Bendamustine and Bortezomib-Containing Regimens Produce Higher Response Rates and More Durable Responses Versus Cyclophosphamide-Based Therapy in Frontline Waldenstrom Macroglobulinemia

Jorge J. Castillo, Joshua N. Gustine, Kirsten Meid, Toni E. Dubeau, Patricia Severns, Steven P. Treon
Bing Center for Waldenstrom Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA, USA

Introduction
Waldenstrom macroglobulinemia (WM) is an incurable IgM-secreting lymphoplasmacytic lymphoma. Primary therapy for symptomatic WM patients often consists of combination therapy with an alkylating agent or proteasome inhibitor with rituximab. However, randomized studies comparing these treatment regimens are lacking in WM patients.

Methods
• We retrospectively searched our database for WM patients who received primary therapy with bendamustine-rituximab (Benda-R), bortezomib-dexamethasone-rituximab (BDR), or cyclophosphamide-dexamethasone-rituximab (CDR) between 2005 and 2016.
• Pertinent clinical data were collected.
• Response was assessed based on current criteria.
• Univariate and multivariate regression models were fitted to evaluate the association between clinical variables and response.
• Time to events was estimated using the Kaplan-Meier method.

Results (I)
Table. 1 Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Benda-R</th>
<th>BDR</th>
<th>CDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>36 (63%)</td>
<td>32 (37%)</td>
<td>19 (50%)</td>
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<tr>
<td>Male sex</td>
<td>35 (61%)</td>
<td>27 (31%)</td>
<td>20 (53%)</td>
</tr>
<tr>
<td>Hemoglobin &lt;11.5 g/dl</td>
<td>22 (40%)</td>
<td>17 (29%)</td>
<td>10 (26%)</td>
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<tr>
<td>Platelets &gt;100 K/ul</td>
<td>9 (16%)</td>
<td>8 (8%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>Serum B2A &gt;3 mg/l</td>
<td>39 (64%)</td>
<td>43 (49%)</td>
<td>16 (42%)</td>
</tr>
<tr>
<td>IgM &gt;4,000 mg/dl</td>
<td>21 (37%)</td>
<td>22 (31%)</td>
<td>15 (39%)</td>
</tr>
<tr>
<td>Marrow &gt;50%</td>
<td>33 (58%)</td>
<td>38 (45%)</td>
<td>17 (45%)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>25 (44%)</td>
<td>15 (17%)</td>
<td>14 (37%)</td>
</tr>
<tr>
<td>MYD88 L265P mutation</td>
<td>18 (32%)</td>
<td>6 (7%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>IPSSWM</td>
<td>17 (89%)</td>
<td>23 (68%)</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>CXCR4 mutations</td>
<td>10 (53%)</td>
<td>11 (42%)</td>
<td>7 (54%)</td>
</tr>
</tbody>
</table>

Best response
• Complete response | 11 (19%) | 9 (11%) | 2 (5%) |
• Very good PR | 14 (26%) | 20 (24%) | 14 (37%) |
• Partial response | 28 (49%) | 40 (48%) | 16 (42%) |
• Minor response | 2 (4%) | 6 (7%) | 2 (5%) |
• No response | 2 (4%) | 8 (10%) | 4 (11%) |
• Received maintenance | 35 (61%) | 55 (65%) | 26 (68%) |

Results (II)
Figure 1. PFS Benda-R, BDR, CDR

Log-rank p<0.001

Figure 2. PFS maintenance R

Log-rank p=0.06

Results (III)
Figure 3. OS Benda-R, BDR, CDR

Log-rank p=0.03

Figure 4. OS maintenance R

Log-rank p=0.10

Conclusions
• Primary therapy with Benda-R, BDR, and CDR produces high response rates and durable PFS in patients with WM.
• The risk of progression is lower in patients treated with Benda-R and BDR when compared to CDR.
• There is a trend towards a better OS in patients treated with BDR versus CDR.
• Maintenance rituximab is associated with both major and deep responses to therapy as well as superior PFS and OS.

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