Messages about Macroglobulinemia

Morie Gertz
HB = hemoglobin; PLT = primed lymphocyte testing; WBC = white blood cell; mg/dL = milligrams per deciliter; CP = centipoise; Fe = iron.

How common is WM?

- MGUS & Smoldering excluded
- The age-adjusted incidence rate for males was 0.92 per 100,000 person-years and for females was 0.30 per 100,000 person-years
- Prevalence of IgM MGUS at age 70 is 0.5%
How common is Smoldering WM?

• ~28% of WM patients in the US are smoldering at diagnosis

• The median age at diagnosis 71 years
How does MYD88 impact outcomes in WM?

- 174 MYD88m 17 smoldering; 45 MYD88wt 1 smoldering
- The number of patients treated with ibrutinib was very small
- \( MYD88^{L265P} \) mutation status does not impact OS, disease severity, or TTNT.
- Patients with \( MYD88^{WT} \) genotype, appear to have similar outcomes and largely overlapping clinical features in comparison to the \( MYD88^{L265P} \).
- A higher frequency of transformation to high-grade lymphoma, or the development of therapy-related myelodysplastic syndrome in the \( MYD88^{WT} \) cohort.
- \( MYD88 \) gene is a predictor for response in patients with WM that are treated with a BTK inhibitor-based regimen, it does not appear to be a disease-defining feature in WM.
Somatic Mutations in MYD88 and CXCR4:

<table>
<thead>
<tr>
<th></th>
<th>MYD88\textsuperscript{MUT} \n\textsuperscript{CXR4\textsuperscript{WT}} (50-60%)</th>
<th>MYD88\textsuperscript{MUT} \n\textsuperscript{CXR4\textsuperscript{MUT}} (30-40%)</th>
<th>MYD88\textsuperscript{WT} \n\textsuperscript{CXR4\textsuperscript{WT}} (5-10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow Involvement</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Serum IgM Levels</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Hyperviscosity</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Acquired VWD</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Risk of DLBCL</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

VWD = Von Willebrand disease; DLBCL = diffuse large B-cell lymphoma.
MYD88 mutation status does not impact rate of progression to symptomatic Waldenström macroglobulinemia
MYD88 mutation status does not impact overall survival in Waldenström macroglobulinemia

A

Surviving

100%
80%
60%
40%
20%
0%

MYD88

\text{L}^{265P}\text{ status known}

MYD88

\text{L}^{265P}\text{ status unknown}

MYD88

\text{L}^{265P}\text{ status known}

HR 1.05 (95% CI 0.7-1.5), p=0.75

Time in Years

B

Surviving

100%
80%
60%
40%
20%
0%

MYD88

\text{W}^{T}\text{ status known}

MYD88

\text{W}^{T}\text{ status unknown}

MYD88

\text{W}^{T}\text{ status known}

HR 0.86 (95% CI 0.46-1.5), p=0.62

Time in Years

C

Surviving

100%
80%
60%
40%
20%
0%

MYD88

\text{L}^{265P}\text{ status known}

MYD88

\text{L}^{265P}\text{ status unknown}

MYD88

\text{W}^{T}\text{ status known}

HR 0.81 (95% CI 0.4-1.5), p=0.54

Time in Years

MYD88 mutation status does not time to second treatment in Waldenström macroglobulinemia
MYD88 and transformation risk

• Of 1147 patients with WM, 50 patients (4.3%) transformed to a high-grade lymphoma, with a median time-to-transformation of 4.5 yrs from dx of WM.
• Transformation risk was higher in patients with MYD88WT status [odds ratio 6.1 ].
• MYD88WT status alone was an independent predictor of transformation.
• MYD88WT status was independently associated with shorter time-to-transformation, with a 5-year transformation rate of 16% for MYD88WT versus 2.8% with MYDL265P mutated patients [risk ratio 9.8]
How common is hyperviscosity and when is therapy required

- Patients with IgM levels above 6000 mg/dL who are otherwise asymptomatic can be safely observed.
- Serum viscosity can vary widely among patients with similar IgM levels.
- Serum viscosity, and not serum IgM level at the time of diagnosis of WM appears to be an independent predictor of the time to development of subsequent symptomatic hyperviscosity.
- Survival outcome of patients with WM appears to be unaffected by the development of symptomatic hyperviscosity.
Predictors of symptomatic hyperviscosity in Waldenström macroglobulinemia

Time to development of active disease in a cohort of smoldering WM patients with serum IgM > 6000 mg/dL at diagnosis.
WM and the kidney

- Kidney involvement is seen in 5% of WM patients.
- Most Common are related to amyloidosis 33% followed by cryoglobulinemia 28%.
- Patients present with protein in the urine, high blood pressure and fluid retention.
What are the kidney manifestations in patients with Waldenström Macroglobulinemia?

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>57 kidney biopsies in patients with Waldenström macroglobulinemia and other IgM secreting B-cell lymphoproliferative disorders</td>
<td><strong>83%</strong> Monoclonal gammopathy related kidney lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amyloid Glomerulopathy</th>
<th>Non-Amyloid Glomerulopathy</th>
<th>Tubulointerstitial lesions</th>
<th>Non-monoclonal gammopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waldenström macroglobulinemia n=19</td>
<td>17</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Monoclonal gammopathy of renal significance n=9</td>
<td>2</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Other n=6</td>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

**Conclusions** This study demonstrates a diverse variety of kidney lesions in patients with monoclonal IgM gammopathy.

Larissa Higgins et al. CJASN 2018;13:1037-1046
### Demographics and characteristics at kidney biopsy of cohort of patients with Waldenström macroglobulinemia and other IgM monoclonal gammopathy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Monoclonal Gammopathy–Related Kidney Diseases</th>
<th>Amyloid</th>
<th>Nonamyloid</th>
<th>Tubulointerstitial Nephritides</th>
<th>Nonmonoclonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>47</td>
<td>19</td>
<td>20</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Age (IQR), yr</td>
<td>63 (61–70)</td>
<td>64 (58–70)</td>
<td>63 (55–68)</td>
<td>64 (59–73)</td>
<td>63 (61–70)</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>31/18</td>
<td>14/5</td>
<td>12/8</td>
<td>5/3</td>
<td>8/2</td>
</tr>
<tr>
<td>Serum creatinine (IQR), mg/dl</td>
<td>1.8 (1.1–2.8)</td>
<td>1.8 (1–2.8)</td>
<td>1.4 (0.9–2.1)</td>
<td>2.3 (2–5.4)</td>
<td>2.1 (1.8–3.6)</td>
</tr>
<tr>
<td>eGFR (IQR), ml/min per 1.73 m²</td>
<td>35 (22–71)</td>
<td>41 (18–79)</td>
<td>42 (28–77)</td>
<td>25 (10–28)</td>
<td>30 (16–37)</td>
</tr>
<tr>
<td>Kidney impairment, %</td>
<td>67</td>
<td>63</td>
<td>58</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Advanced kidney failure, %</td>
<td>16</td>
<td>16</td>
<td>11</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>History of CKD, %</td>
<td>13</td>
<td>11</td>
<td>11</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Proteinuria (IQR), g/d</td>
<td>2.8 (1.1–8.0)</td>
<td>6.8 (2.4–12.4)</td>
<td>2.5 (0.8–3.6)</td>
<td>2.2 (0.2–4.6)</td>
<td>3.4 (1.8–17)</td>
</tr>
<tr>
<td>Nephrotic-range proteinuria, %</td>
<td>45</td>
<td>72</td>
<td>26</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Hematuria, %</td>
<td>49</td>
<td>53</td>
<td>62</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Median serum albumin (IQR), g/dl</td>
<td>3.2 (2.3–3.6)</td>
<td>2.6 (1.7–3.8)</td>
<td>3.3 (2.8–4.1)</td>
<td>3.4 (3.1–3.7)</td>
<td>3.2 (2.3–3.9)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>66</td>
<td>42</td>
<td>85</td>
<td>75</td>
<td>38</td>
</tr>
<tr>
<td>Edema, %</td>
<td>65</td>
<td>84</td>
<td>68</td>
<td>13</td>
<td>50</td>
</tr>
</tbody>
</table>
Chemotherapy treatment of WM

• In contrast to ibrutinib, the \( MYD88 \) mutation status does not appear to impact the activity of BR or DRC.

• A trend towards superior PFS was seen with the use of BR, without associated increased toxicity.
• Therapy-related MDS or transformation to high-grade lymphoma occurred in 5 (8%) patients at a median of 30 months (range 17–59) after BR and 5 (5%) patients at a median of 7 months (range 5–12) after DRC ($p = 0.5$). Of the patients who developed t-MDS or transformed to high-grade lymphoma, 4 patients in the BR group and 5 in the DRC group also received alkylating agents and/or nucleoside analogs.

• No patients with t-MDS progressed to AML.
Fig. 1
Best response rates from BR and DRC. CR complete response, VGPR very good partial response, PR partial response, MR minor response, SD stable disease, PD progressive disease.
How long responses last until new therapy is required
Strategies to Monitor and Manage Adverse Events Associated With Novel Therapies for WM

- Monitor IgM to detect IgM flare cycles 1&2
- Ekg monitoring for atrial fibrillation
- Track for onset of peripheral neuropathy
- CBC monitoring for myelosuppression requiring dose modification
- Inquire about rash, swelling, joint pain, bleeding, pneumonia
## Clinically Relevant Endpoints

<table>
<thead>
<tr>
<th></th>
<th>DRC</th>
<th>R-Benda</th>
<th>BDR</th>
<th>( p, ) DRC vs. R-Benda</th>
<th>( p, ) DRC vs. BDR</th>
<th>( p, ) BDR vs. R-Benda</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, (%)</strong> ( \epsilon )</td>
<td>76</td>
<td>95</td>
<td>81</td>
<td>0.002</td>
<td>0.57</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>MRR, (%)</strong> ( \epsilon )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYD88^L265P/MYD88^W^T (%)</td>
<td>46</td>
<td>93</td>
<td>63</td>
<td>&lt;0.00</td>
<td>0.12</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>45/20</td>
<td>93/100,</td>
<td>45/50,</td>
<td>p=0.27</td>
<td>p=0.46</td>
<td>p=0.86</td>
</tr>
<tr>
<td><strong>Event free survival, range; y^</strong>*</td>
<td>4.3 (3.0-6.8)</td>
<td>NR (4.1-NR)</td>
<td>2.1 (0.6-5.1)</td>
<td>0.003</td>
<td>0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Progression free survival, range; y^</strong>*</td>
<td>4.9 (3.0-7.6)</td>
<td>NR (4.1-NR)</td>
<td>4.5 (1.0-6.8)</td>
<td>0.004</td>
<td>0.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Time-to-next therapy, range; y^</strong>*</td>
<td>5.3 (3.3-7.7)</td>
<td>NR (4.5-NR)</td>
<td>4.5 (0.9-7.0)</td>
<td>0.007</td>
<td>0.07</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Time to best response, range; m^</strong>*</td>
<td>6.9 (4.6-8.1)</td>
<td>4.5 (3.8-5.3)</td>
<td>5.8 (4.6-8.5)</td>
<td>0.003</td>
<td>0.23</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Duration of response, range; y^</strong>*</td>
<td>5.1 (2.6-NR)</td>
<td>NR (4.5-NR)</td>
<td>4.1 (0.9-NR)</td>
<td>0.004</td>
<td>0.49</td>
<td>0.0006</td>
</tr>
<tr>
<td><strong>4 year OS %</strong> ( \epsilon )</td>
<td>87</td>
<td>88</td>
<td>88</td>
<td>0.76</td>
<td>0.97</td>
<td>0.92</td>
</tr>
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\( \epsilon \) Response data was available in 63 patients in the DRC arm, 58 patients in the R-Benda arm and 32 patients in the BDR arm.

* Variables were not different based on MYD88^L265P mutation status within the respective groups.
CONCLUSION

• ORR, MRR, TTNT and EFS with frontline R-Benda are superior in comparison to frontline DRC or BDR in patients with WM.
• OS was similar for the patients in the 3 groups.
• *MYD88*^{L265P} mutation did not affect outcomes with any of the three regimens.
• Toxicity profile across 3 groups was comparable barring higher neuropathy leading to premature treatment discontinuation in 15% patients receiving BDR.