# Waldenstrom's Macroglobulinemia

## Questions and Answers

International Waldenstrom's Macroglobulinemia Foundation

# WALDENSTROM'S MACROGLOBULINEMIA QUESTIONS AND ANSWERS

## The IWMF Vision Statement

*A world without WM (Waldenstrom's macroglobulinemia).*

## The IWMF Mission Statement

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

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# FOREWORD

This 2022 edition of *Questions and Answers* 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.

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# INTRODUCTION

*Questions and Answers* is designed to address common questions about Waldenstrom's macroglobulinemia (WM) for people with the disease, their families, friends, and interested others. 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 IWMF *Glossary and Abbreviations* booklet that can be found at https://iwmf.com/publications/. Should readers have questions not found in this *Questions and Answers* booklet or seek further explanation on a particular topic, they should direct their inquiries to a healthcare professional.

# WHAT IS WALDENSTROM'S MACROGLOBULINEMIA (WM)?

Waldenstrom's macroglobulinemia (WM) is a rare white blood cell cancer defined by the World Health Organization (WHO) and the Revised European American Lymphoma (REAL) classifications as a lymphoplasmacytic lymphoma, a type of B-lymphocyte (B cell) non-Hodgkin's lymphoma. It is often compared with other white blood cell cancers, especially chronic lymphocytic leukemia, and multiple myeloma. A defining characteristic of the disease is the presence of an elevated immunoglobulin called IgM, also referred to as an IgM paraprotein or monoclonal IgM.

Dr. Jan Gosta Waldenström first described the disease that bears his name in 1944. He discussed two patients who experienced bleeding from the mouth and nose and had changes in the retina of the eye. They also had enlarged lymph nodes and several abnormal laboratory values, including low hemoglobin, low platelet counts, and increases in an unknown protein which was later identified as IgM.

Despite advances in research, a cure for WM is still elusive. Unlike many cancers for which early detection and treatment are important for survival, WM is usually an indolent (slow growing) cancer that can be effectively managed for years with appropriate treatment and frequently affords the patient time to seek out competent medical advice, including second opinions. Multiple treatment options are available, but there is currently no "gold standard" of treatment. Rather, treatments are tailored to particular disease symptoms, the urgency for disease control, and the age and overall health status of a patient.

# WHAT ARE BLOOD CELLS? HOW DO THEY CHANGE IN WM?

In order to understand this rare disease, one needs to understand blood components, which are summarized briefly in this section. More information on blood, blood components, and blood tests can be found in the booklet Waldenstrom's Macroglobulinemia Medical Tests, available for downloading from the IWMF website at https://iwmf.com/publications/.

Blood has both a liquid portion and a solid portion. The liquid (plasma) portion of the blood contains proteins such as immunoglobulins, clotting factors, hormones, and albumin, as well as electrolytes such as sodium, chloride, potassium, calcium, and magnesium. When the plasma clots, the remaining liquid is called serum. The solid portion of the blood contains blood cells such as red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes).

The different types of blood cells perform different functions. Red blood cells deliver oxygen from the lungs to other areas of the body. Hemoglobin is a large iron-containing protein found in red blood cells and is the carrier molecule for oxygen. Platelets help blood to clot. When a blood vessel is broken, platelets bind to the broken blood vessel surface, clump together, and help to stop the bleeding. Both red blood cells and platelets are found primarily in the blood, whereas some white blood cells are found not only in the blood but also in other body tissues. The primary function of all white blood cells is to eliminate foreign substances such as bacteria, viruses, and fungi from the body. Neutrophils, eosinophils, basophils, monocytes, macrophages, T-lymphocytes (T cells), natural killer cells, and B-lymphocytes (B cells) are all different types of white blood cells.

Red blood cells, platelets, and white blood cells develop from primitive blood cells called hematopoietic stem cells. These stem cells are unique because they are also able to produce other blood stem cells. The process of blood cell development, called hematopoiesis, is illustrated in Figure 1.

Hematopoiesis occurs primarily in the bone marrow, a spongy tissue located inside the bones. Hematopoiesis occurs in all bones at birth. By adulthood, however, it occurs only in the backbone (vertebrae), ribs, skull, hips, shoulders, breastbone (sternum), and the long bones (femur and humerus).

Patients with WM may experience a reduced capacity to produce one or more of the different types of blood cells in the bone marrow because the lymphoplasmacytic cells of WM infiltrate the bone marrow, interfering with normal hematopoiesis.

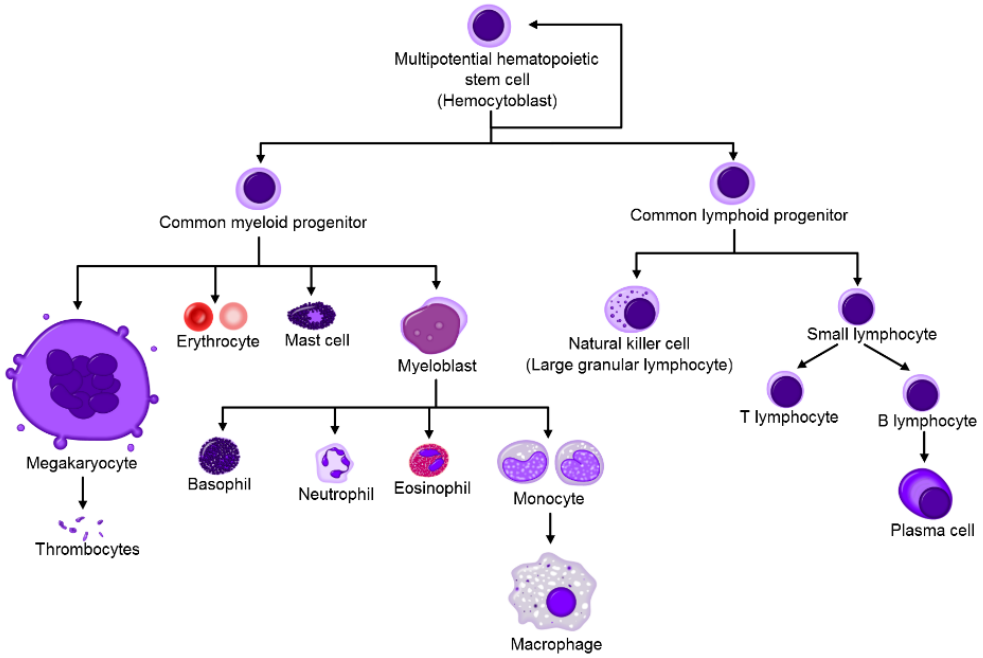


*Figure 1. Hematopoiesis, the process of blood cell differentiation.*

Normally, B cells develop into plasma cells as shown in Figure 1. The role of plasma cells is to secrete immunoglobulins (also referred to as antibodies), which are proteins produced when a foreign substance or antigen is detected in the body. The immunoglobulins coat the foreign substance so that other types of white blood cells can eliminate it. Five classes of immunoglobulins have been identified, IgA, IgD, IgE, IgG, and IgM.

In WM, the normal development of a B cell is altered at a point right before it develops into a plasma cell, resulting in the typical lymphoplasmacytic cell of WM which then proliferates instead of undergoing a normal planned cell death.

Immunoglobulin IgM, which is excessively produced in WM, is the immunoglobulin that usually predominates early in the course of an infection. It is referred to as a macroglobulin because of its size – it is the largest of the immunoglobulins – and this size is the reason why it can cause increased thickening of the blood in WM patients. WM patients frequently have lower levels of normal immunoglobulins for reasons not completely understood.

This excessive circulating IgM may interfere with one or more laboratory tests performed on liquid-based automated analyzers, either by precipitating during the analysis, or by virtue of specific binding properties. The most common artifacts are a low value for HDL cholesterol, a high value for bilirubin, as well as altered measurement of inorganic phosphate. Other examples include interference with measurement of LDL cholesterol, C-reactive protein, antistreptolysin-O, creatinine, glucose, urea nitrogen, iron, and inorganic calcium. These events may occur in patients whose clinicians are unaware of the presence of the underlying monoclonal protein or its possible interference with these tests and could result in the mismanagement of patients with monoclonal gammopathy, especially as regards measurement of HDL and LDL cholesterol and estimation of cardiovascular risk. Re-analysis of specimens using a different test method or a dilution of the sample can be employed for obtaining accurate measurements.

## WHAT IS THE PREVALENCE OF WM?

WM is a rare cancer. Analyses of new cancers reported in the United States show that blood cell or hematologic cancers such as leukemia, lymphoma, and multiple myeloma account for about 10.2% of all cancers, and WM accounts for only about 0.1% of all cancers. These numbers mean that almost 1,700 people in the United States are diagnosed with WM each year. This compares to about 281,000 diagnosed with breast cancer and 248,530 diagnosed with prostate cancer in 2021.

## WHAT IS THE PROGNOSIS FOR WM?

Although WM is incurable, in most cases it can be effectively treated to provide a good quality of life for many years. WM is an indolent, chronic disease in most patients. The median survival has varied in studies, most recently from 16 to 20 years. 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. Mortality is associated with the development of symptoms; the mortality of asymptomatic patients is similar to that of the general population, whereas it is significantly higher in symptomatic patients.

Prognosis is a prediction of the probable course of a condition or disease. Several studies have attempted to determine factors that affect the prognosis for patients with WM, and one international study (2009) developed the widely accepted International Prognostic Scoring System for WM (IPSSWM). This study did not include asymptomatic patients who had not yet received treatment but instead only those patients who had symptoms of disease. Five adverse survival factors were identified: advanced age (more than 65 years), hemoglobin level less than or equal to 11.5 g/dL, platelet count less than or equal to 100 K/uL, beta-2 microglobulin more than 3 mg/L, and serum monoclonal IgM concentration more than 7.0 g/dL (or 7,000 mg/dL). Based on these factors, patients were categorized into three groups. Low risk patients at treatment presented with not more than one adverse factor and age less than or equal to 65 years – these patients had a 5-year survival rate of 87%. Intermediate risk patients had two adverse factors or age older than 65 years and had a 5-year survival rate of 68%. High risk patients had three or more adverse factors and had a 5-year survival rate of 36%.

In 2009 the Southwest Oncology Group identified increased serum lactate dehydrogenase (LDH) as another variable adversely affecting prognosis. The normal range for LDH is 104-333 IU/L.

Based on a prospective study of 72 patients, von Willebrand factor (VWF) antigen level was identified as a prognostic factor in WM. High levels were associated with poor prognosis that did not improve with disease control. Low levels, on the other hand, were associated with increased bleeding risk but improved with lowering of serum IgM levels. The normal range for von Willebrand's factor antigen level is 55-200%. It should be noted that individuals of blood group "O" may have lower plasma von Willebrand factor antigen than those of other ABO blood groups, such that apparently normal individuals of blood group "O" may have plasma VWF antigen as low as 40-50%.

In 2019, researchers studied 439 patients with asymptomatic WM (AWM). During the 23-year study period, with a mean follow-up of 7.8 years, 317 patients progressed to symptomatic WM (72%). To assess progression risk in patients with AWM, they used a proportional hazards model with bone marrow infiltration, immunoglobulin M, albumin, and beta-2 microglobulin values as measures. The model divided the cohort into three distinct risk groups: a high-risk group with a median time to progression (TTP) of 1.8 years, an intermediate-risk group with a median TTP of 4.8 years, and a low-risk group with a median TTP of 9.3 years. This classification system is useful for patient monitoring and care and to identify patients with high-risk AWM who may need closer follow-up or might benefit from early intervention. The research leading to this risk stratification was funded in part by the IWMF. Patients may try out this predictive model by going to the website www.awmrisk.com and entering their own data. For the score to be helpful, all values should be collected at approximately the same time.

## ARE THERE ANY KNOWN RISK FACTORS FOR DEVELOPING WM?

A risk factor is anything that increases the chances of developing a disease. The only risk factors that have been definitively identified in WM are male sex, increasing age, white race, and a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) of IgM class.

The risk is significantly higher in men than in women, and the incidence of the disease is also higher in older people. The median age at diagnosis is 62 although patients as young as 18 have been reported. The annual incidence increases dramatically as age increases. Race appears to be a risk factor, as the incidence is higher in whites than in blacks. Reliable figures for other races are not available.

People with IgM MGUS have an increased risk of developing WM. In one long-term study of IgM MGUS, the incidence of progression to WM and other lymphoid malignancies was 10% at 5 years, 18% at 10 years, and 24% at 15 years.

Several reports suggest a link between WM and certain viruses or to genetic and environmental factors. Research findings report an element of familial susceptibility that is more significant than with other B-lymphocyte cancers, with studies suggesting that almost 20% of WM patients have first-degree relatives with WM or related B cell disorders. Some evidence links the disease to a deletion in part of chromosome 6, although this abnormality is not present in all cases of WM. Environmental factors such as radiation exposure and occupational exposure to leather, rubber, paints, the herbicide Agent Orange, and dyes have also been implicated in some studies, as have certain autoimmune diseases and viruses such as hepatitis C. However, none of these factors has consistently been determined to increase risk.

Discoveries about the biology and genetics of WM indicate that a particular mutation in one gene is prevalent in approximately 90-95% of WM patients. The gene involved is called MYD88, which stands for myeloid differentiation primary response 88. The acquired (not congenital) mutation in this gene changes one specific amino acid to another and is called MYD88 L265P. It plays an important role in the proliferation and survival of WM cells by leading to over-activation of proteins in cell signaling pathways involved in B cell development and activation. Treatments have been and are continuing to be developed to target some of the downstream pathways of this gene, and they are proving to be quite effective in controlling the disease. The IWMF sponsored the research that led to the identification of the MYD88 L265P mutation.

Research is ongoing to discover additional genetic mutations in WM and their significance as possible risk factors for developing the disease or for influencing its progression. One such important gene is CXCR4; several studies suggest that close to 40% of WM patients have acquired mutations in this gene and that these mutations may adversely impact response to certain treatments. CXCR4 mutations 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, where conditions are favorable for the growth of WM cells and stick there. CXCR4 mutations have not been associated with worse survival but might be associated with lower efficacy when treated with Bruton tyrosine kinase (BTK) inhibitors. The IWMF is currently sponsoring research to study CXCR4 as well as other genetic mutations in WM.

## WHAT ARE THE SIGNS AND SYMPTOMS OF WM?

WM can cause a wide variety of signs and symptoms, the most common of which is fatigue due to anemia, caused by a decrease in the number of red blood cells. Because red blood cells are produced in the bone marrow, infiltration of the marrow with WM cells can adversely affect their production. Typical signs and symptoms of WM are listed in Table 1. Most of these are attributable to the proliferation of the lymphoplasmacytic cells of WM or to the secretion of monoclonal IgM.

| | |
|---|---|
| Abnormal bleeding from gums and nose | Dizziness |
| Decreased red blood cell count | Neurological symptoms |
| Enlarged liver | Visual impairment |
| Enlarged lymph nodes | Weakness |
| Enlarged spleen | Weight loss |
| Fatigue | Night sweats |

*Table 1. Common signs and symptoms of Waldenstrom's macroglobulinemia*

There are several conditions which may be associated with WM, although not necessarily so. They can occur in some but not all patients. These include hyperviscosity syndrome, peripheral neuropathy, cryoglobulinemia, cold agglutinin disease, and amyloidosis, all briefly described below.

Hyperviscosity syndrome is reported to occur in approximately 10-30% of patients, depending on the study, and is a result of the increased IgM concentration. As noted previously, IgM molecules are large and contribute to the increase in blood thickness (viscosity). Signs and symptoms of hyperviscosity include chronic bleeding from the nose, gums, and less commonly, the gastrointestinal tract; headache; ringing in the ears (tinnitus); dizziness (vertigo); impaired hearing; blurring or loss of vision; distended, sausage-shaped veins in the retina; and swelling of the optic disk at the back of the eye (papilledema). In severe cases, heart failure, sleepiness (somnolence), stupor, and coma can develop. Symptoms of hyperviscosity occur most commonly at IgM concentrations greater than 4,000 mg/dL. However, such concentrations are not necessarily associated with hyperviscosity, as there is considerable variability in the amount of IgM that will produce hyperviscosity symptoms in an individual.

Peripheral neuropathy is a commonly reported complication of WM – the incidence varies according to the study but is generally about 20-30%. The clinical features of peripheral neuropathy are predominantly sensory, with abnormal sensations such as burning, prickling, itching, tingling, or numbness that are usually first noticed in the feet. The sensations are usually symmetrical, affecting both feet equally, and slowly progress to the upper legs, hands, and arms. Strength is often normal. The peripheral neuropathy in WM is usually caused by the targeting of specific antigens on the nerve coating (myelin) by the circulating IgM, leading to nerve dysfunction. Symptoms can be reduced with gabapentin (Neurontin), pregabalin (Lyrica), amitriptyline (Elavil), opiates, and others. These medications mask the symptoms but do not slow the progression of peripheral neuropathy. The treatment of IgM-related neuropathy is directed toward the reduction of circulating IgM, usually by either plasmapheresis or WM-directed therapy, both of which are further explained in the section of this booklet entitled "**How Is WM Treated?"**

Cryoglobulinemia literally means “cold antibody in the blood” and refers to the physical and chemical properties of the antibody involved. Cryoglobulins precipitate at temperatures below body temperature and then re-dissolve upon warming. Cryoglobulinemia is most often due to unknown causes but may in some cases be associated with an underlying disease such as WM. Frequently, the type of cryoglobulinemia associated with WM does not cause symptoms until the concentration of antibody reaches high levels, at which point it can produce a variety of symptoms because the precipitated antibody physically obstructs smaller blood vessels. When present, symptoms can include blueness of hands and feet from the cold, Raynaud phenomenon (whiteness and numbness of the fingers and toes from the cold), purpura (purple skin marks), bleeding, ulcers, and gangrene of the fingers and toes. WM patients should be tested for cryoglobulinemia at diagnosis, since it can complicate treatment and affect the results of other laboratory testing.

Cold agglutinin disease is sometimes confused with cryoglobulinemia because both conditions involve antibodies (usually of the IgM-type) that react at lower temperatures. However, the antibodies responsible for cold agglutinin disease are specifically directed against proteins found on one’s own red blood cells. It is this characteristic that is responsible for one of its primary manifestations: hemolytic anemia. Cold agglutinins occur naturally in nearly everyone, but at low levels that seldom cause problems. High concentrations can cause anemia because red blood cells are destroyed faster than the bone marrow can replace them. Clinical signs and symptoms of cold agglutinin disease vary according to the severity of the disease. These may include Raynaud phenomenon, painful fingers and toes, anemia, fatigue, shortness of breath, jaundice, and dark urine caused by the presence of hemoglobin. A few of these symptoms, such as Raynaud, are similar to those of cryoglobulinemia, but hemolytic anemia is not a consequence of cryoglobulins.

Amyloidosis is a group of diseases caused by the deposition of an abnormal protein called amyloid in various tissues and organs of the body. The amyloid protein forms abnormal fibers that may injure certain tissues and organs or interfere with their normal function. The protein may be deposited in a localized area or systemically (throughout the body). The most common tissues and organs involved are the kidneys, heart, gastrointestinal tract, peripheral nerves, and liver. Symptoms can vary widely, based on which tissues and organs have the abnormal protein deposits. Clinical signs and symptoms of amyloidosis may be vague, such as weakness, fatigue, weight loss, shortness of breath, abnormal sensations in the feet, enlarged liver and/or spleen, bleeding under the skin, and anemia. More specific signs and symptoms might include swelling of the extremities, an enlarged tongue, carpal tunnel syndrome, food malabsorption, skin thickening, unexplained congestive heart failure, and unexplained kidney failure.

WM patients may have kidney, gastrointestinal, eye, or skin involvement. Bone lesions are uncommon and reported in less than 5% of cases. Kidney involvement occurs infrequently. Rarely, tumors with WM-like cells have been reported in other parts of the body, such as the spine, breast, extremities, etc.

An unusual complication of WM is Bing-Neel syndrome, which involves infiltration of the central nervous system (brain and spinal cord) by WM cells. Manifestations of Bing-Neel syndrome may include mental deterioration, confusion, visual disturbances, irritability, personality changes, convulsions, and coma.

## HOW IS WM DIAGNOSED AND MONITORED?

The diagnosis of WM is made upon demonstration of bone marrow infiltration with lymphoplasmacytic cells, the presence of an IgM monoclonal protein regardless of its concentration and supporting immunophenotypic analysis (flow cytometry or immunohistochemistry) that looks for specific surface proteins, called cluster of differentiation (CD) markers, on the lymphoplasmacytic cells of the bone marrow. Each type of cancer, including B lymphocyte cancers such as WM, has its own identifying pattern of CD markers, and this pattern helps to confirm the diagnosis. The typical CD pattern for WM is CD19+, CD20+, CD5-, CD10-, CD22+, CD23-, and CD79+ (+ means the marker is present on the cell, whereas – means it is absent), although some variation from this typical pattern can occur.

The presence of lymphoplasmacytic cells in the bone marrow is determined by means of a bone marrow aspiration and biopsy. This procedure typically involves inserting a needle into a bone and removing a piece of bone and some bone marrow, usually from the back of the pelvis (iliac crest). While a bone marrow aspiration and biopsy is essential for diagnosis, it is generally not often used for disease monitoring because of its invasive nature, except in special circumstances such as a clinical trial protocol.

Laboratory tests of blood, serum, and urine are also used in the diagnosis. Imaging studies (X-rays, CT scans, or PET scans) of the chest, abdomen, pelvis, and other areas look for evidence of enlarged lymph nodes, enlarged liver and/or spleen, or soft tissue tumors. Recommendations from the National Comprehensive Cancer Network® (an alliance of leading cancer centers in the United States) and the biennial International Waldenstrom Macroglobulinemia Workshop (a consensus panel of international WM experts appointed to update recommendations for diagnosis, staging and treatment of WM patients) suggest that AS-PCR (allele-specific polymerase chain reaction) testing should be performed at diagnosis to determine the presence of the MYD88 L265P mutation, which can be useful to differentiate WM from non-IgM lymphoplasmacytic lymphoma, other B cell lymphomas, and multiple myeloma. It is also suggested that patients who are contemplating BTK inhibitor treatment should be tested for mutations in the CXCR4 gene, as these mutations can negatively impact response to these drugs.

In Table 2 common laboratory tests that may be used to diagnose or monitor WM are listed, as well as normal reference range values.

Laboratory reference ranges are not nationally standardized and therefore may vary slightly from laboratory to laboratory. Some ranges vary by age and gender as well. Patients should follow the trends of their laboratory test results over time. All laboratory tests have an inherent degree of imprecision, some more than others, and depend on proper specimen collection, handling, and interpretation for accurate results. If a laboratory test result is in doubt, it should be repeated.

More information on laboratory tests can be found in the booklet *Waldenstrom's Macroglobulinemia Medical Tests*, available for downloading from the IWMF website at https://iwmf.com/publications/.

| Blood Test | Normal Value | Normal Value in Metric System | WM Abnormality |
|---|---|---|---|
| White blood cell (WBC) count | 3.5-6.1 K/uL | 3.5-11.0 x $10^9$/L | May be decreased |
| WBC differential: | | | |
| Neutrophils | 50-70% of WBC count | 0.50-0.70 fraction of WBC's | May be decreased |
| Lymphocytes | 20-30% of WBC count | 0.20-0.30 fraction of WBC's | May be decreased or increased |
| Monocytes | 2-9% of WBC count | 0.02-0.09 fraction of WBC's | May be decreased |
| Basophils | <1% of WBC count | 0-0.03 fraction of WBC's | May be decreased |
| Eosinophils | 0-7% of WBC count | 0-0.08 fraction of WBC's | May be decreased |
| Red blood cell count | 4.7-6.1 M/uL | 4.7-6.1 x $10^{12}$/L | May be decreased |
| Hemoglobin | 14-18 g/dL | 8.1-11.2 mmol/L | May be decreased |
| Hematocrit | 39-51% | 0.37-0.51 fraction of RBC's | May be decreased |
| Platelets | 130-400 K/uL | 130-400 x $10^9$/L | May be decreased |
| Erythrocyte sedimentation rate | 0-20 mm/hr | 0-20 mm/hr | Increased |
| IgM | 50-300 mg/dL | 0.4-3.0 g/L | Increased |
| Serum viscosity | 1.4-1.8 cP | same | May be increased |
| Beta-2 microglobulin | <2 mg/L | same | May be increased |
| | Abbreviations: K, thousand; uL, microliter; M, million; g, gram; dL, deciliter; mm, millimeter; hr, hour; mg, milligram; cP, centipoise; L, liter | | |

*Table 2. Common laboratory tests used to diagnose and monitor Waldenstrom's macroglobulinemia*

# HOW IS WM TREATED?

## Approach to Treatment

The goal of treatment for WM is to provide disease control and thereby improve quality and duration of life. This section focuses on drug therapies that are used for disease control. There is no single standard of therapy to treat WM; instead, there are many drug options available to WM patients, including the following:

- **Chemotherapy** with alkylating agents, such as cyclophosphamide and bendamustine, or with nucleoside analogs, such as fludarabine and cladribine;
- **Biologic therapy** with monoclonal antibodies such as rituximab;
- **Proteasome inhibitors** such as bortezomib, carfilzomib, and ixazomib;
- **Targeted therapies to the B cell signaling pathways**, including BTK inhibitors such as ibrutinib, acalabrutinib, and zanubrutinib and BCL-2 inhibitors such as venetoclax.

Newer targeted therapies being tested (including third generation BTK inhibitors pirtobrutinib and tirabrutinib and CXCR4 inhibitors) and combinations of these drugs with older therapies are being added to the treatment arsenal.

Some of these drugs may be used as single agents (monotherapy); however, combinations of drugs are frequently used, and many lead to improved overall responses to therapy, either for initial (also called first-line, induction, or primary) treatment or for therapy after previously treated (relapsed) WM.

Treatment is typically required when patients with WM become symptomatic and should not be initiated based on blood test results alone. This applies not only to consideration of first-line treatment but also to treatment for relapsed WM. Initiating treatment early in the course of the disease in most asymptomatic patients does not prolong survival and may result in a range of unpleasant or even serious side effects. Some patients may remain stable and continue to be asymptomatic for years without treatment.

The following symptoms and conditions are considered appropriate reasons to begin treatment:

- Hyperviscosity syndrome (symptoms related to excessive thickness of the blood due to high IgM).
- Anemia (low red blood cell count and low hemoglobin) due to infiltration of the bone marrow with WM cells or destruction of red blood cells due to the abnormal IgM. Anemia is the most frequent condition that leads to treatment for WM. A hemoglobin level less than 10 g/dL may be used as an indication to begin therapy.
- Thrombocytopenia (platelet count less than <100,000) due to bone marrow infiltration.
- Constitutional symptoms – weakness, fatigue, night sweats, fever, or weight loss.
- Systemic light-chain (AL) amyloidosis, symptomatic cryoglobulinemia, cold agglutinin disease, or moderate to severe peripheral neuropathy. (Explanations about these conditions can be found in the section of this booklet entitled “What Are the Signs and Symptoms of WM?”)
- Bing-Neel syndrome (infiltration of WM cells into the brain, lining around the brain and/or spinal cord, or fluid surrounding the spinal cord and brain).
- Progressive, symptomatic enlargement of the lymph nodes, liver, or spleen.
- Kidney disease (nephropathy) related to WM.
- Masses of WM cells outside the bone marrow or pleural effusions (fluid in the chest) – treatment is initiated based on the location, size, and rate of cell growth.

Given that WM remains a very heterogeneous disease and no two patients are alike, patients and clinicians must decide which treatment to use based on the individual patient’s situation and disease characteristics. These may include the presence of one or more cytopenias (decreased production of blood cells); the need for rapid control of aggressive disease; age; co-morbidities (other chronic health conditions); overall health status; and candidacy for a possible autologous stem cell transplant.

When immediate IgM reduction is required (such as for hyperviscosity syndrome, symptomatic cryoglobulinemia, severe hemolysis due to cold agglutinin disease, etc.), the most rapidly acting therapy is plasmapheresis, which is a procedure to withdraw plasma containing excess IgM from the blood. After plasmapheresis, IgM levels can be reduced significantly, but the effect is only transient, and systemic drug therapy is required for disease control. In some cases, a surgical procedure may be needed to place a central catheter for plasmapheresis. More information about plasmapheresis can be found in a separate Fact Sheet on the IWMF website at https://iwmf.com/publications/.

Drug treatment can usually be administered in an outpatient setting or at home. The treatment may be given orally, by intramuscular or subcutaneous injection, or by intravenous therapy depending on the specific therapy chosen. Some treatments require that certain medications be taken the day before or the day of treatment in order to minimize associated side effects. Traditionally, treatment may take months to complete, depending on the course of therapy chosen. Targeted therapies such as ibrutinib, acalabrutinib and zanubrutinib are oral and require regular daily dosing until relapse or significant toxicities develop.

Outside of clinical trials, the choice of therapy after relapse is dependent on first-line therapy use, the quality and duration of response achieved during that therapy, and other variables such as age, tolerance of initial therapy, candidacy for stem cell transplant, etc. Reuse of a first-line single agent therapy or combination is reasonable if a patient achieved a durable or long-lasting response; for patients who had short responses or resistance to first-line therapy, relapse therapy may consist of agents of a different class, either alone or in combination with other drugs.

At the biennial IWWM, a consensus panel of international WM experts is appointed to update recommendations for both first line and relapsed/refractory therapy in WM patients. These recommendations are developed after extensive review of published and ongoing clinical trials in WM. A similar set of clinical practice guidelines for treatment of WM/LPL is updated regularly by the National Comprehensive Cancer Network (NCCN®), a not-for-profit alliance of the leading US cancer centers. The recommendations discussed in this booklet are based on both sets of guidelines.

In 2015, Imbruvica (ibrutinib) became the first treatment specifically approved for WM by the US Food and Drug Administration (US FDA), and it was subsequently also approved by the European Medicines Agency (EMA) and Health Canada. In 2018, the US FDA approved the combination of ibrutinib and rituximab for WM. More recently, zanubrutinib has been approved by the US FDA, EMA, and Health Canada for the treatment of WM, and China National Medical Products Administration granted it conditional approval for treatment of patients with relapsed or refractory WM. Most of the other treatments in use for WM were previously approved for related cancers such as chronic lymphocytic leukemia, lymphoma, and multiple myeloma.

Individual patient considerations are important when deciding on a treatment – these include the presence of low blood counts, the need for rapid disease control, age, overall general health, patient preferences, genomic profile, and the possibility for future autologous stem cell transplantation.

The following are summaries of treatment options in current use or in clinical trials for WM patients. For a more comprehensive review, refer to the Treatment Options Guides and various Fact Sheets on treatments, available for downloading on the IWMF website at https://iwmf.com/publications/.

## Chemotherapy – Alkylating Agents

Chemotherapy owes its origin to the mustard gas of World War I, followed by an air raid in World War II involving mustard gas that produced a marked reduction of white blood cells in those exposed. This led to the use of nitrogen mustard in the treatment of low-grade lymphomas. Chemicals in this category are known as alkylating agents. These are cell-cycle non-specific drugs which target fast-growing cells throughout the body. Thus, they

not only affect many malignant cells but also the rapidly dividing cells of the bone marrow, stomach lining, and hair follicles, often causing neutropenia (low neutrophil count), nausea and mouth sores, and hair loss. The commonly used alkylating agents in the treatment of WM include cyclophosphamide and bendamustine, and Table 3 lists selected chemotherapy drugs. Alkylating agents are frequently used in combination with other drugs, such as purine nucleoside analogs, corticosteroids, and/or monoclonal antibodies.

Cyclophosphamide (Cytoxan) is an alkylating agent that has been used for many years, most frequently given as part of combination therapy. The drug may be administered either orally or intravenously. Typically, it is given in one cycle every three weeks for a total of six to eight cycles. The use of cyclophosphamide in any regimen can cause reduction of IgA and IgG levels, thereby increasing the risk of infections. Rarely, extended treatment may result in an increased risk of bladder cancer. Cyclophosphamide does not appear to harm stem cell collection and can therefore be used in patients who may be candidates for autologous stem cell transplant.

The combination of dexamethasone, rituximab, and cyclophosphamide (referred to as DRC, CDR, or RCD) was evaluated in a study of 72 previously untreated WM patients. An overall response rate of 83% was observed. The median time to response was long, about four months, which suggests that this combination is not the best to use if rapid control of disease is necessary. Toxicities with DRC were mild, with the only moderate to severe toxicity being neutropenia in 9% of patients. This study was recently updated, showing a time to disease relapse of 35 months. Most relapsing patients were still sensitive to rituximab-based therapies. Long-term toxicities, including transformation to aggressive disease or to myelodysplasia, were low. This combination has become widely used as first-line and relapse therapy in the treatment of WM and is one of the preferred regimens in both settings, according to the NCCN Guidelines and the IWWM Consensus Panel Treatment Recommendations. It can be helpful in frail patients requiring combination therapy.

Cyclophosphamide combined with hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone is called CHOP, and if rituximab is added, referred to as CHOP-R or R-CHOP. It can be used as relapse therapy but is not a preferred regimen in the NCCN® Guidelines or the IWWM Consensus Panel Treatment Recommendations. Because vincristine is associated with a high risk of peripheral neuropathy, cyclophosphamide-based regimens without vincristine may be preferred.

The combination of rituximab, fludarabine, and cyclophosphamide (called FCR) is effective in WM, with rapid response rates. However, due to the potential toxicities of fludarabine in this combination (discussed below under Nucleoside Analogs, FCR is not a preferred regimen in the NCCN® Guidelines or the IWWM Consensus Panel Treatment Recommendations in either first-line or relapse settings, although it can be used as an alternate option in patients with high-risk disease who are not candidates for autologous stem cell transplant. Prophylaxis to prevent *Pneumocystis* pneumonia and herpes zoster (shingles) should be seriously considered for patients on FCR.

Bendamustine (Bendeka, Treanda or Levact), although classified as an alkylating agent, also has some characteristics of a nucleoside analog. The US FDA approved bendamustine in late 2008 for the treatment of patients with indolent B cell non-Hodgkin lymphoma.

Bendamustine is an intravenous medication. A rapid-infusion (10-minute) formulation of bendamustine called Bendeka was also approved for use. Bendamustine has been used as single agent therapy or in combination with other agents, including rituximab (a regimen referred to as Benda-R).

The Benda-R combination was compared to CHOP-R in a Phase 3 study of 546 patients with indolent non-Hodgkin's lymphoma, including 41 WM patients. A similar overall survival but a longer progression- free survival was reported for the Benda-R arm of the study (a median of 69.5 months) vs. CHOP-R (a median of 28 months). Progression-free survival is the length of time during and after treatment that a patient lives with the disease but does not show signs or symptoms of disease progression, whereas overall survival is the length of time after diagnosis that a patient survives. Toxicities, including neutropenia, infections, peripheral neuropathy, and hair loss, were less for the Benda-R patients.

The outcome of 30 WM patients with relapsed/refractory disease who received bendamustine with an anti-CD20 monoclonal antibody (such as rituximab) was also examined. An overall response rate of 83% and a median progression-free survival of 13 months were reported.

Another study looked at Benda-R in 71 previously treated WM patients. The overall response rate was 80%, and the major toxicity was moderate to severe neutropenia in 13% of patients. The median progression-free survival was not reached after a median follow-up of 19 months. Among responders, the median time to 50% reduction in monoclonal IgM was three months, and no IgM flare (temporary increase in IgM) was observed. No patients developed aggressive lymphoma or myelodysplasia, but in three cases, a solid cancer was observed.

No randomized clinical trials have directly compared cyclophosphamide, rituximab, and dexamethasone to bendamustine and rituximab. However, two retrospective studies have suggested a higher activity rate, but also higher toxicity, associated with bendamustine and rituximab.

As a result of these and other studies (and including extensive clinical use of bendamustine by physicians treating WM patients), the NCCN® Guidelines and the IWWM Consensus Panel Treatment Recommendations list bendamustine in combination with rituximab as one of the preferred treatment regimens in both first line and relapse therapy, with bendamustine alone as a recommended option in both settings for patients who are intolerant or refractory to rituximab. Treatment is well tolerated even in elderly patients, but the dose of bendamustine may need to be lowered for these patients, as well as for those with renal impairment. Four to six cycles of Benda-R are usually sufficient to achieve adequate response in most WM patients.

Prophylaxis to prevent *Pneumocystis* pneumonia should be considered for patients on Benda-R, and the use of bendamustine in any regimen can cause reduction of IgA and IgG levels, resulting in increased risk of infections. Patients have reported redness, pain, and swelling at the intravenous site due to bendamustine and should be monitored for this side effect during and after each infusion.

Bendamustine is particularly useful for people with WM who have enlarged lymph nodes, livers, or spleens, or when a rapid response to treatment is needed. Another advantage is that it is useful for a fixed duration of time, not a lifetime therapy. Additionally, Bendamustine is not contraindicated in potential candidates for autologous stem cell transplant (ASCT), as it is unlikely to affect stem cell collection. A possible disadvantage of bendamustine is that

approximately 1 percent of people with WM who were treated with this drug developed a secondary cancer like leukemia. It is not known if bendamustine caused this effect; people with WM may also develop secondary cancers that are not related to drug treatments.

## Chemotherapy – Nucleoside Analogs

Purine nucleoside analogs mimic several of the normal building blocks of DNA and, when incorporated into the DNA of rapidly dividing cancer cells, will stop their reproduction. The most used purine nucleoside analogs for WM have been fludarabine and cladribine. Purine nucleoside analogs are also used in varying combinations with other drugs, such as monoclonal antibodies.

Purine nucleoside analogs, especially in combination therapy, have provided patients in clinical trials with response rates of 60-95%, and the responses tend to be durable. There is no clear indication as to which, fludarabine or cladribine, is superior to the other in the treatment of WM, but most physicians lean toward the drug with which they are more familiar.

A marked reduction in white blood cells (particularly neutrophils and T cells) and reduction of IgA and IgG levels following nucleoside analog therapy may result in increased susceptibility to infections. Outbreaks of herpes zoster (shingles) infections are common; it is therefore strongly recommended to use antiviral therapy during and for an extended period after nucleoside analog therapy. Antibiotic therapy to prevent bacterial infections, especially *Pneumocystis* pneumonia, is similarly recommended.

Studies have reported an increased incidence of myelodysplasia and acute leukemia, as well as an increased frequency of disease transformation to aggressive lymphoma in WM patients treated with nucleoside analogs. Because the risk is upwards of 8-15%, limiting the exposure of these agents in WM patients is strongly recommended. They are not preferred regimens for either first-line or relapse therapy in the NCCN® Guidelines or the IWWM Consensus Panel Treatment Recommendations.

Fludarabine (Fludara) is typically administered intravenously for four or five consecutive days in three- or four-week cycles. Fludarabine may also be given orally, more commonly in countries outside the US. The number of cycles is determined by the patient's response; but, as mentioned, information on long-term toxicity of nucleoside analogs has resulted in minimizing the number of cycles received by the patient. Delayed maximum treatment responses are quite common with fludarabine; it is not unusual to see a patient's IgM continue to drop for 6-12 months following the end of therapy. This continued improvement after the conclusion of treatment is not unique to nucleoside analogs. It is also seen after other WM treatments, including rituximab (a monoclonal antibody therapy), alkylating agents, and proteasome inhibitors.

Fludarabine alone, fludarabine and rituximab (FR therapy), and fludarabine in combination with cyclophosphamide, and rituximab (FCR therapy) are effective in first line and relapse therapy, with high response rates and median progression-free survivals in some studies exceeding 50 months. Fludarabine-based treatments can be considered in fit, older WM patients with previously treated disease who have failed other, less toxic treatments. In patients who are eligible for autologous stem cell transplant, stem cells should be

collected before fludarabine administration. More information about stem cell transplantation can be found in a separate Fact Sheet on the IWMF website at https://iwmf.com/publications/.

Cladribine (2CdA or Leustatin) is administered intravenously, usually on five consecutive days, and can be used alone or in combination with rituximab to treat WM. It has also been given as a seven-day treatment through a continuous pump worn by the patient. The usual treatment consists of two to four or more such cycles, spaced four weeks apart. Toxicities are similar to those of fludarabine, and current practice favors limiting the number of cycles to the fewest required by the individual patient.

| GENERIC NAME (TRADE NAME) | ROUTE OF ADMINISTRATION | COMMON SIDE EFFECTS |
|---|---|---|
| **Alkylating Agents:** | | |
| Cyclophosphamide (Cytoxan) | Infusion or oral | Nausea, vomiting, decreased blood cell counts, fatigue, hair loss, nail or skin discoloration, bladder irritation |
| Bendamustine (Treanda or Levact) | Infusion | Nausea, vomiting, decreased blood cell counts, increase in bilirubin, fatigue, diarrhea, rash |
| **Nucleoside Analogs:** | | |
| Fludarabine (Fludara) | Infusion or oral | Nausea, decreased blood cell counts, fatigue, neurotoxicity, infections, rash |
| Cladribine or 2 CdA (Leustatin) | Infusion | Nausea, decreased blood cell counts, fatigue, infections, rash |

*Table 3. Selected chemotherapy agents used in the treatment of Waldenstrom's macroglobulinemia*

## Monoclonal Antibody Therapy

Monoclonal antibody therapy is based on the use of identical antibodies that are engineered and manufactured in a laboratory in large amounts to be directed against a specific antigen found on the surface of the targeted cell. Once the monoclonal antibody has attached to the targeted cell's surface, it can either destroy the cell directly or activate the immune cells of the body to kill it. Monoclonal antibodies used in the treatment of WM are listed in Table 4.

Rituximab (Rituxan or Mabthera) was the first monoclonal antibody to receive FDA approval for the treatment of relapsed non-Hodgkin lymphoma in 1998. It is prescribed off-label for WM and is now commonly used as single agent therapy as well as in combination therapies and as maintenance therapy for both first line and relapsed/refractory treatment. Rituximab targets the CD20 surface antigen on B cells.

Two schedules for single agent rituximab have been studied in WM: the standard one, in which one weekly infusion of 375 mg/$m^2$ is administered for four weeks; and the extended one, in which responding patients receive four more weekly infusions during weeks 12-16. Reported response rates vary between 25-45%.

Recently, subcutaneous administration of rituximab was FDA approved for several blood cancers and may also be prescribed off-label for WM. In a recent study with WM patients, ixazomib and dexamethasone were given in combination with subcutaneous rituximab (after an initial intravenous dose). The subcutaneous formulation is called Rituxan Hycela and is given by injection in 5-7 minutes rather than the typical several hours needed for intravenous infusion. The approval stipulates that the subcutaneous option can be used only after patients have received and tolerated at least one treatment of rituximab intravenously. In clinical trials, the effectiveness of the subcutaneous formulation was equivalent to that of intravenous rituximab. The side effects of subcutaneous administration, in addition to those seen with intravenous administration, include skin issues such as rash, blistering, and peeling.

About 50% of WM patients treated with rituximab experience a transient increase (greater than 25%) in serum IgM levels—referred to as the IgM "flare" phenomenon. This flare may lead to symptomatic hyperviscosity, as well as worsening of other IgM-related conditions. Flare occurs mostly during the first 2-4 months of treatment; it is not associated with a higher risk of treatment failure, and one should be cautious not to interpret flare as a lack of response or even disease progression.

To avoid complications from flare, patients with symptomatic hyperviscosity or with serum IgM concentrations greater than 4,000 mg/dL should avoid single agent rituximab when possible. If serious IgM flare during single agent or combination treatment is considered a possibility, plasmapheresis prior to therapy should be considered to reduce the IgM level, or rituximab should be avoided during the first one or two cycles of combination therapy until the IgM declines to a safer level.

Rarely, patients may be intolerant to rituximab, meaning that they have worsening infusion reactions that result in the therapy becoming unsafe. For such patients, slow infusion rates should be tried, or other drugs considered.

Late-onset neutropenia (low neutrophil count) has been observed with rituximab, mostly when combined with chemotherapy. The underlying mechanism is not well understood. Reactivation of hepatitis B virus has also been observed, and screening for prior hepatitis B exposure is recommended Hepatitis B carriers should be closely monitored for clinical and laboratory signs and symptoms of active infection during therapy and for several months afterward.

Rituximab has been combined with alkylating agents, nucleoside analogs, proteasome inhibitors, and targeted therapies to B cell signaling pathways. It is a part of almost every combination regimen for both first line and relapsed/refractory WM.

Biosimilars for rituximab have been approved in Europe and the US. A biosimilar is a biological product that is highly similar to and has no clinically meaningful difference from an existing approved reference product. As patent protections for rituximab and similar drugs are expiring, biosimilars are being developed to provide more treatment options, increase access to medications, and potentially lower health care costs through competition. Although

rituximab biosimilars are considered equivalent to the original product and may be prescribed off-label for WM, they have not been specifically studied in WM patients.

While rituximab maintenance therapy has been studied extensively in other blood cancers, there has been controversy about its role in WM. Maintenance therapy is prolonged treatment given after the initial treatment course (typically combination therapy including rituximab) has resulted in a response. The rationale for its use has been to prolong the amount of time before disease progression occurs.

There is no standardized rituximab maintenance dosing schedule for WM; in clinical practice, it has varied from one weekly infusion every two or three months to four weekly infusions every six months. The duration of maintenance is typically two years.

A randomized Phase 3 trial of maintenance rituximab in 218 WM patients used bendamustine and rituximab as front-line therapy. Participants who achieved at least a partial response to treatment were randomly assigned to either two years of maintenance rituximab given every two months or to observation (no maintenance). The median progression-free survival in the maintenance arm of the study was 101 months and in the observation arm was 83 months; however, this difference was not statistically significant. The median overall survival had not yet been reached in either arm. The current IWWM consensus panel opinion is that maintenance rituximab should not be recommended for WM patients who have achieved a partial response or better after chemoimmunotherapy. This is based on the risk vs benefit of long-term rituximab use, which can lead to an increased risk of infection for continuous B cell depletion due to maintenance.

| GENERIC NAME (TRADE NAME) | ROUTE OF ADMINISTRATION | COMMON SIDE EFFECTS |
|---|---|---|
| | | |
| Rituximab (Rituxan or Mabthera) | Infusion | Shortness of breath, chills, facial flushing, fatigue, fever, headache, decreased blood pressure, nausea, itching, infections |

*Table 4. Monoclonal antibody agent used in the treatment of Waldenstrom's macroglobulinemia*

## Proteasome Inhibitors

A proteasome is a large protein complex found inside almost all cells, and its main function is to degrade unneeded or damaged proteins by chemically breaking them down with enzymes. Degradation of such proteins is a normal, necessary, and orderly cellular process. Studies have shown that because cancer cells tend to accumulate proteins more quickly, they are more susceptible to the action of proteasome inhibitors than normal cells.

Bortezomib (Velcade) was the first proteasome inhibitor, developed in 1995 and approved by the FDA in 2003 for the treatment of refractory multiple myeloma. It has since been approved for relapsed mantle cell lymphoma and as first-line therapy for multiple myeloma. It is prescribed off-label for WM. Additional proteasome inhibitors

have since been developed or are currently under development to improve potency and ease of administration and to reduce side effects.

The earliest clinical trial protocol of bortezomib for WM therapy administered it intravenously twice a week along with dexamethasone and rituximab (abbreviated BDR) in 23 previously untreated patients. The overall response rate and major response rate were 96% and 83%, respectively. Sixty percent of patients discontinued treatment after 4 cycles because of treatment-related peripheral neuropathy. The median progression-free survival was 66 months.

Subsequent studies of bortezomib combination therapy for first line and relapsed/refractory WM patients administered bortezomib intravenously once a week, with response rates comparable to those seen with twice-weekly administration. Once weekly bortezomib regimens have been associated with lower rates of serious peripheral neuropathy.

According to the NCCN® Guidelines, the combination of bortezomib, rituximab, and dexamethasone is one of the preferred treatment options for both first line and relapsed/refractory WM. However, bortezomib regimens should be used with caution in WM patients who have pre-existing neuropathy. Bortezomib only, bortezomib with dexamethasone, or bortezomib with rituximab can be considered as alternatives for those who are intolerant to rituximab and/or dexamethasone.

Because neuropathy is a major concern with bortezomib treatment, subcutaneous (under the skin) administration of bortezomib once a week is now the preferred method of administration, based on study results in multiple myeloma patients that reported less neuropathy with this method. Subcutaneous bortezomib is currently being evaluated in trials of WM patients as a part of several combination regimens, including cyclophosphamide and rituximab or cyclophosphamide, dexamethasone, and rituximab.

Plasmapheresis followed by bortezomib therapy can be particularly helpful for rapid reduction of serum IgM levels in patients with symptomatic hyperviscosity, symptomatic cryoglobulinemia, symptomatic cold agglutinin disease, amyloidosis, and renal impairment. Another advantage of bortezomib is that it is not toxic to bone marrow stem cells and therefore can be used as treatment for patients who are considering autologous stem cell transplantation as a future option. Long-term follow-up in multiple myeloma patients does not suggest a risk for secondary malignancies.

Bortezomib treatment is associated with a high rate of herpes zoster (shingles), and prophylactic treatment with an antiviral is strongly recommended during treatment. Bortezomib treatment can decrease normal levels of IgA and IgG, and these levels should be carefully monitored during therapy.

Carfilzomib (Kyprolis) is a second-generation proteasome inhibitor associated with a lower risk of neuropathy in multiple myeloma patients. It was evaluated in combination with rituximab and dexamethasone (CaRD regimen), in a Phase 2 trial of 31 previously untreated WM patients. The overall response rate was 87%, similar to response rates seen in bortezomib-based regimens and was not impacted by MYD88 L265P mutation status. IgM flare was reported in 23% of patients. No significant neuropathy was observed. Carfilzomib is associated with an increased risk of cardiovascular events in multiple myeloma patients and should be used with caution in patients who have WM and cardiovascular disease, particularly if they are older than 65 years.

Carfilzomib was approved by the EMA (European Medicines Agency) in 2015 for the treatment of multiple myeloma. Within the US, CaRD therapy is not a preferred regimen for first line use in the NCCN® Guidelines, but it is an alternate option in the first-line setting. Prophylactic treatment with an antiviral agent is strongly recommended during treatment to prevent shingles. Carfilzomib-based therapy can reduce IgA and IgG levels, necessitating the use of immunoglobulin therapy or discontinuation of CaRD treatment.

Ixazomib (Ninlaro) is a newer proteasome inhibitor administered orally that has been approved by the FDA for the treatment of relapsed/refractory multiple myeloma. Ixazomib combined with dexamethasone and rituximab (IDR regimen) was evaluated in a Phase 2 clinical trial of 26 previously untreated WM patients. All participants had the MYD88 L265P mutation, and 58% also had a CXCR4 mutation. The overall response rate was 96%, which was unaffected by CXCR4 mutation status. The median time to response was longer in patients with CXCR4 mutations (12 weeks vs. 8 weeks). There was no statistically significant difference in progression-free survival based on CXCR4 mutation status. The most common adverse events were mild gastrointestinal symptoms and rituximab-related infusion reactions.

IDR was also evaluated in a Phase 2 trial of 59 relapsed/refractory WM patients in The Netherlands, Belgium, and Greece. The first dose of rituximab was intravenous, with subsequent doses administered subcutaneously. The overall response rate was 71%. Serious adverse events occurred in 16 patients and were mainly infections. There was new onset or worsening of peripheral neuropathy in 16 patients, which was reversible in 10 of them. In this study, there was no statistically significant difference in progression-free survival based on CXCR4 mutation status, although there was a tendency for the patients with CXCR4 mutations to have shorter progression-free survival.

Ixazomib was approved by the EMA in 2016 for the treatment of multiple myeloma. IDR is not a preferred regimen for first line use in the NCCN® Guidelines, but it is an alternate option in the first-line setting. As is true with other proteasome inhibitors, prophylaxis for shingles is strongly recommended, and reduction in IgA and IgG levels can occur.

## Corticosteroids

Corticosteroids such as prednisone or dexamethasone are rarely used alone in treating WM. Corticosteroids or combination alkylating agent-corticosteroid therapy may be beneficial in people who also have or who develop certain hematologic complications, such as autoimmune hemolytic anemia, that can be associated with WM. Side effects are common and are dependent upon dosage and length of therapy. Despite the potential side effects of long-term therapy, their use in short-term therapy in combination with monoclonal antibodies or chemotherapy agents is widespread.

## Targeted Therapies to B Cell Pathways

To live and multiply, B cells rely on a very complex series of molecular signals via proteins on their surfaces that in turn initiate a series of reactions inside the cells to enable the cells to carry out their normal functions. This signaling cascade is an essential requirement for the survival of malignant B cells, and in many cases, several of these signals are enhanced, suppressed, or turned on and off by malignant B cells so that they can survive and grow. As researchers have revealed more about genes and their protein expression in WM, they are beginning to understand the complicated pathways involved in the disease and develop treatments that target specific portions of these pathways, thereby interfering with survival and growth of WM cells. They are also discovering that responses to certain targeted treatments may depend upon the cells' genetic makeup, for example, the presence or absence of mutations in the genes MYD88 and CXCR4 in WM cells.

Targeted treatments are different from traditional therapies in several ways, and these differences have important implications for patients. Targeted therapies are more specific for tumor cells than chemotherapy. Almost all the targeted therapies directed to B cell signaling pathways are daily oral medications, which means that they can be taken at home. This makes them more convenient, but it also means that patients must be diligent about when and how they take their medication. These treatments do not damage stem cells in the bone marrow, although they can have side effects that may require dose reduction or treatment discontinuation. These treatments can result in dramatic improvements in disease status, but they appear to slow or arrest tumor cell growth rather than eliminate the cancer. This means that once patients begin these treatments, they may need to continue until the treatments no longer work or until the side effects become intolerable. This represents a significant change from the older therapies that, while not eradicating the cancer, are typically administered cyclically for a finite period and then discontinued if a patient achieves a response that significantly reduces the disease burden.

Although these targeted agents are currently being administered clinically for WM as single-agent therapies, researchers are investigating whether targeted agents can be used in combination with each other or with other therapies. It may be that combinations can clean out the bone marrow better. If so, combinations may permit patients to go off treatment for extended periods of time, rather than taking targeted agents indefinitely.

The oral targeted agents are very expensive, and not all insurers pay for them. They are not available in all countries. US federal and state regulations are being changed so that Medicare, Medicaid, and private insurers may eventually be required to cover their cost to the same extent that they cover intravenous and injectable drugs, but for now availability and cost remain ongoing issues for many cancer patients in the US and internationally.

## Ibrutinib, Acalabrutinib, and Zanubrutinib

Ibrutinib is an inhibitor of an enzyme in the B cell signaling pathway called BTK. There was a strong rationale to begin testing this drug in WM patients because BTK is excessively activated by MYD88 L265P, an acquired gene mutation found in approximately 90-95% of WM patients. Activated BTK enhances the survival of WM cells by subsequent activation of an important protein called NF-kappa B in the B cells. Ibrutinib was approved for WM in 2015 by the US FDA and became the first drug to receive approval for the treatment of WM.

Ibrutinib alone, as well as the combination of ibrutinib with rituximab, are included in the NCCN® Guidelines as a Category 1 (preferred regimen) for the treatment of both first line and relapsed/refractory WM. The standard dose of ibrutinib for WM patients is 420 mg per day.

The clinical trial that led to ibrutinib approval was a Phase 2 study of the drug in 63 symptomatic WM patients who had received at least one prior treatment. The median time to response was four weeks. The overall response rate was 90.5%, with a major response rate of 73%. Treatment-related side effects of grade 2 (moderate) or higher included neutropenia (low neutrophil count) (22%), thrombocytopenia (14%), post-procedural bleeding (3%), nosebleeds associated with the use of fish-oil supplements ( 3%), and atrial fibrillation associated with a history of arrhythmia (5%). Similar results were observed in other studies. An update to this study after median long-term follow-up of almost 47 months reported overall and major response rates of 90.5% and 79.4%, respectively. No complete responses were observed, but 30.2% achieved a very good partial response.
Another Phase 2 study evaluated ibrutinib in 30 symptomatic WM patients who had not been previously treated. The overall response rate was 100%, and the major response rate was 83%. Side effects reported in this study included arthralgias (joint pain), bruising, neutropenia, upper respiratory tract infections, urinary tract infections, atrial fibrillation, and hypertension (high blood pressure).

Overall, treatment with ibrutinib is well tolerated in WM patients. Patients have reported skin rashes and skin and nail changes. New or worsening hypertension (high blood pressure) has been observed. An effect on platelet aggregation, resulting in bleeding complications, has been described. The use of ibrutinib in patients requiring anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and care should be taken if anticoagulant therapy is used. Acquired von Willebrand disease is a bleeding disorder that may occur with a high IgM level. It is recommended that testing for von Willebrand activity in WM patients with a history of bleeding be considered before starting ibrutinib. In some cases, dose reduction of ibrutinib may help to alleviate some of its side effects.

In a series of 112 WM patients on ibrutinib, the cumulative risk of atrial fibrillation at one, two, and three years was 5.4%, 7.1%, and 8.9%, respectively. Patients with a prior history of atrial fibrillation had a shorter time to recurrence compared to those without such a history. Nearly all patients who developed atrial fibrillation were able to continue ibrutinib following cardiac intervention and/or ibrutinib dose reduction. In patients with pre-existing conditions requiring anticoagulant therapy, alternative treatment options can be considered, although anticoagulation is not a contraindication to the use of ibrutinib. Patients should be monitored closely for bleeding and direct oral anticoagulants, such as apixaban and rivaroxaban, are preferred over warfarin in patients requiring anticoagulation.

Both MYD88 and CXCR4 mutations can impact overall and major responses to ibrutinib. WM patients who have wild-type (unmutated) MYD88 have a lower overall response rate and an absence of major responses, compared to patients with a MYD88 mutation. WM patients with CXCR4 mutations, especially with those termed "nonsense" CXCR4 mutations, have a lower overall response rate and fewer major responses to ibrutinib, as well as delayed responses, than do patients without CXCR4 mutations. "Nonsense" mutations involve a change in the DNA genetic code that introduces a "stop" signal. When new CXCR4 proteins are made, the protein is truncated, resulting in an incomplete protein. The part of the protein that follows a "nonsense" mutation is missing altogether. This differs from a "frameshift" mutation, which is due to a genetic mutation that causes an alteration in the way that the DNA is read, resulting in a scrambled sequence of amino acids. It is recommended (by NCCN® and IWWM) that testing of bone marrow for the MYD88 L265P mutation by AS-PCR (allele specific polymerase chain reaction) or other specialized PCR techniques should be an essential part of the workup of newly diagnosed patients and that patients with an unknown MYD88 and CXCR4 mutation status should be tested for both prior to ibrutinib therapy, as the status of the MYD88 and CXCR4 mutations can affect disease response.

Ibrutinib should not be discontinued, except temporarily for surgical and invasive dental procedures, unless unacceptable toxicity or disease progression occurs. Increase in serum IgM and reduction in hemoglobin can occur if ibrutinib is temporarily withheld and should not necessarily be regarded as treatment failure. Patients may experience withdrawal symptoms such as fatigue, fever, or night sweats, which can be managed with oral prednisone (10 mg twice daily) during the period that ibrutinib is withheld. The current recommendations for withholding ibrutinib for surgical procedures depend upon the invasiveness of the procedure and typically vary from 3-5 days before and after.

In patients who discontinue ibrutinib because of disease progression or unacceptable toxicity, 50% have an IgM rebound within the first four weeks afterward. It is suggested that subsequent treatment needed because of disease progression should be started promptly, and consideration should be given to bridging therapy using ibrutinib in combination with the next line of treatment for one or two cycles before completely stopping ibrutinib.

The combination of ibrutinib with the monoclonal antibody rituximab (Rituxan) was approved for WM by the US FDA and the EMA in 2018. Approval was based on the Phase 3 iNNOVATE clinical trial, in which the combination of ibrutinib and rituximab was associated with faster time of response, higher rates of response, and improved progression-free survival than placebo and rituximab. However, the absence of a study arm of ibrutinib with placebo has led to a continuing debate on the merits of single agent ibrutinib vs this combination.

Ibrutinib has been shown to penetrate the central nervous system (brain and spinal cord). Studies have suggested that ibrutinib is effective in the treatment of WM patients with the rare neurological complication of Bing-Neel syndrome (BNS), in which the lymphoplasmacytic cells of WM cells invade the central nervous system. A retrospective study evaluated ibrutinib in 28 patients with BNS; approximately half of the patients took ibrutinib at 560 mg daily and approximately half took the standard dose at 420 mg. Symptomatic improvements were seen in 80% of patients within three months of starting treatment. The 2-year event free survival (survival without additional symptom development related to disease progression) was 80%.

Resistance to ibrutinib has been described in WM patients, especially after several years of treatment. One mechanism of resistance is a mutation of the BTK gene, resulting in one altered amino acid in the BTK protein. This is called the C481S mutation, in which a cysteine at position 481 is changed to serine. Other causes of ibrutinib

resistance are under investigation. Acalabrutinib and zanubrutinib, like ibrutinib, rely on binding to the amino acid cysteine in position 481 of BTK. So, if resistance to ibrutinib is based on the BTK C481S mutation, there also will likely be resistance to acalabrutinib and zanubrutinib.

Many of the side effects of ibrutinib occur because it not only inhibits BTK, the desired target, but also non-specifically inhibits several other similar cellular proteins (called kinases). These so-called off-target effects can cause some of the adverse effects seen with ibrutinib. Newer, more specific BTK inhibitors have been and are being developed to improve responses, reduce some of the side effects seen with ibrutinib, and overcome resistance.

Zanubrutinib, another second generation BTK inhibitor, was also designed to reduce side effects by more selectively inhibiting BTK while minimizing inhibition of other kinases.

A recent Phase 3 study compared zanubrutinib to ibrutinib in symptomatic WM patients. Although a very good partial response was attained in patients on zanubrutinib (28%) vs patients on ibrutinib (19%), that result was not statistically significant. Zanubrutinib was associated with a lower rate of atrial fibrillation than ibrutinib (2% vs 15%). Multiple other side effects, such as muscle spasms, contusions, diarrhea, peripheral edema (leg swelling), and pneumonia were seen in fewer patients on zanubrutinib compared to ibrutinib. On the other hand, there was a higher rate of neutropenia (low neutrophil counts in the blood) with zanubrutinib than ibrutinib (29% vs 13%), but an increase in infections, which might be expected when there is neutropenia, was not seen. A separate arm of this study evaluated WM patients without the MYD88 L265P mutation and found that zanubrutinib was able to induce responses in these patients, with an overall response rate of 77%. Zanubrutinib dosing in WM is 160 mg twice daily or 320 mg once daily.

Zanubrutinib has approval in the treatment of WM patients by the US FDA, EMA, Health Canada, Australia, and has conditional approval from China National Medical Products Administration (NMPA) for the treatment of relapsed or refractory WM. Zanubrutinib has been added to the National Comprehensive Cancer Network (NCCN®) guidelines as a Category 1 (preferred) treatment for patients that are previously untreated and those with relapsed disease.

Zanubrutinib, like acalabrutinib and ibrutinib, relies on cysteine for binding at position 481 of BTK. So, if resistance to ibrutinib is based on the BTK C481S mutation, there will be resistance to zanubrutinib and acalabrutinib as well.

Acalabrutinib, a second generation BTK inhibitor, was designed to reduce side effects by more specifically inhibiting BTK while minimizing inhibition of other kinases. This targeted therapy was evaluated in a Phase 2 study of 106 WM patients, of whom 14 were treatment naïve and 92 previously treated. At a median follow-up of 27 months, acalabrutinib was associated with an overall response rate of 93% in both groups of patients, with a major response rate of 79% in treatment naïve and 80% in previously treated patients. Common adverse events included headache, diarrhea, bruising, fatigue, nausea, and muscle aches. The most serious adverse events of grade 3 or worse included neutropenia and lower respiratory tract infections. The proportion of patients who had atrial fibrillation was 5%. Typical dosing for WM patients is 100 mg twice daily.

Acalabrutinib is approved for the treatment of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and mantle cell lymphoma. It is not approved for WM, but it can be prescribed off-label. Although it is not a

preferred regimen in the NCCN® Guidelines, it is listed as one of the other recommended regimens for previously treated WM patients. Acalabrutinib, like ibrutinib and zanubrutinib, relies on binding to the amino acid cysteine in position 481 of BTK. So, if resistance to ibrutinib is based on the BTK C481S mutation, there also will likely be resistance to acalabrutinib.

## Other BTK inhibitors

Several other BTK inhibitors are in development. Tirabrutinib (Velexbru) was evaluated at a dose of 480 mg once daily in 27 WM patients, both treatment naïve and previously treated. The overall response rate was 94% and the major response rate was 78% in treatment naïve patients, whereas the overall response rate was 100% and the major response rate was 89% in previously treated patients. Rash was reported in 41% of patients, and serious neutropenia was reported in 7%.

Because mutations in BTK can be acquired by patients on ibrutinib and lead to treatment resistance, third generation BTK inhibitors that bind differently to BTK are now being evaluated. These include ARQ 531 and pirtobrutinib (LOXO-305), both are which are in clinical trials with WM patients whose disease has progressed while on ibrutinib.

## BCL-2 inhibitors

Venetoclax is an inhibitor of BCL-2 (B cell lymphoma 2), a member of the BH3 family of proteins that regulate cell death (apoptosis). BCL-2 prevents normal apoptosis, resulting in cells that live longer. If cancer cells over-express BCL-2, extended survival of the cancer cells causes the population of cancer cells to expand. The drug has been approved in the US for the treatment of CLL and SLL. Venetoclax has been studied in a multicenter, prospective Phase 2 trial of relapsed/refractory WM, where it has shown promising interim results (2 years of a 4-year study), with an overall response rate of 84%, a major response rate of 81%, and very good partial response rate of 19%. The major response rate was lower in refractory versus relapsed disease (50% vs. 95%). The median follow-up time was 33 months, and the progression-free survival was 30 months. CXCR4 mutation did not affect treatment response or progression-free survival. The only recurring grade 3 or worse adverse event was neutropenia (45%), including one episode of febrile neutropenia. No deaths were reported among the 32 patients over the course of the study.

Although it is not a preferred regimen in the NCCN® Guidelines, venetoclax is listed as one of the other recommended regimens for previously treated WM patients.

Venetoclax dosing is somewhat unusual, in that at the beginning of treatment, it must be ramped up from a low dose to a higher dose over a period of several weeks in order to avoid an adverse event called tumor lysis syndrome. Tumor lysis syndrome (TLS) is a condition that occurs when a large number of cancer cells die quickly**.** The dying cells release large amounts of potassium, phosphate, and uric acid into the blood, which can cause heart or kidney problems, lead to kidney failure, and become life-threatening. In the Phase 2 trial of WM patients, only one TLS event was reported, and that was based on laboratory evidence of the condition; no clinical symptoms of TLS occurred. To help prevent TLS, it is recommended that patients be treated prophylactically with the drug allopurinol and maintain good hydration during venetoclax ramp-up dosing. Dosing after ramp-up in this trial was 800 mg once daily.

Based on promising results seen with the combination of ibrutinib and venetoclax in CLL patients, a Phase 2 study using this combination in treatment naive WM patients with the MYD88 mutation has begun. Both drugs are being administered for a fixed duration of two years, with four years of follow-up. The hoped-for outcome is that this combination will eliminate most malignant cells in the bone marrow and result in a treatment response that may allow patients to have a prolonged treatment break. Second generation BCL-2 inhibitors are now in development.

## CXCR4 inhibitors

About 90% of patients with WM present with mutations in the MYD88 gene, while 30-40% of patients present with additional mutations in the CXCR4 gene, leading to overexpression of the CXCR4 pathway. Aberrant CXCR4 expression on cancerous B cells contribute to sequestration of malignant B cells in the bone marrow as well as an increased survival proliferation, and migration of cancer cells to lymph nodes and other sites. Patient with WM who have CXCR4 mutations tend to have increased bone marrow disease burden, higher serum IgM levels, and a higher risk of developing symptomatic blood hyperviscosity.
No current treatments show a complete response for patients with WM. The oral BTK inhibitor ibrutinib, which inhibits the MYD88-Bruton tyrosine kinase (BTK) mediated pathway, has shown major response rates (decrease in serum IGM levels from baseline of more than 50%) of up to 80%. Yet, major response rates in patients with WM with both MYD88 and CXCR4 mutations are only as high as 60%, and these patients have a four-fold likelihood of ibrutinib discontinuation.

The first clinical trial of ulocuplumab was an evaluation of the drug with ibrutinib. Ulocuplumab is a monoclonal antibody drug that binds to CXCR4, which not only blocks stimulation of CXCR4 but also causes apoptosis (cell death) in cells with excessive CXCR4 expression. The response to therapy was more rapid than is ordinarily seen with ibrutinib alone, although this was not a head-to-head trial, so no formal conclusions can be made about whether the combination was more effective than ibrutinib alone. The median time to a major response was 1.2 months, whereas with ibrutinib alone, the median time to a major response is generally 4.7 to 7.3 months. The major response rate was 100% (defined as partial response or better), with four of the 12 patients achieving a very good partial response (VGPR). Even the highest dose was well tolerated, with no accentuation of the adverse events commonly seen with ibrutinib therapy. Unfortunately, Bristol-Myers Squibb, the company that makes ulocuplumab, discontinued its development, so a planned Phase 2 study could not be conducted. However, a CXCR4 inhibitor called mavorixafor was available from another company, X4 Pharmaceuticals,

Mavorixafor is an oral, once-daily treatment for WM that is being evaluated in combination with ibrutinib in patients with MYD88 and CXCR4 mutations. Mavorixafor targets the CXCR4 pathway directly and the current clinical trial evaluates the drug's ability to mobilize white blood cells out of the bone marrow and improve treatment response.

## PI3K/AKT/mTOR inhibitors

Everolimus blocks mTOR, a protein in the PI3K/AKT/mTOR pathway that promotes cell growth and survival. This pathway is present in several cell types, including B cells, and is therefore used to treat solid cancers as well as B cell cancers. The effectiveness of PI3K inhibition in B cell cancers appears to result from interference with the ability of the cancer cells to respond to signaling in the tumor microenvironment.

A Phase 2 trial of everolimus in 60 relapsed/refractory WM patients reported a partial response rate of 50% and a major response rate of 23%. Toxicities included grade 3-4 (severe) anemia (27%), leukopenia (22%) thrombocytopenia (20%), diarrhea (5%), fatigue (8%), and pneumonitis (5%). Among previously untreated, symptomatic WM patients, the overall and major response rates were 72% and 60%, respectively. A discordance (lack of agreement) between serum IgM levels and bone marrow response was common and made response assessment difficult. Mouth sores frequently occurred (8%), and an oral dexamethasone swish and spit solution was helpful.

Everolimus is recommended as an option for therapy in relapsed/refractory WM, although owing to the toxicities associated with it (see above), everolimus is best considered in patients who are unresponsive to, or have progressed after, multiple lines of other, better-tolerated therapies. Serial bone marrow biopsies may help to clarify the disease response to everolimus. The drug is currently accessible in the US as an off-label indication for WM; however, it is not available for WM in many other countries.

Within the PI3K/AKT/mTOR pathway there are components other than mTOR that can be targeted to reduce the growth and survival of cancer cells.

One of the earlier inhibitors developed in this pathway was idelalisib (Zydelig), which is targeted to the enzyme PI3K kinase. Idelalisib is FDA-approved for CLL, relapsed follicular lymphoma, and relapsed SLL. It was evaluated in a Phase 1/2 study in ten previously treated WM patients and was associated with an 80% overall response rate. The most common grade 3 or greater adverse events included neutropenia, diarrhea, and liver toxicity. Another Phase 2 study of 30 previously treated WM patients was terminated early due to liver toxicity.

Newer PI3K inhibitors have been developed to reduce the toxicities associated with idelalisib. They include copanlisib (Aliqopa), duvelisib (Copiktra), and umbralisib (Ukoniq). These newer inhibitors have been FDA-approved for CLL and/or several non-Hodgkin lymphomas and have been studied in WM. However, none are currently included in the NCCN® Guidelines or the IWWM consensus panel recommendations for WM patients.

Because cellular pathways are complex and frequently redundant, it is possible that future treatment regimens will consist of one or more of these newer agents combined with older agents such as monoclonal antibodies and corticosteroids.

## Plasmapheresis

Plasmapheresis involves removal of blood from the body, separation and removal of the liquid (plasma) portion from blood, replacement of plasma (usually with albumin and sodium chloride solutions), and return of the remaining blood components to the body. Plasmapheresis can be thought of as a form of dialysis where the primary aim is the "filtering out" or removal of IgM (which is in the plasma) from the circulation.

Plasmapheresis is widely used to reduce the symptoms associated with hyperviscosity syndrome. In general, plasmapheresis is initiated just prior to or concurrent with chemotherapy; however, some patients have been treated successfully with only plasmapheresis, particularly if they cannot tolerate more toxic therapies. If performed alone, plasmapheresis must be repeated frequently to maintain acceptable IgM levels because the procedure has no effect on the growth and survival of WM cells. The treatment of IgM-related neuropathy may also involve a course of plasmapheresis followed by other treatment.

### Radiation

Radiation therapy has been used in WM, primarily for the selective and targeted reduction of enlarged lymph nodes and in the uncommon instances of tumors developing in other sites, such as the spine. Total body irradiation is not used in the management of WM.

### Stem Cell Transplantation

Stem cell transplantation is feasible in WM and has been shown to be effective for younger patients with relapsed disease or disease which has not responded to several previous lines of therapy. However, there are risks associated with transplantation.

Autologous stem cell transplantation re-infuses a patient's own hematopoietic stem cells collected before he has undergone high-dose chemotherapy to destroy the tumor cells in the bone marrow. Allogeneic stem cell transplantation uses donor stem cells from either a family member (usually) or an unrelated individual. A newer type of allogeneic stem cell transplantation, called non-myeloablative or "mini-allo" transplant does not completely clear the recipient's bone marrow of tumor cells before infusion of the stem cells; it is believed that the donor stem cells will recognize any remaining tumor cells in the marrow as foreign and destroy them. Mini-allo transplant is less toxic than a regular allogeneic transplantation, and recovery time tends to be less.

The major toxicities of stem cell transplantation occur because the patient's immune system is severely depressed during the procedure and for some time afterward. Because an allogeneic transplant uses donor stem cells, there is also a risk of serious complications from graft vs. host disease (GVHD*)*, which occurs when the donor's immune cells see the recipient's cells as foreign and attack them. Graft vs. host disease can be acute or chronic. Both acute and chronic GVHD lead to an increased risk of several complications, either because of GVHD itself or because of the immunosuppressive drugs used to treat it. Allogeneic stem cell transplantation for WM is rarely recommended.

One suggested option for younger patients to consider is collection and "banking" of their own stem cells for possible future transplant, as they can be safely preserved for 20 years or more. Patients who are considering stem cell banking or autologous transplantation should be careful to avoid certain treatments beforehand, especially nucleoside analogs, which can adversely affect the ability to collect adequate numbers of stem cells.

## WHAT ARE SOME OF THE EMERGING THERAPIES IN WM?

Several new regimens and therapies are currently being studied, a few of which will be covered here. It remains to be seen how these will become part of the treatment protocol for WM in the future.

Antibody-drug conjugates (ADCs) are an emerging class of biologic drugs. ADCs combine the advantages of a monoclonal antibody targeted to a specific type of cell with the anti-cancer activity of a small-molecule drug. Some potential drug molecules are highly potent killers of cancer cells ("cytotoxins") but are so toxic that if they were given as a traditional drug and distributed throughout the whole body, they would be too dangerous. Efforts have been underway for more than 30 years to improve safety by attaching ("conjugating") these toxic molecules to antibodies so they can be delivered in a more targeted way. The cytotoxin is attached to an antibody by a linker, a piece of chemical intended to prevent release of the cytotoxin while the ADC circulates in the blood. The linker is cleaved once the ADC gets inside the cancer cell, allowing the cytotoxin to detach inside the cancer cell. If the antibodies bind uniquely to cancer cells and are taken up, then the cytotoxic drugs could be delivered only to the cancer cells, sparing the body's normal cells. This could successfully treat the cancer while avoiding toxicity. This ideal has not yet been achieved—even though ADCs theoretically enter and kill only the cancer cells, there is still some toxicity to normal cells.

However, ADCs are improving, and some ADCs are now approved for treatment of certain types of cancer when other drugs are not working. An ADC called loncastuximab tesirine (Zylonta) consists of a highly potent cytotoxic drug attached to a monoclonal antibody that targets the CD19 protein on the surface of B cells and plasma cells. Zylonta was FDA approved in 2021 for treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma after two or more prior therapies.

Clinical trials of this and other ADCs are being considered for patients with WM. An ADC-like product called CLR 131 is based on a similar approach. In this case, the drug that kills the cancer cells is a radioactive form of iodine, called iodine-131. Instead of attaching the iodine-131 to an antibody to selectively target cancer cells, the iodine-131 is attached to a type of fat molecule called a phospholipid. The phospholipid is intended to bind preferentially to cancer cells, while having limited entry into normal cells. The US FDA granted CLR 131 Fast Track Designation for patients with WM having received two or more prior treatment regimens (first line standard of care that had a suboptimal response or failed BTK inhibitor treatment). Orphan Drug Designations (ODD's) have been granted for this drug in WM in the US and Europe. Data collected before January 8, 2021, in the Phase 2 CLOVER-1 clinical study show that six patients with WM demonstrated an overall response rate (ORR) of 100% and a major response rate of 83.3%, with one patient achieving a complete response (CR) that continues at nearly 27 months post-last treatment. The median treatment free survival is currently at 330 days, as of November 2021.

Bispecifics are another class of biologics that is receiving increased attention. Bispecifics are antibodies (or pieces of antibodies) that are designed so that they can recognize two different antigens at the same time. Some bispecifics consist of one part that binds to a tumor cell and another part that binds to a T cell, a type of immune cell. This brings the T cell close together to the tumor cell, which increases T cell killing of the tumor cells. The first bispecific molecule to be FDA approved was Blincyto (blinatumomab), based on a small piece of an antibody called a bi-specific T cell engager (BiTE). It is approved for several types of aggressive leukemia. Blincyto is rapidly excreted from the body, so it requires 28 days of continuous intravenous infusion. One bispecific antibody under development is Epcoritamab (DuoBody-CD3xCD20), which binds to the CD3 protein on T cells and to the CD20 protein on B cells. This drug is in clinical trials for various B cell cancers and may be considered for WM patients in the future. Other bispecifics under development target the CD3 protein on T cells and a different target protein on plasma cells and some B cells, called BCMA (B cell maturation antigen). Other types of newer bispecifics include molecules that bind at the same time to two different target proteins on a cancer cell, or even to two different sites on the same target protein.

CAR T-cell therapy is a relatively new type of T cell immunotherapy that is being used with some success against certain solid tumors such as melanoma and hematological cancers such as leukemia. CAR T cell therapy comes with some very serious side effects that researchers are working to alleviate.

In this type of therapy, T cells are collected from a patient via apheresis (a process similar to plasmapheresis). They are sent to a laboratory where they are genetically engineered to produce chimeric antigen receptors (CARs) on their surface. The CARs are proteins that allow the T cells to recognize an antigen on the patient's tumor cells, and the re-engineered T cells are known as CAR T cells. The number of CAR T cells is expanded by growing them in the laboratory in the millions, following which they are re-introduced into the patient's bloodstream. The CARs on the T cell surface recognize tumor cells in the patient's body and attack them; they may remain in the body long after the infusion has been completed and can guard against recurrence, frequently resulting in long-term remissions.

In a small National Cancer Institute led trial of CAR T cells primarily in patients with advanced diffuse large B cell lymphoma, more than half had complete responses to the treatment. There has been one case study published in a peer reviewed journal that described a patient with WM that had subsequently transformed to refractory high-grade B cell lymphoma. In this one patient, CD19-directed (CD19 is almost universally expressed on lymphoplasmacytic lymphoma cell of WM) CAR-T therapy was effective in eliminating evidence of both underlying WM as well as transformed high-grade B cell lymphoma at his 6- and 12-month follow-up. The study authors noted that longer term follow-up in this patient will be informative as late relapses have occurred even in patients who achieve a deep response after transplant.

Cancer cells can make proteins that interfere with the ability of T cells to recognize and attack the cancer, in other words they put "brakes" on the T cells. Immune checkpoint inhibitors are substances that remove the "brakes" on the T cells and allow them to kill the cancer cells more effectively. Examples of immune checkpoint inhibitors include nivolumab (Opdivo) and pembrolizumab (Keytruda). Researchers are looking into the use of immune checkpoint inhibitors in WM patients.

## HOW IS RESPONSE TO WM TREATMENT DETERMINED?

The following guidelines for determining the degree of response to treatment were developed by a consensus panel of experts in WM. These guidelines provide a uniform method for measuring responses and reporting the results of clinical trials.

- Progressive disease is characterized by an increase in serum monoclonal IgM of 25% or more and confirmed by a second measurement, and/or by progression of clinically significant signs or symptoms.
- Stable disease is defined as having a detectable monoclonal IgM protein, a less than 25% reduction or a less than 25% increase in serum monoclonal IgM from baseline, no progression of lymph node or spleen enlargement if present at baseline, and no new clinically significant signs or symptoms.
- A minor response is defined as having a detectable monoclonal IgM protein, a reduction in serum monoclonal IgM equal to or greater than 25% but less than 50%, and no new signs or symptoms of active disease.
- A partial response is defined as having a detectable monoclonal IgM protein, a reduction in serum monoclonal IgM equal to or greater than 50% but less than 90%, a decrease in lymph node or spleen enlargement if present at baseline, and no new signs or symptoms of active disease.
- A very good partial response is defined as having a detectable monoclonal IgM protein, a reduction equal to or greater than 90% in serum IgM (or normalization of serum IgM with persistent detectable monoclonal IgM in the electrophoresis), complete resolution of enlarged lymph nodes or organ enlargement if present at baseline, and no new signs or symptoms of active disease.
- A complete response is categorized by the absence of serum monoclonal IgM in the electrophoresis, normal serum IgM level, a normal bone marrow aspirate and biopsy, and resolution of enlarged lymph nodes or spleen if present at baseline.

## WHAT ARE CLINICAL TRIALS? ARE THERE ANY FOR WM?

Without clinical trials, all the new treatment options that are available to patients with WM would not exist. Clinical trials answer questions about what dosage is safest while providing optimal effectiveness with the least number of side effects and risks. Clinical trials are research studies designed to answer questions about diseases and new ways to treat them. Several different types of clinical trials for cancer are available, including treatment, prevention, screening, and quality-of-life or supportive care trials. Treatment trials are designed to evaluate new treatments such as new drugs or new combinations of drugs. Prevention trials are designed to evaluate ways of lowering the risk of developing cancer. Screening trials find the best way of diagnosing cancer. Finally, quality-of-life and supportive care trials identify ways of improving the comfort and quality of life of cancer patients.

Phase I trials are the first step in testing a new treatment in humans. Researchers evaluate what dosages are safe, how new agents should be administered (by mouth, infusion into a vein, injection subcutaneously or into a muscle) and how often the drugs are to be given to the patient. Researchers primarily monitor harmful side effects. The dose of the new therapy or technique is increased a little at a time. The highest dose with an acceptable level of side effects is determined to be appropriate for further testing. Phase I trials usually include only a limited number of patients and are often carried out at a few large academic medical centers.

Phase II trials attempt to determine whether the new agent or technique works for a specific type of cancer and continue to study its safety and effectiveness.

Phase III trials compare the treatment outcomes of patients taking the new therapy with results of people taking standard treatment. Participants are randomly assigned to the standard (also called control) group or to the new treatment group. This method, called randomization, helps to avoid bias and ensures that human choices or other factors do not affect the study's results. In most cases, studies move into Phase III testing only after they have shown promise in Phases I and II. Phase III trials often include large numbers of participants.

Phase IV trials occur after a treatment has been approved and is being marketed. The drug's manufacturer studies it further to evaluate the side effects, risks, and benefits over a longer period and in a larger number of people than in Phase III clinical trials. Because of the small WM patient population, Phase III and Phase IV trials for the disease are uncommon, although a recent example is the pivotal phase III trial that compared zanubrutinib with ibrutinib. To enroll enough patients, the investigators cooperated with hospitals around the world and combined their data together under one protocol.

The details of the clinical trial, including the advantages, disadvantages, and possible treatment-related side effects, must be understood by the participant before he or she enrolls. A person enrolled in a clinical trial can withdraw from the trial at any time.

Some clinical trials are non-interventional (essentially risk-free, as there is no drug involved), such as the PCROWD study or the PROMISE study at Dana-Farber Cancer institute. The PCROWD clinical trial (www.pcrowd.dana-farber.org/) is a medical research databank that studies blood samples and analyzes data from patients diagnosed with blood cancers to identify predictors of cancer progression. The PROMISE clinical trial is a collaborative research project screening individuals at higher risk for WM and multiple myeloma that looks at the genetic and microenvironment characteristics of IgM-MGUS and smoldering WM, how race and obesity affect precursor progression, and how imaging and therapeutics affect detection and interception (www.enroll.promisestudy.org).

More clinical trials are being made available to WM patients as more is learned about the biology and genetics of the disease and as more targeted treatments are being developed. Therefore, it is important to obtain the most current information from resources that are routinely updated. Specific information on clinical trials enrolling people with WM can be found on the National Institutes of Health website at www.clinicaltrials.gov. The Leukemia and Lymphoma Society (LLS) provides a group of expert nurses to discuss clinical trials and help blood cancer patients (including WM patients) to find clinical trials. The LLS Clinical Trial Support Center staff speak with individual patients, try to understand their unique circumstances, and, if appropriate, help them identify trials that are best suited for them. This resource can be found at https://www.lls.org/support-resources/information-specialists/clinical-trial-support-center-ctsc.

## WHAT CAN WM PATIENTS DO TO HELP THEMSELVES?

To the extent that he or she is able, a WM patient should try to become knowledgeable about the disease, partner with his or her physician in its management, and be proactive about reporting problems. This means that, at a minimum, newly diagnosed patients should try to be vigilant regarding signs and symptoms and monitor blood tests

that could indicate disease progression. Patients in treatment should be aware of possible treatment-related side effects. Patients should absolutely familiarize themselves with some of the medical terms, tests, and treatments that apply to WM.

One of the most important decisions a WM patient can make is choosing a physician to manage the disease. This person should be board-certified in hematology-oncology and ideally have some familiarity with WM. A patient and his or her physician should share a common treatment philosophy. Some physicians are more aggressive toward treatment while others may be more conservative in their approach and lean toward older, better-known treatments. A patient's attitude toward the illness and toward treatment should be similar to that of his or her treating physician.

Particularly in the early stages after diagnosis or when considering treatment, a patient should put questions and concerns in writing so that they can be addressed during appointments. It may be helpful to have a caregiver present to record the answers, as it can be difficult for a patient to absorb and remember all the new information being communicated.

Many patients find it helpful to keep track of their blood test results over time, as trends are very important in monitoring disease status. This might be in the form of a file folder, a notebook, or a computer spreadsheet.

Patients may find it useful to ask for a second opinion from a WM expert, especially when considering a course of treatment. Given the rarity of WM, it is not unusual to see local physicians who have never treated the disease, and many do not have the time to do all the reading necessary to keep up on the latest treatments. The IWMF maintains a Directory of WM Physicians on its website, www.iwmf.com. After receiving a second opinion, a WM patient may then opt to be treated by his or her local oncologist who agrees to follow the recommendations provided by the expert who was consulted.

There are no special diets or dietary substances that can be used to treat WM. Instead, patients should follow recommended guidelines for optimal health, including a healthy balanced diet, high in fruits and vegetables and low in fatty foods, sugar, and red meat; adopt a regular program of exercise in consultation with a physician; and recognize that they are at increased risk of infections, especially during treatment, and take appropriate measures to reduce their risk. It is also important for patients to get adequate amounts of sleep.

Patients investigating 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 http://nccam.nih.gov.

Patients may want to seek information and support from others with the disease, and the IWMF has a network of support groups and affiliates in the U.S. and internationally. The IWMF sponsors a telephone support network called the LIFELINE, which deals with topics of special interest to WM patients, and it supports an Internet discussion site for patients and caregivers. The IWMF also organizes an annual Educational Forum that rotates among different locations around the U.S. During this Forum and online webinars, patients and caregivers have the opportunity to hear from and interact with experts in the research and treatment of WM. More information about these programs is available at www.iwmf.com/get-support/.

The next section of this booklet entitled "**What Other Resources Are Available?"** offers various ways in which patients may obtain more information and resources to help them cope with WM.

## WHAT OTHER RESOURCES ARE AVAILABLE?

In addition to this booklet, information on living with cancer (and more specifically with WM) can be obtained from several organizations and on the Internet. The following list is a sampling of available resources. For a list of other worldwide organizations that provide services to the WM community go to www.iwmf.com/partners/ Information can also be obtained from cancer treatment facilities and healthcare professionals.

### Organizations

#### International Waldenstrom's Macroglobulinemia Foundation

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a nonprofit organization founded in 1994 by Arnold Smokler. The IWMF provides numerous services for people with WM, including patient and caregiver support groups, dissemination of information, and promotion of research. The IWMF distributes information to members through its website, the *Torch* newsletter, booklets, an annual Educational Forum, regular webinars, email news alerts, Facebook group, and an Internet discussion site, Connect. Membership in the IWMF is based on voluntary contributions that support the administration, outreach, education, and research programs of the Foundation.

**International Waldenstrom's Macroglobulinemia Foundation**
6144 Clark Center Avenue
Sarasota, FL 34238
Telephone number: 941-927-4963
Fax number: 941-927-4467
Internet address: www.iwmf.com
Email address: info@iwmf.com

#### The Leukemia & Lymphoma Society

The mission of The Leukemia & Lymphoma Society (LLS) is to cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of lives of patients and their families. One service of the LLS is the Clinical Trial

Support Center, established to discuss clinical trials and help blood cancer patients (including WM patients) to find clinical trials. The LLS Clinical Trial Support Center staff speak with individual patients, try to understand their unique circumstances, and, if appropriate, help them identify trials that are best suited for them. https://www.lls.org/support-resources/information-specialists/clinical-trial-support-center-ctsc

**The Leukemia & Lymphoma Society**
Telephone number: 914-821-8217
Internet address: www.lls.org
Email address: gwen.nichols@lls.org

### Lymphoma Research Foundation

The mission of the Lymphoma Research Foundation (LRF) is to eradicate lymphoma and serve those touched by the disease.

**Lymphoma Research Foundation**
Telephone number: 212-349-2910
Internet address: www.lymphoma.org
Email address: mgutierrez@lymphoma.org

### National Comprehensive Cancer Network® (NCCN)

This is an alliance of leading cancer centers devoted to patient care, research, and education. Its mission is to improve and facilitate the quality, effective, efficient, and accessible cancer care so that patients can live better lives. The NCCN recently published a patient-friendly booklet called *NCCN Guidelines for Patients® Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma*, which is currently available in English only and can be downloaded at

www.nccn.org/patients/guidelines/content/PDF/waldenstroms-patient.pdf
National Comprehensive Cancer Network® (NCCN)
Telephone number: 215-690-0300
Internet address: www.nccn.org/patients/

### Cancer*care*

The mission of Cancer*care* is to provide free, professional support services and information to help people manage the emotional, practical, and financial challenges of cancer. Their services include case management, counseling, and support groups over the phone, online and in-person, educational workshops, publications, and financial and co-payment assistance. All Cancer*Care* services are provided by master's-prepared oncology social workers and world-leading cancer experts.

Cancer*care*
Telephone number: 800-813-4673
Internet address: www.cancercare.org

### Lymphoma Coalition (Worldwide Network of Lymphoma Patient Groups)

The Lymphoma Coalition, a worldwide network of patient groups with a full or partial focus on providing support to patients with lymphoma.

**Lymphoma Coalition**
Telephone number: 905-990-0609 (Canada)
Internet address: www.lymphomacoalition.org

### EWMnetwork

The mission of the EWMnetwork is to enable WM patients to represent their interests at the European level: "Patients for Patients". They represent the interests of WM patients in Europe, including: access to treatment and medication, access to information on clinical trials, and research into new methods of treatment.

**EWMnetwork**
Internet address: www.ewmnetwork.eu
Email address: info@ewmnetwork.eu

### Triage Cancer

Triage Cancer provides free education on the practical and legal issues that arise after a cancer diagnosis.

Triage Cancer
Internet address: www.triagecancer.org
Email address: jm@triagecancer.org

## Internet Websites

**www.clinicaltrials.gov** – This U.S. National Institutes of Health website provides general and specific information on clinical trials and can be searched for clinical trials currently enrolling people with WM.

**www.wmworkshop.org** – This is the official website of the International Workshops for Waldenstrom's Macroglobulinemia, which are held every 2 years at a different site around the world. [Note: The 2020 Workshop was cancelled because of Covid. The next Workshop is scheduled for 2022.] These workshops provide a venue for the WM scientific community to collaborate and share their latest research with the goal of advancing the knowledge of the genetic basis and pathogenesis of WM and the development of therapeutics for the disease.

**www.nlm.nih.gov** – The U.S. National Library of Medicine website provides access to various types of health information for both healthcare professionals and consumers. PubMed contains references and abstracts from biomedical journals that can be searched for information on specific diseases and treatments. Medline Plus has excellent health information for consumers.

## IWMF Mission Statement

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

## IWMF Vision Statement

*A world without WM (Waldenstrom's macroglobulinemia).*

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

This information has been provided by the IWMF at no cost to you. Please consider joining and/or contributing to the IWMF to enable us to continue to provide materials like this and to support research toward better treatments and a cure for Waldenstrom's macroglobulinemia. You may join and/or contribute at our website, www.iwmf.com, or you may mail your contribution to: 6144 Clark Center Avenue, Sarasota, FL 34238.

IWMF
International Waldenstrom's Macroglobulinemia Foundation

6144 Clark Center Avenue
Sarasota, FL 34238
Ph: 941-927-4963 Fax: 941-927-4467
www.iwmf.com
Email: info@iwmf.com

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