

IWMF Vision Statement

A world without WM (Waldenstrom's macroglobulinemia).

IWMF Mission Statement

Support and educate everyone affected by Waldenstrom's macroglobulinemia (WM) while advancing the search for a cure.

Published by the International Waldenstrom's Macroglobulinemia Foundation (IWMF)

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Waldenstrom's Macroglobulinemia

Frequently Asked Questions





FREQUENTLY ASKED QUESTIONS

The IWMF Vision Statement

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To offer mutual support and encouragement to the Waldenstrom's macroglobulinemia community and others with an interest in the disease.

To provide information and educational programs that address patients' concerns.

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FOREWORD

This 2019 edition of *Frequently Asked Questions* is published by the International Waldenstrom's Macroglobulinemia Foundation (IWMF), a nonprofit organization founded in 1994 by Arnold Smokler. The IWMF was established to offer mutual support and encouragement to the Waldenstrom's macroglobulinemia community and others with an interest in the disease; to provide information and educational programs that address patients' concerns; and to promote and support research leading to better treatments and ultimately, a cure.

The IWMF is very fortunate to have as Trustees Elena Malunis, Marcia Klepac, Pete DeNardis, Barry Nelson, and Linda Nelson who have diligently created the frequently asked questions and answers about Waldenstrom's macroglobulinemia and patiently developed this very readable aid for us.

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INTRODUCTION

Frequently Asked Questions is designed to support the newly diagnosed and veteran patient with Waldenstrom's macroglobulinemia (WM) and their caregivers. This booklet answers common questions about WM in a very readable format for those who may not have a strong background in biology. Those who are newly diagnosed may want to read the booklet from beginning to end, whereas those who are more familiar with the disease may focus on a specific question.

Answering questions about this disease requires the use of terms that may not be familiar to some readers. Terms related to WM are defined in the booklet, *Glossary and Abbreviations*, which can be found on the IWWMF website www.iwmmf.com/publications/. Should readers have other questions not found in this booklet or seek further explanation on a particular topic, they should direct their inquiries to a healthcare professional.

INITIAL KEY QUESTIONS

What is WM?

Waldenstrom's macroglobulinemia (WM) is a lymphoma or cancer. It occurs in a type of white blood cell called a B-lymphocyte or B-cell, which normally matures into a plasma cell whose job is to manufacture immunoglobulins (antibodies) to help the body fight infection. In WM, there is a malignant change to the B-cell in the late stages of maturing and it continues to proliferate as a clone of identical cells, primarily in the bone marrow, but also in the lymph nodes and other tissues and organs. It is known as lymphoplasmacytic lymphoma (LPL) and must be associated with the production of an antibody protein or immunoglobulin known as IgM in order for WM to be diagnosed.

What's the difference between WM and LPL (lymphoplasmacytic lymphoma)? Are they the same disease?

Sometimes WM and LPL (lymphoplasmacytic lymphoma) are used interchangeably although WM is really an LPL. However, WM comprises about 90-95% of all LPL patients. The cancer cells of LPL have the appearance of both B-lymphocytes and plasma cells, hence the term lymphoplasmacytic. LPL cells can secrete immunoglobulin antibodies (IgM, IgA, IgG, IgE or IgD), but those who secrete IgM are called WM. Currently, the clinical term in cases of LPL with circulating monoclonal IgM is WM. LPL is the term that describes the appearance of the bone marrow or lymph node used by pathologists.

My doctor said WM was a rare disease. How rare is it? What does that mean for me?

WM is a rare cancer seen only in approximately three to five per million people per year with about 1500 new cases diagnosed in the US each year. This disorder is age-dependent and is quite rare under the age of 40 (less than 1 percent of patients). Typically, patients present between the ages of 60 and 70. For reasons that are unclear, WM is almost twice as common in men as in women and is more common in Caucasians than other ethnic groups. There is a familial predisposition to WM, with most studies suggesting that approximately 20-25% of patients have a first degree relative with WM or other B cell disorders. WM is a rare disease and as such it does not command much support for research dollars because there are few financial incentives for pharmaceutical companies.

Is there a cure for WM?

No, although quality of life and survival for WM patients are continuing to improve because of better treatments.

How long do I have left to live?

Although WM is incurable, in most cases it can be effectively treated to provide a good quality of life for many years. In most patients, WM is a fairly indolent, chronic disease. The median survival has varied in studies, from 5 years to 10

years. Median survival suggests that half of all patients survive 5 to 10 years. Another way to answer this question is to look at the 5-year survival rate. The 5-year survival rate tells you what percentage of people live at least 5 years after the cancer is found. Percent is how many out of 100. The 5-year survival rate for people with Waldenstrom's macroglobulinemia is about 75%. However, it is important to note that survival rates vary based on a number of individual factors including the patient's age and whether the patient has other medical problems. It is also important to remember that statistics on the survival rates for people with WM are an estimate. As newer agents and treatments that are more effective and less toxic become available, the life expectancy will continue to increase. The main causes of death because of WM include disease progression, transformation to high-grade lymphoma, or complications of therapy. However, because of the advanced age of patients with WM, many will die of unrelated causes.

Should I get a second opinion? If so when?

It is not unusual for newly diagnosed patients or patients needing treatment to get a second opinion from a recognized WM expert or from a hematologist/oncologist who has an interest and experience with the diagnosis and treatment of WM. WM is a rare disease and as a result, many hematologist/oncologists may have little experience dealing with WM patients. The IWMF magazine, the *Torch*, has published an article on this subject, called "Should I Get a Second Opinion," written by Morie A. Gertz MD, MACP. You can find this article at iwmf.com/wp-content/uploads/2020/12/Gertz5Second.pdf.

How do I find a good doctor for a second opinion?

Generally speaking, large teaching hospitals see more WM patients and have staff physicians more experienced with WM. The IWMF website maintains a list of physicians who have an interest and experience in the management and treatment of WM iwmf.com/directory-of-wm-physicians/.

When should I get treatment?

Patients should be treated when they become symptomatic or infrequently when blood tests results pose a health risk. To some extent, the decision to begin treatment is dependent on a particular patient's tolerance of symptoms and how they are affecting their quality of life. The IgM level in and of itself is not an indication for treatment. Additional treatment indicators can be found at: iwmf.com/reasons-undergo-treatment/ Also, the IWMF magazine, the *Torch*, has published an article on this subject, called "Who Needs Treatment for Waldenstrom's Macroglobulinemia and When?" written by Stephen M. Ansell MD, PhD. This article can be found at iwmf.com/wp-content/uploads/2020/12/BestOfTorch16.2Ansell.pdf.

What treatments are approved for WM?

Currently, Imbruvica (ibrutinib) is the only approved treatment specifically for WM in the US, Israel, Canada and many European countries. Most treatments are based on results achieved for similar diseases such as follicular lymphoma, chronic lymphocytic leukemia and multiple myeloma. There are a number of treatment options available for WM patients, and information regarding many of them can be accessed at iwmf.com/publications/. Also, several major cancer centers have developed guidelines for WM treatment. You can find these at iwmf.com/wm-medical-practice-guidelines-research-articles/. The treatment landscape continues to evolve, with novel therapies being discovered and tested in clinical trials. For an updated list of trials, go to the US government website, www.clinicaltrials.gov which contains all US trials and trials in many other countries.

GENERAL QUESTIONS

Should I get the shingles vaccine?

Yes. The non-live virus shingles vaccine called Shingrix should be considered after consultation with your doctor. In some cases, it may be preferable to stay on prophylactic anti-viral medication to help prevent shingles.

Should I get a flu shot? What about the nasal mist vaccination?

You should get a flu shot annually. This is a killed virus vaccine and is therefore safe to use. The nasal mist vaccination called FluMist is a live virus vaccine and is not recommended for people with WM.

Should I get the pneumonia vaccine?

Yes. In the U.S., the Centers for Disease Control recommends that all adults over the age of 65 receive the pneumococcal polysaccharide vaccine (PPSV) and adults younger than 65 receive it if they have a condition that lowers the body's resistance to infection. Lymphoma is listed as one of these conditions. Re-vaccination is recommended five years after the first dose for individuals under the age of 64 who are at high risk for pneumococcal infection or rapid antibody loss.

What should I do to protect my immune system?

Wash your hands frequently and avoid touching your hands to your face, especially during cold and flu season. Keep up to date on your flu and pneumonia vaccinations. Eat a healthy, well-balanced diet and get the proper amount of sleep. Avoid close contact with people who are exhibiting obvious symptoms of colds, flu, or other diseases. Be sure to wash raw fruits and vegetables before eating and make sure that meat and seafood are cooked to the proper temperature. These are all common sense things that everyone should do, no matter their state of health.

Will I still be able to travel?

You should still be able to travel, but possibly with some limitations or additional precautions. Enclosed places like airplanes, crowded airports, and public transportation are sources of infection, especially during cold and flu season. If your disease is progressing to a point where you require treatment, or if you are currently on treatment that can adversely affect your immune system, you should ask your hematologist/oncologist if any travel restrictions are necessary. Consultation with your physician is suggested if you are planning to travel to unusual or exotic destinations where specific disease alerts might be in effect or where additional vaccinations are required. Also remember to keep up-to-date on your recommended vaccinations and exercise common sense by washing your hands frequently and watching your diet in areas that are prone to food- and water-borne diseases.

How often should I see my hematologist/oncologist?

This depends greatly on your disease status or whether you are receiving treatment. If you have smoldering WM and are stable, you may not need to see your hematologist/oncologist more than a few times a year. If you are newly diagnosed or have progressing disease, your hematologist/oncologist will want to follow you at more frequent intervals, perhaps once every 2-3 months. If you are currently being treated, your hematologist/oncologist may choose to monitor you even more frequently during this period because some treatments can cause side effects, which need to be recognized early and managed appropriately. We advise that you consult with your hematologist/oncologist.

OTHER QUESTIONS ABOUT WM

Who was Waldenström? What does “macroglobulinemia” mean?

Dr. Jan Waldenström (1906-1996) was a Swedish physician who in 1944 first described two patients with symptoms of what is now known as Waldenström’s macroglobulinemia. “Macroglobulinemia” is a compound word – “macro” meaning large and “globulinemia” meaning protein in the blood. In the case of WM, the WM cancer cells over-produce a large protein in the blood which is called IgM.

What is IgM and how does it relate to WM?

Immunoglobulin M, or IgM for short, is one of 5 basic antibodies (IgG, IgA, IgM, IgD and IgE) that is produced by B cells (which are a type of white blood cell). IgM is by far the largest antibody in the human circulatory system. It is the first antibody to appear in response to initial exposure to an antigen or infection. WM affects the B cell when they are in the process of developing into plasma cells. They become abnormal “lymphoplasmacytic (LPL) cells” in the bone marrow. Although they are of no use to the body, these LPL cells keep being made. As the number of LPL cells increase, they build up in the bone marrow, lymph nodes, spleen and other organs. In the bone marrow the result of this build up is that the normal blood cells are “crowded out” and this leads to a gradual reduction of normal blood counts. Large amounts of IgM in the blood can cause it to become thicker than normal (hyperviscosity). Sometimes, the IgM (an antibody) may wrongly recognize the body’s tissues as foreign and attach to them and cause inflammation and damage. If they attach to nerves and cause damage, this is known as neuropathy. If the IgM destroys blood cells, it is known as autoimmune hemolytic anemia. For a deeper understanding of basic immunology and immunoglobulins, you can access the IWMF booklet, Basic Immunology, at iwmf.com/publications.

What causes WM? Is there an environmental cause?

The specific cause(s) of WM are unknown. IgM-MGUS (monoclonal gammopathy of undetermined significance), is the precursor condition to WM. Male sex, Caucasian, race, increasing age and a family history of WM or other B-cell disorders, presence of hepatitis, AIDS, and exposure to certain solvents, dyes, and pesticides are risk factors for the disease.

What is IgM MGUS?

WM is preceded by a condition known as monoclonal gammopathy of undetermined significance (MGUS) of the IgM type and is the very early stage when there are very few LPL cells in the bone marrow. They are often undetectable in tissues even if they are sampled by a biopsy, but there is a detectable amount of abnormal IgM (usually a low level). This may be picked up on a blood sample done for an unrelated reason and at this point patients have no symptoms. The cause of MGUS (and hence WM) is not known, but it is more common as people get older. Over time (usually years), these cells may gradually build up and accumulate. If they accumulate symptoms such as fatigue, weight loss, night sweats, fever or recurrent infections may develop and WM is eventually diagnosed. The risk of IgM MGUS turning into symptomatic WM requiring therapy is 1-2% per year. There are other more common types of MGUS associated with IgG, IgA or rarely, IgD.

Is there a familial predisposition to WM? Do I have to worry about my kids getting it?

There is a familial predisposition to WM, with most studies suggesting that approximately 20-25% of patients have a history of the disease or related B-cell disorders in their families. At this time, there is no test that will predict which, if any, family members of a WM patient will ultimately develop WM, although those with IgM MGUS (monoclonal gammopathy of undetermined significance) are at greater risk. Although the risk of developing WM is greater in families with familial disease, the absolute risk is extremely low due to the rarity of the disease. We recommend that you do not worry about your children as WM is primarily a disease of older people and treatments are improving for it. The IWMF magazine, the *Torch*, has published an article on this subject, called “Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Waldenström’s Macroglobulinemia (SWM),” written by Robert A. Kyle MD. This article can be found at iwmf.com/wp-content/uploads/2020/12/Kyle.pdf.

If I have WM, do I have a greater risk for other cancers?

Several studies have suggested an increased risk for certain cancers, including prostate, breast, skin, lung and thyroid as well as other blood cancers. Some of these, particularly other blood cancers, may be related to certain therapies for WM, including alkylating agents and nucleoside analogs. WM patients should continue routine screening with their health care providers for other types of cancer.

What is MYD88 and what is the MYD88 mutation I've heard about in WM patients?

MYD88 is a normal protein coded by a gene called myeloid differentiation primary response 88. When B-cells are exposed to antigens, MYD88 initiates several downstream cell pathways that result in the expression of factors critical to the development and activation of B-cells, one of which is BTK. A single specific mutation in the MYD88 gene, designated as MYD88 L265P, was found to have a much higher prevalence in WM (approximately 90% of patients) than in other kinds of blood cancers. The IWWMF magazine, the *Torch*, has published an article on this subject, called "Mutation MYD88 L265P," written by Steven Treon MD, PhD. You can find this article at iwmf.com/wp-content/uploads/2020/12/Treon.pdf.

What is the significance of the MYD88 L265P mutation in WM?

Its significance is still not understood. Although it is prevalent in WM (approximately 90% of patients), at this point we do not believe it causes the disease. However, it does appear to play a role in the proliferation and survival of WM cells by leading to over-expression of proteins such as BTK that are involved in B-cell development and activation. Because of its prevalence in WM, its presence or absence may become useful as part of the diagnostic workup of patients with suspected WM or related diseases.

Are there other gene mutations important in WM?

Researchers are looking at several other gene mutations found in WM patients. Such work is still preliminary, but at least one mutation in the gene CXCR4 is found in approximately 30-40% of WM patients. CXCR4 may lead to more bone marrow and less lymph node involvement, higher IgM, and greater likelihood of hyperviscosity and acquired von Willebrand disease. CXCR4 has been likened to the "GPS" of the WM cell in that it causes WM cells to home to the bone marrow and stick there. CXCR4 mutations have not been associated with worse survival but might be associated with lower efficacy when treated with ibrutinib. The IWWMF is currently sponsoring research to study CXCR4.

QUESTIONS ABOUT SIGNS AND SYMPTOMS

What are the common signs and symptoms of WM? What is the connection between WM and fatigue?

WM can cause a wide variety of signs and symptoms. The most common are slowly progressing fatigue and shortness of breath with exertion due to anemia. The anemia is the result of the decrease in red blood cells caused by the increased number of lymphoplasmacytic (LPL) cells in the bone marrow. Other typical signs and symptoms are abnormal bleeding from gums and nose, dizziness, decreased red blood cell count, neurological symptoms such as peripheral neuropathy, enlarged lymph nodes, enlarged spleen, weight loss, and night sweats. Most symptoms are attributable to a decrease in red blood cells caused by the proliferation of the lymphoplasmacytic (LPL) cells of WM or to the secretion of monoclonal IgM (hyperviscosity, peripheral neuropathy and autoimmune hemolytic anemia).

What kind of skin problems are related to WM?

Skin problems are uncommon with WM. Rarely, WM cells can infiltrate the skin or the IgM secreted by WM cells can deposit in the skin. Symptoms may include skin thickening, nodules, or rashes. If you have these symptoms, you should see a dermatologist to rule out other causes of your skin problems. Occasionally, people with WM may have thrombocytopenia (low platelets) or their high IgM may cause bleeding problems in the skin, leading to easy bruising, petechiae (tiny red or purple spots) or purpura (small red or purple areas). The IWWMF magazine, the *Torch*, has published an article on this subject, called “Waldenstrom’s Macroglobulinemia and the Skin” written by Julia S. Lehman MD. You can find this article iwmf.com/wp-content/uploads/2020/12/Lehman.pdf.

What is the cause of night sweats in WM?

Drenching night sweating is one of the B-cell symptoms (the others are fever and unexplained weight loss) associated with lymphoma. We do not have a definitive answer as to the cause, but one possible mechanism is that the progression of lymphoma and the body’s way of fighting infection have some things in common—both may lead to the mobilization of immune cells and associated proteins called cytokines, and their activities may account for fever, muscle aches, and night sweats.

How can WM affect my eyes?

WM can affect the eyes in several ways, especially when one has an elevated serum viscosity level in their blood. The IWWMF magazine, the *Torch*, has published an article on this subject, called “Waldenstrom and the Eye,” written by Maureen Hanley, O.D. You can find this article at iwmf.com/wp-content/uploads/2020/12/Hanley.pdf.

What is peripheral neuropathy? What does it feel like?

The IgM protein in WM can cause peripheral neuropathy (PN). It is estimated that approximately 20-30% of WM patients have PN caused by the IgM protein. This protein causes a dysfunction of nerves that extend from the spinal cord out to the peripheral portions of the body (arms, hands, legs, and feet). PN can also be a consequence of certain WM treatments e. g. bortezomib (Velcade) and thalidomide. The symptoms of PN include tingling or prickling, numbness, cold sensation, tightness, burning, shooting or stabbing pains and increased sensitivity to contact. These symptoms usually begin in both feet and can eventually extend upward so that both hands may be affected. PN can also affect motor nerves and involuntary (autonomic) nerves causing symptoms such as, difficulty in rising from a sitting position, lightheadedness upon standing and decreased grip strength,. The IWWMF magazine, the *Torch*, has published an article on this subject, called “Waldenstrom’s and Peripheral Neuropathy,” written by Todd Levine MD. You can find this article at iwmf.com/wp-content/uploads/2020/12/Levine.pdf.

How can I treat my peripheral neuropathy? Will it improve with treatment?

First, the cause of the peripheral neuropathy (PN) should be determined if possible. If WM is the cause, treating the disease may cause some improvement. It is difficult to restore nerve function once it has been damaged. The goal of most WM treatments is to try to keep the neuropathy stable and prevent it from becoming worse. There are many therapies often tried to palliate the symptoms of neuropathy. There is not general agreement which may be more effective and they range from over the counter remedies to prescribed medications.

What is hyperviscosity? What is plasmapheresis? Why is done? What should I do before, during, and after plasmapheresis?

Hyperviscosity syndrome, rare but unique to WM, occurs when extremely high levels of the IgM protein cause thickening of the blood (more like maple syrup than water) which, if extreme, can cause problems with bleeding, most typically from the gums or nose. Plasmapheresis is often used for the hyperviscosity syndrome to provide temporary relief for the patient. During plasmapheresis (PP) for WM, patients are connected through an IV to a special machine, blood is then processed through the machine where the plasma (which contains the IgM) is removed and discarded, and the remaining blood is returned to the patient. The removed plasma is typically replaced with albumin or fresh frozen plasma in order to maintain the appropriate blood volume. Improvement of symptoms is usually rapid. PP does not reduce the tumor cell burden; therefore, the WM cells continue to make IgM and the WM must be treated. The IWMF magazine, the *Torch*, has published an article on this subject, called "Plasmapheresis and Waldenstrom's Macroglobulinemia," written by Marvin J. Stone MD. You can find this article at iwmf.com/wp-content/uploads/2020/12/Stone.pdf/Stone.pdf. Another reference is the IWMF Fact Sheet on Plasmapheresis that can be found in a number of languages at iwmf.com/publications/.

QUESTIONS ABOUT DIAGNOSIS AND TESTS

How is WM diagnosed?

The diagnosis of WM requires two components. The first is the presence in the serum (the clear, yellowish part of the blood that doesn't clot) of a monoclonal IgM protein, the so-called "macroglobulin protein." The second is the presence of an abnormal cell population in the bone marrow. The abnormal cells (lymphoplasmacytic cells) are in the bone marrow and are responsible for the production of the IgM protein. To make that diagnosis, your doctor will begin with a series of questions, called the medical history. They will then examine you, looking for signs and symptoms of disease (See above: QUESTIONS ABOUT SIGNS AND SYMPTOMS). Based on this information, a series of blood and medical tests will be ordered. If WM is suspected, a bone marrow biopsy is necessary. For more information on how WM is diagnosed please refer to the IWMF booklet, Medical Tests which you can find at iwmf.com/publications/. The IWMF magazine, the *Torch*, has published an article on this subject, called "How is Waldenstrom's Macroglobulinemia is Diagnosed," written by Morie A. Gertz MD, MACP. You can find this article at iwmf.com/wp-content/uploads/2020/12/Gertz4.pdf.

What is a bone marrow biopsy? What should I expect?

A bone marrow biopsy is performed to look for abnormalities in the bone marrow, which is the spongy tissue inside the larger bones where blood cells are produced. This procedure can be performed in a physician's office or a hospital under light sedation or local anesthetic. The specimen is usually obtained from the posterior iliac crest (back of the hip bone) by using a special needle. Both an aspiration and a solid bone marrow sample (biopsy) may be taken. A pathologist examines the bone marrow cells under a microscope and performs additional testing with special stains of the cells to identify the presence of an abnormality. There may be some discomfort or a feeling of pressure if a local anesthetic is given. The biopsy site may be bruised and sore for a few days following the procedure.

How often do I need to have a bone marrow biopsy?

A bone marrow biopsy is necessary to establish the diagnosis of WM. Frequent bone marrow biopsies are not usually recommended for disease monitoring because this is a costly and invasive technique, and normally not necessary to monitor the disease. There may be situations, however, where your hematologist/oncologist may decide that an additional biopsy is warranted to help determine if a patient needs treatment or to learn how a patient's bone marrow is responding to therapy or during the course of a clinical trial.

Which measurement is more reliable/valuable – IgM or SV (serum viscosity)?

The IgM measurement or serum protein electrophoresis (SPEP) is one of the more important parameters used in determining a WM patient's disease status. Many WM patients never develop high serum viscosity but more often have other symptoms associated with their disease (anemia, peripheral neuropathy, etc.). However, the SV measurement is important for those patients who have a high IgM level, usually more than 3 g/dL.

Are IgG and IgA levels an important measurement to follow too?

WM patients usually have low levels of either IgG or IgA or both for reasons that are not known. If a patient has recurrent infections (sinus infections or bronchitis, for example), then low IgG and IgA levels may be playing a role, and treatment could possibly include IVIG (intravenous IgG). If a WM patient is not experiencing recurrent infections, the IgG and IgA levels are of little importance.

What are the key numbers in my blood testing?

Most hematologists/oncologists look at trends in test results more than a specific number. The IgM level, in and of itself, is not an indication for treatment. If there are no symptoms associated with the rising numbers. Treatment may not be needed. Generally speaking, the most important blood tests to monitor are an SPEP spike or the IgM level. Patients with amyloidosis, cryoglobulinemia, enlarged lymph nodes or rarely WM-related kidney disease may need to monitor their disease progression with additional tests. You can find more about these special conditions in the IWMF publication, Medical Test booklet at iwmf.com/publications/.

QUESTIONS ABOUT TREATMENT

Why am I on watch and wait and not being treated if I have a cancer?

Treating asymptomatic (smoldering) WM does not save lives, increase the quality of life, cure the disease, or change the long-term outlook. Furthermore, there may be side effects from the chemotherapy as well as increased costs and inconvenience. Patients without significant symptoms affecting quality of life receive no benefit from early treatment and may suffer from side effects of the treatment. A high IgM does not justify treatment, and a low IgM does not mean that treatment is not required. The rule of thumb is that symptoms not the IgM level should be the determining factor to decide if treatment is necessary. The IWMF magazine, the *Torch*, has published an article on this subject, called “When to Move from Watch and Wait to Treatment,” written by Morie A. Gertz MD, MACP. You can find this article at iwmf.com/wp-content/uploads/2020/12/Gertz6WW.pdf.

What can I expect from treatment for WM?

There is currently no treatment that cures WM. The goal of treatment is to reduce or relieve the severity of symptoms, to improve your quality of life, and to maintain that state for an extended period of time. While you are undergoing treatment and for a while afterward, you may experience symptoms related to treatment side effects. Some of these may occur during an infusion and may be alleviated by certain pre-medications. Others may remain throughout the course of the treatment and for a short while afterward. These may include fatigue, nausea, hair and weight loss, low blood counts, and infections, to name a few. Treatment side effects vary according to the specific type of treatment, and you should consult your physician to determine exactly what to expect. Frequently encountered side effects from WM chemotherapeutics are covered under the drug name at the IWMF Fact Sheets that you can find in several languages at iwmf.com/publications/. The IWMF magazine, the *Torch*, has published an article on side effects, called “WM: Managing the Side Effects,” written by Jeffrey V. Matous MD. You can find this article at iwmf.com/wp-content/uploads/2020/12/Matous.pdf.

What can I do for myself?

FITNESS: There is increasing evidence that patients who are fit (as opposed to frail) do better with treatment. Fit patients can tolerate their treatment with fewer complications and this hopefully will translate into better outcomes. Daily activity in the form of walking, as briskly as is physically possible without the risk of falls, is strongly encouraged. There is also increasing evidence that obesity is linked with cancer.

DIET: Attention to diet (reducing total calories and fat) is important for overall health, and maintaining a normal weight contributes to being fit. Many patients ask about sugar. There is no evidence that sugar feeds cancer. However, consumption of sugar is calories wasted and has little nutritive value. Sugar raises insulin levels which contributes to the deposition of fat in the body and merely adds to the total caloric intake in a day. Eating right, maintaining normal body weight, and aerobic activity are important for improving your outcomes with WM.

SLEEP/STRESS: It is also important for patients to get adequate amounts of sleep, and to pay attention to their stress level and emotional state when coping with a diagnosis of WM.

SUPPORT: There are many sources of support from the IWMF, such as local Support Groups (US and International), online discussion forum (IWMF-Connect) and LIFELINE, one-on-one connection with peer volunteers for specific treatments and WM-related issues. You can find these services on the IWMF website, www.iwmf.com/get-support. Psychological counseling can be very helpful for anyone whose emotional distress is impacting their quality of life.

Are there any foods that are beneficial or harmful to eat while in treatment? Are there any alternative medicine treatments for WM?

Patients considering complementary and alternative medicines should be very careful about their use. Mega-vitamins, over-the-counter medications, and so-called health food remedies should always be discussed with one’s physician.

Some of these substances may alter the effectiveness of conventional treatments for the disease or may worsen treatment side effects. While some complementary and alternative therapies, such as yoga or meditation, are helpful in dealing with the psychological issues associated with a chronic health situation, other so-called alternative therapies have the potential to be harmful. For more information about complementary and alternative treatments, visit the National Institutes of Health National Center for Complementary and Alternative Medicine website at www.nccam.nih.gov.

Are there any treatments that target the MYD88 mutation in WM patients?

Currently there are no treatments that target the MYD88 L265P mutation. However, there are drugs that target some of the downstream proteins in the MYD88 pathway. Ibrutinib (Imbruvica) is an oral therapy developed to inhibit Bruton's tyrosine kinase (BTK). As was noted previously, MYD88 is a normal protein coded by a gene called myeloid differentiation primary response 88. When B-cells are exposed to antigens, MYD88 initiates several downstream cell pathways that result in the expression of factors critical to the development and activation of B-cells, one of which is BTK. MYD88 L265P appears to play an important role in the proliferation and survival of WM cells by leading to over-expression of proteins such as BTK that are involved in B-cell development and activation.

What if my treatment doesn't work?

Some treatments work faster than others, so you should allow adequate time for your treatment to work. Just because you don't see immediate results doesn't mean you have treatment failure. Furthermore, certain treatments work better for some patients than for others for reasons that are not well understood. Since WM is usually slow-growing, it is frequently not necessary to achieve immediate results. Treatment options are increasing all the time, and if your treatment has truly failed, your physician will be able to suggest an alternate course of therapy. You may also obtain the advice of a WM expert. The IWMF website maintains a list of experts that are available for consultation at iwmf.com/directory-of-wm-physicians/.

What are some of the other "late and rare" complications of WM?

Diffuse Large- Cell B-Cell Lymphoma: In a small proportion of patients with WM who have lived with the disease for many years, the WM may transform to a large cell lymphoma which has an aggressive course. It may, however, respond well to chemotherapy.

Amyloidosis: Earlier we mentioned that IgM protein can cause a thickening/syrupy effect on the blood (hyperviscosity) and/or nerve damage (peripheral neuropathy). Occasionally, the IgM protein leads to amyloidosis. All proteins, including the IgM protein, are biodegradable and recyclable. When the light chain component (kappa or lambda) of the IgM monoclonal protein misfolds, it is carried in the blood to different tissues and is deposited. It is now referred to as an amyloid deposit. Amyloid typically deposits in the tissue of the heart, liver, kidney and nerves. In each of these organs, the deposits of amyloid can cause those organs to malfunction. Amyloid deposits can be caused by conditions other than WM and are never normally found in the body. Their presence always indicates an abnormal process. Amyloidosis caused by WM is dealt with by treating the underlying disease (i.e. WM). The IWMF magazine, the *Torch*, has published an article on amyloidosis, called "Amyloidosis associated with Waldenstrom disease or IgM MGUS" written by Giampaolo Merlini, MD. You can find this article at iwmf.com/wp-content/uploads/2020/12/Merlini.pdf.

Cryoglobulinemia ("cryo"): literally means "cold antibody in the blood" and refers to the fact that the antibodies involved precipitate at a temperature below 37°C (body temperature) and then re-dissolve upon warming. Cryoglobulinemia may develop due to unknown causes or may be associated with an underlying disease such as WM. Treatment for cryoglobulinemia can depend upon whether an associated disease is present. Asymptomatic "cryo" does not require treatment. The IWMF magazine, the *Torch*, has published an article called "Cryoglobulinemia" written by Sue Herms. You can find this article at iwmf.com/wp-content/uploads/2020/12/Herms4.pdf.

Hypogammaglobinemia: Reduced levels of the immunoglobulins IgA and IgG are common in patients with WM. It can be due to a decreased number of normal plasma cells producing IgG and IgA. In addition, in most patients, disease

reduction or even a complete remission does not improve the hypogammaglobulinemia. Treatment is done on more of a “watchful waiting” scenario, based on a patient’s frequency of recurrent infections.

Bing Neel Syndrome: When WM cells move out of the bone marrow they tend to collect in certain organs, usually the bone marrow, liver, spleen, and lymph nodes. The presence of WM is generally restricted to these organs because the cells have a peculiar “stickiness” that keeps them within those specific sites. In rare instances late in the disease, the WM cells can lose their sticky quality and begin to involve other organs. When this occurs, the disease is referred to as ‘extramedullary disease’. Occasionally, WM cells can invade the central nervous system (CNS), which consists of the brain, spinal cord, and meninges (the membranes that cover the brain and spinal cord). The development of WM cells in the central nervous system is known as the Bing-Neel Syndrome. Treatment of Bing-Neel varies and includes a number of chemotherapeutic agents delivered either orally, intravenously, or by injection into the spinal canal. The IWMF magazine, the *Torch*, has published an article on complications, called “Late (and Rare!) Complications of Waldenstrom’s Macroglobulinemia” written by Morie A. Gertz MD, MACP. You can find this article iwmf.com/wp-content/uploads/2020/12/Gertz3.pdf.

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 professional medical specialist with experience in the treatment of WM. We discourage the use by a patient of any information contained here without disclosure to his or her medical specialist.
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