

# Waldenstrom's Macroglobulinemia

## Questions and Answers



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**IWMMF**

International Waldenstrom's  
Macroglobulinemia Foundation



## **WALDENSTROM'S MACROGLOBULINEMIA QUESTIONS AND ANSWERS**

### **The IWMF Vision Statement**

*Support everyone affected by Waldenstrom's macroglobulinemia while advancing the search for a cure.*

### **The IWMF Mission Statement**

*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.*

*To promote and support research leading to better treatments and ultimately, a cure.*

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## FOREWORD

This 2017 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 italicized the first time they are used and defined in the "Glossary" section found at the end of this booklet. Should readers have other questions not found in this booklet or seek further explanation on a particular topic, they should direct their inquiries to a healthcare professional.

## 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*.<sup>1</sup>

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 [www.iwmf.com](http://www.iwmf.com). 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.

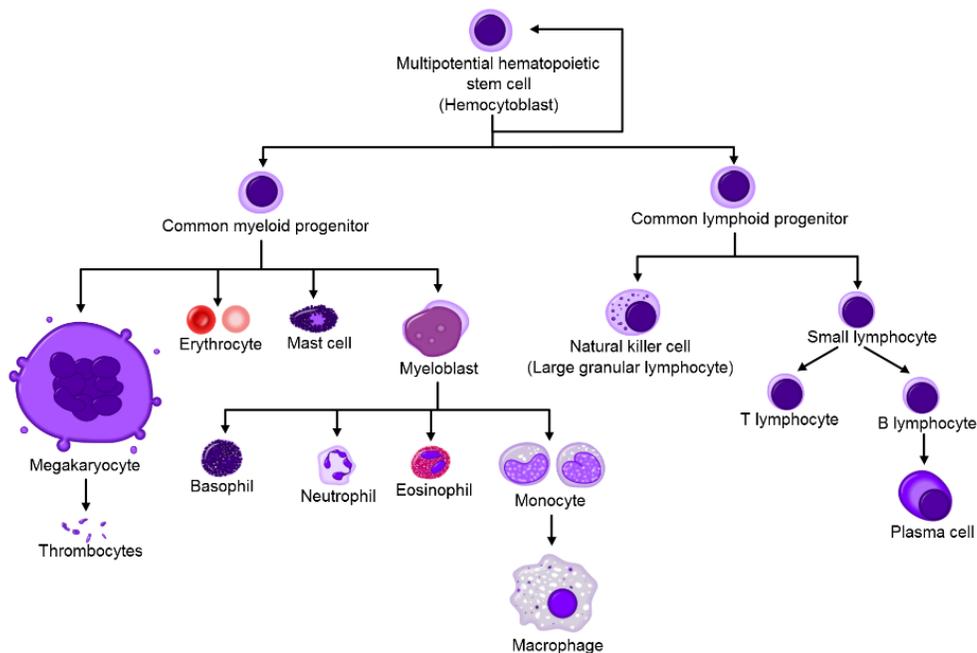


Figure 1. Hematopoiesis, the process of blood cell differentiation.

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 249,000 diagnosed with breast cancer and 181,000 diagnosed with prostate cancer in 2016.<sup>2</sup>

## **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 a fairly indolent, chronic disease in most patients. The median survival has varied in studies, from 5 years to nearly 11 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.<sup>7</sup>

*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 developed the widely accepted International Prognostic Scoring System for Waldenstrom's Macroglobulinemia (ISSWM). 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%.<sup>5</sup>

In 2009 the Southwest Oncology Group identified increased serum lactate dehydrogenase (LDH) as another variable adversely affecting prognosis.<sup>6</sup> The normal range for LDH is 104-333 IU/L.

On the basis of 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%.<sup>8</sup> 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%.

## **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.<sup>9</sup> 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.<sup>10</sup>

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.<sup>11,12</sup> Some evidence links the disease to a deletion in part of chromosome 6, although this abnormality is not present in all cases of WM.<sup>13</sup> Environmental factors such as radiation exposure and occupational exposure to leather, rubber, paints, 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.

More recent 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 mutation in this gene changes one amino acid to another and is called MYD88 L265P.<sup>14</sup> It plays an important role in the proliferation and survival of WM cells by leading to over-expression 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.

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 mutations in this gene and that these mutations may adversely impact prognosis, as well as response to certain treatments.<sup>15</sup>

## 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 rituximab-based therapy, both of which are further explained in the section of this booklet entitled “How Is Waldenstrom’s Macroglobulinemia 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’s 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’s 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’s, are similar to those of cryoglobulinemia, but hemolytic anemia is not a consequence of cryoglobulins.

Amyloidosis is a group of diseases caused by the presence 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.<sup>16</sup> 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.<sup>17</sup>

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*, and *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. Recent recommendations from the National Comprehensive Cancer Network® 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 ibrutinib treatment should be tested for mutations in the CXCR4 gene, as these mutations can negatively impact response to the drug.<sup>18</sup>

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. Generally speaking, 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 [www.iwmf.com](http://www.iwmf.com).

Blood Test	Normal Value	WM Abnormality
White blood cell (WBC) count	3.5-6.1 K/uL	May be decreased
WBC differential:		
Neutrophils	50-70% of WBC count	May be decreased
Lymphocytes	20-30% of WBC count	May be decreased or increased
Monocytes	2-9% of WBC count	May be decreased
Basophils	<1% of WBC count	May be decreased
Eosinophils	0-7% of WBC count	May be decreased
Red blood cell count	4.7-6.1 M/uL	May be decreased
Hemoglobin	14-18 g/dL	May be decreased
Hematocrit	39-51%	May be decreased
Platelets	130-400 K/uL	May be decreased
Erythrocyte sedimentation rate	0-20 mm/hr	Increased
IgM	50-300 mg/dL	Increased
Serum viscosity	1.4-1.8 cP	May be increased
Beta-2 microglobulin	<2 mg/L	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 Therapy

Initiating treatment early in the course of the disease in an asymptomatic patient does not prolong survival; therefore, treatment is delayed until the onset of symptomatic disease. Some patients with increased amounts of IgM or increased numbers of lymphoplasmacytic cells in the bone marrow (measured as % of bone marrow infiltration) may remain stable and continue to be asymptomatic for a long time. Such patients are considered to have smoldering WM and are on *watch and wait*, which means that their disease status and their health are monitored regularly for changes, sometimes for years, before any treatment is initiated.

Signs and symptoms that may require the initiation of treatment include the following: fatigue, recurrent fever, night sweats, weight loss, bulky (enlarged) lymph nodes, greatly enlarged liver or spleen, symptomatic organ or tissue infiltration, hemoglobin less than 10 g/dL, platelets less than 100,000/uL, hyperviscosity, severe peripheral neuropathy, symptomatic cryoglobulinemia, cold agglutinin anemia, IgM-related kidney disease, and amyloidosis.<sup>19</sup> See the section of this booklet entitled "What Are the Signs and Symptoms" for descriptions of several of these conditions.

Treatment may consist of just one drug (single-agent therapy) or of two or more drugs (combination therapy). Most studies seem to indicate that combination therapies are more effective, resulting in better and/or longer-lasting responses.

Treatment can usually be administered in an outpatient setting or at home and may be oral, by intramuscular or subcutaneous injection, or by intravenous therapy. Some treatments require that certain medications be taken the day before or the day of treatment in order to minimize associated side effects from administration. Treatment may result in temporary suppression of the bone marrow and the immune system, leading to low blood counts and greater susceptibility to infection. Supportive therapy to minimize these side effects may be necessary and can include transfusions and medications such as growth factors to increase red blood cell and white blood cell production, antibiotics, anti-viral agents, and anti-fungal agents.

Available treatment options include *chemotherapy; monoclonal antibody therapy; proteasome inhibitors; immunomodulatory drugs; corticosteroids;* and targeted therapies such as B-cell pathway inhibitors; procedures such as plasmapheresis, *splenectomy*, radiation, or *stem cell transplantation*. Newer emerging therapies such as radioimmunotherapy, vaccine therapy, CAR T-cells and immune checkpoint inhibitors are being studied as potential treatment options. Each of these is discussed in greater detail below.

In 2015, Imbruvica (ibrutinib) became the first treatment specifically approved for WM by the US Food and Drug Administration, and it was subsequently also approved by the European Medicines Agency and Health Canada. Most of the other treatments in use for WM were previously approved for related cancers such as chronic lymphocytic leukemia, lymphoma, and multiple myeloma. Once clinical trials have established that these treatments have an acceptable safety profile and are effective for WM patients, they can be prescribed for “off label” use in WM.

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, and the possibility for future autologous stem cell transplantation.

Rituximab-based therapies are the preferred initial (first-line) treatment for many patients with WM. These include therapies with cyclophosphamide such as DRC (dexamethasone, rituximab, and cyclophosphamide). The combination therapy R-CHOP (rituximab, cyclophosphamide, *doxorubicin*, *vincristine*, and prednisone) is no longer considered a first-line choice. Bendamustine and rituximab (BR) is now a primary option, especially for patients with high tumor bulk, and bortezomib alone or in combination with rituximab is appropriate for patients with specific high risk features such as hyperviscosity or in younger patients who might want to avoid alkylating agent therapy. Nucleoside analog-based combinations are not recommended as primary therapy but remain an option for patients with relapsed/refractory disease. In patients who may be candidates for single agent oral therapy, oral fludarabine (if available) is recommended over chlorambucil.<sup>20</sup>

Neuropathy is a symptom in a significant percentage of WM patients; therefore, patients and their physicians should be aware that neuropathy can also be a significant side effect of certain treatment regimens, including those with bortezomib and thalidomide. Careful evaluation of patients for the development or worsening of neuropathy should be emphasized.

Patients with untreated or relapsed WM may wish to participate in clinical trials that explore novel agents or treatment strategies. Outside of clinical trials, the choice of therapy after relapse (called salvage therapy) 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 transplantation, etc. Reuse of a first-line single agent therapy or combination is reasonable if a patient achieved a response that lasted for two years or more; for patients who had short responses or resistance to first-line therapy, salvage therapy may consist of agents of a different class either alone or in combination.<sup>21</sup>

The use of stem cell transplantation in WM requires a more extensive evaluation and selection of individual patients, focusing primarily on patients with high-risk disease or on young patients with aggressive disease. Patients who may be future candidates for autologous stem cell transplantation should be careful not to use treatments that are harmful to their stem cells, such as nucleoside analogs, unless their stem cells have been previously collected and stored. Appropriate first-line therapies may be single-agent rituximab or cyclophosphamide-based combinations, while bortezomib-based regimens may be appropriate salvage therapy.<sup>22</sup>

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 [www.iwmf.com](http://www.iwmf.com).

## Chemotherapy

One of the most common options used in the treatment of WM has been chemotherapy, and Table 3 lists selected chemotherapy drugs.

The commonly used alkylating agents include chlorambucil, cyclophosphamide, and bendamustine. Alkylating agents were one of the earliest classes of drugs used to treat cancer, beginning in the 1940s. They are non-specific drugs which target fast-growing cells throughout the body, causing damage to the DNA at any point in the cell cycle. They not only affect many malignant cells but also the rapidly dividing cells of the bone marrow, stomach lining, and hair follicles, often causing *cytopenias*, nausea, and hair loss. Alkylating agents are frequently used in combination with other drugs, such as purine nucleoside analogs, corticosteroids, and/or monoclonal antibodies.

Chlorambucil (Leukeran) is one of the oldest alkylating agents used for WM. Chlorambucil has produced minor and partial responses in approximately 60% of patients; however, complete responses are rare. Response to chlorambucil therapy occurs slowly and may take from several months to more than one year. The drug is administered orally either as low-dose, daily therapy or as pulse therapy, which consists of a higher dose administered daily for 7 days and repeated every 6 weeks. Treatment is usually administered until the reduction of IgM is maximal and at a stable (plateau) concentration. Treatment is restarted as symptoms warrant. Prolonged administration is associated with an increased risk of developing complications such as abnormal or defective formation of blood cells (*myelodysplasia*) or a secondary leukemia.<sup>23</sup>

Cyclophosphamide (Cytoxan) is a treatment mainstay and has been used in varying combinations with other drugs, such as nucleoside analogs, vincristine, doxorubicin, corticosteroids, and/or rituximab. Cyclophosphamide in combination therapy is very effective in WM, with response rates varying from 75-90%, and appears to confer a lower risk for developing myelodysplasia or a secondary leukemia than chlorambucil. Cyclophosphamide in combination with rituximab and dexamethasone (DRC) is now considered a primary treatment option for WM.<sup>24</sup>

Bendamustine (Treanda or Levact), although classified as an alkylating agent, also has some characteristics of a nucleoside analog. It was developed in the former East Germany in the 1960s but was not approved in the U.S. for B-lymphocyte cancers until 2008. It is now one of the options being used for WM, usually in combination with rituximab, and appears to be quite effective, with response rates of 85-95%. At this time, not much is known about the long-term effects of bendamustine on the bone marrow stem cells or on the risk of developing myelodysplasia or secondary cancers. It should be used with caution in patients where stem cell transplantation is being considered as a future treatment option.<sup>25</sup>

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 replication. The most commonly used purine nucleoside analogs for WM are fludarabine (Fludara) and cladribine or 2CdA (Leustatin). Purine nucleoside analogs are also often used in varying combinations with other drugs, such as alkylating agents, corticosteroids, and/or monoclonal antibodies.

Fludarabine and cladribine each has its champions among respected clinicians, and there is no clear indication as to which may be superior in the treatment of WM. Most physicians lean toward the drug with which they are more familiar. Fludarabine is more commonly used in Europe where it can be conveniently given in oral form. Delayed responses are quite common with fludarabine, and it is not unusual to see a patient's IgM continue to drop for 6-12 months following therapy; cladribine usually results in a faster overall decline in IgM than fludarabine but produces greater bone marrow suppression and is not commonly used today.

Purine nucleoside analogs, especially in combination therapy, provide patients with response rates of 60-95%, and the responses tend to be durable. One of the most common side effects of purine nucleoside analog therapy is suppression of blood cell production by the bone marrow. This side effect increases one's chance of developing an infection. When treatment ceases, normal blood cell production usually resumes, although there may be prolonged suppression of T-lymphocytes. There is an increased risk of developing myelodysplasia or secondary leukemia in WM patients treated with purine nucleoside analogs. There may also be an increased incidence of *transformation* to a more aggressive lymphoma following treatment with these drugs.

If autologous stem cell transplantation is being considered, prior exposure to purine nucleoside analogs is not advisable because of their effect on the ability to procure the number of hematopoietic stem cells necessary for successful transplant.

GENERIC NAME (TRADE NAME)	ROUTE OF ADMINISTRATION	COMMON SIDE EFFECTS
<b>Alkylating Agents:</b>		
Chlorambucil (Leukeran)	Oral	Nausea, decreased blood cell counts, fatigue, rash
Cyclophosphamide (Cytosan)	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
<b>Nucleoside Analogs:</b>		
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.

Alemtuzumab (Campath) is a monoclonal antibody that targets the CD52 antigen expressed on WM cells and on *mast cells*, which are frequently found in association with WM cells in the bone marrow. Initial results indicated that this treatment can be helpful in WM, although toxicity is a major problem. This therapy is very immunosuppressive, with resulting serious infections. Alemtuzumab is rarely used in WM.

Rituximab (Rituxan or Mabthera) is a monoclonal antibody therapy targeted against the CD20 antigen located on many lymphoid cancer cells (as well as on normal B-lymphocytes) and is effective in treating several types of lymphoma. It is now used in almost all treatments for WM, either as a single agent or in combination with other treatments. Responses to rituximab therapy as a single agent for WM have been reported in 40% or more of patients, and more extended administration is associated with higher response rates. Rituximab is used as a first-line treatment in WM because it is less toxic than either alkylating agents or nucleoside analogs. The most typical side effects of rituximab occur during the first infusion of the drug, when patients may experience chills or fever. Subsequent infusions usually cause fewer side effects.

If a WM patient with high IgM and/or hyperviscosity elects to undergo rituximab-based treatment, his physician needs to be aware of a phenomenon known as rituximab "flare," which causes a rapid but temporary increase in IgM, potentially resulting in increased serum viscosity or other IgM-associated complications.<sup>26</sup> This does not represent a treatment failure. A patient at risk for this complication should be closely monitored while undergoing rituximab treatment or consider the use of plasmapheresis beforehand to lower the IgM.

Single agent rituximab may be considered as the first intervention in patients with mild IgM-related neuropathy. In patients with moderate to severe neuropathy, rituximab-based combination therapy may be appropriate.

Some studies have suggested that *maintenance therapy* with rituximab may prolong *progression-free survival* and increase the time-to-next treatment in patients with certain B-lymphocyte lymphomas, especially follicular lymphoma. At this time, it does not appear to increase *overall survival*.<sup>27,28</sup> Although protocols vary, typical maintenance consists of a single rituximab infusion every two or three months for up to two years or more following the end of the primary chemotherapy regimen. While some physicians advocate the use of maintenance rituximab for WM, at present there are no controlled clinical studies that confirm increased progression-free survival or increased overall survival in WM patients.

There are several second and third generation monoclonal antibodies similar to rituximab that also target the CD20 antigen on B-lymphocytes but have been engineered to improve effectiveness or to reduce the infusion side effects associated with rituximab. Recently, ofatumumab (Arzerra) and obinutuzumab (Gazyva) have been approved for certain B-lymphocyte cancers. Ofatumumab is being used in WM patients who cannot tolerate rituximab, but it carries the same risk of IgM flare as rituximab.

Monoclonal antibodies that target other surface antigens, such as CD19, CD38, CD40, and CD70, are also in development for use in B-lymphocyte lymphoma and multiple myeloma, and some or all of these may eventually be applicable to the treatment of WM.

<b>GENERIC NAME (TRADE NAME)</b>	<b>ROUTE OF ADMINISTRATION</b>	<b>COMMON SIDE EFFECTS</b>
Alemtuzumab (Campath)	Infusion or injection	Shortness of breath, chills, facial flushing, fatigue, fever, headache, decreased blood pressure, nausea, vomiting, itching, decreased blood counts, infections
Rituximab (Rituxan or Mabthera)	Infusion	Shortness of breath, chills, facial flushing, fatigue, fever, headache, decreased blood pressure, nausea, itching, infections
Ofatumumab (Arzerra)	Infusion	Shortness of breath, chills, facial flushing, fatigue, fever, headache, decreased blood pressure, nausea, itching, infections

Table 4. Selected monoclonal antibody agents used in the treatment of Waldenstrom's macroglobulinemia

## **Proteasome Inhibitors**

Bortezomib (Velcade) is the first of a newer class of drugs called proteasome inhibitors and provides response rates of approximately 40% as a single agent and 65-85% in combination therapy. It also provides rapid responses. A proteasome is a large protein complex inside most cells which degrades unneeded or damaged proteins. Degradation of such proteins is a normal, necessary, and orderly cellular process. Disruption of normal protein breakdown with a proteasome inhibitor allows certain proteins in the cell to accumulate as “garbage” to the point where they can interfere with cell function and lead to cell death (apoptosis). Normal cells appear better able than cancer cells to tolerate the drug without significant difficulties.

Side effects from bortezomib include temporary bone marrow suppression, dizziness, constipation, diarrhea, and of particular note, peripheral neuropathy.<sup>29</sup> Prophylaxis against shingles is strongly recommended during therapy. Clinical trials using modified dosing schedules (once weekly rather than twice weekly) of bortezomib in combination with rituximab and/or dexamethasone have reduced the incidence and severity of peripheral neuropathy.<sup>30,31</sup> Bortezomib administered subcutaneously rather than intravenously results in less neuropathy in multiple myeloma patients,<sup>32</sup> although no clinical studies have been performed to confirm this finding in WM patients.

Carfilzomib is a newer proteasome inhibitor that has been evaluated in combination with rituximab and dexamethasone (CaRD) in clinical trials of WM patients and represents a novel neuropathy-sparing option for proteasome inhibitor-based therapy for WM. Oral proteasome inhibitors, including ixazomib and oprozomib, are also being developed and tested.

## **Immunomodulatory Drugs (IMiDs)**

Immunomodulatory drugs (IMiDs) kill tumor cells by four described mechanisms of action: they starve the tumor cells by inhibiting the development of blood vessels that feed them; they enhance the tumor killing properties of T-lymphocytes and natural killer cells; they block some of the interactions between tumor cells and other cells in the bone marrow environment; and finally they appear to directly kill tumor cells by a mechanism not yet fully understood.

The best known immunomodulatory drug is thalidomide (Thalomid) which was originally developed in the 1950s as a sedative but was removed from the market when it was discovered to be responsible for birth defects. It was subsequently found to be effective in the treatment of multiple myeloma, a disease closely related to WM. It has shown a response rate of 70% when used in combination with rituximab for WM, but its major side effect is peripheral neuropathy. It is not a choice for primary therapy except in patients with severe cytopenias.

Several newer thalidomide-type drugs have been developed, such as lenalidomide (Revlimid) and pomalidomide (Actimid). These result in less peripheral neuropathy; however, one study indicated that therapy with lenalidomide (in combination with rituximab) appeared to cause the onset of rapid anemia in WM patients.<sup>33</sup> Pomalidomide has been approved for patients with multiple myeloma who are refractory to two chemotherapy regimens.

## **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 Pathway Inhibitors**

There are several cell signaling pathways in B-lymphocytes that can influence their growth and survival. Some proteins in these pathways may be over- or under-expressed in malignant cells, and this abnormal expression can impact the development and growth of the malignant cells. Because cell pathway inhibitors are more targeted, they tend to have fewer systemic side effects than chemotherapy and are not toxic to stem cells. Most are oral medications.

One of the newest treatments of this type is ibrutinib (Imbruvica), an oral therapy that targets the Bruton's tyrosine kinase (BTK) pathway, which is important in B-lymphocyte development and activation. Imbruvica has been approved by the US Food and Drug Administration, the European Medicines Agency, and Health Canada as a treatment for WM patients, primarily those with relapsed/refractory disease, although it is also being evaluated in the front-line setting. It is the first drug to be specifically approved for the treatment of WM. Newer BTK inhibitors are continuing to be developed, including ACP-196 (acalabrutinib) and BGB-3111.

Several other relatively new agents alter other B-lymphocyte signaling pathways and have been or will be tested in clinical trials for WM patients. Some have achieved promising results. Everolimus or RAD001 (Afinitor) targets the mTOR pathway and has been added to the NCCN Guidelines as relapse therapy for WM patients.<sup>34</sup> Venetoclax (Venclexta) targets the B-cell lymphoma 2 (BCL-2) protein, which supports cancer cell growth and is over-expressed in several hematological cancers. It is being tested in 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.

## **Splenectomy**

Surgical removal of the spleen (splenectomy) has been helpful in reducing the IgM concentration for select cases after failure of chemotherapy. Splenectomy is usually considered only to relieve symptoms of a significantly enlarged spleen and certain blood count abnormalities, particularly low platelets (thrombocytopenia).

## **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.<sup>35</sup>

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?**

A number of 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.

## Radioimmunotherapy

*Radioimmunotherapy* combines a monoclonal antibody, such as rituximab or similar agent, with a radioactive particle, called a radioisotope. This radioisotope-antibody targets and binds to an antigen present on B-lymphocytes, delivering a dose of radiation to the targeted cells. Very good results have been achieved from using radioimmunotherapy in certain lymphomas, including a significant number of complete responses. The difficulty in using these agents is that patients who have extensive bone marrow involvement may not be able to receive them without resulting in significant suppression of the bone marrow. This occurs because the radioactive particles also destroy surrounding normal bone marrow cells. Currently, radioimmunotherapy is not being used for WM treatment.

## Vaccine Therapy

The vaccines that most people are familiar with are used to prevent infectious diseases such as measles, mumps, polio, etc. The vaccines being developed for lymphomas differ because they are designed to treat an established disease rather than to prevent it. A lymphoma vaccine is individually made from the patient's own tumor cells and is targeted at a specific set of antigens, or *idiotype*, found only on the surface of the tumor cells. The vaccine then stimulates the T-lymphocytes of the patient's immune system to search for and destroy the tumor cells. The vaccine is typically administered following conventional treatment; once the tumor burden has been reduced and the patient has achieved a response, the vaccine is administered monthly for up to six months to prevent recurrence of the disease. Clinical trials with indolent lymphomas, including WM, are underway, leading to cautious optimism that they will be effective.

## CAR T-Cell Therapy

This is a promising 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.

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. Several clinical trials with CAR T-cells are open to WM patients.

## Immune Checkpoint Inhibitors

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, 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, normal serum IgM level, a normal bone marrow aspirate and biopsy, and resolution of enlarged lymph nodes or spleen if present at baseline.<sup>36</sup>

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

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 of time 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 very uncommon.

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 in a clinical trial. A person enrolled in a clinical trial can withdraw from the trial at any time.

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](http://www.clinicaltrials.gov).

## **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 research necessary to keep up on the latest treatments. The IWFM maintains a list of international experts on its website, [iwmf.com](http://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 [nccam.nih.gov](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, 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 [iwmf.com](http://iwmf.com).

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. 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, email news alerts, and an Internet discussion site. 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

Email address: [info@iwmf.com](mailto:info@iwmf.com)

Internet address: [iwmf.com](http://iwmf.com)

### **The Leukemia & Lymphoma Society**

The mission of The Leukemia & Lymphoma Society (LLS) is to cure leukemia, lymphoma, and myeloma and improve the lives of patients and their families.

The Leukemia & Lymphoma Society  
3 International Drive, Suite 200  
Rye Brook, NY 10573  
Telephone number: 914-949-5213  
Internet address: [www.lls.org](http://www.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  
115 Broadway, Suite 1301  
New York, NY 10006  
Telephone number: 212-349-2910  
Internet address: [www.lymphoma.org](http://www.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 the quality, effectiveness, and efficiency of 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/waldenstroms/index.html](http://www.nccn.org/patients/guidelines/waldenstroms/index.html).

National Comprehensive Cancer Network® (NCCN)  
275 Commerce Drive, Suite 300  
Fort Washington, PA 19034  
Telephone number: 215-690-0300  
Internet address: [www.nccn.org](http://www.nccn.org)

### **CancerCare**

The mission of CancerCare is to provide free, professional support services including counseling, support groups, educational workshops, publications, and financial assistance to anyone affected by cancer. All CancerCare services are provided by oncology social workers and world-leading cancer experts.

CancerCare  
275 Seventh Avenue  
New York, NY 10001  
Telephone number: 800-813-4673  
Internet address: [www.cancercares.org](http://www.cancercares.org)

Email address: [info@cancercare.org](mailto:info@cancercare.org)

## **Lymphoma Coalition**

The Lymphoma Coalition is a worldwide network of lymphoma patient groups with the express purpose of facilitating lymphoma patient organizations around the world to form a community to support one another's efforts in helping patients with lymphoma receive the care and support needed.

Lymphoma Coalition

8 Stavebank Road N, Unit #401

Mississauga ON L5G2T4

Canada

Internet address: [www.lymphomacoalition.org](http://www.lymphomacoalition.org)

## **EWMnetwork**

The mission of the EWMnetwork is to enable WM patients to represent their interests at the European level, 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](http://www.ewmnetwork.eu)

Email address: [info@ewmnetwork.eu](mailto:info@ewmnetwork.eu)

## **Internet Websites**

[www.clinicaltrials.gov](http://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](http://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. 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.lymphomation.org](http://www.lymphomation.org) – Founded by patients for patients, this website's mission is to provide support and evidence-based information on lymphoma and its treatments, independent from health industry funding – with a focus on helping patients to routinely consider clinical trials.

[www.msmart.org](http://www.msmart.org) – Developed by a consensus of experts from the Mayo Clinic, mSMART includes guidelines for the management of plasma cell disorders, including multiple myeloma, amyloidosis, and WM.

[www.nlm.nih.gov](http://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.

## GLOSSARY

*Albumin* – the most abundant plasma protein, it is produced in the liver and is important in regulating blood volume and carrying molecules such as hormones, fatty acids, calcium, and certain drugs.

*Alkylating agent* – a chemotherapeutic compound such as chlorambucil or cyclophosphamide that targets fast-growing cells throughout the body, causing damage to the DNA at any point in the cell cycle.

*Amyloidosis* – a group of diseases caused by the presence 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.

*Anemia* – a decrease in the number of red blood cells.

*Antibodies* – another name for immunoglobulins.

*Antigen* – a substance that provokes an immune response.

*B-lymphocyte (B-cell)* – a type of white blood cell which develops into a plasma cell that manufactures immunoglobulin when a foreign substance is detected.

*Basophil* – a type of white blood cell that is involved in allergic reactions.

*Beta-2 microglobulin* – a protein found on all cells with a nucleus; it is frequently elevated in people with multiple myeloma and lymphoma.

*Bing-Neel syndrome* – a condition that involves infiltration of the central nervous system (brain and spinal cord) by WM cells; complications of Bing-Neel syndrome may include mental deterioration, confusion, visual disturbances, irritability, personality changes, convulsions, and coma.

*Bone marrow* – the spongy tissue inside the large bones that is the primary site for the production of blood cells.

*Bone marrow aspiration and biopsy (BMB)* – a procedure to collect and examine bone marrow for the presence of abnormalities.

*Chemotherapy* – a chemical used to treat cancer. Traditional chemotherapy acts by killing cells that divide rapidly, one of the main properties of cancer cells; however, this means that it can also kill normal cells that divide rapidly, including cells of the bone marrow, gastrointestinal tract, and hair follicles.

*Chronic lymphocytic leukemia (CLL)* – the most common type of leukemia, this is a cancer of B-lymphocytes that usually occurs in adults and is characterized by increased numbers of B-lymphocytes in the blood.

*Cold agglutinin disease (CAD)* – a condition resulting from immunoglobulins (usually of the IgM-type) that react at lower temperatures; these immunoglobulins are specifically directed against proteins (antigens) found on one's own red blood cells and can cause anemia, among other symptoms.

*Corticosteroids* – man-made drugs that closely resemble cortisol, a steroid hormone; typical corticosteroids used in WM include prednisone, prednisolone, and dexamethasone.

*Cryoglobulinemia* – a condition characterized by immunoglobulins that precipitate at temperatures below body temperature and then re-dissolve upon warming; it is most often due to unknown causes but may in some cases be associated with an underlying disease such as WM; signs and symptoms are due to obstruction of small blood vessels in the extremities and include whiteness, numbness, bleeding, ulcers, and gangrene.

*CT or CAT (Computerized Axial Tomography) Scan* – an imaging procedure that uses narrow X-ray beams to examine a body section from any different angles and produces a precise image of that area. It can be performed with or without contrast medium (X-ray dye).

*Cytopenia* – a condition in which there is a lower-than-normal number of blood cells.

*Cytotoxic* – toxic to cells.

*Doxorubicin* – a drug used in cancer chemotherapy that blocks cell division; it is known by the trade name Adriamycin.

*Eosinophil* – a type of white blood cell that is involved in allergic reactions and is responsible for combating parasites.

*Flow cytometry* – a process in which an instrument uses a laser beam to scatter light from cells as they pass through a liquid in the instrument's chamber; the laser beam light bounces off each cell, is picked up by detectors, and provides information about the cell's characteristics, such as size and inner structure; flow cytometry can also use antibodies tagged with fluorescent stains that bind to specific antigens on the cell surfaces - in the case of leukemia and lymphoma, these fluorescent-tagged antibodies bind with and identify protein surface markers on the immune cells.

*Graft vs. host disease (GVHD)* – a complication that can occur following allogeneic stem cell transplantation (using stem cells from a donor); the donor's immune cells see the recipient's cells as foreign and can attack them, causing a variety of symptoms.

*Hematopoiesis* – the process of blood cell development.

*Hematopoietic stem cells* – primitive blood cells in the bone marrow that can continually reproduce themselves or develop into different types of mature blood cells.

*Hemoglobin* – the oxygen-carrying molecule in a red blood cell.

*Hemolytic anemia* – anemia due to hemolysis, which is the abnormal breakdown of red blood cells either in the blood vessels or elsewhere in the body.

*Hyperviscosity syndrome* – occurs as a result of increased IgM concentration; signs and symptoms include chronic bleeding from the nose, gums, gastrointestinal tract, headache, ringing in the ears (tinnitus), dizziness (vertigo), impaired hearing, blurring or loss of vision, sausage-shaped veins in the retina, and swelling of the optic disk at the back of the eye (papilledema).

*Idiotype* – a unique set of antigens found on the surface of a cell.

*IgM (Immunoglobulin M)* – an immunoglobulin that is produced by B-lymphocytes; it is the largest immunoglobulin and the first one to appear in response to initial exposure to antigen.

*Immunomodulatory drugs (IMiDs)* – a class of drugs based on the structure of thalidomide.

*Immunoglobulin (Ig)* – a protein produced by B-lymphocytes and plasma cells in response to a foreign substance or antigen; the classes of immunoglobulins are IgA, IgD, IgE, IgG, and IgM. Also called an antibody.

*Immunohistochemistry* – refers to the use of special stains to identify antigens in the cells of a tissue section for purposes of identification, exploiting the principle that (labeled) antibodies bind specifically to antigens; immunohistochemical staining is widely used in the diagnosis of abnormal cells such as those found in cancer.

*Immunophenotypic analysis* – a method for dividing lymphoma and leukemia into subgroups on the basis of differences in cell surface antigens. These differences are detected by means of monoclonal antibodies and flow cytometry.

*Lactate dehydrogenase (LDH)* – an enzyme found extensively in tissues such as blood cells and heart muscle; it is released during tissue damage and thus can be a marker of common injuries and disease.

*Lymphoplasmacytic cells* – cancer cells which have characteristics of both B-lymphocytes and plasma cells.

*Lymphoplasmacytic lymphoma (LPL)* – a rare type of indolent non-Hodgkin's B-lymphocyte lymphoma whose cells have characteristics of both B-lymphocytes and plasma cells. WM is the most common type of LPL and is additionally characterized by the secretion of monoclonal IgM.

*Macrophage* – a type of white blood cell, found in the tissues, that engulfs foreign substances and helps to stimulate the immune response.

*Maintenance therapy* – a treatment given at regular intervals after a disease has responded to previous treatment; maintenance therapy is given in order to help prevent spread or recurrence of the tumor.

*Mast cell* – a cell distributed near blood vessels in most tissues, including the bone marrow. Mast cells are often associated with allergic reactions and are believed to offer support to the malignant cells of WM.

*Monoclonal* – a group of cells, produced from a single ancestral cell by repeated reproduction, which share the characteristics of the original cell; also refers to the single protein produced by the clonal cells.

*Monoclonal antibody therapy* – the use of antibodies that specifically bind to a target on cells in order to stimulate the patient's immune system to attack those cells.

*Monoclonal gammopathy of undetermined significance (MGUS)* – a condition characterized by an overproduction of one clone of B-lymphocytes or plasma cells that produce an immunoglobulin but not associated with the presence of an underlying malignancy; IgM MGUS is associated with an increased risk of developing WM.

*Monocyte* – a type of white blood cell that circulates in the blood and can develop into a macrophage when it moves into tissues.

*Multiple myeloma (MM)* – cancer of the plasma cells; most commonly the cancer clone produces immunoglobulin IgG, IgA, or only light chains (kappa or lambda) of these immunoglobulins.

*Myelodysplasia (MDS)* – a group of related disorders of the bone marrow characterized by low numbers of abnormally developed blood cells; myelodysplasia can precede the development of acute leukemia.

*Natural killer (NK) cell* – a type of lymphocyte that directly kills tumor cells and virus-infected cells by enzymes contained in granules found in its cytoplasm.

*Neutrophil* – the most abundant type of white blood cell and one of the first responders to infection; it is the predominant cell in pus.

*Overall survival (OS)* – an indication of the proportion of people within a cancer group who are expected to be alive after a specified time. It takes into account death due to any cause – both related and unrelated to the cancer in question.

*Paraprotein* – another term for monoclonal immunoglobulin.

*Peripheral neuropathy (PN)* – a fairly common manifestation of WM, usually caused by the targeting of antigens on the nerve coating (myelin) by the circulating IgM; clinical features are predominantly sensory, with abnormal sensations such as burning, prickling, itching, tingling, or numbness that are symmetric and usually first noticed in the feet but can progress to the hands and arms.

*PET (Positron Emission Tomography) Scan* – a nuclear medicine procedure that uses gamma rays to produce three-dimensional images of functional processes in the body.

*Plasma cell* – a cell that develops from B-lymphocytes upon recognition of a foreign substance or antigen; plasma cells secrete antibodies to eliminate the foreign substance or antigen.

*Plasmapheresis (PP)* – a procedure that involves removal of blood from the body, separation of the liquid (plasma) portion from blood, replacement usually with albumin and sodium chloride solutions, and return of the remaining blood components to the body. Also called plasma exchange.

*Platelet* – a type of blood cell that helps stop bleeding. Also called a thrombocyte.

*Prognosis* – a prediction of the course of a disease and its outcome.

*Progression-free survival (PFS)* – the amount of time following cancer treatment when a patient's disease remains stable without showing signs of progression.

*Prophylaxis* – a treatment to prevent disease.

*Proteasome inhibitor* – an agent that binds to the core of a cell structure called a proteasome and blocks its enzyme activity, thus interfering with its ability to degrade proteins; disruption of this normal protein breakdown process allows certain proteins in the cell to accumulate to the point where they can interfere with cell reproduction and other functions and lead to cell death.

*Purine nucleoside analog* – part of a larger class of anti-cancer drugs termed antimetabolites, which mimic several of the normal building blocks of DNA and, when incorporated into the DNA of rapidly dividing cancer cells, will stop their replication.

*Radioimmunotherapy (RIT)* – a class of drugs which uses an antibody labeled with a radioactive particle to target and kill a cancer cell.

*Red blood cell (RBC)* – a type of blood cell that contains hemoglobin and carries oxygen from the lungs to other areas of the body. Also called an erythrocyte.

*Splenectomy* – surgical removal of the spleen.

*Stem cell transplantation (SCT)* – a procedure used to restore properly functioning bone marrow by intentionally destroying the patient's diseased bone marrow through chemotherapy and/or radiation and replacing it with stem cells derived from the patient or a donor.

*T-lymphocyte (T-cell)* – a type of white blood cell that matures in the thymus gland and is important in the immune response.

*Thrombocytopenia* – a decrease in the number of platelets.

*Transformation* – the development of a more aggressive lymphoma in a patient with an indolent or slow growing lymphoma; this may occur over time as the cancerous B-lymphocytes acquire additional mutations that cause the disease characteristics to change; some studies suggest that certain chemotherapy treatments can also cause transformation.

*Vincristine* – a drug used in cancer chemotherapy that blocks cell division; it is known by the trade name Oncovin.

*Watch and wait* – the period of time following diagnosis when a patient is not being actively treated but is monitored for disease progression.

*White blood cell (WBC)* – a type of blood cell that eliminates foreign substances or antigens from the body. Also called a leukocyte.

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## IWMF Vision Statement

*Support everyone affected by Waldenstrom's macroglobulinemia while advancing the search for a cure.*

## IWMF Mission Statement

*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.*

*To promote and support research leading to better treatments and ultimately, a cure.*

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6144 Clark Center Avenue  
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Ph: 941-927-4963 Fax: 941-927-4467  
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