Comparative Outcomes Following CP-R, CVP-R and CHOP-R in Patients with Waldenstrom’s Macroglobulinemia

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Introduction

• Randomized studies incorporating Rituximab in indolent lymphomas showed improved overall response, complete response, time to progression and overall survival with CHOP and CVP;

• In WM patients, the German Low Grade Study Group showed improved overall response, complete responses, time to progression were significantly improved in patients receiving CHOP+Rituximab versus CHOP;

• Similar results to those attained with CHOP-R however were seen in a recent study by Dimopoulos et al in patients receiving R-CD;

• These studies raise the question whether Doxorubucin (“H” in CHOP) and Vincristine (“O” in CHOP or “V” in CVP) are necessary in treating indolent lymphomas like WM given their toxicities.
Chemotherapy related Toxicities

- **Doxorubicin**
  Can lead to heart failure, moderate to severe nausea/vomiting, loss of hair, skin irritation at site of injection, decrease in blood counts, susceptibility to infections.

- **Vincristine**
  Significant neuropathy, significant constipation, decrease in blood counts loss of hair.
Study Design

• Comparison of activity and toxicity in WM patients who received cyclophosphamide based therapy with rituximab.

• CHOP-R (n=23)
• CVP-R (n=16)
• CP-R (n=19)

Study Comparison of CHOP-R, CVP-R, CP-R

- Response rates
  - overall, major, and complete response rates

- Progression free survival (PFS)

- Improvements in hematological function

- Treatment related adverse events
  - occurrence of febrile neutropenia, hospitalizations, neuropathy, occurrence of rituximab-related “IgM flare”, and need for plasmapheresis as a result of “IgM flare”
Therapy

CHOP-R
-- Intravenous (IV) Cyclophosphamide (750 mg/m²)
-- Intravenous (IV) Doxorubicin (50 mg/m²)
-- Intravenous (IV) Vincristine (1.4 mg/m²; max 2 mg)
-- Intravenous (IV) Rituximab on day 1 (375 mg/m²)
-- Oral Prednisone (100mg) Days 1-5

CVP-R
-- Intravenous (IV) Cyclophosphamide (750- 1000 mg/m²)
-- Intravenous (IV) Vincristine (1.4 mg/m²; max 2 mg)
-- Intravenous (IV) Rituximab on day 1 (375 mg/m²)
-- Oral Prednisone (100mg) Days 1-5

CP-R
-- Intravenous (IV) Cyclophosphamide (1000 mg/m²)
-- Intravenous (IV) Rituximab on day 1 (375 mg/m²)
-- Oral Prednisone (100mg) Days 1-5
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CHOP-R</th>
<th>CVP-R</th>
<th>CP-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N)</td>
<td>23</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Median Age</td>
<td>54 Years (42-74)</td>
<td>60 Years (32-81)</td>
<td>65 Years (42-74)</td>
</tr>
<tr>
<td>Median Previous Therapies</td>
<td>0 (0-2)</td>
<td>1 (0-3)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>No Previous Therapy</td>
<td>57%</td>
<td>29%</td>
<td>63%</td>
</tr>
</tbody>
</table>

*p* not significant for all comparisons.

## Baseline Characteristics

<table>
<thead>
<tr>
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<th>CHOP-R</th>
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</thead>
<tbody>
<tr>
<td>Median Bone Marrow Involvement</td>
<td>50%</td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td>Serum IgM (mg/dL)</td>
<td>5,190</td>
<td>2,515^a</td>
<td>2,665^b</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>31.3</td>
<td>30.2</td>
<td>33.4</td>
</tr>
<tr>
<td>Platelet count (x (10^9/L))</td>
<td>242</td>
<td>169</td>
<td>270</td>
</tr>
<tr>
<td>B(_2) microglobulin (mg/L)</td>
<td>3.6</td>
<td>3.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Adenopathy and/or Splenomegaly</td>
<td>34.7%</td>
<td>25%</td>
<td>31.6%</td>
</tr>
<tr>
<td>Cycles of therapy</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

\(p\) = Not significant except (a) = 0.015 (CHOP-R vs. CVP-R) and (b) = 0.014 (CHOP-R vs. CP-R)
Response Rates

- **Complete response (CR)**: resolution of all symptoms, normalization of serum IgM levels and disappearance of IgM, and resolution of any adenopathy or splenomegaly.

- **Near-CR (nCR)**: fulfilling all CR criteria but presence of positive immunofixation

- **Very good partial response (VGPR)**: ≥ 90% reduction in serum IgM

- **Partial Response (PR)**: 50-89% reduction in serum IgM

- **Minor Response (MR)**: 25-49% reduction in serum IgM

- **Progressive disease (PD)**: > 25% increase in serum IgM or clinically significant disease parameters.
# Response Assessments for CHOP-R, CVP-R, or CP-R

<table>
<thead>
<tr>
<th></th>
<th>CHOP-R</th>
<th>CVP-R</th>
<th>CP-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N)</td>
<td>23</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Overall Responders</td>
<td>22 (96%)</td>
<td>14 (88%)</td>
<td>18 (95%)</td>
</tr>
<tr>
<td>Major Responders (PR or better)</td>
<td>16 (70%)</td>
<td>12 (75%)</td>
<td>15 (80%)</td>
</tr>
<tr>
<td>Complete/Near Complete Responders</td>
<td>4 (17%)</td>
<td>2 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Median Change in sIgM (%)</td>
<td>-83.2%</td>
<td>-65.5%</td>
<td>-56.2%</td>
</tr>
<tr>
<td>Improvement in Hct (&gt;2%)</td>
<td>19 (83%)</td>
<td>11 (68%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>Time to Progression (months)</td>
<td>19</td>
<td>&gt;35</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>
Kaplan Meier Curve

Without Progression or Going on to Other Therapy (%)

Time from Treatment Initiation (Months)

- CHOP-R
- CVP-R
- CP-R
Inferior outcome associated with higher IgM levels in CHOP-R treated patients.

- CHOP-R cohort had a greater number of patients with elevated serum IgM $\geq$ 5,000 mg/dL;

- Overall and complete responses in CHOP-R patients with IgM $\geq$ 5,000 mg/dL (50%; 0%) were inferior to those patients with IgM < 5,000 mg/dL (91%; 36%); $p=0.06$;

- Time to progression was also shorter in patients with pre-therapy serum IgM levels $\geq$ 5,000 mg/dL versus patients <5000 mg/dL (11.1 vs. 17.8 months); $p=0.42$.

## Treatment Related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Neutropenic Fever</th>
<th>Hospitalization</th>
<th>Therapy Related Neuropathy</th>
<th>Hemorrhagic cystis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CP-R</strong></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>CVP-R</strong></td>
<td>12.5%</td>
<td>25%</td>
<td>68.8%(^b)</td>
<td>0%</td>
</tr>
<tr>
<td><strong>CHOP-R</strong></td>
<td>17%</td>
<td>13%</td>
<td>47.8%(^a)</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

\(^a\) p= not significant (NS) except as follows: (a) and (b) p= <0.001

Rituximab Related “IgM Flare”

<table>
<thead>
<tr>
<th></th>
<th>IgM Flare</th>
<th>Plasma-pheresis due to IgM Flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP-R</td>
<td>25%</td>
<td>16%</td>
</tr>
<tr>
<td>CVP-R</td>
<td>25%</td>
<td>12.5%</td>
</tr>
<tr>
<td>CHOP-R</td>
<td>27%</td>
<td>13.6%</td>
</tr>
</tbody>
</table>

*p= Not significant (NS)*

Summary

• The results of this study demonstrate comparable overall and major response rates among patients who received CHOP-R, CVP-R and CP-R;

• Neuropathy was significantly more pronounced in patients who received CHOP-R and CVP-R versus CP-R;

• The incidence of febrile neutropenia and hospitalizations was also higher in patients treated with CHOP-R and CVP-R versus CP-R;

• The addition of doxorubicin and/or vincristine did not prevent rituximab induced “IgM flare” and interventional plasmapheresis.
Summary

• The use of doxorubicin and vincristine sparing regimens such as CP-R or R-DC may represent reasonable treatment options to more intense cyclophosphamide based regimens while minimizing treatment related complications.

• Randomized studies to address the optimal cyclophosphamide based rituximab combinations are warranted.
Acknowledgements

Steven Treon, MD, PhD
Patricia Sheehy, NP
Christopher Patterson
Diane Warren
Zachary Hunter
Robert Manning
Christina Hanzis
Bryan Ciccarelli
Phil Brodsky
Lian Xu
Jenny Sun, MD
Guang Yang, MD
Yang Sheng Zhou, PhD
Hsuiyi Tseng
Ping Gong
Xia Liu, MD