WALDENSTROM'S MACROGLOBULINEMIA

ESSENTIAL INFORMATION:
A PHYSICIAN'S GUIDE

WMFC
Waldenstrom's Macroglobulinemia Foundation of Canada

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CONTENTS

This document is provided as a reference guide to assist medical professionals in discussions with patients with WM.

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Highlighted text indicates there is a Canadian clarification added in the appendix.

ABOUT THE CONDITION
Waldenstrom's Macroglobulinemia

What is Waldenstrom's Macroglobulinemia (WM)?

WM is an indolent lymphoma characterized by the presence of lymphoplasmacytic cells that 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 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 at 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?

WM 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 patients with WM, 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 in 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, ß-2-microglobulin and IgM.[14] In recent years, this scoring system was revised (rIPSSWM) and now includes age, ß-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 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), ß-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 the time to response, depth of hematologic response and length of progression-free survival are shorter with Bruton's tyrosine kinase (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 who 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 ß-2-microglobulin to calculate the median time to disease progression to assist asymptomatic patients in understanding when they may require treatment (**www.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 hemoglobin ≤10 g/dL (secondary to the WM), platelets <100,000mm^3, 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 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 patients with IgM >6,000 mg/dL at the time of diagnosis, the median time to symptomatic hyperviscosity is approximately 3 months compared with patients with IgM of 5,000-6,000 mg/dL who 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 coloured 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 my patient has symptomatic hyperviscosity?

If there is concern for hyperviscosity, serum IgM level and serum viscosity can be measured. Typically, serum viscosity ≤4 centipoise does not lead to clinical symptoms of hyperviscosity. Serum viscosity is often not readily available, and in most cases serum IgM level is sufficient to determine the risk of hyperviscosity, with 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 for WM?

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, comorbidities 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.**[2] 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 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[3] 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, is also a potential treatment option, 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 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**[4] can be substituted for rituximab **per the NCCN guidelines.**[5,46]

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 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] BNS can occur at the time of initial WM diagnosis or later in the disease course. The clinical presentation of BNS can vary widely, but common symptoms include cognitive changes, behavioural changes, seizures, headaches, gait/balance abnormalities, cranial nerve deficits or paresis. Evaluation for potential BNS 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 tumoural 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 BNS 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 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.

APPENDIX: CANADIAN UPDATES

1. See the WMFC's discussion of second opinions at **https://www.wmfc.ca/about-wm/common-canadian-questions-answered**, under the headings "Can I request an Oncologist / Hematologist Second Opinion?" and "Examples of US Medical Institutions Offering Second Opinions".
2. Recognizing that BTK inhibitors and bendamustine-rituximab have equal effectiveness, Canada's public health care system has chosen bendamustine-rituximab as being much more cost effective as a first-line therapy.
3. Recognizing that BTK inhibitors and bendamustine-rituximab have equal effectiveness, Canada's public health care system has chosen bendamustine-rituximab as being much more cost effective as a first-line therapy.
4. As of 2023, ofatumumab is not yet approved for WM in Canada.
5. The NCCN guidelines are generally not used in Canada.

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The WMFC is an all-volunteer organization, and is the only Canadian charity dedicated solely to the support and education of WM patients and their families, and to fund research for a cure for WM.

Our Mission

The mission of the WMFC is to support Canadians with WM, and their families, by offering a range of services that can enhance the quality of life of those with WM through education and Support Groups across Canada.

The WMFC is committed to creating a world without WM by finding a cure. Since 2002, the WMFC has invested over $1.3 million in WM research projects. Doing our part in a worldwide research initiative, WM patients are living longer and have better treatment options that can lead to longer-lasting remissions, with fewer side effects.

Visit our website www.wmfc.ca and join the WMFC to:

- Find and join a local WMFC Support Group
- Read our articles and view our recorded presentations to keep up to date on WM
- Join the WMFC Facebook group
- Get alerted to our national Zoom educational seminars
- Attend our annual WMFC Education Forum and our online webinars
- Receive our periodic emails and newsletters
- Keep current on changes in treatments and research

WM is a rare disease, but with the WMFC

you are never alone.

PATIENT RESOURCES

The IWMF, the only international organization dedicated solely to WM, is a patient-founded and patient-directed nonprofit with a simple but compelling vision and mission.

OUR VISION

A world without WM

OUR MISSION

Support and educate everyone affected by WM 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 $21 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.

www.iwmf.com

Lymphoma Canada (LC) is a national Canadian registered charity whose mission is to empower patients and the lymphoma community through education, support, advocacy and research. Based out of Mississauga, ON, we collaborate with patients, caregivers, healthcare professionals and other organizations and stakeholders, to promote early detection, find new and better treatments for lymphoma patients, help patients access those treatments, learn about the causes of lymphoma and work together to find a cure. Resources are provided in both English and French.

www.lymphoma.ca

The Leukemia and Lymphoma Society of Canada

Our mission

We won't stop until there is a cure for leukemia, lymphoma, myeloma, myelodysplastic syndromes and myeloproliferative neoplasms, and are able to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services and support.

What we do

In Canada, there are currently over 155,000 people living with or in remission from one of the 137 types of blood cancers. Today, we are the largest registered charitable health agency dedicated to supporting the blood cancer community in Canada. Our focus includes:

- Funding research from bench to bedside
- Rethinking how a person navigates their blood cancer experience and provide 1:1 personalized support
- Providing easy to understand and vetted blood cancer information
- Offering tools for psychological and emotional support
- Empowering Canadians to take charge of their blood cancer experience through practical support and advocacy

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Lymphoma Coalition is a worldwide network of patient organizations that support those affected by lymphoma. Lymphoma Coalition 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 organizations from over 50 countries.

www.lymphomacoalition.org

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