Frontline treatment options in Waldenström Macroglobulinemia

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• Biogen IDEC
• Alexion Pharmaceuticals

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• 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

- 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

↓HCT, ↓PLT, ↓WBC

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

- Hemoglobin $\leq 10$ g/dL on basis of disease
- Platelets $< 100,000$ mm$^3$ on basis of disease
- Symptomatic hyperviscosity
- Moderate/severe peripheral neuropathy
- Symptomatic lymphadenopathy or hepatosplenomegaly
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloidosis
- Symptomatic extramedullary disease (kidney, lungs, central nervous system, etc.)

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
Hot off the press!

Olszewski Oncologist 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

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>• BDR; N=25</td>
<td>• N=59</td>
</tr>
<tr>
<td>• Bortezomib: IV twice weekly</td>
<td>• Bortezomib: IV weekly</td>
</tr>
<tr>
<td>• ORR 96%</td>
<td>• First cycle without rituximab</td>
</tr>
<tr>
<td>• CR 12%</td>
<td>• ORR: 85%</td>
</tr>
<tr>
<td>• Progression-free survival 66 months</td>
<td>• CR: 3%</td>
</tr>
<tr>
<td></td>
<td>• Progression-free survival 42 months</td>
</tr>
</tbody>
</table>

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.

Problems:
Infusion reactions, increased risk of infections, hypogammaglobulinemia.
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></th>
<th>METHOD</th>
<th>TISSUE</th>
<th>WM</th>
<th>IGM MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treon</td>
<td>WGS/Sanger</td>
<td>BM CD19⁺</td>
<td>91%</td>
<td>10%</td>
</tr>
<tr>
<td>Xu</td>
<td>AS-PCR</td>
<td>BM CD19⁺</td>
<td>93%</td>
<td>54%</td>
</tr>
<tr>
<td>Gachard</td>
<td>PCR</td>
<td>BM</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>Varettoni</td>
<td>AS-PCR</td>
<td>BM</td>
<td>100%</td>
<td>47%</td>
</tr>
<tr>
<td>Landgren</td>
<td>Sanger</td>
<td>BM</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Jiminez</td>
<td>AS-PCR</td>
<td>BM</td>
<td>86%</td>
<td>87%</td>
</tr>
<tr>
<td>Poulain</td>
<td>PCR</td>
<td>BM CD19⁺</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Argentou</td>
<td>PCR-RFLP</td>
<td>BM</td>
<td>92%</td>
<td>1/1 MGUS</td>
</tr>
<tr>
<td>Willenbacher</td>
<td>Sanger</td>
<td>BM</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>Mori</td>
<td>AS-PCR/BSiE1</td>
<td>BM</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Ondrejka</td>
<td>AS-PCR</td>
<td>BM</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Ansell</td>
<td>WES/AS-PCR</td>
<td>BM</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Patkar</td>
<td>AS-PCR</td>
<td>BM</td>
<td>85%</td>
<td></td>
</tr>
</tbody>
</table>
MYD88 L265P Signal Pathway

Yang et al, Blood 2013
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

Hemoglobin (g/dL)

Median of 12 (range 1-21) Cycles

N=63
Bone Marrow Disease Burden following Ibrutinib

At Best Response 60% to 30%; p< 0.001
WHIM-like CXCR4 C-tail mutations in WM

Warts, Hypogammaglobulinemia, Infection, and Myelokathexis.

Most common: CXCR4$^{C1013G}$ (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; CXCR4&lt;sup&gt;WT&lt;/sup&gt;</th>
<th>MYD88&lt;sup&gt;L265P&lt;/sup&gt; CXCR4&lt;sup&gt;WHIM&lt;/sup&gt;</th>
<th>MYD88&lt;sup&gt;WT&lt;/sup&gt; CXCR4&lt;sup&gt;WT&lt;/sup&gt;</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<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
## Selected studies in untreated patients with Waldenstrom macroglobulinemia

<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>

Castillo Ther Adv Hematol 2016
Frontline clinical trials at DFCI

Ixazomib, dexamethasone, rituximab
- N=26/26 enrolled
- 20 have completed induction treatment
- Minimal toxicity
- Overall response 80%
- Major response 50%

Ibrutinib
- N=18/30 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 assembly 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

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