Waldenstrom's Macroglobulinemia

Essential Information: A Nurse's Guide

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Shayna Sarosiek, MD
Bing Center for Waldenstrom Macroglobulinemia
Division of Hematological Malignancies, Dana-Farber Cancer Institute
Assistant Professor, Harvard Medical School

Catherine A. Flynn, NP
Bing Center for Waldenstrom Macroglobulinemia
Division of Hematological Malignancies, Dana-Farber Cancer Institute
Assistant Professor, Harvard Medical School

Jorge J. Castillo, MD
Clinical Director, Bing Center for Waldenstrom Macroglobulinemia
Division of Hematological Malignancies, Dana-Farber Cancer Institute
Associate Professor, Harvard Medical School

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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 and how is it diagnosed?

Waldenstrom's macroglobulinemia (WM) is an indolent non-Hodgkin lymphoma characterized by the presence of lymphoplasmacytic cells which secrete an IgM monoclonal paraprotein.[1] The malignant cells in WM can reside in the bone marrow, lymph nodes, spleen, liver, or other locations outside the bone marrow.

Typically a diagnosis of WM is made by obtaining a serum immunofixation electrophoresis (to confirm the presence of an IgM clone), and a bone marrow biopsy to confirm the presence of a lymphoplasmacytic lymphoma. The bone marrow sample should also be tested for MYD88 L265P and CXCR4 mutations, which are frequently detected in WM. An MYD88 mutation is found in >90% of patients with WM and can help distinguish WM from other hematologic disorders, such as multiple myeloma, in which MYD88 mutations are not found.[2-5] CXCR4 mutations can be found in approximately 30-40% of patients with WM. MYD88 and CXCR4 mutational status may affect the clinical manifestations and treatment options.[6-10]

Patients with a clone of IgM in the blood, but without a detectable bone marrow clone and no associated clinical signs or symptoms related to the IgM, are characterized as having a monoclonal gammopathy of undetermined significance (MGUS). A MYD88 mutation is detectable in up to 50% of patients with IgM MGUS. Patients with IgM MGUS have a small chance of progressing to WM over the course of many years.

How common is WM and who is at risk?

WM is a rare lymphoma that affects 3-4 persons per million.[11] It is more common in men than women and in White patients, particularly of European descent, compared with other races/ethnicities.[12] The average age of diagnosis is approximately 70 years.[13] In most patients, the etiology of WM is not well understood. However, approximately 19% of all patients with WM have a first-degree relative with WM or another B-cell disorder.[14] Despite this slightly increased risk of hematologic disorders in family members of patients with WM, in the absence of concerning signs or symptoms, it is generally not recommended that other family members be screened for WM.[15]

What is the life expectancy of patients with WM?

Most patients with WM will live for many years and potentially even decades. In many cases life expectancy is matched with gender-specific, age-specific matched cohorts, and patients will likely die from something unrelated to WM.[16]

Does everyone need treatment at the time of diagnosis?

Not everyone who is diagnosed with WM requires treatment. Within two years of diagnosis, approximately 30% of patients will require treatment, but about 20-30% will not require treatment even ten years after the diagnosis of WM.[17,18] 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 (https://awmrisk.com).

Why not treat everyone with WM?

We currently have no curative therapy for WM and initiation of treatment may lead to adverse effects that negatively affect a patient's quality of life. In patients with WM that are asymptomatic and remain without WM-related symptoms or

disease progression, it is best to have a "watchful waiting" approach and monitor the patient closely without treatment. These patients may be able to live for many years, and some patients for the remainder of their lifetime, without the need for therapy.

What are the criteria for the treatment of WM?

There are official guidelines for initiation of therapy, including the development of symptomatic anemia with hemoglobin ≤10 g/dL (secondary to the WM), platelets <100,000 mm^3, symptomatic hyperviscosity, moderate to severe neuropathy, symptomatic extramedullary disease, or other symptomatic complications of the disease such as cold agglutinin syndrome, cryoglobulinemia, or amyloidosis.[19,20] These guidelines, in addition to patient specific factors such as laboratory results and symptoms, are used to determine when treatment should be initiated.

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, it is important to ensure there is no other cause for the anemia before offering WM-directed therapy. Work-up should be performed to evaluate for other etiologies 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 hepcidin overproduction from the malignant cells.[21,22] In such cases, intravenous iron may be given to improve the patient's hemoglobin.

What symptoms should I and my patient 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:[23]

- 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 syndrome (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, seizures, facial paralysis, limb weakness)

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

Neuropathy is present in approximately 25% of patients with WM at diagnosis.[24] Typically, IgM-related neuropathy is bilateral and symmetric, 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.

Still, a thorough evaluation by a neurologist, including an EMG/NCS, as well as history, phys-

ical exam, and labs, is important in patients with rapidly progressive neuropathy or neuropathy that is affecting a patient's quality of life. It is important to confirm the etiology of the neuropathy and confirm its relationship to the IgM paraprotein before initiating therapy for WM-directed therapy to improve the neuropathy.

Beyond definitive care of the underlying IgM paraprotein, symptomatic care of neuropathy is important. Many patients use medications such as gabapentin, pregabalin, or amitriptyline for pain control. Other patients may benefit from additional therapies, such as acupuncture, physical therapy, topical analgesics, or massage.

What is hyperviscosity and when does it need treatment?

An elevated serum IgM level can cause hyperviscosity or thickened blood, which can have clinical consequences in some patients. It is important to recognize that although patients have an increased risk of hyperviscosity when IgM reaches ≥4,000 mg/dL, there is no specific serum IgM level that necessitates therapy.

Instead, treatment decisions are based on clinical symptoms associated with hyperviscosity, including bleeding (commonly nosebleeds or spontaneous oral bleeding), vision changes, or central nervous system symptoms such as headache, dizziness, seizure, or cognitive changes. Blurred vision can be related to retinal vessel engorgement or retinal bleeding. Patients at risk for hyperviscosity should have an annual or semi-annual dilated eye exam with an ophthalmologist to ensure there are no signs of hyperviscosity, such as retinal vessel hemorrhages, retinal or optic nerve head edema, or retinal vein dilation.[25] Such findings could warrant initiation of WM treatment.

In those patients with an IgM >4,000 mg/dL, especially those with bleeding, it is reasonable to evaluate for acquired von Willebrand disease to help determine the patient's risk of bleeding.

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

If there is a concern for hyperviscosity, 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. 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%.[26] An exam and thorough history should be performed in patients with elevated serum IgM levels to evaluate for clinical signs or symptoms of hyperviscosity.

In the case of symptomatic hyperviscosity, patients should be treated urgently with plasmapheresis to temporarily 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 most common treatment options for WM?

Treatment options 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.

Chemoimmunotherapy, such as DRC (dexamethasone, rituximab, cyclophosphamide) or BR (rituximab, bendamustine), are common treatment regimens in treatment-naïve patients or those with relapsed or refractory disease. Proteasome inhibitors, such as bortezomib or ixazomib, can also be used in combination with rituximab in some patients, although these agents are used less

frequently due to the increased risk of peripheral neuropathy associated with these medications.

In recent years, BTK inhibitors have become a mainstay in first-line or relapsed 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.[27-29] There are also data for using acalabrutinib in WM, although it is not FDA-approved in WM.[30] BTK inhibitors are used in many patients, although alternative options can be considered, especially in patients with MYD88 wild-type or CXCR4 mutated disease.

Additionally, a two-year course of venetoclax can also be used to treat relapsed or refractory WM.[31] Many ongoing clinical trials are exploring the use of new medications or new combinations of therapies in WM, and participation in clinical trials should always be encouraged for eligible patients. Patient enrollment in clinical trials is incredibly important for developing new therapies for rare diseases such as WM.

What treatment side effects might I see in my patients?

In most patients, BTK inhibitors are well tolerated, but adverse effects may develop in some patients. Common symptoms of BTK inhibitors are easy bruising/bleeding, diarrhea, arthralgias, and myalgias.[32] Additional adverse effects of note include infection, arrhythmias (most commonly atrial fibrillation), hypertension, and cytopenias such as neutropenia or thrombocytopenia.

When side effects develop, supportive measures are initially employed prior to changing therapy.[33] For diarrhea, patients could initiate dietary fiber supplementation, probiotics, or anti-diarrheal medications. If palpitations are reported, cardiac monitors should be used to evaluate for arrhythmias, and appropriate cardiology referral and medical or procedural management should occur if an arrhythmia is documented. For arthralgias, patients may require the use of acetaminophen or prednisone. Rashes may be managed with topical steroids or oral antihistamines. If supportive care is ineffective, temporary holds or dose reductions can be utilized. Referral to an appropriate specialist should be considered to further assess the symptoms before a permanent dose reduction in the BTK inhibitor.

BR and DRC are therapies given for a finite duration (4-6 cycles) and are typically efficacious and well tolerated. Some common side effects can occur with these regimens, such as infusion reactions, gastrointestinal symptoms, cytopenias, and infection.[34,35]

Rituximab-bortezomib-dexamethasone, in addition to other proteasome inhibitor-based regimens, are also potential treatment options. However, consideration must be made for the potential side effect of neuropathy, especially in patients with baseline neuropathy related to their WM.[36,37]

The most common side effects of venetoclax include cytopenias (most commonly neutropenia, followed by anemia, lymphopenia, and thrombocytopenia), nausea, diarrhea, upper respiratory infection, sinusitis, and headache.[31]

What is rituximab intolerance, how common is it, and how can it be managed?

The monoclonal antibody rituximab is known to have a risk of infusion reactions. Infusion reactions occur in up to 77% of patients, most of which occur during the initial infusion.[38] Typically, these reactions will lessen with time, but in some patients with WM, reactions can persist after the initial infusion or may recur during later infusions.[39]

Some patients may respond to additional supportive medications (such as antihistamines or steroids), slower infusion rates, or split rituximab dosing. Still, in other patients, the reactions may worsen over time and prevent the safe use of rituximab in these patients. In those cases, ofatumumab can be substituted for rituximab per NCCN guidelines.[39]

What is Bing Neel syndrome and how is it treated?

Bing Neel syndrome (BNS) is a rare manifestation of WM that occurs in approximately 1% of patients and is characterized by infiltration of the cancer cells into the central nervous system.[40,41] BNS can occur at the time of the initial WM diagnosis or later in the disease course. The clinical presentation of BNS can vary widely, but common symptoms include cognitive changes, behavioral changes, seizures, headaches, gait/balance abnormalities, cranial nerve deficits, or paresis. Evaluation for BNS should include cerebral spinal fluid (CSF) evaluation by lumbar puncture 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. CSF analysis can show the presence of WM cells, definitively diagnosing BNS. The lumbar puncture should always be scheduled after the MRI to ensure that changes on the MRI that are related to the procedure itself do not interfere with the interpretation of the MRI.

If BNS is diagnosed the preferred first-line therapy is a BTK inhibitor. The most robust data in this setting support using ibrutinib, although early data suggest that zanubrutinib may also be a potential treatment.[42] In the case of relapsed or refractory BNS, other chemotherapy-based regimens such as bendamustine/rituximab or fludarabine/rituximab can be considered. It is important to know that patients will not have immediate relief from their symptoms from BNS and that it can take weeks to months to improve symptoms. Follow-up MRI can be performed to assess improvement from baseline.

International Waldenstrom's Macroglobulinemia Foundation

Website: iwmf.com
Email: info@iwmf.com
Phone: 941-927-4963 • International: 001-941-927-4963

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:

- Download a free Newly Diagnosed Info Pak.
- Learn about WM and download free publications available in multiple languages.
- Find curated resources to help support your mental, physical, and financial health.
- Join a local IWMF Support Group or IWMF International Affiliate.
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- Participate in the annual IWMF Educational Forum or our online webinars.
- Join IWMF Connect, an online community offering a wide variety of moderated WM-related email discussions, or the IWMF Facebook Discussion Group.
- 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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The IWMF is a 501(c)(3) tax-exempt nonprofit organization, Fed ID #54-1784426

CancerCare

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Cancer Support Community (CSC)

CancerSupportCommunity.org
Phone: 888-793-9355

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.

Leukemia & Lymphoma Society® (LLS)

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The Leukemia & Lymphoma Society® (LLS) is the global leader in the fight against blood cancer. The LLS mission: Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families. LLS funds lifesaving blood cancer research around the world, provides free information and support services, and is the voice for all blood cancer patients seeking access to quality, affordable, coordinated care.

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

lymphomacoalition.org

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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6144 Clark Center Avenue, Sarasota, FL 34238
Phone: 941-927-4963
International: 001-941-927-4963
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