Goals of talk

• What is Waldenström Macroglobulinemia?
• How do we make a diagnosis?
• When do we need to treat Waldenström Macroglobulinemia?
• How do we treat, and what kind of treatments
• What happens when the treatments stop working?
What is WM?
(and what is lymphoplasmacytic lymphoma?)

• B-cell disorder
  – Accumulation of clonal (clones) cells (lymphoplasmacytic/LPL) that secrete IgM protein
WHO Criteria for Lymphoplasmacytic Lymphoma and Waldenström Macroglobulinemia

• Lymphoplasmacytic lymphoma (LPL)
  – Neoplasm of small B lymphocytes, plasmacytoid lymphocytes, plasma cells
  – Usually involves bone marrow, lymph nodes, spleen

• Waldenström Macroglobulinemia
  – LPL with bone marrow involvement and
  – IgM monoclonal gammopathy (any level!)

Diagnostic Studies

• Bone Marrow biopsy
• Blood work to evaluate for:
  – Anemia
  – Monoclonal Protein
  – Viscosity
  – Total protein
  – Quantitative immunoglobulins (IgM)
• CT imaging to evaluate lymph nodes & spleen size
• No role for MRI or PET at diagnosis
• MYD88 L265P AS-PCR testing of bone marrow
What is IgM?

• Largest of the immunoglobulins (pentamer)
• Serum viscosity
• Auto-antibody activity
  – Can attack nerves
• Interaction with other proteins
• Precipitation on cooling
• Cold Agglutinemia
• Deposition in tissues
Risk factors for development of WM

• Gender (Women > men)
• Ethnicity (Ashkenazi Jewish 20%; AA <5%)
• Genes (Familial 27%)
• Chronic antigen stimulation (HIV, HCV, Rickettsiosis)
• Common Variable Immunodeficiency Disorder (CVID)
Familial B-cell Disorders among First and Second Degree Relatives of Patients with WM.
How do patients find out they have WM?

Typical symptoms:
Weakness, fatigue,
Mouth and nasal bleeding
Blurred vision
Recurrent infections
Numbness and tingling in hands and feet
Who needs treatment for WM?

• Symptomatic:
  – Treatment indicated

• Asymptomatic:
  – No treatment indicated!
Indications for treatment

• Disease related cytopenias
  – Anemia (Hb < 10)
  – Thrombocytopenia (Plt count < 100k)
• Hyperviscosity
• Secondary amyloidosis
• Cryoglobulinemia
• Cold agglutinemia
• Extramedullary disease involving the CNS (Bing Neel)
• Paraprotein-related peripheral neuropathy
• Disease transformation
• IgM level > 6000 mg/dL → if sole abnormality, consider treatment

Treon Blood 2015
Anemia

- Bone marrow replacement
- Hemodilution (high IgM)
- Hemolysis

- If out of proportion to level of disease:
  - Evaluate for other causes
    - Iron deficiency
      - Common (can be refractory to oral iron)
Hyperviscosity
Hyperviscosity

- Headache, loss of balance, mental confusion
- Retinal changes can occur as low as 3.0 cp
- Variables aside from level of IgM can affect viscosity (ie cryoglobulinemia)
- Usually not symptomatic <4.0 cp (but not absolute)
Peripheral Neuropathy

- 20-25% of patients
- Usually sensory
  - Anti-myelin associated glycoprotein (MAG)
  - Anti-sulfatide IgM
  - Anti-ganglioside M1 (GM1)
  - Others?
- EMG
- Avoid sural nerve biopsy
- Amyloidosis
- Myopathy rare
  - Anti-decorin IgM
Ophthalmological Issues:

• Retinal changes due to hyperviscosity
  – Reported at as low as IgM =3000
• Prompt resolution with plasmapheresis
• Retinal exam useful to follow effect of both chemotherapy and plasmapheresis
Treatment options

• Plasmapheresis
  – Symptomatic hyperviscosity
  – Cryoglobulinemia
  – IgM level > 5000

• Systemic treatments
  – Chemo-immunotherapy
  – Targeted agents
  – Transplant
Selecting a treatment:

• Is transplant a future option?
• What are the side effects?
• What are the long term risks?
• How fast do you need to get a response?
• What are the financial implications?
**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 x 10⁹/L
- **Constitutional symptoms**
- **Hyperviscosity symptoms**

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**Observation**

**Single Agent Rituximab†**
(1 cycle; no maintenance therapy)
†plasmapheresis if hyperviscosity develops with treatment

**Bendamustine + Rituximab (BR)† x 4-6 cycles**
No rituximab maintenance therapy

**Plasmapheresis**

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*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*

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v4  Revised April 2015
NCCN Guidelines Version 1.2017
Waldenström's Macroglobulinemia/
Lymphoplasmacytic Lymphoma

SUGGESTED TREATMENT REGIMENS
(Order of regimens is alphabetical and does not indicate preference)

Primary Therapy: Non-stem cell toxic

- Bortezomib ± rituximab\(^1,2,3,4\)
- Bortezomib/dexamethasone\(^3,4\)
- Bortezomib/dexamethasone/rituximab\(^1,2,3,4\)
- Carfilzomib/rituximab/dexamethasone\(^1,3,5\)
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab\(^1,4,6\)
- Ibrutinib\(^7\)
- Rituximab\(^1\)
- Rituximab/cyclophosphamide/prednisone\(^1\)
- Rituximab/cyclophosphamide/dexamethasone\(^1\)
- Thalidomide ± rituximab\(^1,4\)

Possible stem cell toxicity and/or risk of transformation (or unknown)

- Bendamustine ± rituximab\(^1\)
- Cladribine ± rituximab\(^1,3,8,9\)
- Chlorambucil\(^7,8\)
- Fludarabine ± rituximab\(^1,3,8,9\)
- Fludarabine/cyclophosphamide/rituximab\(^1,3,8,9\)

Previously Treated WM/LPL:
Non-stem cell toxic

- Alemtuzumab
- Bortezomib ± rituximab\(^1,2,3,4\)
- Bortezomib/dexamethasone\(^3,4\)
- Bortezomib/dexamethasone/rituximab\(^1,2,3,4\)
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab\(^1,4,6\)
- Everolimus
- Ibrutinib
- Ofatumumab (for rituximab-intolerant individuals)\(^1,10\)
- Rituximab\(^1\)
- Rituximab/cyclophosphamide/prednisone\(^1\)
- Rituximab/cyclophosphamide/dexamethasone\(^1\)
- Thalidomide ± rituximab\(^1,4\)

Possible stem cell toxicity and/or risk of transformation (or unknown)

- Bendamustine ± rituximab\(^1\)
- Cladribine ± rituximab\(^1,3,8,9\)
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Stem cell transplant

- In selected cases stem cell transplantation may be appropriate either:
  - High-dose therapy with stem cell rescue
  - Allogeneic stem cell transplant (ablative or nonablative)\(^11\)

See Suggested References (WMLPL)
Ibrutinib

- Mechanism: small-molecule inhibitor of BTK that triggers apoptosis of Waldenstrom’s cells with MYD88 (L265P).
- Approved for frontline and relapsed/refractory WM
- Dose: 420 mg daily
- Side effects:
  - Bleeding – affects platelet aggregation
  - Atrial fibrillation – reported rates 5-10%

Castillo Ther Adv Hematology 2016
## Chemoimmunotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate</th>
<th>Complete Remission</th>
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<tbody>
<tr>
<td>Rituximab 4 cycles</td>
<td>25-30%</td>
<td>0%</td>
</tr>
<tr>
<td>Rituximab 8 cycles</td>
<td>40-45%</td>
<td>0%</td>
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<tr>
<td>R+CHOP or CVP, or CP or CD</td>
<td>70-80%</td>
<td>8-10%</td>
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<tr>
<td>R+ fludarabine</td>
<td>70-80%</td>
<td>5-10%</td>
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<tr>
<td>R+thalidomide</td>
<td>70%</td>
<td>55</td>
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<tr>
<td>R+ bortezomib</td>
<td>70-90%</td>
<td>10-25%</td>
</tr>
<tr>
<td>R+bendamustine</td>
<td>90%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Bendamustine

• Bi-functional agent
Bendamustine and rituximab

Bortezomib, dexamethasone, rituximab (BDR)

- **Chemotherapy**
  - Bortezomib: proteasome inhibitor (PI)
  - Rituximab: Monoclonal antibody directed against CD20
  - Dexamethasone: Corticosteroid

- **Regimen** — studied in untreated patients
  - Bortezomib 1.3 mg/m2 days 1, 4, 8, 11
  - Rituximab 375 mg/m2 day 11
  - Dexamethasone 40 mg on days 1, 4, 8, 11

Treon SP Blood 2015
IgM Flare

Autologous SCT in Waldenstrom’s Macroglobulinemia

- Very limited data
- Consideration primarily in patients with multiply relapsed, but not yet refractory, disease
- Allogeneic SCT associated with significant toxicity and should be considered investigational
Autologous transplant for WM

• Analysis from the EBMT for WM undergoing ASCT
• 158 adult patients
• Median time diagnosis to ASCT 1.7 years
• Median age at time of ASCT was 53 years
• Responses
  – CR in 34 (22%)
  – VGPR in 77 (50%)
  – PR in 23 (15%)

Kyriakou JCO 2010