Waldenstrom's Macroglobulinemia

Essential Information: A Physician's Guide

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Medical Disclaimer: The information presented here is intended for educational purposes only. It is not meant to be a substitute for professional medical advice. Patients should use the information provided in full consultation with, and under the care of a physician with experience in the treatment of WM. We discourage the use by a patient of any information contained herein without disclosure to his or her medical specialist.

What is Waldenstrom's macroglobulinemia (WM)?

Waldenstrom's macroglobulinemia (WM) is an indolent lymphoma characterized by the presence of lymphoplasmacytic cells which secrete an IgM monoclonal paraprotein.[1] The clonal lymphoplasmacytic cells in WM can be present in the bone marrow at any concentration, but may also be found in the lymph nodes, spleen, liver or other extramedullary locations. Patients with a serum monoclonal IgM in the absence of a detectable bone marrow clone and with no associated clinical signs or symptoms related to the IgM paraprotein are characterized as having a monoclonal gammopathy of undetermined significance (MGUS). An MYD88 L265P mutation is detectable in up to 50% of patients with IgM MGUS, but is found in >90% of patients with WM. The presence of an MYD88 mutation can help distinguish WM from other hematologic disorders, such as multiple myeloma, in which MYD88 mutations are not found.[2-5]

How common is WM and who is at risk?

WM is a rare lymphoma that affects 3-4 persons per million.[6] It is more common in men than women and is also more common in White patients, particularly of European descent, compared with other races/ethnicities.[7] This is a disease that occurs in older patients with an average age of diagnosis of approximately 70 years.[8] Having an IgM MGUS poses a cumulative risk of developing WM of 1% per year.[9]

Why did my patient get WM?

The exact etiology of WM is unclear. It develops spontaneously with no known predisposing factors or causes in most cases, although there are data relating the development of WM to underlying chronic inflammation or autoimmune disorders.[10,11] Additionally, familial clustering has been reported in WM with approximately 19% of all patients with WM having a first-degree relative with WM or another B-cell disorder.[11]

Are my patient's children at risk for developing WM?

Waldenstrom's macroglobulinemia is typically not directly inherited. Having a family member with WM does increase the risk of developing WM, another non-Hodgkin lymphoma, or MGUS, but the relative risk remains low.[11,12] Despite this slightly increased risk of hematologic disorders in family members of WM patients, in the absence of concerning signs or symptoms it is generally not recommended that other family members be screened for WM.[10]

What is the life expectancy of a person with WM?

Most patients with WM will live for many years and potentially even decades. In many cases, especially young patients with WM, life expectancy is matched with gender-specific, age-specific matched cohorts and patients will likely die from something unrelated to WM.[13] The International Prognostic Scoring System for WM (IPSSWM) can be used to further define a patient's risk group by using age, hemoglobin, platelets, β-2-microglobulin, and IgM.[14] In recent years this scoring system was revised (rIPSSWM) and now includes age, β-2-microglobulin, lactate dehydrogenase (LDH), and albumin.[15] In both of these scoring systems age is weighed most heavily as a risk factor. When using the IPSSWM or rIPSSWM it must be taken into account that these systems were developed at a time before the current, most effective standard therapies were widely available, so it is expected that prognosis has improved since the development of these scoring systems. In addition, these prognostic tools aim at estimating survival from first line therapy initiation and not at diagnosis.

How can I confirm a diagnosis of WM and what tests should be performed prior to treatment?

The criteria to confirm a diagnosis of WM include the presence of a monoclonal IgM paraprotein (which can be detected on serum immunofixation electrophoresis) and a lymphoplasmacytic infiltrate in the bone marrow.[16] The clonal infiltration in the bone marrow is typically positive for expression of surface IgM, CD19, CD20, CD25 and CD27.[17] Although CD5, CD10 and CD23 are not typically expressed they may be present in a minority of cases. In addition to the diagnostic utility of a bone marrow biopsy, a bone marrow aspirate should also be obtained in patients with suspected WM to evaluate the MYD88 mutational status, in addition to evaluating the mutational status of CXCR4. An MYD88 mutation will be detected in more than 90% of patients with WM.[2,3] CXCR4 mutations are found in approximately 30-40% of patients with WM. The MYD88 and CXCR4 mutational status may influence clinical manifestations of the disease as well as treatment options.[18-22]

Additional baseline labs, such as complete blood counts, comprehensive metabolic panel, serum immunofixation electrophoresis, serum protein electrophoresis, immunoglobulins, serum viscosity (if concern for symptomatic hyperviscosity), β-2-microglobulin, cryoglobulins, and cold agglutinins may be helpful for full disease assessment. Prior to initiating therapy, it is also important to obtain baseline CT scans to evaluate for sites of extramedullary disease and splenomegaly. This imaging is not required at the time of diagnosis for asymptomatic patients.

Of note, in an era of rapidly evolving research it can be helpful to have the input of a specialist with an in-depth understanding of the nuances and complexities of the highly variable clinical presentation of WM, as well as the genetic and molecular characteristics of the disease. There are multiple physicians throughout the US and in other countries who specialize in WM and would be willing to evaluate your patient and continue to collaborate with you for ongoing patient care. Contact information for many WM specialists can be found through the International Waldenstrom's Macroglobulinemia Foundation (IWMF) Physician Directory.

Why should CXCR4 status be evaluated?

Patients with CXCR4 mutations are more likely to present with higher serum IgM levels, increased bone marrow burden of disease, increased risk of hyperviscosity, and increased risk of acquired von Willebrand syndrome.[23] Knowing the CXCR4 mutational status can help predict responses to therapy, as it has been noted that the time to response, depth of hematologic response, and the length of progression free survival is inferior with BTK inhibitors such as ibrutinib.[24] The rate of major response was also shown to be lower in patients with CXCR4 mutations treated with either ibrutinib or zanubrutinib when compared with patients that have wild-type CXCR4.[25]

Does everyone need treatment at the time of diagnosis?

Not everyone who is diagnosed with WM requires treatment at the time of diagnosis. Within two years of diagnosis approximately 30% of patients will require treatment, but there are about 20-30% of patients that will not require treatment even 10 years after diagnosis of WM.[26,27] It can be helpful to use albumin serum IgM level, percent of bone marrow infiltration, and β-2-microglobulin to calculate the median time to disease progression to assist asymptomatic patients in understanding when they may require treatment. (awmrisk.com)

What are the criteria for treatment of WM?

There are specific guidelines for initiation of therapy, including the development of symptomatic anemia with a hemoglobin ≤10 g/dL (secondary to the WM), platelets <100,000 mm3, symptomatic hyperviscosity, moderate to severe neuropathy, symptomatic extramedullary disease, or other symptomatic complications of the disease such as cold agglutinemia, cryoglobulinemia, or amyloidosis.[28,29]

It is also important to recognize that although patients have an increased risk of hyperviscosity when IgM reaches ≥4,000 mg/dL, there is no need to treat asymptomatic patients based only on the serum IgM level or serum viscosity. The risk of hyperviscosity increases with the IgM level and for those patients with an IgM >6000 mg/dL at the time of diagnosis the median time to symptomatic hyperviscosity is approximately 3 months compared with those patients with an IgM of 5000-6000 mg/dL that have a median time of 3 years until development of symptomatic hyperviscosity.[30]

What work-up should be done in the setting of worsening anemia in a patient with WM?

If a patient with WM has developed significant anemia, prior to offering WM-directed therapy it is important to ensure there is no other cause for the anemia. Work-up should be performed to evaluate for other etiologies of anemia such as B12, folate or iron deficiency. If iron deficiency is discovered a thorough work-up for bleeding, especially gastrointestinal, should be performed. If no alternative source of iron deficiency is discovered the iron deficiency may be a result of the WM. Approximately 25% of patients with WM develop iron deficiency related to production of hepcidin from malignant cells.[31,32] In such cases, intravenous iron may be used to improve the patient's hemoglobin. Hemolysis is a rare cause for anemia in patients with WM and could be associated with warm auto-antibodies or cold agglutinins.

What symptoms should I and my patients monitor for?

Although symptomatic anemia is the most common presentation of WM, additional signs and symptoms of the disease can vary widely and may include:[33]

- Constitutional symptoms (fatigue, weight loss, night sweats, and unexplained fevers)
- Splenomegaly (early satiety, left upper quadrant pain or fullness)
- Hyperviscosity (nosebleeds, headaches, blurred vision)
- Peripheral neuropathy (bilateral, symmetrical, length-dependent, sensory deficits)
- Cold agglutinin disease (anemia and dark colored urine when exposed to cold temperatures)
- Cryoglobulinemia (livedo reticularis, discoloration of hands, feet, nose tip, or ears when exposed to cold temperatures)
- Amyloidosis (nephrotic syndrome, cardiomyopathy, rapidly progressing neuropathy)
- Bing Neel syndrome (headaches, seizure, facial paralysis, limb weakness)

How common is neuropathy in WM and how should it be evaluated?

Neuropathy is present in approximately 25% of patients with WM at the time of diagnosis.[34] Typically, IgM-related neuropathy is bilateral and symmetrical, slowly progressive (years), length-dependent, and predominantly sensory.

In many cases the neuropathy is related to the presence of an anti-myelin associated glycoprotein (anti-MAG) antibody, but anti-ganglioside and anti-sulfatide antibodies have also been reported. Neuropathy mediated by an anti-MAG antibody typically presents as a sensorimotor polyneuropathy with demyelinating features on electromyography and nerve conduction studies (EMG/NCS). Less commonly, neuropathy can be related to amyloidosis or cryoglobulinemia. A thorough evaluation by a neurologist, including an EMG/NCS, history and physical exam, is important in patients with rapidly progressive neuropathy or neuropathy that is significantly affecting a patient's quality of life to confirm the etiology of the neuropathy prior to initiating therapy for WM.

What are the most common symptoms of hyperviscosity?

Hyperviscosity symptoms can include bleeding (commonly nosebleeds or spontaneous oral bleeding), vision changes, or central nervous system symptoms such as headache, dizziness, or seizure. Blurred vision can occur, usually related to retinal vessel engorgement or retinal bleeding. Patients at risk for hyperviscosity should have annual or semi-annual eye exams to ensure there are no signs of hyperviscosity, such as retinal vessel hemorrhages, retinal or optic nerve head edema or retinal vein dilation.[35]

What should be done if I am concerned that my patient has symptomatic hyperviscosity?

If there is concern for hyperviscosity then serum IgM level and serum viscosity can be measured. Typically, a serum viscosity ≤4 centipoise does not lead to clinical symptoms of hyperviscosity. Serum viscosity is often not readily available and in most cases a serum IgM level is sufficient to determine the risk of hyperviscosity with an IgM ≥6,000 mg/dL having an incidence of hyperviscosity of approximately 67%.[30] An exam and thorough history should be performed in patients with elevated serum IgM to evaluate for clinical signs or symptoms of hyperviscosity.

In the case of symptomatic hyperviscosity patients should be treated with plasmapheresis to reduce the serum IgM and alleviate clinical signs/symptoms of hyperviscosity. At least 1-2 sessions of plasma exchange can be performed as a bridging therapy while definitive treatment is initiated.

What are the treatment options?

Treatment options for WM vary and should be chosen based on each patient's disease characteristics and patient-specific factors, such as age, performance status, co-morbidities, and treatment preferences.

In recent years, as cancer directed therapies have moved more towards targeted treatments, BTK inhibitors have become a mainstay in first-line therapy of WM. The FDA has approved both ibrutinib (+/- rituximab) and zanubrutinib as options for first line therapy in WM due to the high response rate and acceptable safety profile.[25,36,37] There are also data for using acalabrutinib in WM, although it is not FDA approved in WM.[38] BTK inhibitors are a preferred treatment option in many patients, although alternative options can be considered especially in patients with MYD88 wild-type or CXCR4 mutated disease. The adverse effects associated with BTK inhibitors include risks of bleeding, infection, gastrointestinal symptoms, cytopenias, arthralgias or myalgias, and atrial fibrillation. Recent data confirm that newer BTK inhibitors, such as zanubrutinib, have the same disease efficacy as ibrutinib but with less off- target effects.[25]

Bendamustine-rituximab is also a common first-line treatment option that has a finite duration of

treatment (4-6 cycles) and has efficacy, independent of the CXCR4 mutational status.[39-41] Rituximab-bortezomib-dexamethasone, in addition to other proteasome inhibitor-based regimens, are also potential treatment options, although consideration must be made for the potential side effect of neuropathy especially in patients with baseline neuropathy related to their WM.[42,43] In patients with an IgM >4,000 mg/dL rituximab should not typically be given due to the risk of IgM flare.[44,45] In those cases, bendamustine or the proteasome inhibitor can be given for 1-2 cycles with rituximab added at a later date. Of note, approximately 10% of patients with WM will develop intolerance to rituximab and in this case ofatumumab can be substituted for rituximab per the NCCN guidelines.[46]

In the relapsed setting any of the above mentioned therapies can be considered if not previously utilized.[47-49] In addition, a two year course of venetoclax can also be used for treatment of relapsed or refractory WM.[50]

Importantly, when feasible clinical trials should be considered for patients with newly diagnosed or relapsed disease, as patient enrollment in clinical trials is incredibly important for the development of new therapies in rare diseases such as WM.

How is Bing Neel syndrome diagnosed and treated?

Bing Neel syndrome (BNS) is a rare manifestation of WM that occurs in approximately 1% of patients and is characterized by the infiltration of malignant cells into the central nervous system.[51,52] Bing Neel syndrome can occur at the time of initial WM diagnosis or later in the disease course. The clinical presentation of Bing Neel syndrome can vary widely, but common symptoms include cognitive changes, behavioral changes, seizures, headaches, gait/ balance abnormalities, cranial nerve deficits, or paresis. Evaluation for potential Bing Neel syndrome should include cerebral spinal fluid (CSF) evaluation and MRI (with gadolinium) of the brain and the spine, including cervical, thoracic, and lumbar regions. Typical findings of BNS on MRI may include either tumoral involvement or leptomeningeal enhancement. Lumbar puncture should be performed for complete evaluation and CSF should be sent for flow cytometry, cytology, IGH rearrangement, and MYD88 testing. If Bing Neel syndrome is diagnosed the preferred first-line therapy is a BTK inhibitor. The most robust data in this setting support the use of ibrutinib, although early data suggest that zanubrutinib may also be a potential treatment.[53] In the case of relapsed or refractory BNS, other chemotherapy based regimens such as bendamustine/ rituximab, fludarabine/rituximab, or intrathecal therapy can be considered.

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The IWMF, the only international organization dedicated solely to Waldenstrom's macroglobulinemia, is a patient-founded and patient-driven nonprofit with a simple but compelling vision and mission.

VISION: A world without Waldenstrom's macroglobulinemia.

MISSION: Support and educate everyone affected by Waldenstrom's macroglobulinemia to improve patient outcomes while advancing the search for a cure.

The IWMF is committed to creating a world without WM by finding a cure. Since 1999, the IWMF has invested over $23 million in WM research projects throughout the world. Thanks to this research, WM patients are living longer and have better treatment options that can lead to longer-lasting remissions with fewer side effects.

Visit the IWMF website to:

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- Find contact information for our partner organizations.

The IWMF relies on donor contributions to fulfill its mission, and we welcome your support. You can contribute to the organization by visiting our website or by mailing a check to:

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Cancer Support Community (CSC)

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As the largest professionally led nonprofit network of cancer support worldwide, the Cancer Support Community (CSC), including its Gilda's Club affiliates, is dedicated to ensuring that all people impacted by cancer are empowered by knowledge, strengthened by action, and sustained by community. CSC achieves its mission through three areas: direct service delivery, research, and advocacy. The organization's Institute for Excellence in Psychosocial Care includes an international network of affiliates that offer the highest quality social and emotional support for people impacted by cancer, as well as a community of support available online and over the phone. The Research and Training Institute conducts cutting-edge psychosocial, behavioral, and survivorship research. CSC furthers its focus on patient advocacy through its Cancer Policy Institute, informing public policy in Washington, D.C. and across the nation.

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Founded in 1949 and headquartered in Rye Brook, NY, LLS has regions throughout the United States and Canada. To learn more, visit lls.org. Patients should contact the Information Resource Center at (800) 955-4572, Monday through Friday, 9 a.m. to 9 p.m. ET.

For additional information visit lls.org/lls-newsnetwork.

Lymphoma Coalition

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Lymphoma Coalition is a worldwide network of patient organisations that support those affected by lymphoma. LC acts as a central hub for reliable and current information, as well as advocating for equitable care globally. Its mission is to enable global impact by fostering a lymphoma ecosystem that ensures local change and evidence-based action. Today, there are more than 80 member organisations from over 50 countries.

Lymphoma Research Foundation (LRF)

lymphoma.org

LRF Helpline: 800-500-9976

The Lymphoma Research Foundation (LRF) is the nation's largest non-profit organization devoted exclusively to funding lymphoma research and supporting the lymphoma community through evidence-based education, support services, and resources.

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