Update on Waldenström Macroglobulinemia (WM)

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Disclosures

Stephen M. Ansell, MD, PhD has nothing to disclose.
Waldenström macroglobulinemia

Treatment approaches for newly diagnosed and relapsed disease

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Topics to be covered -

• What is Waldenström macroglobulinemia?
• Who needs treatment?
• Standard treatment options –
  • Newly diagnosed patients
  • Relapsed patients
What is Waldenström macroglobulinemia?

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−.
- exclude CLL and mantle cell lymphoma
- MYD88 L265P is the most common genetic abnormality seen
- del(6)(q21) and CXCR4 mutations are also seen


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.
MYD88 Mutations in Waldenström macroglobulinemia

MYD88 L265P mutations are almost universal in Waldenström macroglobulinemia

- Whole genome sequencing in 30 patients – MYD88 L265P mutation found 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 similar to WHIM syndrome

A

MEGISYTSNDYTEEMGSGDYDMSKICPFCREENAANFKIIFLPTI YSIIFLTGIVGVLIVLMGYQKLRSDTKYRLHLSVADLLFI TLPFWADAVANWYFGNFLCKAVHVTYVNLYSVLAMFLSILD RYLAIVHATNSQPRKLLAEKVVYYGVWIPALLLITPDIFANVS EADDRIYCDRFYPNDLWVVFQGHIMVGLIPGTVSCLCVISSLKLSHSGHOKRKLKTVILILAFFACWLPYIGISIDSFILLEI1K QGCEFENTVHKWSITEALAFFHCLNPILYAFLGAKFMSAQH ALFESURIKSSKEFCNKTQESSAFSSFFHSS

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

C

Frame shift mutation
Nonsense mutation

S338 Mutation Types
- Nonsense C/G
- Nonsense A/G
- Frame shift

Overall survival of 175 WM patients stratified by MYD88 and CXCR4 mutation status

Treon et al. Blood 2014;123:2791-2796
Waldenström macroglobulinemia – present symptoms

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


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 lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid 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 lymphoplasmacytic 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 lymphoplasmacytic 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; …IWM)
MGUS (217 patients) and indolent Waldenström's macroglobulinemia (201 patients) groups

Baldini L et al. JCO 2005;23:4662-4668
Risk of progression from IgM MGUS to WM or another B-cell malignancy

The overall average risk for progression is approximately 1.5% per year.

Survival of 587 symptomatic patients with Waldenström macroglobulinemia

Who needs treatment?

Patient 1

- 66 year old man
- Went for an executive physical – in good health with no symptoms
- Found to be mildly anemic (Hgb 12.8 g/dl). Other blood counts – normal
- Also noted to have increased total protein with an increased gammaglobulin level.
- Monoclonal IgM – 1.4 g/dl
- Bone marrow biopsy – 20% involvement by lymphoplasmacytic lymphoma
- CT scan – no lymph nodes
Patient 2

- 67 year old man
- Severe fatigue, nausea, visual difficulties, increasing confusion and sleepiness, gums bleed easily.
- Anemic (Hgb 8.8g/dl). Platelets decreased to 96,000.
- Ulcers have developed on his ankles
- Monoclonal IgM – 6.6 g/dl. Viscosity – 5.8
- Bone marrow biopsy – 85% involvement by lymphoplasmacytic lymphoma
- CT scan – enlarged liver and spleen and multiple bulky lymph nodes in the abdomen

Many treatment options

- Watch and wait
- Single agent rituximab
- Chemoimmunotherapy combinations
- Ibrutinib
- Plasmapheresis
- Clinical trials with new agents
- Stem cell transplantation

- Which approach is best?
Does everyone need treatment at diagnosis?

Watch and wait in Patients with Waldenström macroglobulinemia

Half of the patients who had no symptoms had not yet been treated at 3 years after their diagnosis

10% of the patients had not yet been treated at 10 years

What clinical findings suggest that treatment should be started?

- Fever, night sweats, or weight loss.
- Lymphadenopathy or splenomegaly.
- Hemoglobin ≤ 10 g/dL or a platelet count < 100 x 10^9/L due to marrow infiltration.
- Complications such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia.

Kyle et al. Semin Oncol. 2003 Apr;30(2):116-20

Before starting therapy –

Does the patient have hyperviscosity and do they need plasmapheresis?
Plasmapheresis for Waldenström patients with hyperviscosity

- Symptoms of hyperviscosity –
  - Visual deterioration
  - Neurological symptoms
  - Bleeding

- Rarely seen with IgM <4g/dL

Efficacy of Plasmapheresis for Waldenström patients with hyperviscosity

Before plasmapheresis - optic disc edema (arrowheads), central retinal hemorrhages (bold arrows), and venous “sausaging” (thin arrows).

Initial treatment for untreated symptomatic WM patients

Common Treatments used as initial therapy for WM

- Purine analogue based combinations – FCR/FR
- Alkylating agent based combinations – R-CHOP, DRC, R-Bendamustine
- Bortezomib based combinations – BDR
- Rituximab alone
- Ibrutinib
**Bendamustine plus rituximab compared with R-CHOP in WM patients**

- A subset analysis in the prospective randomized STIL trial - bendamustine plus rituximab (BR) compared with R-CHOP


**Rituximab alone for Waldenström macroglobulinemia**

69 symptomatic WM patients – rituximab x 4 doses

ORR 52% - 27% PR, 25% MR

Median duration of response – 27 months

**Gertz et al, Leuk Lymphoma. 2004 Oct;45(10):2047-55.**

Same study – evaluated IgM levels for “flare”

54% had an increase in IgM

27% still elevated at 4 months

No factors predicting an increase in IgM levels could be identified.

**Ghobrial et al. Cancer. 2004 Dec 1;101(11):2593-8.**
### Ibrutinib in Waldenström macroglobulinemia

- 63 previously treated patients received 420 mg of oral ibrutinib daily for 2 years or until progression.
- ORR was 90.5%, with a major response rate (PR or better) of 73% and a median time to response of 4 weeks.
- 2-year progression-free and overall survival rates among all patients were 69.1% and 95.2%, respectively.
- Toxicities > grade 2 - thrombocytopenia; neutropenia; atrial fibrillation and epistaxis.

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### Consensus for Newly Diagnosed Waldenström Macroglobulinemia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Observation</th>
<th>Single Agent Rituximab*</th>
<th>Bendamustine + Rituximab (BR)*</th>
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<tbody>
<tr>
<td>IgM MGUS (&lt;10% lymphoplasmacytic infiltration)</td>
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<tr>
<td>Asymptomatic/smoldering Waldenström’s</td>
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<td>Hemoglobin ≤11 g/dL</td>
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<td>Platelets ≥120 x 10^9/L</td>
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<td>Bulky Disease</td>
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<tr>
<td>Profound cytopenias –</td>
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<tr>
<td>- Hemoglobin ≤10 g/dL</td>
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<tr>
<td>- Platelets ≤100 x 10^9/L</td>
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<tr>
<td>Constitutional symptoms</td>
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<td>Hyperviscosity symptoms</td>
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</tbody>
</table>

| Hyperviscosity symptoms         | Yes          | Plasmapheresis            | Bendamustine + Rituximab (BR)* |
|                                 | No           |                          |                                |

> *Dexamethasone + Rituximab+ Cyclophosphamide (DRC)* is an alternative if disease burden is low

ASCT = autologous stem cell transplantation

v4 Revised March 2015
Subsequent treatment in relapsed WM patients

Newer drugs with promise

- BTK inhibitors - ibrutinib
- PI3kinase inhibitors - Idelalisib
- mTOR inhibitors - Everolimus
- New anti-CD20 antibodies - ofatumumab
- Anti-bcl2 agents - venetoclax
- New HDAC inhibitors - panobinostat
- New proteosome inhibitors - carfilzomib
- New Imids - Pomalidomide
Therapeutic opportunities afforded by the biology of Waldenström macroglobulinemia

Ibrutinib in Waldenström macroglobulinemia

- 63 patients received 420 mg of oral ibrutinib daily for 2 years or until progression,
- ORR was 81% (4 VGPR; 32 PR, 15 MR), with a major response rate (PR or better) of 57.1% and a median time to response of 4 weeks.
- 59 patients remain on study with 7 on reduced doses of ibrutinib.
- Toxicities - thrombocytopenia; neutropenia; stomatitis; atrial fibrillation; diarrhea; herpes zoster; hematoma; hypertension and epistaxis.
Waldenström Macroglobulinemia Consensus for Off-Study Salvage Therapy

Time to next therapy ≥ 4 years from previous therapy

Yes

Repeat Original Therapy

No

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

Autologous stem cell transplant in select patients

DRC = Dexamethasone + Rituximab + Cyclophosphamide; BR = Bendamustine + Rituximab; BDR = Bortezomib (weekly)
Dexamethasone + Rituximab
* If not previously used.

v4 Revised March 2015

Transplantation in relapsed Waldenström macroglobulinemia.

Autologous transplant –
158 WM patients
Non-relapse mortality – 3.8%
5-year PFS – 40%
5-year OS – 68%


Allogeneic transplant –
86 WM patients (37 MAC and 49 RIC)
Non-relapse mortality – 33%(MAC), 23% (RIC)
5-year PFS – 56%
5-year OS – 62%

Update on Waldenström Macroglobulinemia (WM)

Q&A Session

The Leukemia & Lymphoma Society Offers:

• Information Resource Center: Information Specialists, who are master’s level oncology professionals, are available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  ➢ EMAIL: infocenter@LLS.org
  ➢ TOLL-FREE PHONE: 1-800-955-4572

• Free Education Booklets:
  ➢ www.LLS.org/booklets

• Free Telephone/Web Programs:
  ➢ www.LLS.org/programs

• Live, weekly Online Chats:
  ➢ www.LLS.org/chat
The Leukemia & Lymphoma Society Offers:

• Support Resources: LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support

• LLS Podcast, The Bloodline with LLS: Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.LLS.org/thebloodline

• Education Video: Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos

• Patti Robinson Kaufmann First Connection Program: Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

• Free Nutrition Consults: Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition

• What to ask: Questions to ask your treatment team: www.LLS.org/whattoask

We have one goal: A world without blood cancers

THANK YOU FOR PARTICIPATING!