MCL

2) Non-nodal MCL presenting with
   – isolated lymphocytosis
   – no symptoms
   – no cytopenias

(MBL of MCL type?)
Conclusions 2

In all other MCL you can *consider* watch and wait.

<table>
<thead>
<tr>
<th>useful for decision</th>
<th>not useful for decision</th>
</tr>
</thead>
<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 SOX11</td>
<td>Genetic abnormalities</td>
</tr>
<tr>
<td>-no altered blood counts</td>
<td></td>
</tr>
<tr>
<td>-...</td>
<td></td>
</tr>
</tbody>
</table>

(MIPI ?)
And if you want to remain on the edge …

13-ICML
13th International Conference on Malignant Lymphoma

Palazzo dei Congressi
Lugano (Switzerland)
www.lymphcon.ch

SAVE THE DATE: June 17-20, 2015