Updates on Waldenström macroglobulinemia

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Mr. W, 68 y/o male

- 2 months weight loss (20 lbs), night sweat, decreased appetite, fatigue, and dizziness, worsening more acutely in the past few days.

- PMH: PTSD, gout, Reynaud's, HLP

- Hemodynamically stable, mild tachycardia, no skin & neurological changes

- P/E: Splenomegaly

- CT: 20.1 cm spleen, Mildly enlarged periportal lymph nodes
Labs

- DAT positive, hapto <10
- Cold agglutinin positive, titer 1:4096
- High retic, LDH 346
- SPEP, M protein 3.03 g/dL, immunofixation: IgM Kappa
- IgA 60, IgG 396, IgM 3279
- Cannot measure viscosity due to hemolysis
- ANA, HIV/HCV/HBV negative, normal coag
Peripheral Flow

INTERPRETATION
Peripheral blood:
1. Abnormal B cell population identified (see comment).
2. No abnormal T cell population identified (see comment).

COMMENT
Flow cytometry reveals an abnormal mature B cell population having abnormal expression of kappa light chain restriction with normal expression of CD19, CD20, CD38, and CD45 without definite CD5 or CD10. The abnormal B cell population represents 76.6% of the total white cells. The immunophenotype is not specific, although primary consideration may include marginal zone lymphoma, lymphoplasmacytic lymphoma and large B cell lymphoma (although uniform large size is not appreciated). Give the lack of CD5, CLL/SLL and mantle cell lymphoma would be less likely, and given the lack of CD10, follicular lymphoma would also be less likely. Nonetheless, clinical and morphologic correlation will be necessary (with tissue biopsy if indicated), to further subclassify this B lymphoid neoplasm. The patient has splenomegaly and hairy cell evaluation will be performed and reported in an addendum. The findings are discussed with Dr. Woo on 12/5/2014.
Labs

- Cold agglutinin associated hemolytic anemia
- Clonal lymphocytosis, splenomegaly
- Monoclonal IgM
- Cannot measure viscosity due to hemolysis
- Stable vital signs and no neurological symptoms

- Declined bone marrow
- Diagnosis: *Waldenström macroglobulinemia*
- ISSWM: high risk (age(2), hgb(1), plt(1)) 5yr survival 36%
1\textsuperscript{st} line treatment in Symptomatic Patients
1st line Phase II trial in 72 WM patients

DRC (dexamethasone, rituximab, and cyclophosphamide)

- ORR 83% (CR 7%, PR 67%)
- mTTR: 4.1 months
- 2-year PFS 67%, (responder 80%)
- 2-year ds-Survival 90%

For patient with cytopenias or organomegaly and paraprotein-related neuropathy
Primary Therapy of Waldenström Macroglobulinemia With Bortezomib, Dexamethasone, and Rituximab: WMCTG Clinical Trial 05-180

N=23, induction 4 cycles followed by maintenance 4 cycles, m-cycles=7

- ORR 96% (CR 13%, nCR 8%, PR 61%)
- mTTR: 1.4 months
- 18/23 patients remained free of disease progression
- Peripheral Neuropathy (Gr>=2) 69%, 81% resolved within 6 months

For patients with symptomatic hyperviscosity, cryoglobulinemia, or cold agglutinin disease.

Steven P. Treon et al. JCO 2009;27:3830-3835
Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

22 patients with WM

For patients with bulky disease requiring rapid disease control

Figure 3 Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D) B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.


http://dx.doi.org/10.1016/S0140-6736(12)61763-2
Molecular Pathogenesis, Targeted treatment
GEP of WM is closer to CLL than MM

unsupervised clustering of normal B cells, PCs, MGUS, and SMM

MYD88 and WM
MYD88 L265P Somatic Mutation in Waldenström’s Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

No MYD88 L265P mutation in non-IgM MGUS or lymphoplasmacytic lymphomas, CLL, MM, including IgM MM, GC-DLBCL, DLBCL NOS, HCL.

Three of 14 splenic marginal zone lymphomas, nine of 48 ABC DLBCLs (non-GC type)

⇒ MYD88 L265P is a marker highly characteristic of, but not restricted to, Waldenstrom's macroglobulinemia

Leukemia (2013); 27: 1722–1728.
MYD88-Directed NF-κB Signaling.
A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenstrom macroglobulinemia. Phospho-BTK as a binding partner of MYD88 in L265P-expressing WM cells, and abrogation of MYD88-BTK binding following treatment with ibrutinib in MYD88 L265P-expressing cells.
Ibrutinib in Previously Treated Waldenström’s Macroglobulinemia

Kaplan–Meier Curves for Progression-free and Overall Survival.

ORR 90.5%
2-year PFS 69.1% , OS 95.2%
mTTR : 4 weeks

68% improved adenopathy
57% decreased splenomegaly

Symptomatic improvement in Rituxan-unresponsive neuropathy

CXCR4 and WM
Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease

Paolo A. Hernandez, Robert J. Gorlin, John N. Lukens, Shoichiro Taniuchi, Jože Bohinjec, Fleur Francois, Mary E. Klotman & George A. Diaz
Somatic CXCR4 mutations in WM are similar to those found in WHIM syndrome.

Zachary R. Hunter et al. Blood 2014;123:1637-1646

LEGEND
A - Germline variant in WHIM syndrome
B - Transmembrane helix
C - Somatic frame shift or nonsense WM variant

S338 Mutation Types

Frame shift mutation
Nonsense C/G
Nonsense C/A
Frame shift
C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma

WM cells harboring the C1013G/CXCR4 somatic variant present with drug resistance.
BMS936564-MDX1338 targets C1013G/CXCR4-mutated cells in vivo and targets survival- and apoptosis-related signals in WM cells.
MYD88, CXCR4 and WM
BM disease involvement and serum IgM levels at diagnosis for WM patients stratified by MYD88 and CXCR4 mutation status.

Steven P. Treon et al. Blood 2014;123:2791-2796
Effect of MYD88 and CXCR4 Mutation Status on Ibrutinib-Related Changes in Serum IgM and Hemoglobin Levels.

**A**

- Serum IgM Level Normalized to Baseline
- MYD88L265P CXCR4WT
- MYD88L265P CXCR4WHIM
- MYD88WT CXCR4WT
- Minor response
- Partial response
- Very good partial response

- P-values: P=0.06, P=0.32, P=0.003

**B**

- Hemoglobin Level Normalized to Baseline
- MYD88L265P CXCR4WT
- MYD88L265P CXCR4WHIM
- MYD88WT CXCR4WT
- Very good partial response
- Partial response
- Minor response

- P-values: P=0.03, P=0.03, P=0.20

n=34  n=21  n=7

### Overall and Major Response Rates

**MYD88<sup>L265P</sup>CXCR4<sup>WT</sup>** (100% and 91.2%)
**MYD88<sup>L265P</sup>CXCR4<sup>WHIM</sup>** (85.7% and 61.9)
**MYD88<sup>WT</sup>CXCR4<sup>WT</sup>** (71.4% and 28.6%)

![Graph showing response rates](image)

- **BTK dependence on MYD88<sup>L265P</sup>-triggered signaling**
- **Intrinsic resistance conferred by CXCR4<sup>WHIM</sup> mutations**

STAY TUNED,
NEW THERAPIES COMING !!!
Q & A
Table 1

Primary differential diagnoses of IgM monoclonal gammopathies.*

<table>
<thead>
<tr>
<th></th>
<th>IgM MGUS</th>
<th>Smoldering/Asymptomatic WM</th>
<th>WM</th>
<th>IgM multiple myeloma</th>
<th>IgM amyloidosis</th>
<th>Splenic marginal zone lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IgM gammopathy</td>
<td>&lt;3 g/dL</td>
<td>≥3 g/dL</td>
<td>Any level</td>
<td>Any level</td>
<td>Any level</td>
<td>Low level</td>
</tr>
<tr>
<td>Bone marrow LPL infiltrate (%)</td>
<td>&lt;10%</td>
<td>≥10%</td>
<td>≥10%; predominately plasmacytic PCs,</td>
<td>Normal or slight increase of PC or LPL</td>
<td>Intertrabecular and intrasinusoidal infiltrate</td>
<td>Yes</td>
</tr>
<tr>
<td>End organ damage/symptoms</td>
<td>No</td>
<td>No</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hyperviscosity</td>
<td>No 6q deletion absent, MYD88 L265P (upto 80%)</td>
<td>No 6q deletion, MYD88 L265P (90%), CD56 —</td>
<td>Yes 6q deletion (30–50%), IgH translocations absent, MYD88 L265P (90%), CD56 —, CD25 + (88%), CD103 —</td>
<td>Uncommon May have t(11;14) or other IgH translocations, MYD88 L265P negative, CD56 +, CD138 +, CD19 —, CD45 —</td>
<td>Uncommon May have t(11;14)</td>
<td>Uncommon + 3q (19%) and +5q (10%); MYD88 L265P negative, CD22 +, CD11c +, CD25 —, Del 7q (19%), CD25 + (44%), CD103 ± (40%) 13–19% life-time risk in small series</td>
</tr>
<tr>
<td>Differentiating genetic features and markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Risk of transformation</td>
<td>1.5% per year</td>
<td>12% per year for the first 5 years, 68% within 10 years</td>
<td>5%–10% risk for DLBCL</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IgM, Immunoglobulin M; LPL, lymphoplasmacytic lymphoma; MGUS, monoclonal gammopathy of undetermined significance; N/A, not applicable; PC, plasma cells; WM, Waldenström macroglobulinemia.

* The table lists a few important differential diagnoses of IgM monoclonal gammopathies. IgM paraprotein can be present in virtually all B cell lymphoproliferative disorders.

a Constitutional symptoms: hepatosplenomegaly, lymphadenopathy, anemia, hyperviscosity, solid organ involvement, and rarely lytic lesions.

b CRAB features (hypercalcemia, renal failure, anemia and bone lesions).

c Organs typically involved are kidneys, heart, nerves, tongue, GI tract, and liver. Patients with IgM Amyloid Light-chain (AL) amyloidosis have higher frequency of pulmonary, lymph node, peripheral nerve, and lower cardiac involvement. Concentration of free light-chain tends to be lower compared to non-IgM AL amyloidosis.

d Primarily involves spleen; lymphadenopathy is rare.
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Common/universe toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Chlorambucil</td>
<td>Cytopenias, Myelodysplastic syndrome (MDS) and acute leukemias</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>Vomiting, hypersensitivity</td>
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<tr>
<td></td>
<td>Bendamustine</td>
<td>Myelosuppression, infections due to immunosuppression, fever, MDS, AML and large cell transformation (10%-15%) and stem cell toxicity</td>
</tr>
<tr>
<td>Nucleoside analogs</td>
<td>Fludarabine</td>
<td>Cytopenias, infusion reactions</td>
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<td></td>
<td>Cladribine</td>
<td>IgM flare</td>
</tr>
<tr>
<td>Monoclonal Ab</td>
<td>Rituximab</td>
<td>Rash, fatigue, infections, including CMV reactivation, esophageal candidiasis, cytopenias, including autoimmune thrombocytopenia</td>
</tr>
<tr>
<td>Anti-CD20</td>
<td>Ofatumumab</td>
<td>IgM flare</td>
</tr>
<tr>
<td>Anti-CD52</td>
<td>Alemtuzumab</td>
<td></td>
</tr>
<tr>
<td>Proteasome inhibitors (PIs)</td>
<td>Bortezomib</td>
<td>Peripheral neuropathy, GI disturbance</td>
</tr>
<tr>
<td></td>
<td>Carfilzomib</td>
<td>Reactivation of herpes zoster, thrombocytopenia</td>
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<tr>
<td></td>
<td>Oprozomib</td>
<td></td>
</tr>
<tr>
<td>Immunomodulatory drugs (IMIDs)</td>
<td>Thalidomide</td>
<td>Neuropathy, sedation, bradycardia, constipation, thrombosis and fatigue</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide</td>
<td>Hemolytic anemia, rash, fatigue, thrombosis and cytopenias</td>
</tr>
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<td></td>
<td>Pomalidomide</td>
<td></td>
</tr>
<tr>
<td>Mammalian target of rapamycin (mTOR) inhibitors</td>
<td>Everolimus</td>
<td>Cytopenias, mucosal ulceration/stomatitis, IgM discordance fatigue, diarrhea, hyperlipidemia and dyspnea (± pleural effusion) that responds to steroids, therapy cessation or dose reduction</td>
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<tr>
<td></td>
<td>Temsirolimus</td>
<td></td>
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<tr>
<td>Histone deacetylase (HDAC) inhibitors</td>
<td>Panobinostat</td>
<td>Excessive or prolonged myelosuppression</td>
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<tr>
<td>AKT inhibitor</td>
<td>Perifosine</td>
<td>Gastrointestinal toxicity (diarrhea, nausea, vomiting), cytopenias, fatigue, arthritis/joint effusion</td>
</tr>
<tr>
<td>PI3 kinase delta inhibitor</td>
<td>Idelalisib</td>
<td>Diarrhea, pneumonia, elevation in aminotransferases, pyrexia, rash, colitis, intestinal perforation and neutropenia</td>
</tr>
<tr>
<td>Serine/threonine kinase inhibitors</td>
<td>Enzastaurin</td>
<td>Fatigue, gastrointestinal toxicity, leukopenia and infection</td>
</tr>
<tr>
<td>Bruton's tyrosine Kinase inhibitors</td>
<td>Ibrutinib</td>
<td>Thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, atrial fibrillation, epistaxis, respiratory tract infection and rash</td>
</tr>
</tbody>
</table>