Frontline treatment options in Waldenström Macroglobulinemia

Jorge J. Castillo, MD
Assistant Professor of Medicine
Harvard Medical School
Disclosures

Consulting
• Otsuka Pharmaceuticals
• Biogen IDEC
• Alexion Pharmaceuticals

Research Funding
• Millennium Pharmaceuticals
• Gilead Sciences
• Pharmacyclics Inc.
• Abbvie Inc.
Waldenström’s Macroglobulinemia – first described by Jan Gosta Waldenström in 1944.
Lymphoplasmacytic Lymphoma

- **Cellular Morphology:** lymphocytes, lymphoplasmacytic cells, plasma cells
- **BM Pattern:** interstitial with diffuse or nodular infiltrates with excess mast cells associated with lymphoid aggregates.
- **LN/SP:** diffuse pattern
Manifestations of WM Disease

↓HCT, ↓PLT, ↓WBC

Adenopathy, splenomegaly ≤20% (at Dx)

Hyperviscosity Syndrome:
Nosebleeds, headache, Impaired vision >4.0 CP

IgM Neuropathy (22%)
Cryoglobulinemia (10%)
Cold Agglutininemia (5%)

Hepcidin ↓Fe Anemia

Treon, Hematol Oncol 2013
NCCN Guidelines for Initiation of Therapy in WM

- Hb $\leq 10\text{ g/dL}$ on basis of disease
- PLT $< 100,000\text{ mm}^3$ on basis of disease
- Symptomatic hyperviscosity
- Moderate/severe peripheral neuropathy
- Symptomatic lymphadenopathy or hepatosplenomegaly
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloidosis.

Kyle, Semin Oncol 2003
Anderson, JNCCN 2016.
Rituximab

Characteristics

- Anti-CD20 monoclonal antibody
- CD20 is expressed in all B-cells, normal and malignant
- Activates the immune system to kill cancer cells
- Accumulates in the body

Treon et al (2001)

- N=30, retrospective study
- 1-11 infusions; single agent
- IgM went from 2400 to 1500 mg/dl
- Bone marrow involvement went from 60% to 15%
- 60% response rate

Treon J Immunother 2001
Rituximab

• N=17; prospective
• 4 weekly doses; repeat at 3 months
• 40% response rate
• Time to response was 3 months
• Time to progression was 16 months

Treon et al (2005)
• N=29; prospective
• 4 weekly doses; repeat at 3 months
• 65% response rate
• Time to best response was 17 months

Dimopoulos Clin Lymphoma 2002
Treon Ann Oncol 2005
Rituximab

**Adverse events**
- Infusions reactions
- Increased risk of infections
- Low blood counts
- Hepatitis B reactivation

**Disadvantages**
- Delayed responses
- IgM flare
  - 40% of patients
  - Avoid Rituximab until IgM in “safe range”
- Rituximab Intolerance
  - 7% of patients
  - Consider Ofatumumab

Treon Ann Oncol 2004
Castillo Br J Haematol 2016
Cyclophosphamide-Based Therapy

Greek experience
- N=72; untreated
- Cyclophosphamide/Dexamethasone/Rituximab
- ORR 83%
- CR 7%
- Median PFS 3 years

A German study
- N=64; untreated
- R-CHOP (n=34) vs. CHOP (n=30)
- Response: R-CHOP 94%; CHOP 67%
- Time to failure: R-CHOP 63 months; CHOP 22 months

Dimopoulos J Clin Oncol 2007
Kastritis Blood 2015

Buske Leukemia 2009
Cyclophosphamide-Based Therapy

Disadvantages

• Hair loss
• Low blood counts
• Nausea and vomiting
• Increased risk of infections
• Secondary leukemia ~1%
Proteasome inhibitor-based therapy

Mechanism of action

- Targets the proteasome, among others
- Proteasome is the garbage disposal of the malignant cell
- “Trash” accumulates in the cell and forces it to die

Chen et al (2007)

- N=27
- Bortezomib: IV twice weekly
- ORR: 70%
- CR: 0%
- Nodal response lagging
- Time to response: 2 cycles

Chen J Clin Oncol 2007
Proteasome inhibitor-based therapy

Treon et al (2009)
- BDR; N=25
- Bortezomib: IV twice weekly
- ORR 96%
- CR 12%
- Time to progression: 66 months

Dimopoulos (2015)
- N=59
- Bortezomib: IV weekly
- First cycle without rituximab
- ORR: 85%
- CR: 3%
- Progression-free survival 42 months

Treon, JCO 2009
Treon, ASH 2015
Dimopoulos, Blood 2013
Disadvantages

- Peripheral neuropathy
  - Less when given weekly or SC instead of IV
- Low platelet counts
- Steroids
- Zoster prophylaxis
  - Acyclovir or valacyclovir
Proteasome inhibitor-based therapy

Carfilzomib

- CARD; N=31
- Intravenous twice weekly
- ORR 87%
- CR 3%
- Less neuropathy (<5%)
- Responses less durable in patients with lymphadenopathy

Disadvantages

- Increases glucose and cholesterol
- Hypogammaglobulinemia
- Heart problems: HTN, CAD
- Steroids
- Zoster prophylaxis

Treon, Blood 2014
Bendamustine and rituximab

Another German study

• Bendamustine-R (N=22) vs. CHOP-R (N=19)
• Good option for patients with lymphadenopathy or enlarged liver/spleen
• ORR 80%
• Progression-free survival 69 months

Rummel, Lancet 2013
Disadvantages

• Potential stem cell toxicity
• Low blood counts
• Infusion reactions
• 1/200 chances of secondary leukemia
To Maintain or Not to Maintain?

Maintenance in progress
Sorry for the inconvenience

ThyssenKrupp Escalator
Observation vs. maintenance rituximab therapy in rituximab-naïve patients treated with rituximab regimen.

**PFS**

- **Alive or without progression (%)**
  - Time from treatment initiation (months)
  - Rituximab Maintenance
  - No Rituximab Maintenance

**OS**

- **Alive (%)**
  - Time from treatment initiation (months)
  - Rituximab Maintenance
  - No Rituximab Maintenance

**Problems:**
- Infusion reactions, increased risk of infections, hypogammaglobulinemia.

Treon Br J Haematol 2011
New Directions in WM
MYD88 L265P Somatic Mutation

- 91% of WM pts
- 10% IGM MGUS
- No difference sporadic vs. familial pts

Treon, NEJM 2012
## MYD88 L265P in WM/IGM MGUS

<table>
<thead>
<tr>
<th>Method</th>
<th>Tissue</th>
<th>WM</th>
<th>IGM MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>WGS/Sanger</td>
<td>BM CD19⁺</td>
<td>91%</td>
<td>10%</td>
</tr>
<tr>
<td>AS-PCR</td>
<td>BM CD19⁺</td>
<td>93%</td>
<td>54%</td>
</tr>
<tr>
<td>PCR</td>
<td>BM</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>AS-PCR</td>
<td>BM</td>
<td>100%</td>
<td>47%</td>
</tr>
<tr>
<td>Sanger</td>
<td>BM</td>
<td>100%</td>
<td>54%</td>
</tr>
<tr>
<td>AS-PCR</td>
<td>BM</td>
<td>86%</td>
<td>87%</td>
</tr>
<tr>
<td>PCR</td>
<td>BM CD19⁺</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>PCR-RFLP</td>
<td>BM</td>
<td>92%</td>
<td>1/1 MGUS</td>
</tr>
<tr>
<td>Sanger</td>
<td>BM</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>AS-PCR/BSiE1</td>
<td>BM</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>AS-PCR</td>
<td>BM</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>WES/AS-PCR</td>
<td>BM</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>AS-PCR</td>
<td>BM</td>
<td>85%</td>
<td></td>
</tr>
</tbody>
</table>
MYD88 L265P
Signal Pathway

Yang et al, Blood 2013

TNFAIP3
HIVEP2

SURVIVAL
Ibrutinib in Previously Treated Waldenström’s Macroglobulinemia

Serial Serum IgM Levels Following Ibrutinib

Best IgM Response: 3,610 to 915 mg/dL; p<0.0001

Median of 12 (range 1-21) Cycles
N=63

Median time to MR=4 weeks
Serial Hemoglobin Levels Following Ibrutinib

Best Hemoglobin Response: 10.5 to 13.5; p<0.0001

Median of 12 (range 1-21) Cycles

N=63
Bone Marrow Disease Burden following Ibrutinib

At Best Response 60% to 30%; p< 0.001
Ibrutinib Related Adverse Events

Early
- Anemia
- Neutropenia
- Thrombocytopenia
- Rash
- Nausea
- Diarrhea
- Arthralgias

Delayed
- Increased risk of bleeding
- Atrial fibrillation
- Hypertension
WHIM-like CXCR4 C-tail mutations in WM
Warts, Hypogammaglobulinemia, Infection, and Myelokathexis.

Most common: CXCR4<sup>C1013G</sup> (S338X)

Somatic WHIM-CXCR4 Mutations were detected in 21/63 patients (34%) on ibrutinib study.

Hunter Blood 2014
**MYD88 and CXCR4 mutation status and Responses to Ibrutinib**

<table>
<thead>
<tr>
<th></th>
<th>MYD88&lt;sup&gt;L265P&lt;/sup&gt;</th>
<th>MYD88&lt;sup&gt;L265P&lt;/sup&gt;</th>
<th>MYD88&lt;sup&gt;WT&lt;/sup&gt;</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXCR4&lt;sup&gt;WT&lt;/sup&gt;</td>
<td>CXCR4&lt;sup&gt;WHIM&lt;/sup&gt;</td>
<td>CXCR4&lt;sup&gt;WT&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>N=</td>
<td>34</td>
<td>21</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Overall RR</td>
<td>100%</td>
<td>80.9%</td>
<td>57.1%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Major RR</td>
<td>88.2%</td>
<td>57.1%</td>
<td>28.6%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Treon NEJM 2015
<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Overall response rate</th>
<th>Major response rate</th>
<th>Time to response</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>29</td>
<td>66%*</td>
<td>48% (untreated and treated)</td>
<td>3-6 months</td>
<td>14 months</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>27</td>
<td>85%*</td>
<td>48% (treated)</td>
<td>1.4 months</td>
<td>8 months</td>
</tr>
<tr>
<td>CDR</td>
<td>72</td>
<td>83%</td>
<td>74% (untreated)</td>
<td>4 months</td>
<td>35 months</td>
</tr>
<tr>
<td>BDR twice weekly</td>
<td>23</td>
<td>96%</td>
<td>83% (untreated)</td>
<td>1.4 months</td>
<td>66 months</td>
</tr>
<tr>
<td>BDR once weekly</td>
<td>38</td>
<td>85%</td>
<td>68% (untreated)</td>
<td>Not reported</td>
<td>42 months</td>
</tr>
<tr>
<td>Bendamustine/rituximab</td>
<td>22</td>
<td>Not reported</td>
<td>Not reported (untreated)</td>
<td>Not reported</td>
<td>69 months</td>
</tr>
<tr>
<td>CARD</td>
<td>31</td>
<td>87%</td>
<td>68% (untreated)</td>
<td>2.1 months</td>
<td>Not reached at 36 months</td>
</tr>
</tbody>
</table>

Selected studies in untreated patients with Waldenstrom macroglobulinemia
Frontline clinical trials at DFCI

IDR
- Ixazomib, dexamethasone, rituximab
- N=26/26 enrolled
- Minimal toxicity
- Data to be presented at ASH 2016

Ibrutinib
- N=10/30 enrolled
- WGS in all patients on a yearly basis
- MYD88 +/- CXCR4
Novel pathways: novel agents

- Oral proteasome inhibitors – ixazomib, marizomib
- BTK inhibitors – acalabrutinib, BGB-3111
- PI3K-delta – idelalisib, TG-1202
- BCL2 antagonism – venetoclax
- Anti-CD38 therapy - daratumumab
- Anti-CXCR4 therapy – ulocuplomab
- TLR inhibitor – IMO8400
- IRAK1/4 inhibitor
- MYD88 binding inhibitor
Summary

- There are multiple effective options for the frontline treatment of Waldenstrom Macroglobulinemia.
- Rituximab can be used as a single agent.
- Bendamustine, bortezomib, carfilzomib and cyclophosphamide are highly effective when combined with rituximab.
- Exciting clinical trials with oral agents are ongoing.
- Future treatments are likely to be less toxic and more effective.
Frontline treatment options in Waldenström Macroglobulinemia

Jorge J. Castillo, MD
Assistant Professor of Medicine
Harvard Medical School