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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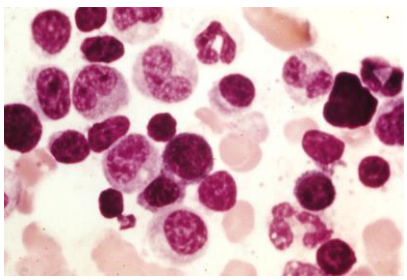
Topics to be covered -

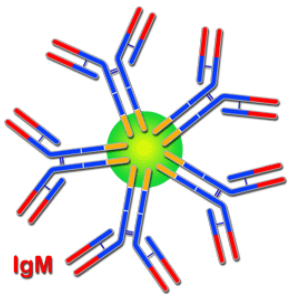
- What is Waldenström macroglobulinemia?
- Who needs treatment?
- Standard treatment options –
  - Newly diagnosed patients
  - Relapsed patients

What is Waldenström macroglobulinemia?

Waldenström macroglobulinemia
"A disease with two problems"



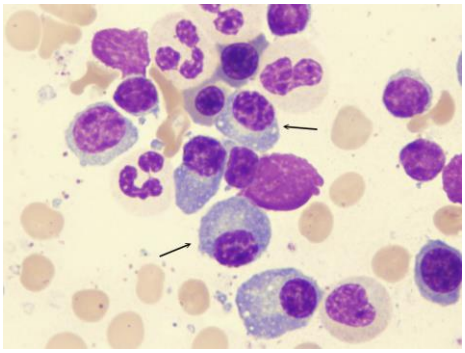
Lymphoplasmacytic infiltrate



Monoclonal IgM protein

Gertz et al. The Oncologist 2000;5:63-67

Waldenström macroglobulinemia Morphology and Immunophenotype

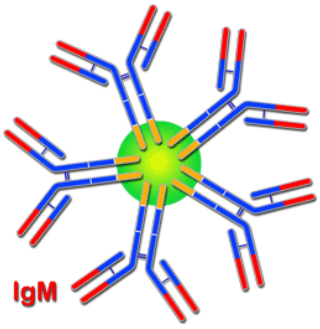


- Lymphoplasmacytic infiltrate (usually intertrabecular)
- Immunophenotype - surface IgM+, CD19+, CD20+, CD79a+ and PAX5+. CD5−, CD10−, CD23−.
- exclude CLL and mantle cell lymphoma
- MYD88 L265P is the most common genetic abnormality seen
- del(6)(q21) and CXCR4 mutations are also seen

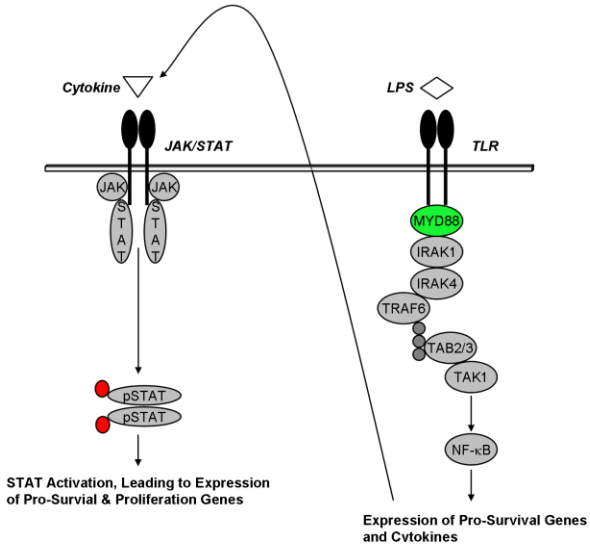
Treon et al. N Engl J Med. 2012;367(9):826-33.
Hunter et al. Blood. 2014;123(11):1637-46.

Waldenström macroglobulinemia Monoclonal IgM

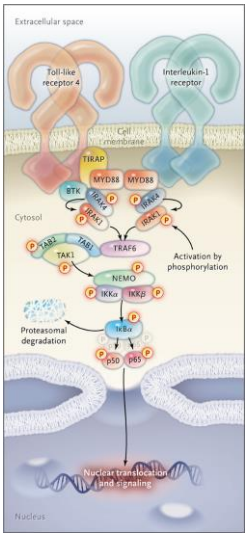
- Symptoms related to the monoclonal IgM protein are attributable to -
  - its characteristics in the circulation,
  - its interaction with various body tissues when deposited,
  - and its autoantibody activity.



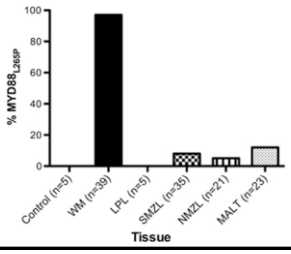
MYD88 Mutations in Waldenström macroglobulinemia



MyD88 L265P mutations are almost universal in Waldenström macroglobulinemia

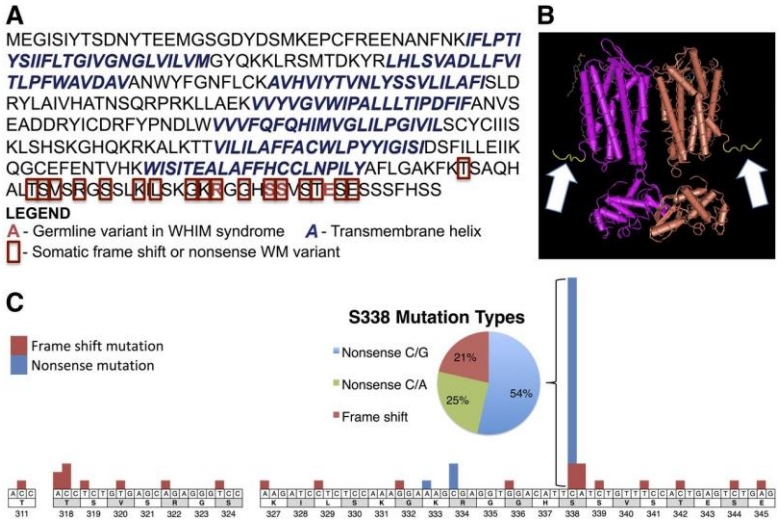


- Whole genome sequencing in 30 patients – MYD88 L265P mutation found in 27/30.
- High frequency confirmed in 49/54 additional cases (91%)
- Rarely expressed in myeloma, MZL, or IgM MGUS



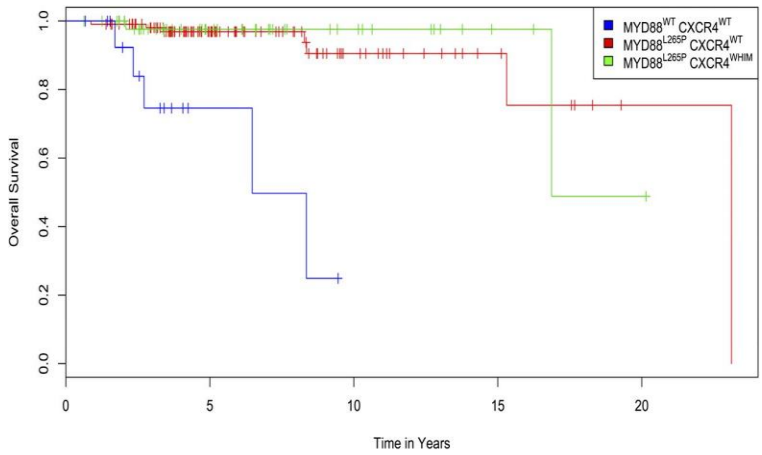
Treon SP et al. N Engl J Med 2012;367:826-833.
Ansell et al. Blood Cancer J. 2014 Feb 14;4:e183.

CXCR4 mutations in Waldenström macroglobulinemia similar to WHIM syndrome



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

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



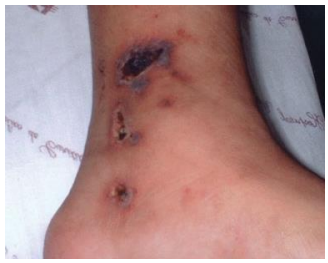
Treon et al. Blood 2014;123:2791-2796

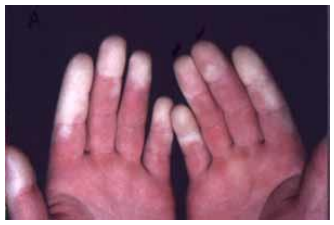
Waldenström macroglobulinemia – presenting symptoms

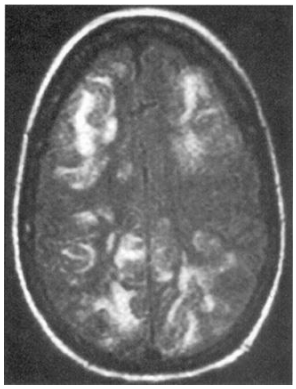
- 217 patients with serum monoclonal IgM protein ≥ 3 g/dl and > 20% bone marrow involvement -
  - Asymptomatic (27%)
  - Anemia (38%),
  - Hyperviscosity (31%),
  - B symptoms (23%),
  - Bleeding (23%)
  - Neurological symptoms (22%)

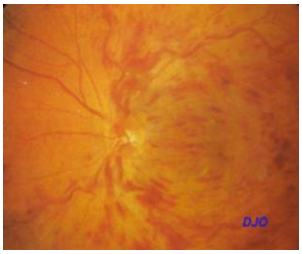
García-Sanz et al. Brit J Haematol. 115: 575-582, 2001

Hyperviscosity due to Waldenström macroglobulinemia

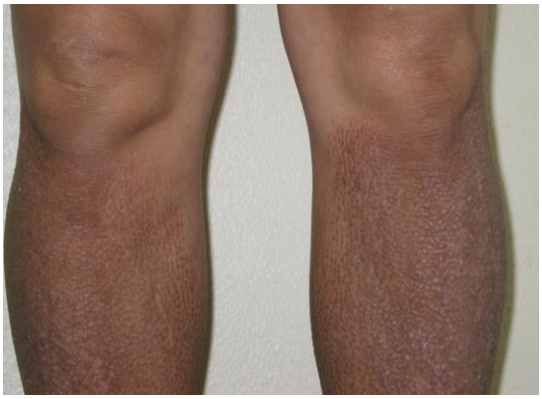


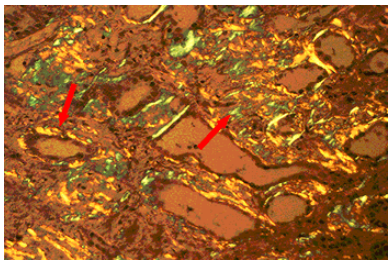




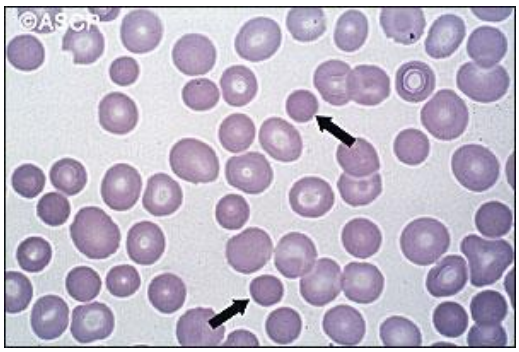


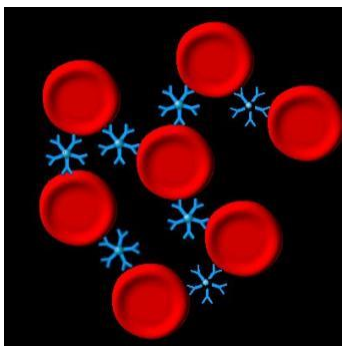
IgM deposition due to Waldenström macroglobulinemia





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

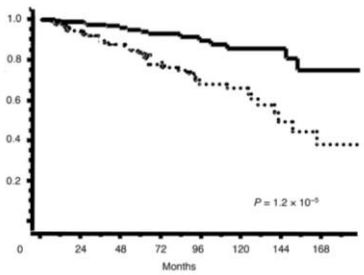
IgM MGUS
Serum IgM monoclonal protein level <3 g/dL, bone marrow lymphoplasmacytic infiltration <10%, and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly

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

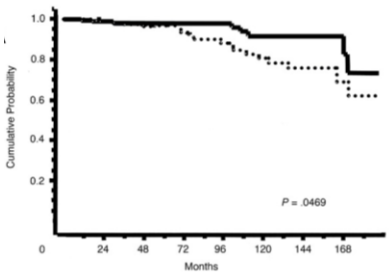
Kyle et al. Leukemia. 2009 Jan;23(1):3-9.

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

Time to evolution



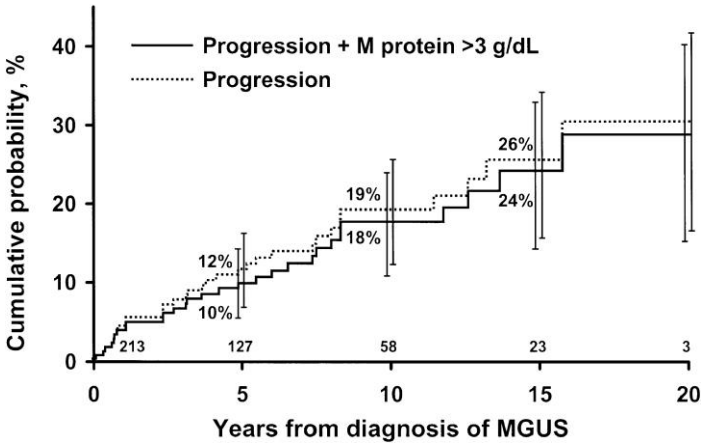
Overall survival



(— MGUS; ···IWM)
MGUS (217 patients) and indolent Waldenström's macroglobulinemia (201 patients) groups

Baldini L et al. JCO 2005;23:4662-4668

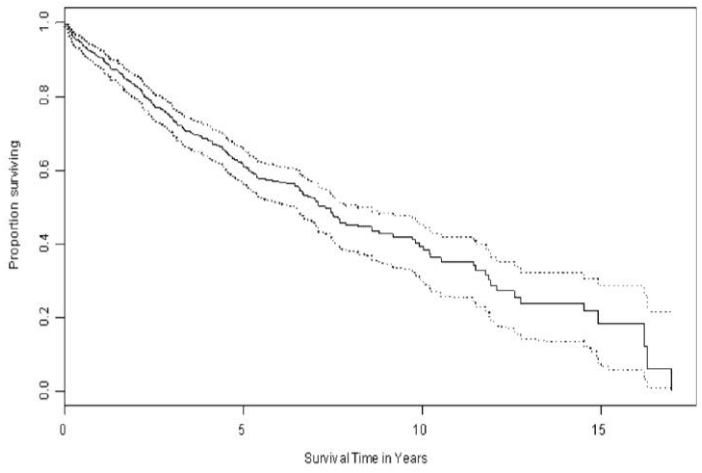
Risk of progression from IgM MGUS to WM or another B-cell malignancy



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

Kyle R A et al. Blood 2003;102:3759-3764

Survival of 587 symptomatic patients with Waldenström macroglobulinemia



Morel P et al. Blood 2009;113:4163-4170

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 12.8g/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

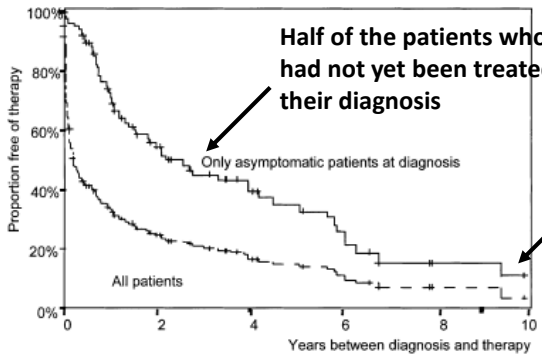
Many treatment options

- 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

García-Sanz et al. Brit J Haematol. 115: 575-582, 2001

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

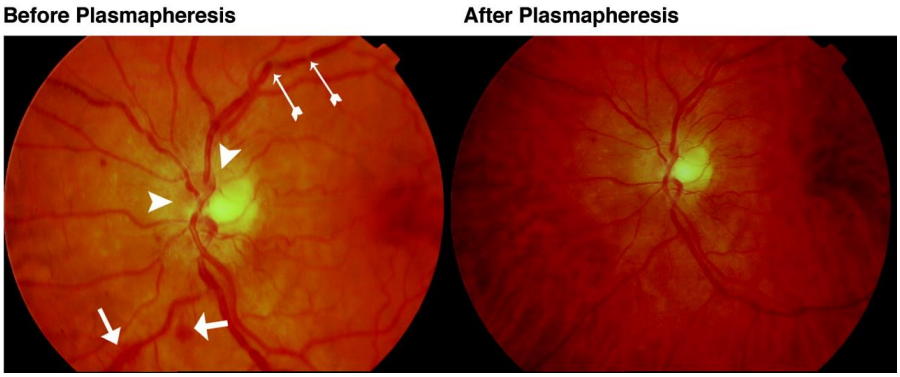
Before starting therapy –

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).

Menke et al. Invest Ophthalmol Vis Sci. 2008Mar;49(3):1157-60.

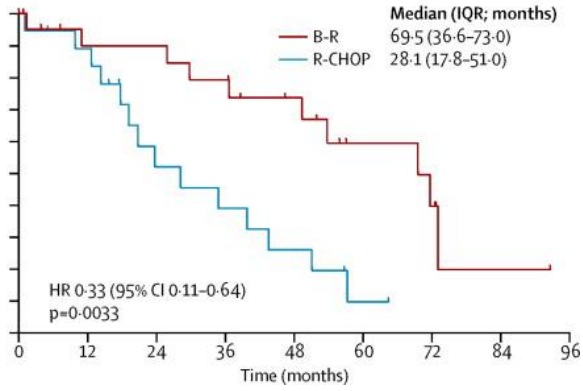
Initial treatment for untreated symptomatic WM patients

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



Rummel MJ, et al. Lancet. 2013 Apr 6;381(9873):1203-10.

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.

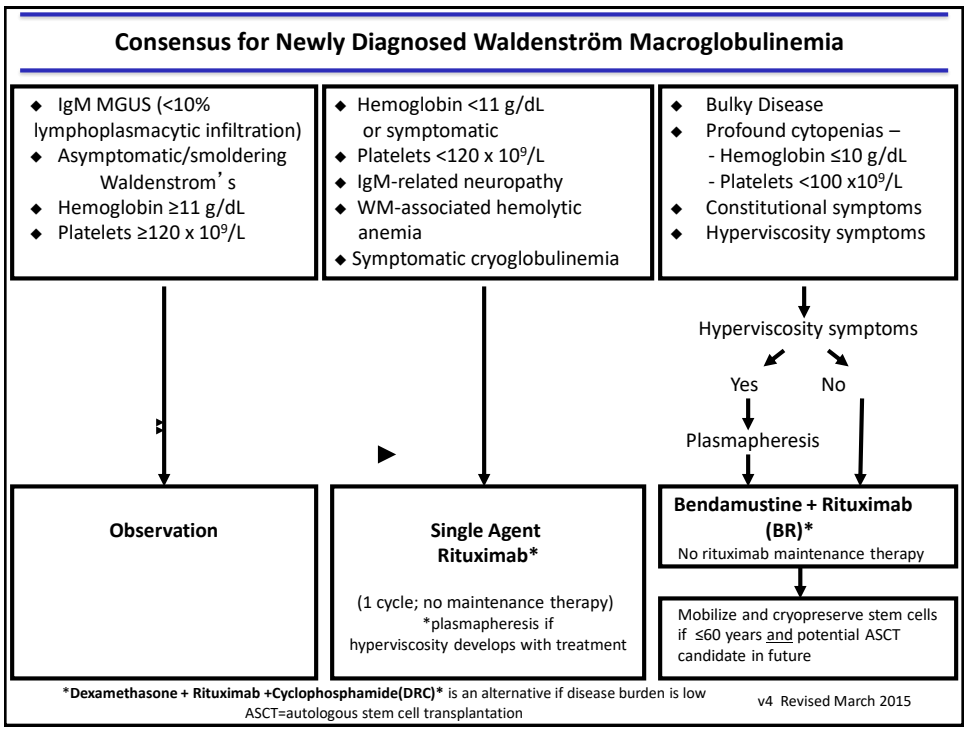
Same study – evaluated IgM levels for "flare"
54% had an increase in IgM
27% still elevated at 4 months
No factors predicting an increase in IgM levels could be identified.

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.

Treon et al. N Engl J Med. 2015 Apr 9;372(15):1430-40.

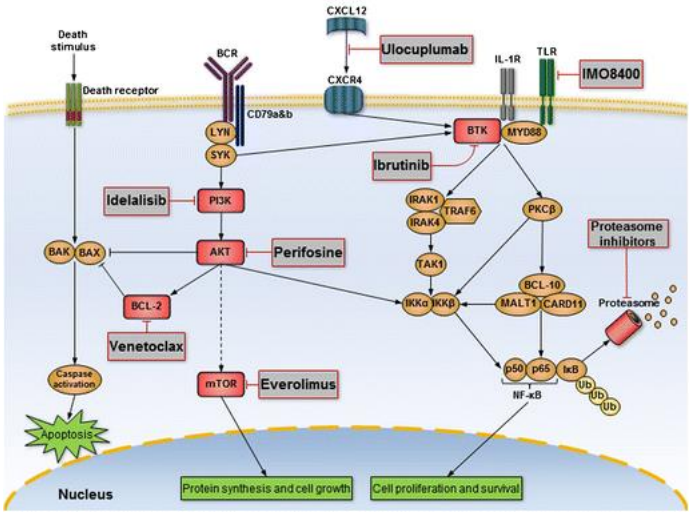


Subsequent treatment in relapsed WM patients

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



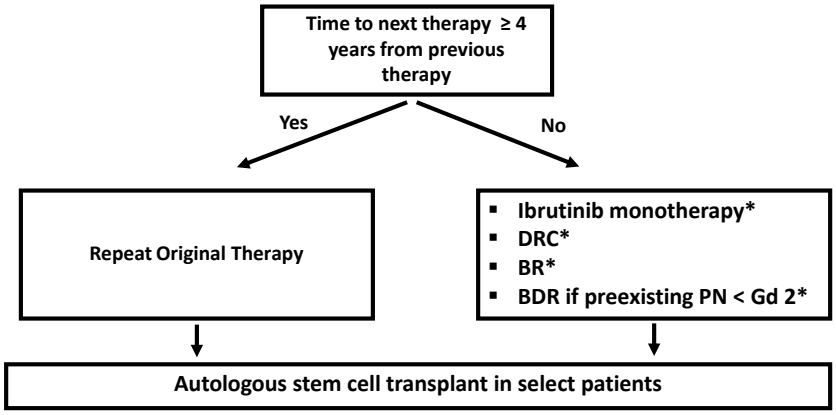
Kapoor et al. Curr Treat Options Oncol. 2016 Mar;17(3):16.

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.

Treon et al. ASH. 2013 Abstract 251.

Waldenström Macroglobulinemia Consensus for Off-Study Salvage Therapy



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%

Kyriakou et al, J Clin Oncol. 2010 May 1;28(13):2227-32.

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%

Kyriakou et al. J Clin Oncol. 2010 Nov 20;28(33):4926-34.

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LEUKEMIA & LYMPHOMA SOCIETY®

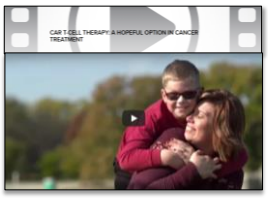
Q&A Session

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**



THANK YOU FOR PARTICIPATING!

We have one goal:
A world without blood cancers

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