Waldenström Macroglobulinemia
Discussion
Clinical Case Presentation

C Buske
Comprehensive Cancer Center Ulm
University Hospital Ulm
Ulm, Germany
Disclosures

Honoraria from Roche, Janssen, Pharmacyclics

Research funding from Roche, Janssen
First identified in 1944 by Swedish physician, Jan G. Waldenström

Observations based on 2 patients presenting with:
- Lymphadenopathy
- Nasopharyngeal bleeding
- Increased blood viscosity
- Infiltration of bone marrow by neoplastic B-cells

Jan G. Waldenström, MD
Case Report

2002: 51 years

- Arterial hypertension, BP=160/90 mmHg, systolic BP: sometimes 190 mmHg
- IgM kappa “MGUS” (no marrow assessment)
- Hb=12.7 g/dL, WBC=6.2 $10^9$/L, PMN=3.16 $10^9$/L, Platelet=289 $10^9$/L, IgM concentration: 9g/L
May 2011:

- Epistaxis, No other symptoms
- No lymph nodes
- Hb = 10.2 g/dL, WBC = 3.7 $10^9$/L, PMN = 2.07 $10^9$/L, Platelet = 198 $10^9$/L
- SEP: $\beta_2$-globulin: 11.3 g/L; IgM concentration: 60.9 g/L; $\beta_2$-microglobulin: 2.4 mg/L
  FLC kappa: 300 mg/L, lambda: 6.59 mg/L
- Bone marrow biopsy:
  - diffuse lymphoid infiltration (>80%)
  - CD20 positive
  - MYD88 (L265P) positive (posterior assessment)
  - Trisomy 4, del(6q)
May 2011 (continued)

- **Cryoglobulin**: positive, high titer, preventing the identification of the type

- **Fundoscopic**:
  
  February 2011 (at this time done at home for arterial hypertension): central retinal hemorrhages, tortuous blood vessels
  
  Adjust treatment of arterial hypertension → good control of BP
  
  May 2011: small blot-like retinal hemorrhages, tortuous blood vessels with venous sausaging

June 2011:

- **Hb=9.1 g/dL, Platelet=214 10^9/L, WBC=3.9 10^9/L, PMN=1.99 10^9/L**
Q 1: Please indicate indisputable criteria for initiating therapy in May 2011

1. Epistaxis
2. Fundoscopic abnormalities
3. Anemia
4. IgM concentration
5. none
not be based on IgM level per se
-- recurrent fever, night sweats, fatigue due to anemia
-- weight loss
-- presence of progressive symptomatic lymphadenopathy or splenomegaly
-- presence of anemia (Hb ≤ 10 g/dL) or platelet count ≤ 100 x 10⁹/L
-- symptomatic sensorimotor peripheral neuropathy
-- systemic amyloidosis, renal insufficiency or symptomatic cryoglobulinemia
-- hyperviscosity syndrome
Q 2: Please indicate the ISSWM subgroup

1. Low
2. Intermediate
3. High
<table>
<thead>
<tr>
<th>Risk Score WM</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>0-1 (except age)</td>
<td>Age or 2</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Survival</td>
<td>87 %</td>
<td>68 %</td>
<td>36%</td>
</tr>
<tr>
<td>Factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 65 yrs</td>
<td>--</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hb ≤ 11.5 g/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombos &lt; 100x 10⁹/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b₂M &gt; 3 mg/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM &gt; 70g/l</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Every factor counts as 1
Q 2: Please indicate the ISSWM subgroup

1. Low (Score 1 → Hb)
2. Intermediate
3. High
Response Criteria?
DRC regimen (Dexamethasone, Rituximab, Cyclophosphamide) is initiated

<table>
<thead>
<tr>
<th></th>
<th>Date</th>
<th>Hb (g/dL)</th>
<th>IgM (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st cycle DRC</td>
<td>25/06/2011</td>
<td>9.1</td>
<td>66.4</td>
</tr>
<tr>
<td>6th cycle DRC</td>
<td>05/12/2011</td>
<td>11.7</td>
<td>19.4</td>
</tr>
<tr>
<td>Best response</td>
<td>22/05/2013</td>
<td>13.6</td>
<td>6</td>
</tr>
</tbody>
</table>
### Response Criteria in WM

<table>
<thead>
<tr>
<th>Response category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>Absence of serum monoclonal IgM protein by immunofixation&lt;br&gt;Normal serum IgM level&lt;br&gt;Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline&lt;br&gt;Morphologically normal bone marrow aspirate and trephine biopsy</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>Monoclonal IgM protein is detectable&lt;br&gt;≥ 90% reduction in serum IgM level from baseline&lt;br&gt;Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline&lt;br&gt;No new signs or symptoms of active disease</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>Monoclonal IgM protein is detectable&lt;br&gt;≥ 50% but &lt;90% reduction in serum IgM level from baseline&lt;br&gt;Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline</td>
</tr>
<tr>
<td>Minor response (MR)</td>
<td>Monoclonal IgM protein is detectable&lt;br&gt;≥ 25% but &lt;50% reduction in serum IgM level from baseline&lt;br&gt;No new signs or symptoms of active disease</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Monoclonal IgM protein is detectable&lt;br&gt;&lt;25% reduction and &lt;25% increase in serum IgM level from baseline&lt;br&gt;No new signs or symptoms of active disease</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>≥ 25% increase in serum IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease</td>
</tr>
</tbody>
</table>

*Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry.

**Best response**

sometimes very delayed
If we have to treat....., which treatment would we choose?
1. DRC regimen (Dexamethasone, Rituximab, Cyclophosphamide) is initiated

<table>
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<th>IgM (g/L)</th>
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<td>25/07/2011</td>
<td>9,1</td>
<td>66,4</td>
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<td>6th cycle DRC</td>
<td>05/12/2011</td>
<td>11,7</td>
<td>19,4</td>
</tr>
<tr>
<td>Best response</td>
<td>22/05/2013</td>
<td>13,6</td>
<td>6</td>
</tr>
</tbody>
</table>
Published Data

a. Chemotherapy alone
   -- alkylating agents
   -- purine analogues

b. Rituximab alone

c. Rituximab plus Chemotherapy
CHOP vs. R-CHOP in WM

- TTF -

Buske et al., Leukemia 2009
PFS Waldenström

Rummel et al., Lancet 2013
De-escalating treatment?

DRC
Results
Response to DRC

- CR: 7%
- PR: 67%
- MR: 9%
- ORR: 83%
Progression Free Survival

Median PFS: 35 months
(95% CI 22-48 months)

Median follow up for patients still alive is 87 months (range 73-110 months)
Overall Survival

Median OS: 95 months
7-year OS 58%
Table 2. Toxicity of Treatment With DRC (percentage of patients affected)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>66</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>93</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>62</td>
</tr>
<tr>
<td>Chills/fever</td>
<td>84</td>
</tr>
<tr>
<td>Headache</td>
<td>81</td>
</tr>
<tr>
<td>Hypotension</td>
<td>94</td>
</tr>
<tr>
<td>Alopecia</td>
<td>78</td>
</tr>
</tbody>
</table>

Abbreviation: DRC, dexamethasone, rituximab, and cyclophosphamide.

Dimopoulos et al., JCO 2007
How can we improve….. ‘novel agents’?

1. Thalidomid
2. Lenalidomid
3. Bortezomib
4. Enzastaurin
5. Ibrutinib
Case Report - Outcome...

1. Plasmapheresis from December 5-11, 2013,
2. December 16, 2013: fever, blood culture staphylococcus lugdunensis despite Augmentin® (amoxicillin/clavulanate potassium)
3. Endocarditis with abscess of aortic valve
4. Cardiac surgery
5. February 20, 2014: asthenia, no lymph node,
   1. Hb=7.4 g/dL, platelet=130 10⁹/mm³, WBC=2.47 10⁹/mm³, PMN =1.16 10⁹/mm³

2. BDR

<table>
<thead>
<tr>
<th>Date</th>
<th>SEP: M-spike (g/L)</th>
<th>IgM conc (g/L)</th>
<th>Viscosity (cSt)</th>
<th>Protein (g/L)</th>
<th>comment</th>
</tr>
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<tbody>
<tr>
<td>02/04/2014</td>
<td>13,5</td>
<td>84,6</td>
<td></td>
<td></td>
<td>104</td>
</tr>
<tr>
<td>16/04/2014</td>
<td>16</td>
<td>90,1</td>
<td>4,14</td>
<td></td>
<td>102</td>
</tr>
<tr>
<td>22/04/2014</td>
<td>13,8</td>
<td>56,13</td>
<td>2</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>07/05/2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/05/2014</td>
<td>12,2</td>
<td>49,24</td>
<td>1,88</td>
<td>83</td>
<td>No cryoglobulin</td>
</tr>
<tr>
<td>25/06/2014</td>
<td>4,8</td>
<td>43,54</td>
<td></td>
<td></td>
<td>88</td>
</tr>
</tbody>
</table>
BDR – rapidly acting and effective

Median Time to Response = 3 months

Median PFS 42 months

3-yrs OS 82 %

Clinical Intergroup

The ECWM is based on a clinical intergroup connecting all major clinical national study groups such as:

- BNLI
- Czech Myeloma Group
- FIL Italian Intergroup
- FCGCLLWM Group
- GLSG/OSHO
- Greek Myeloma Study Group
- HOVON
- Nordic Lymphoma Group
- Portuguese Lymphoma Study Group
Study Flow

Registration

Randomisation

Standard Arm
6 x DRC

Experimental Arm
6 x Bortezomib - DRC

Follow – up

SD, PD
Follow-up for survival

For response until progression
For OS until death

SD, PD
Follow-up for survival
**Newly diagnosed WM**

- **Asymptomatic WM**
  - Observation
  - **Symptomatic WM**
    - Medically Fit
      - Consider clinical trial
    - **Symptomatic WM**
      - Medical Non-Fit
        - Consider clinical trial
      - **Hyperviscosity**
        - Yes
          - Plasmapheresis
          - **mild Rituximab/chemotherapy e.g. (DRC)**
        - No
          - **Single agent therapy e.g.,**
            - Rituximab
            - Chlorambucil
            - Fludarabine
          - Bortezomib combination e.g., Bortezomib/Rituximab

* In case of hyperviscosity consider plasmapheresis before Rituximab application

**Buske et al., ESMO Guidelines, 2014**
**Treatment Algorithms - WM**

**Relapsed WM**

- **Asymptomatic WM**
  - Observation

- **Symptomatic WM**
  - **Medically Fit**
    - Consider clinical trial
  - **Rituximab/chemotherapy**
    - Response > 12 months
      - Repeat first line treatment
    - Response < 12 months
      - Change to alternate Rituximab/chemotherapy
    - Response < 12 months and aggressive clinical course
      - Consider ASCT
      - 2nd relapse, failure after ASCT discuss allograft (within clinical trials)
    - Chemoresistant disease
      - Consider clinical trials with novel compounds

- **Medically Non-Fit**
  - Consider clinical trial

- **Hyperviscosity**
  - Yes
    - Plasmapheresis
  - No
    - Depending on first line therapy
      - Novel compounds within clinical trials
      - Mild rituximab/chemotherapy
        - Or chemotherapy alone (e.g. Chlorambucil, fludarabine, rituximab)
      - Bortezomib combination e.g. Bortezomib/Rituximab

*In case of hyperviscosity consider plasmapheresis before Rituximab application*
Many thanks!
Bruton’s Tyrosine Kinase (BTK): A Critical Kinase for Lymphoma Cell Survival and Proliferation

- Bruton’s tyrosine kinase (BTK) is an essential element of the BCR signaling pathway
- Inhibitors of BTK block BCR signaling and induce apoptosis
- PCI-32765 (ibrutinib) forms bond with cysteine-481 in BTK
  - Highly potent BTK inhibition at IC$_{50}$ = 0.5 nM
  - High degree of B-cell specificity
  - Orally administered once daily dosing
MULTICENTER PHASE II STUDY OF IBRUTINIB IN RELAPSED/REFRACTORY WM

Screening

Informed Consent and Registration

Ibrutinib 420 mg po daily

Progressive Disease or Unacceptable Toxicity

Stop Ibrutinib

Event Monitoring

Stable Disease or Response
Continue x 26 four week cycles

Event Monitoring

N=35, expanded to 63.

OPENED MAY 2012
DFCI, MSKCC, STANFORD
<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGPR</td>
<td>4</td>
<td>11.4</td>
</tr>
<tr>
<td>PR</td>
<td>19</td>
<td>54.3</td>
</tr>
<tr>
<td>MR</td>
<td>6</td>
<td>17.1</td>
</tr>
<tr>
<td>SD</td>
<td>5</td>
<td>14.3</td>
</tr>
<tr>
<td>NON-RESPONDER</td>
<td>1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**ORR**: 83%  **MAJOR RR (≥ PR)**: 66%
### POSSIBLY, PROBABLY, OR LIKELY RELATED (N=35)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>≥Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>6 (17.1%)</td>
<td>3 (8.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (17.1%)</td>
<td>2 (5.7%)</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1 (2.9%)</td>
<td>1 (2.9%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>1 (2.9%)</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>
A randomized phase III study of Ibrutinib p.o. versus extended Rituximab i.v. therapy in patients with previously treated WM

ECWM-R1
ECWM-R1 / Relapse

**Rituximab 375 mg/m² IV weekly for 4 consecutive weeks – week 1-4 and week 13-16 plus Placebo**

**Rituximab plus oral Ibrutinib 420 mg qD continuously until evidence of progressive disease plus Ibrutinib**

*Crossover*: Patients who are randomized in the rituximab arm and demonstrate progressive disease, will be allowed to receive ibrutinib