HOW I TREAT WALDENSTRÖM MACROGLOBULINEMIA IN THE ERA OF NOVEL THERAPEUTICS

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Outline

- Case presentation
- Diagnosis
- Treatment for newly diagnosed WM
- Biology and targeted therapy
- Summary
Case presentation

- 59 year-old man with elevated total protein of 10.9 g/dL
  - Hgb: 9.2 g/dL Hct 28% (MCV 91)
  - Creatinine: 1.39
  - SPEP/immunofixation: 4.1 g/dL IgM kappa monoclonal protein
- Past Medical History: HTN, CVA, CKD stage 2
- Social History: no tobacco, EtOH, occasional cannabis
- Family History: negative
# Review of Systems

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Implication/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Anemia</td>
</tr>
<tr>
<td>Headache, blurry vision, confusion</td>
<td>Hyperviscosity</td>
</tr>
<tr>
<td>Easy bruising, bleeding gums, epistaxis</td>
<td>Thrombocytopenia, platelet dysfunction</td>
</tr>
<tr>
<td>Acrocyanosis</td>
<td>Cryoglobulinemia, cold agglutinemia</td>
</tr>
<tr>
<td>Numbness, tingling</td>
<td>IgM-related neuropathy</td>
</tr>
</tbody>
</table>

Case presentation

- Physical Examination: unremarkable
- Referred to ophthalmology: normal retinal exam
- Serum viscosity: 3.4 CP & B2-microglobulin: 2 mcg/mL

Hyperviscosity related retinal changes in WM

“Sausaging”

Courtesy of Dr. Dan Sabath
Bone marrow examination

- **Flow cytometry**
  - B cell: CD19+ CD20+ CD45+ CD38+ surface kappa light chain restriction CD5- CD10-
  - Plasmacytic: CD19+ CD45+ CD38+ CD138+ cytoplasmic kappa light chain restriction

- **IFISH**
  - del 1p32, gain/amplification 1q21, t(4;14), t(14;16), del 13q, del 17p13

- **MYD88 not tested** as all material was used
Lymphoplasmacytic lymphoma AND any serum IgM level

No relationship between IgM level and BM involvement

Treatment Options for Newly Diagnosed WM
### Indications for treatment

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional symptoms (fever, night sweats, weight loss, fatigue)</td>
</tr>
<tr>
<td>Symptomatic lymphadenopathy or splenomegaly</td>
</tr>
<tr>
<td>Hemoglobin $\leq 10$ g/dL</td>
</tr>
<tr>
<td>Platelet count $&lt;100 \times 10^9$/L</td>
</tr>
<tr>
<td>Hyperviscosity syndrome</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Amyloidosis related to WM</td>
</tr>
<tr>
<td>Cold agglutinin anemia</td>
</tr>
<tr>
<td>Symptomatic cryoglobulinemia</td>
</tr>
</tbody>
</table>

Considerations for treatment

- Rapid disease control
- Autologous stem cell transplantation
- IgM level
- Neuropathy
Frontline Treatment Approach

WM Diagnosis → Asymptomatic → Observation q2-3 months, Year 1 q3-6 months >Year 1, if stable.

WM Diagnosis → Symptomatic → ASCT Eligible

- Avoid oral alkylators
- Avoid nucleoside analogues

Immediate Disease Control Required → Immediate Disease Control Required → Plasmapheresis for symptomatic HV, severe cryoglobulinemia or CAGG¹,
Then 1st choice: IB² or BDR³,⁴
Alternate: Benda-R⁴ or CDR⁴

Immediate Disease Control Not Required → Immediate Disease Control Not Required → 1st choice: IB² or BDR³,⁴
Alternate: Benda-R⁴, CDR⁴, FR⁴

ASCT Ineligible → Immediate Disease Control Required

- Immediate Disease Control Required

- Immediate Disease Control Not Required

Plasmapheresis for symptomatic HV, severe cryoglobulinemia or CAGG¹,
then 1st choice: IB² or BDR³,⁴
Alternate: Benda-R⁴, CDR⁴, FR⁴

CAGG = cold agglutinemia
IB = ibrutinib

## Primary therapy with rituximab

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR</th>
<th>VGPR/CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab only</td>
<td>25-45%</td>
<td>0-10%</td>
</tr>
<tr>
<td>Rituximab/cyclophosphamide</td>
<td>70-80%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Rituximab/nucleoside analogues</td>
<td>70-90%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Rituximab/proteosome inhibitor</td>
<td>70-90%</td>
<td>20-40%</td>
</tr>
<tr>
<td>Rituximab/bendamustine</td>
<td>90%</td>
<td>30-40%</td>
</tr>
</tbody>
</table>

**European Myeloma Network: Bortezomib, Dexamethasone and Rituximab**

<table>
<thead>
<tr>
<th><strong>N</strong></th>
<th><strong>59</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>85%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>10%</td>
</tr>
<tr>
<td>Median time to response</td>
<td>3 months</td>
</tr>
<tr>
<td>Median PFS after 32 months</td>
<td>42 months</td>
</tr>
<tr>
<td>Peripheral neuropathy (grade ≥2)</td>
<td>32%</td>
</tr>
</tbody>
</table>

### Phase II Study of Cyclophosphamide, Dexamethasone and Rituximab

<table>
<thead>
<tr>
<th>N</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR 7% PR 67%)</td>
<td>83%</td>
</tr>
<tr>
<td>Median time to response</td>
<td>4.1 months</td>
</tr>
<tr>
<td>2-year PFS (all patients)</td>
<td>67%</td>
</tr>
<tr>
<td>2-year PFS (responders)</td>
<td>80%</td>
</tr>
<tr>
<td>Grade 3-4 neutropenia</td>
<td>9%</td>
</tr>
</tbody>
</table>

![Graph A](image1.png)

![Graph B](image2.png)

Bendamustine-R vs. CHOP-R: Subgroup Analysis

Progression-free survival in WM patients

IgM flare

- >25% increase in serum IgM
- Cut off is 4 g/dL
- May potentiate symptomatic hyperviscosity, cryoglobulinemia and cold agglutinemia

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>40-60%</td>
</tr>
<tr>
<td>Rituximab/Cyclophosphamide</td>
<td>30-40%</td>
</tr>
<tr>
<td>Rituximab/Proteosome inhibitors</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

IgM flare

Avoid rituximab until IgM is <4 g/dL either by plasmapheresis or chemotherapy without rituximab
IgM flare with rituximab: an ECOG study

- Can persist for up to 4 months
- Not indicative of treatment failure
- No difference in progression-free and overall survival

Biology and targeted treatment
MYD88<sup>L265P</sup> Somatic Mutation

- Found in >90% of WM
- Activates NFkB

Other MYD88 mutations

Ibrutinib in previously treated Waldenström macroglobulinemia

<table>
<thead>
<tr>
<th>N</th>
<th>63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of treatment</td>
<td>2 (range 1-9)</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>91%</td>
</tr>
<tr>
<td>Major response rate (≥PR)</td>
<td>73%</td>
</tr>
<tr>
<td>Median time to response</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Progression-free and overall survival for 63 previously treated WM patients with ibrutinib

2 year PFS = 69%

2 year OS = 95%

FDA expands approved use of Imbruvica for rare form of non-Hodgkin lymphoma
First drug approved to treat Waldenström
January 29, 2015

CXCR4 mutation in WM

- Similar to WHIM syndrome
  (Warts, Hypogammaglobulinemia, Infections and bone marrow Myelokathexis)

- 30-40% of WM patients

- Almost always occur with MYD88L265P

## MYD88 and CXCR4 mutations and response to Ibrutinib

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>Mutated MYD88 and Wild-type CXCR4 (N=36)</th>
<th>Mutated MYD88 and CXCR4 (N=21)</th>
<th>Wild-type MYD88 and CXCR4 (N=5)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>100%</td>
<td>85.6%</td>
<td>60%</td>
<td>0.005</td>
</tr>
<tr>
<td>Major</td>
<td>91.7%</td>
<td>61.9%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Blocking CXCR4

- Combined with ibrutinib
- Anti-CXCR4 antibody or CXCR4 receptor inhibitor
- Other therapies: BCL-2 inhibitor, PI3-kinase\textsubscript{\textdelta} inhibitor, IRAK1 inhibitor
Rituximab-based regimens are the mainstay of treatment.

Rituximab may induce IgM flare but does not indicate treatment failure.

Ibrutinib is FDA-approved for initial and second-line treatment for WM.

MYD88 and CXCR4 mutations are present in >90% and 30-40% of WM patients & impact response to ibrutinib.

Inhibitors for MYD88 and CXCR4 represent novel treatment strategies in WM.
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