Treatment Advances in Waldenstrom’s Macroglobulinemia

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6th International Workshop on Waldenström’s Macroglobulinemia
Venice, Italy • October 6-10, 2010
www.wmworkshop.org
Case Presentation

This 63 year old went for a routine physical exam and was found to have an elevated total protein. An IgM\(\lambda\) monoclonal spike was discovered, and his total serum IgM level was 4,010 mg/dL. Hematocrit was 37.9%. A bone marrow biopsy showed 30% involvement with LPC. He was diagnosed with WM and placed on watch and wait.

One year later his IgM is 4,820 mg/dL, hematocrit is 35.1%. He has more fatigue, nosebleeds, and is hearing “tree frogs”. He also is experiencing numbness and tingling in his feet. Exam shows “plump retinal vessels”. Neurological exam shows diminished sensation to touch over his soles. Fat pad biopsy with congo red staining is negative. Anti-MAG IgM antibody screen is positive with titer >102,400. He undergoes plasmapheresis and reports improvement in his neuropathy, and also states his “thinking” has improved.
Case Presentation

What is the most appropriate course of action for this patient?

1. Continue watch and wait
2. Gabapentin or Pre-Gabapentin for symptomatic relief
3. Continue with periodic plasmapheresis
4. Treat with rituximab alone
5. Treat with cyclophosphamide based rituximab therapy (CPR or RCD)
6. Treat with fludarabine or cladribine based rituximab therapy
7. Treat with bortezomib based rituximab therapy (BDR or VR)
8. Treat with bendamustine plus rituximab

Clinicopathological Manifestations of WM

- HCT, PLT, WBC
- Adenopathy, splenomegaly ≤15%
- Fatigue, Constitutional Sxs
- Cytokinemia?
- Hyperviscosity Syndrome: Epistaxis, HA, Impaired vision >4.0 CP
- IgM Neuropathy (~20%)
- Cryoglobulinemia (<5%)
- Cold Agglutinemia (<10%)

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Anemia in Waldenstrom’s macroglobulinemia

- Bone marrow replacement
- Hemodilution (high IgM levels)
- Hemolysis (cold agglutinin; warm antibody)
- Therapeutic injury (nucleoside analogue mediated hemolysis; MDS)
- Iron deficiency (Hepcidin)

Actions of Hepcidin

IL-6

\[ \text{increased iron accumulation} \rightarrow \text{macrophage} \]

\[ \text{hepcidin} \]

\[ \text{reduced iron absorption} \rightarrow \text{enterocyte} \]
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**Hepcidin vs. BM involvement and Anemia in WM**

Ciccarelli et al, ASH 2009.

**Ferrlicit improves Hematocrit in Oral Iron Refractory WM patients who display high hepcidin levels.**

Ciccarelli et al, ASH 2009.
Consensus Panel Recommendations for Initiation of Therapy in WM

- Hb ≤ 10 g/dL on basis of disease
- PLT < 100,000 mm³ on basis of disease
- Symptomatic hyperviscosity (> 4.0 cp)
- Moderate to severe peripheral neuropathy
- Symptomatic cryoglobulinemia, cold agglutinemia, amyloidosis, or symptomatic autoimmune related events on the basis of disease


First published report of response to rituximab in WM

Semin Oncol. 1999; 26:97-106.
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**Serum IgM Levels Following Rituximab in Patients With WM**

![Graph showing serum IgM levels following Rituximab in patients with WM.](image)

- P denotes patient-required plasmapheresis for hyperviscosity.

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**IL-6 blockade leads to inhibition of IgM release in Co-Culture Studies with WM cells and Rituximab Stimulated Monocytes.**

![Diagram illustrating IL-6 blockade affecting IgM release.](image)
Primary Therapy of WM with Rituximab Based Options

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab x 4</td>
<td>25-30%</td>
<td>0%</td>
</tr>
<tr>
<td>Rituximab x 8</td>
<td>40-45%</td>
<td>0%</td>
</tr>
<tr>
<td>Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, RCD</td>
<td>70-80%</td>
<td>8-10%</td>
</tr>
<tr>
<td>Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R</td>
<td>70-90%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Rituximab/thalidomide</td>
<td>70%</td>
<td>5%</td>
</tr>
<tr>
<td>Rituximab/bortezomib i.e. BDR, VR</td>
<td>70-90%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Rituximab/bendamustine</td>
<td>90%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Dexamethasone, Rituximab, Cyclophosphamide in WM

- N=72
- Dexamethasone 40 mg IV D1; Rituximab 375 mg/m² D1; Cyclophosphamide 100 mg/m² PO BID D1-5.
- ORR: 83% CR: 7%.
- Median PFS: 35 months; TTNT: 51 months.
- Short-term toxicities included:
  - Myelosuppression (9% G≥3 Neutropenia); PNA (1 death).
- Long-term hematological toxicities: DLBCL (1).

Dimopoulos et al, ASH 2008; Abstract 2887
**Fludarabine and Rituximab in WM**

- **N=43** (63% untreated).
- 6 cycles (25 mg/m² per day for 5 days) of fludarabine and 8 infusions (375 mg/m² per week) of rituximab.
- **ORR:** 95.3%; **CR/VGPR:** 37%
- Short-term toxicities included:
  - Myelosuppression (G≥3 neutropenia 62%).
  - PNA (6). Including 2 deaths due to non-PCP PNA.
- **Long-term toxicities:** *DLBCL (3)*; *MDS/AML (3).*

*Treon et al, Blood 2008; Updated IWWM6, 2010*
## Disease transformation following nucleoside analogues in WM

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N=</th>
<th>Median F/U (mo)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leleu et al, JCO 2009</td>
<td>Prev treated with NA vs. non-NA or untreated</td>
<td>439</td>
<td>60</td>
<td>Histological Transformation (5%) MDS/AML (2%)</td>
</tr>
<tr>
<td>Tamburini et al, Leukemia 2005</td>
<td>Firstline with Fludara/Cyclo</td>
<td>49</td>
<td>41</td>
<td>Histological Transformation (10%)</td>
</tr>
<tr>
<td>Leblond, JCO 1998</td>
<td>Previously treated with Fludara</td>
<td>71</td>
<td>34</td>
<td>Histological Transformation (10%)</td>
</tr>
<tr>
<td>Rakkhit et al, ASH 2008</td>
<td>Untreated; 2CDA based therapy</td>
<td>111</td>
<td>NA</td>
<td>Histological Transformation (9%)</td>
</tr>
</tbody>
</table>

## Thalidomide and Rituximab in WM

- **N=25**

- Thalidomide at 200 mg, increase to 400 mg and 8 infusions (375 mg/m² per week) of rituximab.

- **ORR: 72%; CR/VGPR: 4%**

- **Short-term toxicities included:**
  - Sensory neuropathy (11); resolved grade 1 or less: 10.
  - Confusion (3), tremors (2), bradycardia (2).

- **Dose reduction in all pts. 50-100 mg/day tolerated.**

*Blood 2008; 112:4452*
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Thalidomide and Rituximab in WM

- Median PFS: 41.9 months
- Median Follow-up: 40.4 months

Lenalidomide (Revlimid)-Induced Anemia in WM

- Decreased Hct observed in 10/12 pts following first week of lenalidomide monotherapy
- Median Hct decrease: 3.9% (31.9% to 28.0%; \( P = .003 \))
- No evidence for hemolysis; concurrent thrombocytopenia observed in 1 pt
- 4 patients hospitalized for anemia related complications (Afib, syncope, CHF)

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Bortezomib combination therapy in WM

- **Primary**
  - Bortezomib (1.3 mg/m²/biweekly)/Dexamethasone/Rituximab
    - ORR 95%; CR 22%; TTP >3 yrs; 30% Grade 3 PN
  - Bortezomib (1.6 mg/m²/wk)/Rituximab
    - ORR 92%; CR 8%; 80% 1 Y PFS; No Grade 3 PN

- **Salvage**
  - Bortezomib (1.6 mg/m²/wk)/Rituximab
    - ORR 81%; CR 5%; TTP 12 mos; 5% Grade 3 PN.
  - Bortezomib (randomized weekly vs. biweekly)/Rituximab
    - ORR 80%; CR 0%; TTP ?; 0% Grade 3 PN.

Treon et al, JCO 2009; Ghobrial et al, AJH 2010; Ghobrial et al, JCO 2010; Agathocleous et al, ASH 2007
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PFS: Benda-R vs CHOP-R in frontline WM

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Progression Free Survival (n=159)

<table>
<thead>
<tr>
<th>Response</th>
<th>Estimated PFS (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>&gt;90</td>
</tr>
<tr>
<td>VGPR</td>
<td>&gt;75</td>
</tr>
<tr>
<td>PR</td>
<td>42.6</td>
</tr>
<tr>
<td>MR</td>
<td>30.8</td>
</tr>
<tr>
<td>NR/SD</td>
<td>10.6</td>
</tr>
</tbody>
</table>

Proc ASCO 2010; 28: 15s; Updated IWM6, 2010

Treon et al, Clin Lymph Myeloma 2010
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FcγRIIIA-158 polymorphisms predict response in WM

Proc ASCO 2010; 28: 15s

PGx Health
www.clda.com

“Your polymorphism results are back”
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GA101 --- a Novel Third Generation Humanized Type II CD20 Monoclonal Antibody

- Rituximab
- Ofatumumab (Arzerra®)
  a second generation fully humanized antibody approved by FDA for CLL therapy in 2009

Glycoengineered Fc domain
  Enhanced ADCC effect

modified elbow hinge
  - Apoptosis induction

In vitro ADCC efficacy for GA101 vs. Rituximab with primary BM WM patient cells using autologous NK cells.

Yang et al, ASCO 2010
To Maintain or Not to Maintain?

PFS in rituximab naïve WM patients who underwent observation or maintenance rituximab therapy.

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Maintenance</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated (Median PFS)</td>
<td>29.6 months</td>
<td>54.6 months</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prev Treated (Median PFS)</td>
<td>25.8 months</td>
<td>56.7 months</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
RAD001 in Relapsed/Refractory WM

- N = 50 (DFCI and Mayo)
- 10 mg QD
  - Reduce to 5 mg for AE
- Median prior therapies: 3
- Median IgM: 3330 mg/dL
- ORR: 72%
- Median response:
  - NR (3-22+ mos)
- Grade >3 thrombocytopenia, pneumonitis, mucositis, and hyperglycemia.

Ghobrial et al, JCO 2010

RAD001 for Primary Therapy of WM

- N = 60
- Eligibility: symptomatic, untreated WM
- Dose: 10 mg QD
  - Reduction to 7.5, 5.0 mg for AE
- Duration: 4 yrs to progression
- Primary endpoints: safety, ORR, and 2- and 4-yr PFS
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**IgM changes following RAD001 in untreated WM patients.**

![Graph showing IgM changes](image)

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**IgM Related Neuropathies in WM**

- Observed in about 20% of WM patients
- IgM can often be found to react with specific neural antigens; these autoantibodies define very specific clinical syndromes.
  - Myelin Associated Glycoprotein (MAG)
  - Ganglioside M1 (GM1)
  - Sulfatide

Courtesy Todd Levine, MD
Clinical characteristics of paraprotein related PN in WM.

- 900 consecutive WM Pts; Pts with treatment and non-disease related PN excluded.
- 199 (22.1%) had disease related PN.

122 had NP Ab testing
24.5% MAG+
1.6% GM1+
0.8% Sulfatide+

61 had FP or BM Congo Red Stain
21.3% +
Only 1 pt also MAG+


Symptomatic Improvement following Therapy: Subset Analysis

Treon et al, ASCO 2010.
### Treatment Outcome of WM related PN.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=</th>
<th>Overall RR</th>
<th>Major RR</th>
<th>Improved PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral alkylator</td>
<td>21</td>
<td>33.3%</td>
<td>19.0%</td>
<td>19.0%</td>
</tr>
<tr>
<td>Nucleoside analogue</td>
<td>11</td>
<td>45.5%</td>
<td>36.4%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>57</td>
<td>59.6%</td>
<td>35.1%</td>
<td>42.1%</td>
</tr>
<tr>
<td>Rituximab/nucleoside analogue</td>
<td>26</td>
<td>50.0%</td>
<td>46.0%</td>
<td>54.0%</td>
</tr>
<tr>
<td>Rituximab/cyclophosphamide</td>
<td>18</td>
<td>83.3%</td>
<td>50.0%</td>
<td>55.6%</td>
</tr>
<tr>
<td>Rituximab/thalidomide</td>
<td>7</td>
<td>71.4%</td>
<td>71.4%</td>
<td>71.4%</td>
</tr>
<tr>
<td>Rituximab/bortezomib</td>
<td>8</td>
<td>75%</td>
<td>50.0%</td>
<td>75.0%</td>
</tr>
</tbody>
</table>

Treon et al, ASCO, 2010.

### Treatment Score Card

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the patient a candidate for ASCT?</td>
<td>✔️</td>
</tr>
<tr>
<td>Is an immediate response needed?</td>
<td>✔️</td>
</tr>
<tr>
<td>Does the treatment meet the goals of therapy?</td>
<td>✔️</td>
</tr>
<tr>
<td>Is the patient able to tolerate myelosuppressive therapy?</td>
<td>✔️</td>
</tr>
<tr>
<td>Are potential side effects prohibitive for the patient?</td>
<td>✔️</td>
</tr>
<tr>
<td>Are long term treatment risks reasonable?</td>
<td>✔️</td>
</tr>
<tr>
<td>Is treatment covered by insurance?</td>
<td>✔️</td>
</tr>
</tbody>
</table>
Summary

- Watch and wait is appropriate for asymptomatic patients.
- Bendamustine, Bortezomib Cyclophosphamide, and Thalidomide based rituximab therapies are active and can be considered in the upfront treatment of WM.
- Use of nucleoside analogues should be carefully considered due to potential long-term consequences.
- Better categorical responses are associated with improved PFS in rituximab naïve WM patients receiving rituximab based therapy, and may reflect underlying FcγRIIIA-158 polymorphisms.
- Patients with IgM related PN benefit with earlier treatment with rituximab combination therapy.