Options in Mantle Cell Lymphoma Therapy

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My Disclosures:

**ADVISOR OR ADVISORY BOARDS:**
Lundbeck Canada Inc, Celgene Europe, Mundipharma International

**RESEARCH FUNDS:**
Mundipharma Pharmaceuticals Italy
Mantle cell lymphoma (MCL)

• About 6% of non Hodgkin’s lymphomas
• Predominantly elderly (>60), male patients
• Advanced Ann Arbor stage
• Extranodal involvement (bone marrow, gastrointestinal tract, liver, spleen)
Model of molecular pathogenesis of MCL

Genetically stable t(11;14), SOX11- cells

Modified from Jares et al, JCI 2012
Patients in whom treatment may be postponed (iMCL)

- Long history of asymptomatic disease
- Non-nodal leukemic disease (++) spleen
- Low proliferation rate
- Hypermutated IGHV
- Noncomplex karyotypes
- SOX11-negative

Fernandez V, Cancer Res 2010
Seto M, Blood 2013
Ferrando A, Blood 2013
Vegliante et al, Blood 2013
Cause-specific survival of the main B-cell lymphoma subtypes

Significant improvement in OS in the last 10 years:
1) introduction of dose-intensive strategies upfront in younger patients
2) availability of novel agents in older patients or in the r/r setting.
Standard 1st line in younger patients with MCL

INDUCTION CHEMOTHERAPY

ARA-C including

R-Hyper-CVAD

ASCT
LyMa trial

MCL, 18 to 65 years old

If < VGPR
If > VGPR

R-DHAP  R-DHAP  R-DHAP  R-DHAP  R-BEAM

R-CHOP

OBSERVATION

RITUXIMAB MAINTENANCE
every 2 months during 3 years

W1  W4  W7  W10

Le Gouill et al. ASH 2012
IIL MCL 0208 trial

CHOP21 | CHOP21 | CHOP21 | HD-CTX | HD Ara-C | HD Ara-C | BEAM+ ASCT | ±IFRT 36-40 Gy

0 | 3 | 6 | 9 | 13 | 17 | 21 | 29 wks

R | R | R | R | R | R | R | R

Len 15 mg days 1-21 every 28 days /2 yrs

Observation

Cortelazzo et al. ongoing
Elderly (≥65)/unfit patients
CHOP vs Rituximab-CHOP

<table>
<thead>
<tr>
<th></th>
<th>ORR (%)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>94</td>
<td>34</td>
</tr>
<tr>
<td>CHOP</td>
<td>75</td>
<td>7</td>
</tr>
</tbody>
</table>

Median age 61 (1/3>65)

No difference in DOR or OS*

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Lenz et al, JCO 2005
Treatment of Older Patients with Mantle-Cell Lymphoma


≥60 years

1st: is Flu-regimen better than CHOP?

2nd: does maintenance with Rituximab prolong remission?
R-CHOP vs R-FC in elderly patients with MCL

<table>
<thead>
<tr>
<th></th>
<th>ORR (%)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>86</td>
<td>34</td>
</tr>
<tr>
<td>R-FC</td>
<td>78</td>
<td>40</td>
</tr>
</tbody>
</table>

Cause of death | R-FC | R-CHOP |
--- | --- | --- |
Died in CR/PR | 10% | 4% |
Infections    | 7%  | 4%  |
Second cancer | 3%  | 1%  |

Kluin-Nelemans HC et al. NEJM 2012;367:520-31
Maintenance therapy: Rituximab vs Interferon α

Kluin-Nelemans HC et al. NEJM 2012;367:520-31
Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Lusem, Dorothea Kofahl-Krause, Gerhard Hell, Manfred Welsch, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Dürk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StIL)

**Histology**

<table>
<thead>
<tr>
<th>Type</th>
<th>B-R</th>
<th>R-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>139 (53%)</td>
<td>140 (55%)</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>46 (18%)</td>
<td>48 (19%)</td>
</tr>
<tr>
<td>Marginal zone</td>
<td>37 (14%)</td>
<td>30 (12%)</td>
</tr>
<tr>
<td>Lymphoplasmacytic*</td>
<td>22 (8%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Small lymphocytic</td>
<td>10 (4%)</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Low grade, unclassifiable</td>
<td>7 (3%)</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

Median (IQR; months)

- **B-R**: 35.4 (28.8–54.9)
- **R-CHOP**: 22.1 (15.1–33.8)

**Median age of the MCL pts**

70 years (65-74)
Bendamustine plus Rituximab (BR) vs R-CHOP/CVP

**BRIGHT study**

447 patients with indolent NHL or MCL randomized to 6-8 cycles of BR or R-CHOP/R-CVP

<table>
<thead>
<tr>
<th>Population, Analysis</th>
<th>Complete Response Rate</th>
<th>Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR %</td>
<td>R-CHOP/R-CVP %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized MCL</td>
<td>50</td>
<td>27</td>
<td>1.95 (1.01-3.77)</td>
</tr>
</tbody>
</table>

Flinn IW et al. Blood 2014;123:2944-52
B-R + Observation vs B-R + 2 years Rituximab Maintenance

NHL 7-2008 - MAINTAIN

- Waldenström’s Marginal zone
- Mantle cell (for patients not eligible for APBSCT)

- Bendamustine-Rituximab + Observation
- Bendamustine-Rituximab + 2 years Rituximab q2 mo

Rummel et al, ASH 2012 [Abstr 2739]
## Bendamustine including combinations

### Ongoing studies in elderly MCL

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Treatment</th>
<th>Primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>BERT (University Mainz)</td>
<td>II</td>
<td>Temsirolimus plus bendamustine and rituximab for patients with FL or MCL in first to third relapse</td>
<td>Mar 2015</td>
</tr>
<tr>
<td>LENA-BERIT (NLG-MCL4 Trial)</td>
<td>I/II</td>
<td>Lenalidomide, bendamustine and rituximab as first-line therapy for patients over 65 years with MCL</td>
<td>Sep 2014</td>
</tr>
<tr>
<td>R2-B (FIL)</td>
<td>II</td>
<td>Lenalidomide, bendamustine and rituximab as a second-line therapy for 1st relapsed-refractory MCL</td>
<td>Jul 2014</td>
</tr>
<tr>
<td>R-BAC500 (FIL)</td>
<td>II</td>
<td>Age-adjusted rituximab, bendamustine, cytarabine as induction therapy in older patients with MCL</td>
<td>Mar 2014</td>
</tr>
<tr>
<td>RIBVD (GOELAMS)</td>
<td>II</td>
<td>Study of MCL treatment by Rituximab, Velcade, Bendamustine and Dexamethasone (1st-line)</td>
<td>Apr 2015</td>
</tr>
<tr>
<td>Ohio State University</td>
<td>I</td>
<td>Rituxan/Bendamustine/PCI-32765 in Relapsed DLBCL, MCL, or Indolent Non-Hodgkin's Lymphoma</td>
<td>Oct 2015</td>
</tr>
<tr>
<td>North American Intergroup Trial</td>
<td>III</td>
<td>Rituximab, bendamustine ± Velcade ± R2 maintenance as 1st line therapy for elderly MCL patients</td>
<td>Apr 2015</td>
</tr>
</tbody>
</table>
E1411 North American Intergroup Trial

Accrual to E1411 is ongoing and may define a new standard of care, particularly in older individuals with MCL.

**Diagram:**

- **Registration**
  - **BR x 6** → **Rituximab**
  - **BVR X 6** → **Rituximab**
  - **BR x 6** → **Lenalidomide + Rituximab**
  - **BVR x 6** → **Lenalidomide + Rituximab**

*B=bendamustine, R=rituximab, V=bortezomib*

Schema of E1411. Maintenance therapy is administered for 2 years.
Bendamustine and Ara-C
Mechanism of action

Alkylator group

Benzimidazole ring

Bendamustine

Ara-C

Visco et al, BCMD 2012
Hiraoka, et al, PLOS 2014
Rituximab, Bendamustine, Cytarabine (R-BAC)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR (%)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>R/R</td>
<td>80</td>
<td>70</td>
</tr>
</tbody>
</table>

- Median age 71 (54-82)
- Median F/U 48 months (28-63)

Visco C et al, JCO 2013

Previous untreated (n=20)

Relapsed/Refractory (n=20)

Visco C et al. Unpublished data
Elderly MCL-Provocative comparison

<table>
<thead>
<tr>
<th>Grade 3 or 4 Event</th>
<th>Cycles (N = 182)</th>
<th>Patients (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>87</td>
<td>48</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>56</td>
<td>31</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>138</td>
<td>76</td>
</tr>
<tr>
<td>Anemia</td>
<td>48</td>
<td>26</td>
</tr>
</tbody>
</table>

Time (months)
Phase 2 study of age-adjusted R-BAC (RBAC500)

- Two stages, phase 2 study
- Introduction of MRD and CGA assessment
- **Ara-C dose reduction to 500 mg/m^2**
- Previously untreated >65 years or 60-65 unfit
- 57 patient enrolled [2 May 2012 - 25 Feb 2014]
- Expected 1st report Lugano 2015
Active «biologic» agents

Proteasome Inhibitors [Bortezomib]

M-TOR inhibitors [Temsirolimus]

B-cell receptor downstream pathways inhibitors [Ibrutinib, Idelalisib]

Immunomodulators [Lenalidomide]
Lenalidomide + Rituximab for relapsed or refractory MCL: a phase I/II trial

44 patients, median age 66 (46-85)
Phase 1: MTD 20 mg
Phase 2: ORR 57%, CR 36%

<table>
<thead>
<tr>
<th>Haematological events</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>31 (70%)</td>
<td>6 (14%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 (45%)</td>
<td>22 (50%)</td>
<td>16 (36%)</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (2%)</td>
<td>7 (16%)</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>23 (52%)</td>
<td>9 (20%)</td>
<td>8 (18%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>26 (55%)</td>
<td>14 (32%)</td>
<td>10 (23%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>27 (61%)</td>
<td>21 (48%)</td>
<td>12 (27%)</td>
<td>4 (9%)</td>
</tr>
</tbody>
</table>

PFS 11.1 months
DOR 19 months

Wang, Lancet Oncol 2012
Chemo-free approach

Combination Biologic Therapy Without Chemotherapy As Initial Treatment For Mantle Cell Lymphoma: Multi-Center Phase II Study Of Lenalidomide Plus Rituximab

- Induction phase (Lena 20 mg) + maintenance phase (Lena 15 mg)
- 31 subjects with previously untreated MCL, median age 65 years (range 42-86)
- Median follow-up 12 months (range 5-23 months)
- ORR 77% with 40% CR/CRu
- Median time to objective response was 2.8 months
- 87% remain on study without evidence of progression

Martin P, ASH 2013
Ibrutinib, a Bruton tyrosine kinase inhibitor

Phase 2 study

- Open-label, multicenter international study (18 sites)
- Patients with **R/R MCL** (N = 115)
- Median 3 prior therapies
- Patients received a daily dose of ibrutinib until disease progression or unacceptable levels of adverse events (AEs)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>No Prior Treatment with Bortezomib (n = 63)</th>
<th>Prior Treatment with Bortezomib (n = 48)</th>
<th>All Patients (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>19%</td>
<td>23%</td>
<td>21%</td>
</tr>
<tr>
<td>PR</td>
<td>49%</td>
<td>44%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Wang ML, NEJM 2013
Ibrutinib
Efficacy: PFS

13.9 months

Wang ML, NEJM 2013
NLG-MCL6 (PHILEMON)
Ibrutinib+Lenalidomide+Rituximab
Phase II study in R/R MCL

Maintenance until progression

Courtesy of M Jerkemann
Conclusions

• Intensified protocols containing Ara-C ensure prolonged remissions in younger/fit patients
• For them, the role of maintenance and of autotransplant still debated (results soon)
• R-CHOP + R maintenance standard therapy for many groups in the elderly/unfit
• R-Benda is significantly challenging R-CHOP
• A list of biologic agents that target tumor cells and microenvironment
• Many low-toxic associations emerging
• Chemo-free approaches next step
Thank you!

Enjoy Toronto and CHC 2014