Strategic Research Roadmap Overview & the Bone Marrow/Tumor Microenvironment in Waldenström macroglobulinemia

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Topics to be covered -

• What is Waldenström macroglobulinemia?
  – Disease phenotype and clinical characteristics

• What is the WM Roadmap and why do we need one?

• What is unique about the bone marrow microenvironment?
  – Genetic mutations and cytokine dysregulation

• Therapeutic opportunities –
  – Targeting BTK signaling
  – Targeting TLR signaling
  – Targeting PI3k signaling
Waldenström macroglobulinemia
“A disease with two problems”

Lymphoplasmacytic infiltrate

Monoclonal IgM protein

Gertz et al. The Oncologist 2000;5:63-67
Waldenström macroglobulinemia
Morphology and Immunophenotype

- Lymphoplasmacytic infiltrate (usually intertrabecular)
- Immunophenotype - surface IgM+, CD19+, CD20+, CD79a+ and PAX5+. CD5−, CD10−, CD23−.
- MYD88 L265P is the most common genetic abnormality seen
- del(6)(q21) and CXCR4 mutations are also seen

Waldenström macroglobulinemia – presenting symptoms

- 217 patients with serum monoclonal IgM protein $\geq 3 \text{ g/dl}$ and $> 20\%$ bone marrow involvement -
  - Asymptomatic (27%)
  - Anemia (38%),
  - Hyperviscosity (31%),
  - B symptoms (23%),
  - Bleeding (23%)
  - Neurological symptoms (22%)

Waldenström macroglobulinemia
Monoclonal IgM

Symptoms related to the monoclonal IgM protein are attributable to:
- its characteristics in the circulation,
- its interaction with various body tissues when deposited,
- and its autoantibody activity.
Hyperviscosity due to Waldenström macroglobulinemia
IgM deposition due to Waldenström macroglobulinemia
Autoimmune hemolysis secondary to Waldenström macroglobulinemia
Diagnostic Criteria for Waldenström macroglobulinemia

Waldenström macroglobulinemia
IgM monoclonal gammopathy (regardless of the size of the M protein) with >10% bone marrow lymphoplasmacytoid infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytid or plasma cell differentiation and a typical immunophenotype (surface IgM+, CD5−, CD10−, CD19+, CD20+, CD23−) that satisfactorily excludes other lymphoproliferative disorders, including chronic lymphocytic leukemia and mantle cell lymphoma

IgM MGUS
Serum IgM monoclonal protein level <3 g/dL, bone marrow lymphoplasmacytoid infiltration <10%, and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly

Smoldering Waldenström macroglobulinemia (also referred to as indolent or asymptomatic Waldenström macroglobulinemia)
Serum IgM monoclonal protein level ≥3 g/dL and/or bone marrow lymphoplasmacytoid infiltration ≥10% and no evidence of end-organ damage, such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly, that can be attributed to a lymphoplasmacytic proliferative disorder

Time to developing WM and Survival in patients with Indolent WM or IgM MGUS

Time to evolution

Overall survival

MGUS (217 patients) and indolent Waldenström macroglobulinemia (201 patients) groups

Baldini L et al. JCO 2005;23:4662-4668
Survival of symptomatic patients with Waldenström macroglobulinemia (n=587)

WM Roadmap and why we need it

- Signaling
- ‘- omics’ – genomics, epigenomics, proteomics
- Immunology
- Bone marrow microenvironment
Molecular mechanisms of cancer

Signaling
Omics

**Cartoon:**

Two figures are shown. One, with a DNA double helix, is saying, "Do these genes make me look fat?"
Genomics, Epigenomics, Proteomics, Metabolomics
"According to all our tests, your immune system is 'out to lunch'."
Getting the Immune System to target WM

[Diagram showing immune system cells and their interactions, including Tumor, DC/MΦ, T reg cell, MDSC, and specific markers like IDO, Arginase, PD-L1/2, CTLA-4, PD-1, LAG-3, TGFβ, IL-6, IL-10, VEGF, and antigen-specific CTLs.]
Bone marrow microenvironment
Bone Marrow offers Therapeutic Targets
What is unique about the bone marrow microenvironment in WM?

- Whole genome sequencing – MYD88 L265P mutation in 27/30.
- High frequency confirmed in 49/54 additional cases (91%)
- Rarely expressed in myeloma, MZL, or IgM MGUS

CXCR4 mutations in Waldenström macroglobulinemia in 40%

A
MEGSIYTSNDYTEEMGSGDYMKEPCFRENAFNKIFLPIT
YSIIIFLTGIVGNGVILVILVMGYKQKLPRTMDKRYRLHLSVADLLFVI
TPLFWAVDANWYFGNFLCALKAVHYITYTVNYSSVLILAFS
RYLAIHVATNSQRPRKLLAEKVVYGWVWIPALLTIPDFIANVS
EADDRYICDRFPNDLWVVVFQFQHIMVGLILPGIVILSCYCIIS
KLSHSHGQRKALKTTVILLAFACWLPPYIGISIDSFILLEIIK
QGCEFENTVHKWISITEALAFFHCCLNPILYAFLGAKFKTISAHQ
ALTSMRSGLSKLSKCKGCHSTVSTSESSSFHSS
LEGEND
A - Germ line variant in WHIM syndrome  A - Transmembrane helix
■ - Somatic frame shift or nonsense WM variant

B

C

\[
\text{S338 Mutation Types}
\]

- Frame shift mutation
- Nonsense mutation

Hunter et al. Blood 2014;123:1637-1646
CXCR4/C1013G Mutations Drive Adhesion and Survival of Waldenström cells

Roccaro et al. Blood 2014;123:4120-4131
Overall survival of 175 WM patients stratified by MYD88 and CXCR4 mutation status

Treon et al. Blood 2014;123:2791-2796
MYD88 Mutations in Waldenström macroglobulinemia modulate cytokine function

**Diagram:**
- Cytokine
- LPS
- MYD88
- IRAK1
- IRAK4
- TRAF6
- TAB2/3
- TAK1
- NF-κB
- JAK/STAT
- pSTAT

**Text:**
- STAT Activation, Leading to Expression of Pro-Survival & Proliferation Genes
- Expression of Pro-Survival Genes and Cytokines
Cytokines are dysregulated in Waldenstrom macroglobulinemia
Cytokine-induced differentiation of B cells

BLyS/BAFF stimulates IgM production and malignant B-cell growth in Waldenstrom macroglobulinemia

IL-6 expression increased in Waldenstrom macroglobulinemia

IL-21 is expressed in WM and promotes proliferation and IgM secretion

Hodge L S et al. Blood 2012;120:3774-3782
The role of cytokines in regulating IgM levels in Waldenström macroglobulinemia
Therapeutic opportunities afforded by the biology of Waldenström macroglobulinemia
Ibrutinib in Waldenström macroglobulinemia

- 63 previously treated patients received 420 mg of oral ibrutinib daily.
- ORR was 90.5%, with a major response rate (PR or better) of 73%.
- 2-year progression-free and overall survival rates among all patients were 69.1% and 95.2%, respectively.

IMO-8400 in Patients with Relapsed Waldenstrom Macroglobulinemia

- IMO-8400 is an oligonucleotide antagonist of endosomal TLRs 7, 8, and 9.
- 17 patients (6 female, 11 male) enrolled in three dose cohorts.
- 6 of 15 evaluable patients (40%) had an objective response.
- Generally well tolerated. Main effects were transient flu-like symptoms and injection site reactions.

Thomas et al. ASH 2015, #1540
Everolimus in Waldenström macroglobulinemia

- 60 patients received everolimus 10 mg PO daily.
- ORR was 50% (all PR); the clinical benefit rate including MR or better was 73% (95% CI: 60-84%) with 23% MR.
- The median duration of response has not been reached and median progression-free survival (PFS) was 21 months.

Idelalisib in Waldenström macroglobulinemia

Summary

• MYD88 and CXCR4 mutations associated with Waldenström macroglobulinemia transmit signals to and from the bone marrow microenvironment.

• IgM production and cell growth in WM is regulated by cytokines from the bone marrow including BAFF/BLyS, IL-6, and IL-21.

• Inhibiting signals from the microenvironment are therapeutic opportunities in WM.
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[Image: IWMF logo]