My WM is Back:

Treatment Options for Relapsed Waldenström macroglobulinemia

Sheeba Thomas, MD
<table>
<thead>
<tr>
<th>History</th>
<th>Other Diseases/Signs</th>
<th>Other Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt; 101 F</td>
<td>Amyloidosis</td>
<td>Hemoglobin ≤ 10g/dL</td>
</tr>
<tr>
<td>Drenching Night Sweats</td>
<td>Transformation</td>
<td>Platelets &lt; 100 x 10⁹/L due to WM</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>Kidney Impairment</td>
<td>Bulky lymph nodes/liver/spleen</td>
</tr>
<tr>
<td>Severe Neuropathy</td>
<td>Cryoglobulinemia</td>
<td>Hyperviscosity with signs (&gt;4 cp)</td>
</tr>
<tr>
<td>Severe Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>Monoclonal Protein</td>
<td></td>
</tr>
<tr>
<td>Fundoscopic exam</td>
<td>IgM by Densitometry</td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>- No Certain Level</td>
<td></td>
</tr>
<tr>
<td>Organomegaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kyle, Semin Oncol, 2003
Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

Conventional Chemotherapy
- Cyclophosphamide
- Bendamustine
- Fludarabine
- Cladribine
- Stem Cell Transplant
- Autologous SCT
- Allogeneic SCT

Monoclonal Antibodies
- Rituximab
- Ofatumumab
- Alemtuzumab
- BTK inhibitor
- Ibrutinib
- mTOR inhibitor
- Everolimus

Proteasome inhibitors
- Bortezomib
- Carfilzomib

Immunomodulators
- Thalidomide
- Lenalidomide
- ? Pomalidomide

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Treatment Decision Considerations

- **Disease related**
  - Slow vs. rapid progression
  - Neuropathy
  - Cranial nerve involvement

- **Patient related**
  - Performance status
  - Kidney/Liver function
  - Blood counts
  - Other medical conditions
  - Convenience/Practical considerations

- **Treatment related**
  - Length of response to prior therapy (>12 months)
  - Prior drug exposure (relapsed/progressive disease on therapy)
  - Ongoing side effects from prior therapy
Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

Monoclonal Antibodies
- Rituximab
- Ofatumumab
Rituximab: Backbone of Treatment

Multicenter Phase 2 Trial of Rituximab for Waldenström Macroglobulinemia (WM): An Eastern Cooperative Oncology Group Study (E3A98)

- N = 35 previously treated patients (none with prior rituximab)
- Regimen: Weekly rituximab x 4 doses
- Partial Response rate = 20%

Impact of Rituximab on the Treatment of Waldenström’s Macroglobulinemia


Department of Lymphoma/Myeloma, The University of Texas M. D. Anderson Cancer Center

Overall Survival

![Graph showing overall survival rates with Rituximab and various treatment combinations.]

- B + Rituximab (44)
- NA +/- AA + Rituximab (52)
- NA +/- AA (85)
- AA (118)
- Rituximab combinations (96)
- Without Rituximab (203)

Retrospective evaluation of 312 pts. who received primary therapy with:

- Alkylating agents (AA) - CHOP, CVP, melphalan-prednisone, chlorambucil-prednisone
- Nucleoside analogs (NA) +/- AA - 2CdA, 2CdA + prednisone, 2CdA + cyclophosphamide
- NA +/- AA + Rituximab - 2CdA + rituximab, 2CdA + cyclophosphamide + rituximab
- Bortezomib (B) + Rituximab +/- dexamethasone

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Median OS (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA alone</td>
<td>4.5</td>
</tr>
<tr>
<td>NA +/- AA</td>
<td>6.5</td>
</tr>
<tr>
<td>NA +/- AA + Rituximab</td>
<td>Not reached</td>
</tr>
<tr>
<td>B + Rituximab</td>
<td>Not reached</td>
</tr>
<tr>
<td>Rituximab combinations</td>
<td>&gt;13</td>
</tr>
<tr>
<td>Without rituximab</td>
<td>5.6</td>
</tr>
</tbody>
</table>
Rituximab Intolerance: Ofatumumab in Relapsed WM

- Fully human monoclonal anti-CD20 antibody

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Median Prior Rx</th>
<th>No. Evaluable</th>
<th>Major Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) OFA 300 mg wk 1 and 1000 mg wks 2–4 or B) OFA 300 mg wk 1 and 2000 mg wks 2–5</td>
<td>3 (1-5)</td>
<td>28</td>
<td>57%</td>
</tr>
</tbody>
</table>

Treatment A - lower response rate if had prior rituximab

Treatment B - equal response regardless of prior rituximab or other prior therapy

* 2 patients developed an IgM flare

Furman et al. ASH Annual Meeting Abstracts 2011
Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

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- Cladribine

Monoclonal Antibodies
- Rituximab
- Ofatumumab

NCCN Clinical Practice Guidelines in Oncology, v.3.2015
## Dexamethasone-Rituximab-Cyclophosphamide

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen (28 day cycle)</th>
<th>No. Evaluable*</th>
<th>Major Response Rate</th>
<th>2 year Progression Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimopoulos et al. 2007</td>
<td>Dexamethasone 20mg Rituximab 375mg/m2 Cyclophosphamide 100mg/m2</td>
<td>72</td>
<td>74%</td>
<td>67% (all patients) 80% (responders)</td>
</tr>
</tbody>
</table>

* All patients were previously untreated for Waldenstrom’s
# Bendamustine +/- Rituximab

<table>
<thead>
<tr>
<th>Regimen (28 day cycle)</th>
<th>Median Prior Rx</th>
<th>No. Evaluable</th>
<th>Major (Complete) Response Rate</th>
<th>Progression Free Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine-Rituximab</td>
<td>0</td>
<td>22</td>
<td>93 (40)*</td>
<td>69.5</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CHOP</td>
<td></td>
<td>19</td>
<td>91 (30)*</td>
<td>28.1</td>
</tr>
</tbody>
</table>

*Response rate is for all patients on study – includes different types of low grade lymphomas

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Median Prior Rx</th>
<th>No. Evaluable</th>
<th>Major (Complete) Response Rate</th>
<th>Progression Free Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine-Rituximab</td>
<td>2 (1-9)</td>
<td>24</td>
<td>79</td>
<td>13.2 (all)</td>
</tr>
<tr>
<td>Bendamustine-Ofatumumab</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Bendamustine</td>
<td>4</td>
<td>4</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>No. Evaluable</th>
<th>Major (Complete) Response Rate</th>
<th>Time to Treatment Failure</th>
<th>% MDS/AML or Transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimopoulos et al.</td>
<td>Cladribine X 2 cycles</td>
<td>20</td>
<td>40%</td>
<td>Not reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Laszlo et al.</td>
<td>Cladribine-Rituximab x 4 cycles</td>
<td>13</td>
<td>84.6%</td>
<td>Not Reached (50 mos of follow-up)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2-CdA</th>
<th>2-CdA/Cy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>38</td>
<td>54</td>
</tr>
<tr>
<td>Relapsed</td>
<td>12</td>
<td>19</td>
<td>31</td>
</tr>
<tr>
<td><strong>Retreated</strong></td>
<td>10</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>8</td>
<td>10</td>
<td>18 (78%)</td>
</tr>
<tr>
<td><strong>Remission Duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median # mos.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>23.5</td>
<td>37.7</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>24</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

# Fludarabine Based Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen (28 day cycle)</th>
<th>No. Evaluable</th>
<th>Major Response Rate</th>
<th>Long Term Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LeBlond et al. 2001</td>
<td>Fludarabine</td>
<td>45</td>
<td>30%</td>
<td>Duration of Response = 19 months</td>
</tr>
<tr>
<td>Dhodapkar et al.</td>
<td>Fludarabine 30mg/m2 x 5 days x 4-8 cycles</td>
<td>64</td>
<td>33%</td>
<td>Estimated 5 year PFS = 41%</td>
</tr>
<tr>
<td>Treon et al.</td>
<td>Fludarabine x 6 cycles Rituximab x 8 infusions</td>
<td>16</td>
<td>81%</td>
<td>Time to progression = 33.4 months</td>
</tr>
</tbody>
</table>

LeBlond et al. Blood 2001, Blood 98(9)
2nd Cancers after Cladribine/Fludarabine

**Treon et al. Fludarabine + Rituximab (n=43 patients)**
- Median follow-up of 40.3 months:
  - 2nd cancers seen in 8

**Rakhitt et al. Cladribine alone, + Cyclophosphamide, or + Cyclophosphamide-Rituximab (n=111 patients)**
- 10 patients (9%) had transformation to large cell lymphoma.
  - 4 pts had transformation of disease within 13 months.
- An additional 13 pts (12%) developed a second cancer.
  - Median time to 2nd cancer was 85.5 months

**Leleu et al. (n= 193 patients with Nucleoside Analog exposure; 136 without NA exposure)**
- 12 patients (6.2%) had transformation or t-MDS/AML in NA treated group
- 1 patient (0.4%) had transformation in the non-NA treated group ($P < .001$)

Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

- **Conventional Chemotherapy**
  - Cyclophosphamide
  - Bendamustine
  - Fludarabine
  - Cladribine

- **Monoclonal Antibodies**
  - Rituximab
  - Ofatumumab

- **Stem Cell Transplant**
  - Autologous SCT
  - Allogeneic SCT

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Stem Cell Transplantation

Autologous

Stem cell collection from patient

Allogeneic

Stem cell collection from donor
Stem Cell Collection

www.mysct.net
High Dose Chemotherapy

- To destroy the cancer cells in your body
- Varied chemotherapy drugs can be used.
- 24-72 hours for the chemotherapy to clear from your body before infusing the stem cells.
- The amount of time between your last dose of chemotherapy and your transplant is determined by what drugs you receive.

Photo courtesy of www.msnbc.msn.com
Stem Cell Transplantation
# Autologous Stem Cell Transplant in Relapsed WM

<table>
<thead>
<tr>
<th>EBMT registry</th>
<th>Transplant Dates</th>
<th>No. Evaluable</th>
<th>Median time from diagnosis to ASCT</th>
<th>Median Prior Rx</th>
<th>Major (Complete) Response Rate</th>
<th>Estimated 5 year PFS Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/1991-12/2005</td>
<td>75</td>
<td>1.7 yrs (0.3-20.3)</td>
<td>3</td>
<td>87 (22%)</td>
<td>40%</td>
</tr>
</tbody>
</table>

Factors predicting longer PFS:
- Having <3 prior therapies for WM
- Having chemosensitive disease at time of transplant

8.4% incidence of 2\textsuperscript{nd} cancers at 5 years

## Allogeneic Stem Cell Transplant

**Review of EBMT registry from 1/1998-12/2005**

- 86 patients (Myeloablative Conditioning, 37pts; Reduced Intensity Conditioning, 49 pts)
- Median time from diagnosis to Allo SCT = 37 months
- Median Age = 49 yrs (23-64 yrs)

<table>
<thead>
<tr>
<th>Conditioning Regimen</th>
<th>Major Response Rate (%)</th>
<th>Estimated 5 Year Progression Free Survival</th>
<th>Estimated 5 Year Overall Survival</th>
<th>Incidence of Graft vs. Host Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloablative</td>
<td>76%</td>
<td>56%</td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td>Reduced Intensity</td>
<td></td>
<td>49%</td>
<td>64%</td>
<td>33%</td>
</tr>
</tbody>
</table>

47 patients had ≥ 3 prior therapies

59 patients (69%) had chemotherapy-sensitive disease at the time of alloSCT.
8 patients had relapsed after prior autologous stem cell transplant

**Non-Relapse Mortality Rate: 33% MAC; 23% RIC**

Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

**Conventional Chemotherapy**
- Cyclophosphamide
- Bendamustine
- Fludarabine
- Cladribine

**Monoclonal Antibodies**
- Rituximab
- Ofatumumab

**Proteasome inhibitors**
- Bortezomib
- Carfilzomib

**Stem Cell Transplant**
- Autologous SCT
- Allogeneic SCT
Proteasome: Present and Future Therapies

Deubiquitylating Enzymes (DUBs)

- P5091 target USP-7

UB enzymes E1, E2 and E3-UB-Ligases

Poly-ubiquitinated proteins (proteasome substrates)

ATPases/Cdc48

Potential Therapeutic Targets

ATP → ADP

Immunoproteasome

Bortezomib, Carfilzomib, Ixazomib, Oprozomib

Marizomib: β5, β2

PR-924

Six Protease activities

β5, β5i, β1, β1i, β2, β2i

Degraded protein

Free Ub for re-cycling

20S

19S

19S

26S PROTEASOME

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>No. Evaluable</th>
<th>Major (Complete) Response Rate</th>
<th>Median Time to Progression/Progression Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al.</td>
<td>Bortezomib 1.3 mg/m² iv twice weekly</td>
<td>15</td>
<td>27%</td>
<td>16.3 months *all patients</td>
</tr>
<tr>
<td>Treon et al.</td>
<td>Bortezomib 1.3 mg/m² iv twice weekly</td>
<td>27</td>
<td>48%</td>
<td>7.9 months</td>
</tr>
<tr>
<td>Dimopoulos et al.</td>
<td>Bortezomib 1.3 mg/m² iv twice weekly</td>
<td>10</td>
<td>60%</td>
<td>&gt;11 months (estimate)</td>
</tr>
<tr>
<td>Ghobrial et al.</td>
<td>Bortezomib 1.6 mg/m² iv</td>
<td>37</td>
<td>51 (5)%</td>
<td>15.6 months (Range = 11-21 mos.)</td>
</tr>
<tr>
<td></td>
<td>Rituximab 375 mg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

Proteasome inhibitor-based

- Carfilzomib
  - Low rates of neuropathy

Side Effects to Consider
- Fatigue
- Nausea
- Low blood counts
- Kidney impairment
  - Seen less commonly now
- Heart problems

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Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

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- Thalidomide
- Lenalidomide
- Pomalidomide

Stem Cell Transplant
- Autologous SCT
- Allogeneic SCT

NCCN Clinical Practice Guidelines in Oncology, v.3.2015
Immunomodulators in WM

• **Thalidomide**
  – Thalidomide alone: ≥ PR of 25%
  – Thalidomide + steroids and/or clarithromycin: ≥ PR of 25-83%.
  – Thalidomide + Rituximab (Phase II Study): ≥ PR of 64%.
    • 25-44% of patients developed ≥ Grade 2 peripheral neuropathy

• **Lenalidomide**
  – Lenalidomide + Rituximab (Phase II Study): ≥ PR of 25%
    • 56% of patients developed ≥ Grade 2 anemia

---

Treon et al., Clinical Cancer Research 2009 Jan 1;15(1):355-60
Considerations for Thalidomide in Relapsed WM

Clinical Trial of a Novel Agent is a Priority

Immunomodulator-based

Thalidomide-based

- Low blood counts
- Impaired Kidney Function

Side Effects to Consider
- Sleepiness (>12%)
- Blood Clot risk (with steroids)
- Neuropathy (> 44%)
- Constipation
- Birth defects
- Rash


Considerations for Lenalidomide in Relapsed WM

Immunomodulator-based

Lenalidomide

- Underlying peripheral neuropathy
- Adjust dose if kidney function impaired

Side Effects to Consider
- Blood Clot risk (with steroids)
- Constipation or Diarrhea
- Birth defects
- Can lower blood counts
- Rash

NCCN Clinical Practice Guidelines in Oncology, v.3.2015
# Phase I Trial Of Pomalidomide

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen (28 day cycle)</th>
<th>No. Evaluable*</th>
<th>Major Response Rate (%)</th>
<th>Time on Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas et al.</td>
<td>Pomalidomide 1mg</td>
<td>6</td>
<td>1/6</td>
<td>2 years, 1 month +</td>
</tr>
<tr>
<td></td>
<td>Pomalidomide 2mg</td>
<td>3</td>
<td>Not tolerable</td>
<td></td>
</tr>
</tbody>
</table>

*Day 1: 3/2013  PR: 11/2014*

Thomas et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 8536)
Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

Monoclonal Antibodies

- Alemtuzumab
- BTK inhibitor
  - Ibrutinib
- mTOR inhibitor
  - Everolimus

NCCN Clinical Practice Guidelines in Oncology, v.3.2015
Alemtuzumab in Relapsed WM

- Humanized monoclonal antibody to CD 52

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. Evaluable</th>
<th>Median Prior Rx</th>
<th>Major Response Rate</th>
<th>Median Time to Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg iv 3x/week for up to 12 wks</td>
<td>23</td>
<td>2</td>
<td>36%</td>
<td>14.5 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46% refractory to last therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Toxicities of Note:**

- Cytomegalovirus reactivation occurred in 18%, leading to 3 deaths
- New-onset autoimmune thrombocytopenia in 14% (4 pts), leading to 1 death

Everolimus in Relapsed WM

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. Evaluable</th>
<th>Major Response Rate</th>
<th>Median Progression Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus 10mg/day</td>
<td>60</td>
<td>50%</td>
<td>21 months</td>
</tr>
</tbody>
</table>

Toxicities

- Lung Toxicity (5%)
- Mouth Sores (8%)
- Diarrhea (5%)
- Fatigue (8%)

Grade 3-4 toxicity rate = 67%
- Mostly low blood counts

Ibrutinib in Relapsed WM

Niiro H et al. 2002 Nature Reviews Immunology 2, 945-956
Ibrutinib in Relapsed WM

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen (28 day cycle)</th>
<th>No. Evaluable</th>
<th>Median Prior Rx</th>
<th>Major Response Rate (%)</th>
<th>Median Time to Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treon et al. 2015</td>
<td>Ibrutinib 420mg/day</td>
<td>63</td>
<td>2 (1-6)</td>
<td>57.1</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

- Attainment of major responses was impacted by mutations in CXCR4
- MRR was 77% for pts with wild-type CXCR4 vs. 30% in those with WHIM-like CXCR4 mutations

**Side Effects:**
- Low platelets (14%)
- Low neutrophils (22%)
- Pneumonia (8%)
- Bleeding events – bloody nose, bleeding after procedures (6%)
- Atrial Fibrillation (5%) – all in pts w/history of intermittent afib
  - resolved after stopping drug; drug was later resumed uneventfully

Treon et al. NEJM 2015 Apr 9;372(15):1430-40
FDA expands approved use of Imbruvica for rare form of non-Hodgkin lymphoma

First drug approved to treat Waldenström’s macroglobulinemia
Recommendations for Treating Relapsed WM

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- Pomalidomide

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Available Trials for Relapsed WM on ClinicalTrials.Gov

Clinical Trial of a Novel Agent is a Priority

- Carfilzomib-Rituximab-Dexamethasone
- Oprozomib
- BTK inhibitors
  - Ibrutinib + Rituximab
  - ACP196
- TLR antagonists – IMO 8400
Thank you for your attention... and making these advances possible!