Waldenström Macroglobulinemia: The Burning Questions

IWMF Ed Forum May 2017
Morie Gertz MD, MACP
Are my kids going to get this?
• Familial seen in approximately 5–10% of all CLL patients and can be associated with earlier age of diagnosis, more female prevalence, and increased incidence of other lymphoproliferative disorders (LPD), such as non-Hodgkin Lymphoma. 6 per 100,000 persons per year
Relative risk of lymphoproliferative malignancies and MGUS among first-degree relatives of LPL/WM patients

<table>
<thead>
<tr>
<th>Risk among first-degree relatives</th>
<th>Relatives of LPL pts only</th>
<th>Relatives of WM pts only</th>
<th>Relatives of LPL/WM pts combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts</td>
<td>Co</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----</td>
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<td>------------------</td>
</tr>
<tr>
<td>LPL/WM</td>
<td>4</td>
<td>1</td>
<td>16.6 (1.7-162.2)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>15</td>
<td>26</td>
<td>2.3 (1.2-4.3)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>7</td>
<td>6</td>
<td>4.8 (1.6-14.1)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>3</td>
<td>2</td>
<td>5.9 (1.0-36.0)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>6</td>
<td>11</td>
<td>2.2 (0.8-5.9)</td>
</tr>
<tr>
<td>MGUS</td>
<td>2</td>
<td>1</td>
<td>8.1 (0.7-90.6)</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CI, confidence interval; LPL, lymphoplasmacytic lymphoma; WM, Waldenström macroglobulinemia; MGUS, monoclonal gammopathy of undetermined significance; Pts, patients; and Co, controls.

*All estimates were adjusted for sex of first-degree relative.
12/56 patients had a family member affected
My opinion

- first degree relatives can have a serum protein electrophoresis beginning at age 50 repeated every 2 years
How long will I live?
• Since I began practice the survival has more than doubled
• Half of patients with symptomatic WM succumb to the disorders associated with old age
• New drugs are being developed at a rapid pace
  – Oprozomib, IMO-8400, Lenalidomide & everolimus combinations, carfilzomib, bendamustine, ibrutinib
• The danger of medians
  – Height across populations & income
Everolimus

- Active as a single agent
- Active with bortezomib
- Rise in triglycerides
- Consistent with >5 years of use
oprozomib

• Oral proteosome inhibitor
• Not neurotoxic given 2 days a week
• Impressive activity as a single agent
• Nausea and diarrhea managed with a new extended release formulation
What can I do to live longer

• Life style
• Activity
• Nutrition
• Obesity & Chemotherapy
  – clear standards or dosing guidelines are unable to be made for the obese population
• Frailty
  – may be predictive of decreased cancer-independent survival
Obesity and cancer

- 26% increase in men 10% increase in women
- 5 ft 8 in at 164 pounds
- These numbers apply at weight at 196 about 35 pounds overweight
- High levels of insulin like growth factor and adipokine as well as changes in male and female hormones
What are the risks of Imaging (X-rays)

- We are all exposed to radiation daily 0.01 millisieverts
- Chest X ray 0.1 mS
- Mammogram 0.4
- CT abdomen & Pelvis 10 mS
- PET CT 25mS
- Estimated exposure at Fukushima 2011 average 10
Australian study 2013

• 680,000 children that had CT imaging
• Comparator 10,000,000 children no CT
• Scanned children 45 cancers/10,000 over 10 yrs
• Unscanned 39 cancers/10,000 over 10 yrs
• Scanned children had a 24% rise in cancer risk
• Each additional scan increased risk 16%
Moral

• Try to minimize imaging and ask how essential it is
Will my WM transform into something worse?

• Richter's Transformation
  – tumor cells of DLBCL are clonally identical to those of WM/LPL.
  – occur in 6% of patients with WM
  – Role of nucleoside analogs

• MDS
  – Role of chemotherapy and DNA damage 1-3%
Cumulative incidence of (A) secondary malignancies and (B) high-grade lymphomas.

Leblond V et al. JCO 2013;31:301-307
Will I be Disabled?

• Fortunately the overwhelming majority of patients have complications limited to their blood counts and problems of the lymph nodes liver & spleen are much less common

• Neuropathy
  – Not therapy related

• Renal Complications/amyloidosis

• Cryoglobulinemia
What are the complications that can be seen?

<table>
<thead>
<tr>
<th>Classification</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal gammopathy of undetermined significance (MGUS)</td>
<td>242</td>
<td>56 Ratios MGUS:WM=4:1</td>
</tr>
<tr>
<td>Waldenström's macroglobulinemia (WM)</td>
<td>71</td>
<td>17</td>
</tr>
<tr>
<td>Lymphoma (LY)</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Primary amyloidosis (AL)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoproliferative disease (LP)</td>
<td>62</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>430</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

The spectrum of IgM monoclonal gammopathy in 430 cases
<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>WM</th>
<th>LY</th>
<th>CLL</th>
<th>AL</th>
<th>LP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable liver (%)</td>
<td>11</td>
<td>25</td>
<td>32</td>
<td>48</td>
<td>33</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>Palpable spleen (%)</td>
<td>6</td>
<td>20</td>
<td>29</td>
<td>62</td>
<td>17</td>
<td>34</td>
<td>17</td>
</tr>
<tr>
<td>Lymphadenopathy (%)</td>
<td>3</td>
<td>17</td>
<td>43</td>
<td>67</td>
<td>0</td>
<td>39</td>
<td>16</td>
</tr>
</tbody>
</table>

Five percent of all patients had a peripheral neuropathy; more than half the cases occurred in patients with MGUS.
## Viscosity in WM

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>WM</th>
<th>LY</th>
<th>CLL</th>
<th>AL</th>
<th>LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tested</td>
<td>40</td>
<td>51</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>&gt;4.0 cP</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1.8 cP</td>
<td>16</td>
<td>46</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Viscosity (cP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.7</td>
<td>2.8</td>
<td>1.8</td>
<td>1.9</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Range</td>
<td>1.0–2.9</td>
<td>1.2–14.8</td>
<td>1.3–2.8</td>
<td>1.8–2.8</td>
<td>2.0</td>
<td>1.2–6.5</td>
</tr>
</tbody>
</table>
Should I be tested for MYD88 L256P?

• MYD88 is not currently part of the diagnostic criteria
• MYD88- may be less ibrutinib responsive
• Therapy as yet is not determined by MYD88 status
• Does not distinguish WM from IgM MGUS
What are the Triggers for initiating therapy?

Second International Workshop on Waldenström's Macroglobulinemia agreed that initiation of therapy was appropriate for patients with constitutional symptoms such as fever, night sweats, fatigue due to anemia, or weight loss. The presence of progressive, symptomatic lymphadenopathy or splenomegaly provided additional reasons to begin therapy. The presence of anemia with a hemoglobin value of 10 g/dL or lower or a platelet count lower than $100 \times 10^9$/L due to marrow infiltration also justified treatment. Certain complications such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia may also be indications for therapy.

What should I monitor when I see my Provider?

Watch & Wait; Prior Rx

- Hb
- Platelets
- M-Spike
- IgM
- ± Free light Chain
- Monitoring of liver spleen & lymph node size

On Active Rx

- The key monitoring metric should be driven by why therapy was initiated and corroborated by indirect measures of WM including IgM & M spike

Note bone marrow is not part of my routine monitoring schedule
Is Rituxan alone a good therapy?

- N=69 strictly defined WM
- Four doses of rituximab
- 50% fall in IgM in 19 (28%)
- 25-50% fall in IgM in 17 (25%)
- >25% reduction in IgM 36/69=52%
  - Chlorambucil single agent reduction of IgM >50%-39%
  - Fludarabine 48% (second cancers 3.7%)
- Single agent R produces inferior response rates compared with combinations (44% 7 studies 317 patients vs 73% for combinations 700 patients)

How deep a response do I need?

• Controversial and debates on depth of response are ongoing
• Unclear that adding new therapies to deepen response after a plateau has been achieved is indicated and its not part of my practice
Should I get a second opinion?

In Multiple Myeloma centers that averaged > 10.6 patients / year (Canada) Had significantly better outcomes than facilities caring for fewer patients

JCO V34 : 7suppl abs 284
What's the deal with maintenance Rituximab

- Observational study R maint associated with improved outcomes but more frequent infections. No quality of life measure done
- In a survey performed in the Netherlands WM maintenance was recommended by 23% and actually used for their last patient in 8.5%
- The National Institute for Health and Clinical Excellence (NICE) considered it impossible to draw firm conclusions regarding the clinical effectiveness of the intervention -2013
## Results in FL

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Induction regimen</th>
<th>Maintenance schedule</th>
<th>PFS or EFS (MR versus observation)</th>
<th>OS (MR versus observation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hochser et al.</td>
<td>387</td>
<td>CVP</td>
<td>Four weekly doses every 6 months for 2 years</td>
<td>64%* vs 33% (3 years)</td>
<td>91% vs 86% (3 years)</td>
</tr>
<tr>
<td>Martinelli et al.</td>
<td>202</td>
<td>R alone</td>
<td>Single dose at 3, 5, 7 and 9 months</td>
<td>24 months* vs 13 months</td>
<td>Difference not statistically significant</td>
</tr>
<tr>
<td>Ardeshna et al.</td>
<td>720</td>
<td>R alone</td>
<td>Single dose every 2 months for 2 years</td>
<td>79% reduction in the risk of progression with MR*</td>
<td>Not reported</td>
</tr>
<tr>
<td>Salles et al.</td>
<td>1217</td>
<td>R-CVP, R-CHOP, or R-FCM</td>
<td>Single dose every 2 months for 2 years</td>
<td>74.9%* vs 57.6% (3 years)</td>
<td>Not significantly different between the two arms</td>
</tr>
<tr>
<td>Foa et al. [40]</td>
<td>545</td>
<td>Various R based regimens</td>
<td>Single dose every 2 months for 2 years</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Vitolo et al.</td>
<td>242</td>
<td>R-FND</td>
<td>Single dose every 2 months for four doses</td>
<td>80% vs 68% (2 years)</td>
<td>No data available</td>
</tr>
</tbody>
</table>

CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; FCM, fludarabine, cyclophosphamide, mitoxantrone; RND, fludarabine, mitoxantrone, dexamethasone; MR, maintenance rituximab; OS, overall survival; PFS, progression-free survival; R, rituximab.

*Statistically significant value.
Bendamustin-Rituximab Induction Followed by Observation or Rituximab Maintenance for Newly Diagnosed Patients with Waldenstrom’s Macroglobulinemia: Results From an ongoing Prospective, Randomized, Multicenter Study (StiL NHL 7-2008 - MAINTAIN; ClinicalTrials.gov Identifier: NCT00877214)

Matthews J. Rammol, MD, Christian Leuchtmüller, MD, Richard Greif, MD, Martin Görmé, Manfred Hensel, MD, Erik Engel, Ulrich Jürges, MD, Friedhelm Breuer, Bernd Hertenstein, Otto Prummer, MD, PhD, Christian Buske, MD, Juergen Barth, Alexander C. Burchardt, MD and Wolfram Brügger

Background:
Treatment for Waldenstrom’s Macroglobulinemia (WM) typically consists of rituximab in combination with nucleoside analogs with or without alkylating agents or with cyclophosphamide-based therapies or cyclophosphamide and dexamethasone (1, 2). In addition, combination treatments including bortezomib, thalidomide, lenalidomide and bendamustine have shown to have activity in WM.

Bendamustine has demonstrated durable responses in previously treated patients with WM both as monotherapy and in combination with rituximab (3).

In addition, a recent observational study suggests improved clinical outcomes following maintenance rituximab therapy in patients who responded to induction treatment that consisted of a rituximab-containing regimen (4).

We initiated a multicenter, prospective, randomized phase III trial to investigate the impact of adding rituximab maintenance following B-R first-line induction. The trial includes patients with WM, marginal zone, small lymphocytic and mantle cell lymphomas (ClinicalTrials.gov Identifier: NCT00877214).

The trial is currently ongoing and we present first and preliminary results of the induction phase for patients with WM.

Methods:
Treatment consists of a maximum of 6 cycles of B-R (bendamustine 90 mg/m², rituximab 375 mg/m²) administered every 28 days plus 2 cycles of rituximab every 4 weeks.

Responding patients (≥ PR) are eligible for further treatment and are will be randomized to observation or 2 years of rituximab maintenance every two months. The primary endpoint is PFS.

Results:
From April 2009 to July 2012, 57 centers included a total of 162 patients with newly diagnosed WM with a median age of 67 years (31% < 60 years, 69% ≥ 60 years). At baseline/inclusion/screening, the following median values were recorded: β2-Microglobulin 3.3 mg/L, hemoglobin 10.1 g/dL, and IgM 2110 mg/dL, (max. 13400 mg/dL).

The trial is currently ongoing, and we report results for 116 evaluable patients who have completed the induction phase (data cut-off Aug 2012). 43 women (37%) and 73 men (63%). 160 patients have responded to B-R leading to an overall response rate (ORR) of 86%. At the time of response evaluation, the median Lh was 12.6 g/dL and the median IgM was 380 mg/dL (Table 1).

No uncommon toxicities were observed during B-R induction.

To date, 90 patients have undergone randomization after completing the induction phase: 43 to observation and 47 to maintenance. Recruitment and randomization are ongoing. No results can be reported from the maintenance part of the trial.

Conclusion:
Initial results of our trial confirm that for patients with Waldenstrom’s Macroglobulinemia, induction treatment with B-R is efficacious and has a manageable safety profile. The role of rituximab maintenance in this disease is under investigation.

References:
2. Traon JP, Blood. 2004 Sep 1;104(12):2976-86.

Primary Completion Date: April 2017
Consensus for Newly Diagnosed Waldenström Macroglobulinemia

- IgM MGUS (<10% lymphoplasmacytic infiltration)
- Asymptomatic/smoldering Waldenstrom’s
- Hemoglobin ≥11 g/dL
- Platelets ≥120 x 10⁹/L

- Hemoglobin <11 g/dL or symptomatic
- Platelets <120 x 10⁹/L
- IgM-related neuropathy
- WM-associated hemolytic anemia
- Symptomatic cryoglobulinemia

- Bulky Disease
- Profound cytopenias –
  - Hemoglobin ≤10 g/dL
  - Platelets <100 x10⁹/L
- Constitutional symptoms
- Hyperviscosity symptoms

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Observation

- IgM MGUS (<10% lymphoplasmacytic infiltration)
- Asymptomatic/smoldering Waldenstrom’s
- Hemoglobin ≥11 g/dL
- Platelets ≥120 x 10⁹/L

- Hemoglobin <11 g/dL or symptomatic
- Platelets <120 x 10⁹/L
- IgM-related neuropathy
- WM-associated hemolytic anemia
- Symptomatic cryoglobulinemia

- Bulky Disease
- Profound cytopenias –
  - Hemoglobin ≤10 g/dL
  - Platelets <100 x10⁹/L
- Constitutional symptoms
- Hyperviscosity symptoms

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Single Agent Rituximab*

(1 cycle; no maintenance therapy)
*plasmapheresis if hyperviscosity develops with treatment

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Bendamustine + Rituximab (BR)* x 4-6 cycles

No rituximab maintenance therapy

Harvest stem cells if ≤ 70 years and potential autologous stem cell transplantation candidate in future

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* Dexamethasone + Rituximab + Cyclophosphamide (DRC)* x 6 cycles is an alternative if the disease burden is low

v4 Revised March 2015
Waldenström Macroglobulinemia Consensus for Off-Study Salvage Therapy

**Time to next therapy**

≥ 3 years from previous therapy

Yes

- Repeat Original Therapy

No

- Ibrutinib monotherapy*
- BDR if preexisting PN < Gd 2*
- DRC*
- BR*

Autologous stem cell transplant in select patients

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DRC = Dexamethasone + Rituximab + Cyclophosphamide; BR = Bendamustine + Rituximab; BDR = Bortezomib (weekly), Dexamethasone + Rituximab; PN = peripheral neuropathy

* If not previously used.
How about Ibrutinib?

• 1 prior treatment
• Intended therapy consisted of 420 mg of oral ibrutinib daily for 2 years.

<table>
<thead>
<tr>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Response rate: 61.9% (95% CI: 48.8, 73.9)</td>
</tr>
<tr>
<td>• Partial response: 50.8%</td>
</tr>
<tr>
<td>• Very good partial response: 11.1%</td>
</tr>
<tr>
<td>• Median duration of response: not reached (range, 2.8+ - 18.8+ months)</td>
</tr>
</tbody>
</table>

• a median time to response of 4 weeks.
  Median IgM 3610 to 1340. Hb 10.5 to 12.6
Ibrutinib

- MYD 88 status did not impact response
- CXCR4 WT major response of 77% CXCR4- WHIM response 30%
- Mutated WHIM had less benefit in IgM level and Hb improvement
- Neutropenia 19% thrombocytopenia 14%
Ibrutinib

- FDA Breakthrough Therapy Designation
- FDA approved Mantle Cell 11/13 & CLL 2/14
- Diarrhea & Platelets *atrial fibrillation*
- Rash Swelling Joint Pain
- Bleeding, pneumonia
- Final approval Jan 29, 2015
Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial

Median IgM levels of patients treated with ibrutinib. Error bars denote 95% CI.

Meletios A Dimopoulos, Judith Trotman, Alessandra Tedeschi, Jeffrey V Matous, David Macdonald, Constantine Tam, Olivier Tournilhac, Shuo Ma, Albert Oriol, Leonard T Heffner, Chaim Shustik, Ramón García-Sanz, Robert F Cornell, Carlos Fernández de Larrea, Jorge J Castillo, Miquel Granell, Marie-Christine Kyrtonis, Veronique Leblond, Argiris Symeonidis, Efstathios Kastritis, Priyanka Singh, Jianling Li, Thorsten Graef, Elizabeth Bilotti, Steven Treon, Christian Buske

null, 2016, Available online 10 December 2016

http://dx.doi.org/10.1016/S1470-2045(16)30632-5
Carfilzomib

• Combined with rituximab and dexamethasone in NDWM.

• The overall response rate was 87%, with 36% having at least a very good partial response.

• At 2 years, 65% were progression free. The peripheral neuropathy rate and cardiomyopathy rates were both 3%.
Obesity and Cancer: An Exploration of Biological Processes, Clinical Implications and Future Directions

Given the obesity epidemic that is occurring in most of the developed and developing world, the association of obesity and cancer has become increasingly important. The risk of many types of cancers is higher in overweight/obese individuals and there is growing evidence that obesity is also associated with poor outcomes of several cancers.

This JCO Special Series issue reviews associations of obesity with many common cancers, discusses the impact of obesity on cancer treatment, and reviews approaches to management of obesity.

Share your thoughts on this issue @JCO_ASCO
Health and insulin levels

- Levels linked to obesity and are driving by intake of simple sugars (glucose, sucrose)-partially measured by glycemic index
- FDA provides sugar information on almost all products
- Butter 0 g  An egg 0.4 g
- Oatmeal Cherrios 1 g
- Kix 3 g
- Apple Jacks 12 g
- Granola 13 g
• Twinkie 19g
• Unsweetened OJ 20g
• Yogurt 26 g (Strawberry-flavored original Yoplait yogurt, 99 percent fat free)
• Snickers bar, at **30 g of sugar**
• Coke 12 oz 33 g (RDA 36g men less for women)
• Craisins 40 g
1 sugar cube = 4.0g

<table>
<thead>
<tr>
<th>Snack</th>
<th>Calories, total</th>
<th>Sugars, total</th>
<th>Calories from sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Twinkies Snack Cakes</strong></td>
<td>145</td>
<td>18g</td>
<td>74</td>
</tr>
<tr>
<td>1 Twinkie</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2 Twinkies (1 package)</strong></td>
<td>290</td>
<td>37g</td>
<td>148</td>
</tr>
<tr>
<td>6 Donuts (85g)</td>
<td>340</td>
<td>23g</td>
<td>92</td>
</tr>
<tr>
<td>Donettes, Powdered Sugar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 oz Container</td>
<td>170</td>
<td>27g</td>
<td>108</td>
</tr>
<tr>
<td>Yoplait Yogurt, Strawberry</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cream filled and sugar filled.

One donut, one sugar cube.