

No. 20 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- Waldenström macroglobulinemia (WM) is a rare and slow-growing subtype of non-Hodgkin lymphoma that affects white blood cells.
- A main characteristic of WM is the overproduction of a monoclonal protein called “immunoglobulin M” (IgM). Immunoglobulin M can result in a thickening of the blood and may cause several other symptoms.
- Over 90 percent of WM patients have a mutation in the *MYD88* gene in their lymphoma cells. The mutation turns on pathways that sustain the growth and survival of WM cells.
- Some patients with WM do not have symptoms at diagnosis and may not require treatment for years. In these cases, patients are closely monitored for symptoms in an approach known as “watch and wait.” Active treatment is started only when symptoms appear.
- There is no cure for WM, but the disease is treatable. Therapy regimens that include a combination of chemotherapy, targeted therapies and immunomodulatory agents have shown promising results. Patients with WM often live for many years after they are diagnosed.
- Patients who have relapsed WM may be treated with either a single agent (such as ibrutinib) or with a combination regimen that either may or may not include the same agents that were used during the first-line treatment. The choice of treatment agents will depend on the duration of the initial response to treatment.

Introduction

“Lymphoma” is the name for many different types of cancer that originate in lymphocytes (white blood cells). There are three types of lymphocytes: B lymphocytes (B cells), T lymphocytes (T cells) and natural killer (NK) cells. B lymphocytes make antibodies to fight infection; T lymphocytes have many functions, including helping B lymphocytes to make the antibodies that fight infection; and natural killer cells that attack cancer cells and viruses.

Lymphocytes go through several stages of development. They are created in the bone marrow and then move through the blood to the lymphatic system. The final stage of B-lymphocyte development is a mature, immunoglobulin-producing plasma cell.

Lymphoma may arise in any of these types of lymphocytes but, in general, B-cell lymphomas are more common than T-cell lymphomas. Lymphoma is divided into two major categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Waldenström macroglobulinemia (WM) is an uncommon B-cell cancer that is classified by the World Health Organization (WHO) as a subtype of NHL. Waldenström macroglobulinemia is also referred to as a “B-cell lymphoproliferative disease,” and it accounts for approximately 1 to 2 percent of hematologic (blood) cancers.

This fact sheet provides specific information about the diagnosis, treatment and expected outcomes of WM, information about new treatments being investigated in clinical trials, and support resources.

For additional information about WM and other related diseases, please see the free The Leukemia & Lymphoma Society (LLS) booklet *Non-Hodgkin Lymphoma*.

About Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM) is a cancer of the B lymphocytes found in the bone marrow. B-lymphocytes are a type of white blood cell and their normal function is to fight infections in the immune system.

These cells and their more mature forms (the plasma cells and the memory B-cells) produce five different classes of antibodies, also known as immunoglobulins: IgG, IgM, IgA, IgD and IgE. These antibodies are used by the immune system to identify and fight intruders such as bacteria and viruses. Under normal conditions, there are many different types of B-lymphocytes, each responsible for producing their own class of antibodies. In Waldenström's however, there is an abnormal growth (caused by certain mutations) of one particular B-lymphocyte (a "clone") which is responsible for producing IgM antibodies. These B-lymphocytes start crowding out the many different types of healthy blood cells.

As a result, there are too many of the same kind of B-lymphocyte in the blood (along with the same kind of IgM immunoglobulin or macroglobulin produced by these particular cells), and not enough of the other types of healthy cells.

Crowding out the healthy cells in the marrow leads to low levels of red blood cells (called anemia), which can make people feel tired and weak. It can also cause low numbers of white blood cells, which makes it hard for the body to fight infection. The numbers of platelets in the blood can also drop, leading to increased bleeding and bruising.

The WM cells only produce one type of antibody (IgM), so it is called a monoclonal protein, or just an M protein. The buildup of this M protein in the body can lead to many of the symptoms of WM, including excess bleeding, problems with vision, and nervous system problems.

Lymphoplasmacytic Lymphoma (LPL). Waldenström macroglobulinemia is a type of lymphoplasmacytic lymphoma (LPL). Lymphoplasmacytic lymphoma is a slow-growing type of NHL. It is usually found in the lymph nodes. Lymphoplasmacytic lymphoma cells are found at diagnosis and immunoglobulins such as IgG or IgA may be present. Another immunoglobulin, monoclonal IgM, may be found. It is when IgM is identified, along with an involvement of 10 percent or more of LPL cells in the bone marrow, that the disease is referred to as WM.

Incidence, Causes and Risk Factors

Waldenström macroglobulinemia (WM) is a rare non-Hodgkin lymphoma (NHL). It has an incidence rate of about 3 to 4 cases per million people per year in the United States. About 1 to 2 percent of all NHL cases—1,000 to 1,500 people—are diagnosed with WM each year.

There is no known way to prevent WM, nor are the exact causes known. However, certain risk factors may play a role in its development. A risk factor is anything that increases a person's chance of developing a disease.

The following factors may raise a person's risk of developing WM (even though most people with these risk factors will never develop the disease):

- Age—the risk of WM increases with age. The median age at diagnosis is 73 years.
- Gender—WM appears to be twice as common in men as in women.
- Race—WM incidence is highest among Caucasians and is rare in other population groups. The incidence of WM may be higher for individuals of Ashkenazi Jewish descent.
- History of disease—monoclonal gammopathy of undetermined significance (MGUS) is an abnormality of antibody-producing cells that is related to WM and another B-cell blood cancer called "myeloma." In most cases, MGUS does not cause health problems, but up to 25 percent of people with MGUS, especially those with a monoclonal IgM protein, will develop WM, another type of NHL, or myeloma. **See the free LLS booklets *Monoclonal Gammopathy of Undetermined Significance (MGUS) Facts and Myeloma* at www.LLS.org/booklets.**
- Heredity—genetic factors appear to play a role in WM onset, with studies showing a small percentage of patients (4.3 percent) having a first- or second-degree relative with WM or another type of B-cell disorder.
- Environmental factors—the role of the environment in WM onset is unknown. However, the United States Department of Veterans Affairs has listed non-Hodgkin lymphoma as a cancer associated with Agent Orange. For more information, see *We're Here to Help* on page 12.

Signs, Symptoms and Complications

At least 25 percent of people with Waldenström macroglobulinemia (WM) are asymptomatic (have no symptoms), and the cancer is diagnosed because of abnormal results from blood tests that were ordered, usually, during a routine physical examination. Over time, patients are likely to develop complications from WM.

Some patients have signs (a change in the body that the doctor sees in an exam or a test result) and symptoms (a change in the body that the patient can see or feel) that may be similar to those of people with other types of non-Hodgkin lymphoma (NHL). The symptoms of WM are mostly associated with the effects of

- The WM cells in the marrow
- Monoclonal immunoglobulin M (IgM) in the blood.

The most common early symptoms of WM are fatigue and weakness due to anemia. Other common signs and symptoms include

- Fever
- Night sweats
- Weight loss
- Enlarged lymph nodes
- Enlarged spleen and liver
- Peripheral neuropathy—nerve problems that may cause pain and tingling (pins and needles sensation) and numbness in the feet, legs and hands.
- Slow and progressive reduction in kidney function—acute kidney failure is rare.

In some, but not all patients, monoclonal IgM may be present in the blood and tissues and may cause the following disorders:

Hyperviscosity syndrome. This syndrome is caused by the accumulation of IgM proteins (large molecules) in the blood. The buildup of the IgM proteins thickens the blood eventually impairing blood flow. When the blood gets too thick it has trouble traveling through the smallest blood vessels. The resulting poor blood circulation to the brain can lead to problems similar to those of a stroke, including slurred speech and/or weakness on one side of the body. The impaired blood flow can also cause changes in eyesight due to retinal bleeding, headache, and unexplained bleeding (from nose and gums); it may

also strain the heart, causing congestive heart failure. Hyperviscosity syndrome occurs in about 10 to 30 percent of WM patients.

Patients with IgM serum levels greater than 50 grams per liter (g/L) are considered to be at an increased risk for hyperviscosity syndrome. Untreated, long-standing hyperviscosity syndrome can cause life-threatening complications. Testing for hyperviscosity syndrome involves measurements of serum and/or plasma viscosity. Centipoise (cP) is the standard measuring unit and normal serum viscosity is between 1.4 and 1.8 cP. Typically, symptoms of hyperviscosity syndrome develop when the patient's serum viscosity is elevated, exceeding 4 cP. Patients need to be tested periodically for evidence of hyperviscosity syndrome progression. Treatment includes plasmapheresis (see *page 4*).

Amyloidosis. Insoluble protein (amyloid) can accumulate in organs such as the heart or kidney, causing damage. If amyloid builds up in the heart muscle, it can make the heart weaker. In WM, amyloidosis is usually caused by fragments of light chains produced by the monoclonal IgM.

Cold agglutinin disease. Monoclonal IgM destroys red blood cells when the patient is exposed to cold temperatures. This breakdown of red blood cells is a type of hemolytic anemia. Less than 10 percent of WM patients experience this condition.

Cryoglobulinemia. In some people, monoclonal IgM in the blood becomes thick and gel-like when exposed to cold temperatures. That causes circulatory problems in areas exposed directly to the cold, such as fingertips, ears, nose or toes and exposed areas may turn blue or black and cause pain. Up to 20 percent of patients with WM may develop this condition although fewer than 5 percent of patients actually exhibit symptoms.

Raynaud's syndrome (also called "Raynaud phenomenon"). This syndrome is associated with both cold agglutinin disease and cryoglobulinemia. This syndrome is characterized by signs of poor red blood cell circulation in the blood vessels near the nose, ears, fingers and toes in response to cold temperatures. Features of Raynaud's syndrome include feelings of cold, numbness, tingling, discoloration of the affected areas and pain in the hands and feet in cool temperatures.

The following supportive therapy options may be used to help manage symptoms and complications of WM:

Plasmapheresis. Plasmapheresis reduces blood viscosity. It uses a machine that separates the plasma (the liquid part of the blood), which contains the abnormal IgM protein, from the blood cells. The cells are then returned to the patient, while the plasma, which contains the antibodies, is discarded and replaced with other fluids. Medication to keep the blood from clotting (an anticoagulant) is given through a vein during the procedure. Treatment with plasmapheresis alone may be indicated if hyperviscosity is the patient's only symptom. In some cases, plasmapheresis is used when a patient's WM is not controlled by chemotherapy, biological therapy or other treatments.

Red blood cell transfusions. Transfusions use cells donated by healthy volunteers to help replace red cells, platelets and other blood components. Red blood cell transfusions can be used to help a patient who has developed anemia. However, if a patient has hyperviscosity syndrome, he or she may also have reduced capillary blood flow following transfusions. Patients should not be transfused unless treatment for hyperviscosity has first been implemented to reduce high serum IgM levels.

Splenectomy. The surgical removal of the spleen may be needed in WM patients, but it is uncommon. However, this procedure is indicated in some patients with WM who have painful enlargement of the spleen and for whom drug therapy was not helpful. Moreover, splenectomy may also benefit individuals with enlarged spleens who develop severe blood count depletions.

Common Genetic Mutations

Scientists have recently made progress in the understanding of how certain changes in DNA (deoxyribonucleic acid) can cause normal lymphocytes to become lymphoma cells. Scientists are also beginning to understand how changes in the DNA of some lymphoma cells cause them to produce high levels of immunoglobulin M (IgM), a key reason for many symptoms of WM. The following gene mutations are associated with WM:

- *MYD88 L265P* (myeloid differentiation primary response 88 somatic mutation). In WM, the most common mutation occurs in *MYD88 L265P* gene. Over 90 percent of patients carry this mutation

in the WM cells. A mutation in *MYD88 L265P* turns on growth and survival pathways including Bruton tyrosine kinase (BTK), the target of **ibrutinib (Imbruvica®)**.

- *CXCR4* (chemokine receptor type 4 gene). About 30 to 40 percent of WM patients also carry a mutation in *CXCR4*, the gene that turns on growth and survival pathways. More than 40 types of *CXCR4* mutations can be found in patients with WM. Patients with “nonsense mutations” of *CXCR4* can present with higher serum IgM levels and bone marrow involvement. (“Nonsense mutations” are mutations that cause part of the protein to be cut off, thereby a shorter CXCR4 protein exists, which lacks the segment that allows it to be shut off.) Waldenström macroglobulinemia cells with mutations of the *CXCR4* gene show resistance to **ibrutinib**.
- *ARID1A* (AT-rich interacting domain containing protein 1A). This is the third most common mutation in WM patients, occurring in 17 percent of all cases. Protein 1A is a chromatin remodeling protein. Patients who have mutations of both *ARID1A* and *MYD88 L265P* genes, when compared with patients who do not have the *ARID1A* gene mutations, have greater bone marrow disease involvement and lower hemoglobin values and platelet counts.

Novel therapeutic approaches for WM under investigation include therapies targeting these genes.

Diagnosis

Waldenström macroglobulinemia (WM) may be suspected if blood test results show low blood counts or unusually high protein levels. To establish a diagnosis of WM, your doctor will order blood, bone marrow and other tests to determine

- The presence and amount of immunoglobulin M (IgM) monoclonal protein
- The presence of lymphoplasmacytic cells in the bone marrow.

Tests to diagnose WM include

Serum protein electrophoresis (SPEP). This test is used to identify the presence of abnormal proteins, to identify the absence of normal proteins and to determine increases and decreases of different groups of proteins in the blood. This test is typically ordered to identify an excessive production of immunoglobulins (Igs).

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The amounts of all five types of immunoglobulin (IgG, IgA, IgM, IgE, and IgD) are measured by this test. An excessive production of a monoclonal immunoglobulin may be shown on laboratory results as a spike on a graph. Generally, IgM protein levels greater than 3 grams per deciliter (g/dL) are an indication of WM.

Serum viscosity. This test measures the thickness of the blood. High levels of IgM will cause the blood to thicken, leading to abnormal blood flow. Most patients with WM will have an elevated serum viscosity level, which is more than 1.8 cP (centipoise). Typically, patients become symptomatic at levels of more than 4.0 cP. For some patients, even a 3.0 cP viscosity level may cause changes in the retina and bleeding that will require medical treatment.

Other blood tests. These tests may include checking blood counts, the levels of microglobulins and immunoglobulins and may result in the following findings:

- **Red blood cells.** Anemia (a low number of red blood cells) is present in most patients at diagnosis. Hemoglobin and hematocrit levels (measures of the concentration of red cells in the blood) are often low; however, the absolute quantities may be normal or near-normal, because there is an increase in plasma (the fluid portion of the blood).
- **White blood cells.** A reduction in the total white blood cell count (leukopenia) may be present at diagnosis. However, the number of lymphocytes (a type of white cell) is usually increased.
- **Beta₂-microglobulin (B₂M).** Many patients have an elevated serum B₂M level at diagnosis. This protein is found on the surface of many cells including lymphocytes and it is a marker of tumor burden. The B₂M level is also elevated in patients who have abnormal kidney function.
- **Immunoglobulins.** There may be a decrease in the number of uninvolved immunoglobulins (IgG, IgA, IgD and IgE) and an increase of IgM.

Bone marrow aspiration and biopsy. Because the symptoms of WM can also be caused by noncancerous problems, such as infections, or by other kinds of cancer, a diagnosis of WM can only be confirmed by performing bone marrow tests, in which a small amount of bone marrow is removed and examined under a microscope by a pathologist to see if lymphoma cells are present. These tests can be done at the doctor's office or at the hospital, and the patient can usually go home soon

after the procedure is completed. Rarely, a lymph node biopsy, in which tissue is removed from a lymph node, may be used to diagnose WM, although this method is more useful for diagnosing other types of lymphoma.

Other laboratory tests. The following tests are also used in the diagnosis of WM.

- **Immunophenotyping.** This is a method used to identify a specific type of cell in a sample of blood or marrow cells to determine if the abnormal lymphocytes are B cells or T cells. Abnormal B lymphocytes are associated with WM and are characterized by the cell markers CD19, CD20, CD22, CD79 and antibody FMC7. The term "cluster of differentiation (CD)" is used to identify an antigen on the surface of the cell. Expressions of CD5, CD10 and CD23 may be found in 10 to 20 percent of WM cases.
- **Flow cytometry.** In this test, cell properties are measured using a light-sensitive dye and a laser beam or other type of light. The test is often used to look at markers on the surface of cells or inside the lymphocytes. Flow cytometry has become increasingly important in helping doctors to determine a patient's exact type of lymphoma.
- **Allele-specific PCR (AS-PCR).** This is a type of polymerase chain reaction (PCR) test used to detect variations in a specific location of a gene. The National Comprehensive Cancer Network® (NCCN) clinical practice guidelines recommend AS-PCR for the *MYD88 L265P* mutation as an essential test to differentiate WM from lymphoplasmacytic lymphoma (LPL) and other B-cell lymphomas.
- **24-hour urinalysis.** An analysis of urine collected over 24 hours used to detect elevated levels of protein in the urine.
- **Liver function tests.** Patients with WM, in particular those affected by cryoglobulinemia, may have an underlying hepatitis C infection. In addition, **rituximab (Rituxan®)** can activate the hepatitis B virus. Therefore, liver function tests and blood screening to identify hepatitis B or hepatitis C infection are recommended before the start of treatment.

Imaging tests. Imaging tests may include computed tomography (CT or CAT) scan(s). The findings allow the doctor to evaluate the chest, abdomen and pelvis and detect swelling of the lymph nodes and the enlargement of the liver and/or spleen. A skeletal survey (x-rays of the skeleton) can help distinguish between WM and a

similar plasma cell cancer called “myeloma.” In contrast to myeloma, in WM no lytic bone lesions (holes in the bones where the tissue has been destroyed as a result of myeloma) are seen. Magnetic resonance imaging (MRI) and/or positron emission tomography (PET) may be useful tests to determine where the lymphoma is located throughout the body.

For additional information about laboratory and imaging tests, please see the free LLS booklet *Understanding Lab and Imaging Tests*.

Treatment Planning

Every patient’s medical situation is different and should be evaluated individually by a hematologist-oncologist who specializes in treating non-Hodgkin lymphoma (NHL). A patient has two options for treatment: standard of care or a clinical trial. It is important to talk to the healthcare team about the best treatment option.

Treatment plans for Waldenström macroglobulinemia (WM) are developed for each individual patient based on several factors, including

- The nature and extent of symptoms
- The need for more rapid disease control
- The patient’s age, overall health and quality of life. There may be age requirements for treatments such as stem cell transplantation.
- The potential need for a stem cell transplant in the future.

For more information about choosing a doctor or a treatment center, see the free LLS booklet *Choosing a Blood Cancer Specialist or Treatment Center*.

Treatment

There are several treatment options available to prevent or control symptoms of Waldenström macroglobulinemia (WM) and improve the quality of life of patients. Not all newly diagnosed WM patients will need immediate treatment. Twenty-five percent of WM patients are asymptomatic (have no symptoms) at diagnosis, and up to 50 percent of those patients may not require therapy for many years after diagnosis.

Patients who do not present with symptoms (they are asymptomatic) are observed in an approach called “watch and wait.” Active treatment for these patients only begins

when symptoms develop. To date, there is no evidence that suggests that treatment of asymptomatic WM patients provides any greater survival benefit than waiting for symptoms to appear and starting treatment then.

For more information about this topic, see the free LLS information sheet *Watch and Wait*.

According to The National Comprehensive Cancer Network® (NCCN) guidelines for WM, treatment should be initiated when patients have the following symptoms:

- Low blood cell counts
- Symptomatic enlargement of lymph nodes and organs, such as the liver and the spleen
- Severe peripheral neuropathy due to the immunoglobulin M (IgM) protein
- Systemic amyloidosis with organ damage related to the IgM protein
- Hyperviscosity syndrome
- Symptomatic cryoglobulinemia
- Symptomatic cold agglutinin disease.

There are a number of therapies that are effective against WM but there is no single or combination standard treatment that is used for all patients. Patients are advised to discuss with their doctors the most appropriate treatment for their situation. Specific treatments include drug therapy, combinations of drugs, stem cell transplantation and clinical trials.

Drug Therapy

Bruton tyrosine kinase (BTK) inhibitor—This class of drugs targets BTK which is activated by the mutation of the *MYD88 L265P* gene. The US Food and Drug Administration (FDA) approved BTK inhibitor, **ibrutinib (Imbruvica®)**, is taken by mouth for the treatment of symptomatic WM patients. Ibrutinib is also approved in combination with **rituximab (Rituxan®)** for the treatment of adult patients with WM. People with *CXCR4* mutations show lower response rates and delayed responses to ibrutinib. Derivatives of these compounds are also being explored including the drug **acalabrutinib (Calquence®)**.

Monoclonal antibodies—Biological therapies are a type of targeted therapy directed at specific proteins. **Rituximab (Rituxan®)** targets CD20, a protein that is found on the surface of B cells, including WM cells; it is approved by the FDA for use, either alone or in combination with other medications, to treat certain

types of non-Hodgkin lymphoma (NHL). Ibrutinib is also approved in combination with rituximab (Rituxan®) for the treatment of adult patients with WM. Rituximab is also considered a very effective choice for treating patients who have IgM-related neuropathies. An important consideration when using this type of therapy is that when rituximab is used as a single agent, it is associated with the risk of an IgM flare or spike for many patients. This means that when treatment with rituximab is started, there is a temporary rise in the serum level of IgM, which can produce hyperviscosity that requires urgent plasmapheresis therapy.

Another monoclonal antibody, **alemtuzumab (Campath®)**, targets a different protein, CD52, that is found on the membrane of lymphoma cells. Alemtuzumab is FDA approved to treat chronic lymphocytic leukemia (CLL), but it has also been found to help some WM patients. It is being studied in clinical trials.

Alkylating agents—This class of chemotherapy drugs includes **chlorambucil (Leukeran®)**, **cyclophosphamide (Cytoxan®)** and **bendamustine hydrochloride (Bendeka®)**. Bendeka®, given by intravenous (IV) infusion, is indicated for treatment of patients with indolent B-cell NHL that has progressed either during or within 6 months of treatment with rituximab (Rituxan®) or a rituximab-containing regimen. These drugs directly damage the DNA (deoxyribonucleic acid) of cells. People who are candidates for stem cell transplantation should not be treated with alkylating agents—with the exception of cyclophosphamide—because these drugs are likely to decrease the production of functioning red blood cells, white blood cells and platelets.

In addition, alkylating agents are reported to increase the incidence of disease transformation and development of myelodysplastic syndromes (syndromes in which the bone marrow does not effectively produce blood cells) and acute myeloid leukemia (AML) in patients with WM who have received this type of therapy.

Antimetabolites or nucleoside analogues—This category of drugs includes **pentostatin (Nipent®)**, **fludarabine (Fludara®)** and **cladribine (Leustatin®)**. Pentostatin has been found to be effective for patients who are candidates for high-dose chemotherapy with autologous stem cell transplantation. Patients who are candidates for stem cell transplantation should not be treated with fludarabine or cladribine until an adequate number of stem cells has been collected. In addition, a study found that nucleoside analogue-based

combinations may be associated with an increased risk of disease transformation or myelodysplastic syndromes. Because of this consideration, these agents are less frequently used now than they were in the past.

Corticosteroids—Corticosteroids are drugs that are often used to relieve inflammation but they are also toxic to lymphoma cells. Corticosteroids are often part of chemotherapy regimens. **Dexamethasone** and **prednisone** can be useful in the treatment of WM, especially in patients who have extremely low blood cell counts but are not candidates for treatment with drugs that affect normal blood cell production. Corticosteroids also help decrease the nausea and vomiting side effects caused by many chemotherapy agents.

Immunomodulators—These agents modify different parts of the immune system. **Lenalidomide (Revlimid®)** and **thalidomide (Thalomid®)** are examples of immunomodulating drugs that have been shown to be effective in some patients with WM. The best results with thalidomide in WM patients have occurred when it was used in combination with other drugs, such as rituximab or dexamethasone.

mTOR (mammalian target of rapamycin) inhibitors—This class of drugs inhibits the mTOR pathway that promotes growth and survival of cells. **Everolimus (Affinitor®)** is a drug that is taken by mouth and it is FDA approved for treatment of other nonblood cancers; however, it has also shown good responses in patients with previously treated WM.

Proteasome inhibitors—This class of drug blocks the action of proteasomes (cellular complexes that break down proteins). **Bortezomib (Velcade®)** is FDA approved to treat patients with myeloma and patients with mantle cell lymphoma who have received at least one prior therapy. Bortezomib induces apoptosis (cell death) of primary WM lymphoplasmacytic cells. However, neuropathy is a major concern for the patients using this medication. It may also reactivate the herpes zoster (shingles) virus. **Carfilzomib (Kyprolis®)**, a proteasome inhibitor, which has a low risk for neuropathy, was recently shown to be active in WM patients in combination with rituximab and dexamethasone. Carfilzomib is approved by the FDA for the treatment of previously treated myeloma patients.

Combination Therapies

Based on the favorable outcomes reported in recent studies, the use of combination therapy (treatment with

two or more drugs) is increasingly being favored for previously untreated patients or for those whose disease has relapsed.

Some examples of combination therapies commonly used in the treatment of WM patients include

- IR: Ibrutinib (Imbruvica), rituximab (Rituxan)
- BDR: Bortezomib (Velcade), dexamethasone and rituximab (Rituxan)
- VR: Bortezomib (Velcade) and rituximab (Rituxan)
- CaRD: Carfilzomib (Kyprolis), rituximab (Rituxan), dexamethasone.
- RCD: Rituximab (Rituxan), cyclophosphamide (Cytoxan), and dexamethasone
- RCP: Rituximab (Rituxan), cyclophosphamide (Cytoxan), and prednisone
- Benda-R: Bendamustine hydrochloride (Bendeka) and rituximab (Rituxan).
- FR: Fludarabine (Fludara) and rituximab (Rituxan)
- FCR: Fludarabine (Fludara), cyclophosphamide (Cytoxan) and rituximab (Rituxan).

Clinical trials are under way to determine the long-term results and adverse side effects of combination therapy strategies in the treatment of WM.

Certain long-term or late effects have been associated with the use of alkylating agents and antimetabolite agents, such as transformation to a more aggressive lymphoma and/or development of a myelodysplastic syndrome or acute myeloid leukemia. Patients should discuss the benefits and risks of any treatment with their doctors. **See the free LLS booklet *Long-Term and Late Effects of Treatment in Adults* for additional information about potential long-term effects of these and other drug treatments.**

Stem Cell Transplantation

This therapy is not used as a first treatment for WM but is an option for some patients who have relapsed and/or refractory disease, especially younger patients who have had one or more relapses. There are two main types of stem cell transplantation: autologous and allogeneic.

Autologous stem cell transplantation is the type of transplantation most often used in WM patients. This procedure uses the patient's own stem cells to restore blood cell production after intensive chemotherapy.

Based on data from a number of clinical trials, autologous stem cell transplants are showing high response rates, even in patients whose disease was refractory to several regimens of standard chemotherapy.

Allogeneic stem cell transplantation (infusion of donor stem cells into a patient) has more risks and side effects than autologous stem cell transplantation and it is usually reserved for younger patients with advanced disease who have either failed to respond, or no longer respond, to other treatment options.

Talk to your doctor about whether stem cell transplantation is a treatment option for you. **For additional information on stem cell transplantation, please see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Side Effects of Treatment for Waldenström Macroglobulinemia (WM)

The side effects of treatment will depend on many factors, including type of treatment and dosage, the age of the patient and coexisting medical conditions.

Therapy may induce fatigue, nausea, fever, chills, dizziness, shortness of breath, confusion, temporary loss of hair and other side effects. Side-effects management is important. If you are having any concerns about side effects, talk to your doctor to get help. Most side effects are temporary and resolve when treatment is completed. **For specific drug information, see the free LLS booklet *Understanding Side Effects of Drug Therapy*.**

Treatment for Relapsed and/or Refractory Waldenström Macroglobulinemia (WM)

Because Waldenström macroglobulinemia (WM) is not curable and the disease grows slowly, virtually all patients will experience relapse (return of the cancer) and/or refractory disease (the cancer resists treatment) after initial therapy, and will require additional treatment. Many treatment combinations for relapsed and/or refractory WM have been tested, but comparative trials to identify the most effective treatment approach have not been done.

The choice of treatment for a patient who has relapsed and/or refractory WM depends on several factors, including

- The initial treatment used
- The quality and duration of response to the initial treatment
- Tolerance of initial therapy
- Eligibility for stem cell transplantation.

According to the recommendations from the National Comprehensive Cancer Network (NCCN) panel for WM in its NCCN Guidelines for 2018, administering the same therapeutic regimen used for first-line treatment is acceptable for relapsed disease if a patient achieved a response that lasted at least 12 months or more. For WM patients who experienced a short remission or resistance to initial therapy, the use of different classes of drugs, either alone or in combination, is recommended. Also, it is important to avoid using stem cell-damaging agents such as alkylators or antimetabolites in patients who are candidates for autologous stem cell transplantation. Therapies that are not toxic to stem cells must be offered, especially if stem cells have not been previously harvested.

The following are treatment options for relapsed and/or refractory WM.

- **Ibrutinib (Imbruvica®)**
- **Bortezomib (Velcade®)** with or without **rituximab (Rituxan®)**
- **Bendamustine hydrochloride (Bendeka®)**, either as single agent or in combination with rituximab
- **Alemtuzumab (Campath®)**
- **Everolimus (Affinitor®)**

- **Rituximab**
- **Ofatumumab (Arzerra®)**, either given alone or with other drugs to patients who cannot tolerate rituximab
- **Thalidomide (Thalomid®)**, either with or without rituximab.

In several studies, ibrutinib has been found to be an effective treatment option for patients whose disease did not respond to rituximab therapy. Stem cell transplantation is also an option for the treatment of relapsed WM in selected patients. High-dose drug therapy, followed by autologous stem cell transplantation, is the preferred indication for the treatment of these patients.

Disease Transformation

Rarely, Waldenström macroglobulinemia (WM) patients have disease that transforms to diffuse large B-cell lymphoma (DLBCL, a subtype of non-Hodgkin lymphoma). This complication is usually associated with a marked enlargement of the lymph nodes and/or the spleen, an increase in serum lactate dehydrogenase (LDH), and weight loss, fever and night sweats. Cytogenetic abnormalities are often found in involved tissues—for example, the lymph nodes and/or bone marrow—at the time of transformation.

The incidence of transformation in WM patients is approximately 2 percent at 10 years. Transformation may occur at any time during the course of the disease: at diagnosis, before treatment is started, during response to therapy and even 20 years after the diagnosis of WM.

Prior use of nucleoside analogue drugs, such as **fludarabine (Fludara®)** or **cladribine (Leustatin®)**, has been reported as being associated with disease transformation and development of myelodysplastic syndromes and acute myeloid leukemia.

Treatments Undergoing Investigation

Patients are encouraged to explore clinical trials. Clinical trials test new drugs and treatments, many of which are being supported by LLS research programs, before they are approved by the US Food and Drug Administration (FDA) as standard treatments.

Clinical trials are carefully controlled research studies, conducted under rigorous guidelines, to help researchers determine the beneficial effects and possible adverse side effects of new treatments.

Clinical trials are designed to be accurate and very safe. Patient participation in clinical trials is important in the development of new and more effective treatments for Waldenström macroglobulinemia (WM) and may provide patients with additional treatment options.

LLS Information Specialists, at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals. When appropriate, Information Specialists refer patients for personalized clinical-trial navigation by trained nurses, which is available through our Clinical Trial Support Center.

Patients interested in participating in clinical trials are encouraged to talk to their doctors. **For more information about clinical trials, see the free LLS booklet *Understanding Clinical Trials for Blood Cancers* or visit www.LLS.org/clinicaltrials.**

The following novel therapies and drugs are being investigated as treatments for WM.

- **Oprozomib**, taken by mouth, is an epoxyketone proteasome inhibitor that is similar to bortezomib but causes fewer side effects (such as neuropathy). Oprozomib is being evaluated in current trials as a less toxic alternative to bortezomib for the treatment of myeloma and WM.
- **Ixazomib (Ninlaro®)** is a novel, oral proteasome inhibitor, which has shown activity in relapsed/refractory myeloma patients, without significant neuropathy and is being studied in WM.
- **Ixazomib, dexamethasone and rituximab (Rituxan®) (IDR)** is a combination being studied in symptomatic untreated WM patients. Ixazomib is also being studied in combination with **ibrutinib (Imbruvica®)** for relapsed and refractory disease.
- **IMO-8400** is an oligonucleotide directed against the endosomal Toll-like receptors (TLRs) 7, 8 and 9. In WM cells, TLR signaling is overactivated enabling tumor cell survival and proliferation. IMO-8400 is under investigation in clinical trials for treatment of WM that has either relapsed or that has failed to respond to one or more prior therapies.
- **Idelalisib (Zydelig®)** is a PI3K inhibitor currently under study for treatment as a single agent and in combination with **obinutuzumab (Gazyva®)** (a

monoclonal antibody) for the treatment of patients with either relapsed and/or refractory WM.

- **Venetoclax (Venclexta®)** is a B-cell lymphoma 2 (BCL-2) inhibitor that induces cell death in WM cells treated with either ibrutinib or idelalisib. A current study is evaluating the safety and effectiveness of venetoclax in WM patients with previously treated disease.
- **Ulocuplumab** is a monoclonal antibody that targets *CXCR4*. It is being studied in combination with ibrutinib for symptomatic WM patients who have the *CXCR4* gene mutation. **Daratumumab (Darzalex®)** is a monoclonal antibody that binds to cluster of differentiation 38 (CD38). In a current study, investigators are evaluating its efficacy for patients with WM that has either relapsed or has shown no response to previous treatment.
- Chimeric antigen receptor (CAR) modified T-cell therapy has shown promising results in several B-cell malignancies. A second-generation CAR therapy has shown preclinical activity against WM cells, and a clinical trial for patients who have relapsed or refractory WM is under study.

Treatment Outcomes

The prognosis for patients with Waldenström macroglobulinemia (WM) depends on a number of factors, including patient age, rate of disease progression and response to therapy. Some patients may have either stable or slowly progressive disease and may live good-quality lives for many years while under a doctor's care for the management of their WM. Other patients may have a rapidly progressive form of WM.

The International Prognostic Scoring System for Waldenström Macroglobulinemia (IPSSWM) is internationally accepted as a predictive model for long-term outcomes in newly diagnosed patients.

The IPSSWM uses the following factors to estimate survival. Except for age, each factor is worth one point:

- Age greater than 65 years
- Hemoglobin level of 11.5 grams per deciliter (g/dL) or less
- Platelet count of 100,000 platelets per microliter (mCL) or less
- Beta₂-microglobulin (B₂M) greater than 3 milligrams per liter (mg/L)

- Serum monoclonal protein concentration greater than 70 grams per liter (g/L).

According to most studies, immunoglobulin M (IgM) levels have little value in predicting patient outcomes.

Except for age, each of these factors is worth a single point. The points are added to make a score. The score is used to group WM patients into one of the following three risk groups:

- **Low risk**—includes patients younger than 65 years who have no more than one point
- **Intermediate risk**—includes patients who are at least 65 years of age and/or have two points.
- **High risk**—includes patients who have at least three points.

The risk groups of the IPSSWM are used to help estimate “median survival.” Median survival is defined as the time after which 50 percent of people with a particular condition are still living and 50 percent have died. Keep in mind that the most recent survival statistics for WM¹ may underestimate survival, because these data do not incorporate outcomes of current treatment options. It is also important to know that outcome data can show how groups of people with WM responded to treatment, but cannot determine how any one person will respond. For these reasons, patients are advised to discuss survival information with their doctors. It is important to remember that many of these prognostic systems were developed before the availability of some of the newer drugs mentioned, and it is likely that the prognosis has significantly improved since.

¹ The estimated median survival for WM ranges from 4 years (higher risk) to 12 years (lower risk) after treatment begins.

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Rafael Fonseca, MD

Getz Family Professor of Cancer
Chair, Department of Medicine,
Distinguished Mayo Investigator
Mayo Clinic
Phoenix, Arizona

Glossary

Antigen. Any substance that elicits an immune response in the body. An antigen can be either a germ or a toxin.

Beta₂-microglobulin (B₂M). A small protein normally found on the surface of many cells, including lymphocytes. It is also found in small amounts in the blood and urine. An increased amount in the blood or urine may be a sign of certain diseases, including some types of cancer, such as multiple myeloma or lymphoma.

Bone marrow aspiration. A procedure in which a small sample of liquid bone marrow is removed, usually from the hip bone. A small area of skin and the surface of the bone underneath are numbed with an anesthetic. Then, a special needle is inserted into the bone. A sample of liquid bone marrow is removed. The bone marrow is sent to a laboratory to be looked at under a microscope. This procedure is usually done at the same time as a bone marrow biopsy.

Bone marrow biopsy. A procedure in which a small sample of bone with bone marrow inside it is removed, usually from the hip bone. A small area of skin and the surface of the bone underneath are numbed with an anesthetic. Then, a special, wide needle is inserted into the bone and rotated to remove a sample of bone with the bone marrow inside it. The sample is sent to a laboratory to be looked at under a microscope. This procedure is usually performed at the same time as a bone marrow aspiration.

Centipoise (cP). A unit of viscosity of a fluid. The viscosity of blood serum may be elevated in Waldenström macroglobulinemia. Normal blood serum viscosity is 1.8 cP. Water viscosity is 1.0 cP. See *Viscosity*.

Immunoglobulin. A protein made by white blood cells (lymphocytes) that helps the body to fight infection. Also known as an “antibody.”

Lymphoplasmacytic cells. Cells that have characteristics of both lymphocytes and plasma cells.

Plasmapheresis. The process of separating certain cells from the plasma in the blood by a machine; only the cells are returned to the person. Plasmapheresis can be used to remove excess antibodies from the blood. In Waldenström macroglobulinemia treatment, it removes excess immunoglobulin M monoclonal antibody.

Viscosity. The measure of a fluid’s resistance to flow. Thinner liquids like water have lower viscosities while thicker liquids like oil have higher viscosities.

Questions to Ask Your Doctor

It may be helpful to prepare some questions to ask your treatment team at your next appointment. Here are some suggestions of questions to ask.

About the Disease and Testing

1. What tests do I need to have?
2. How do I prepare for these tests?
3. Will my medical insurance pay for the tests?
4. When will I have the results? Who will explain the results?
5. When can I expect to experience Waldenström macroglobulinemia symptoms?
6. I am experiencing symptoms right now, what does that mean for my treatment?

About Treatment Options and Side Effects

1. Do I need treatment for Waldenström macroglobulinemia?
2. Is the “watch-and-wait” approach the right option for me?
3. What treatment options do I have?
4. Are there any available clinical trials for my diagnosis?
5. Does this hospital/center offer treatment for my disease?
6. How long will the treatment last?
7. What are the side effects of this treatment? How long will they last?
8. How will I know if the treatment is effective? What will happen if the treatment does not work?
9. Are there any long-term side effects of this treatment?

About Cost

1. Will my medical insurance pay for my treatment?
2. If I participate in a clinical trial, am I responsible for any of the costs associated with that clinical trial?
3. What additional costs should I be thinking about (for example, transportation, parking, food, etc)?

We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our Web site at www.LLS.org/chapterfind or contact:

The Leukemia & Lymphoma Society
3 International Drive, Suite 200
Rye Brook, NY 10573

Call an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org

LLS offers free information and services for patients and families touched by blood cancers. The following entries list various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, from 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists
- Visit: www.LLS.org/InformationSpecialists

Clinical Trials (Research Studies). New treatments for patients are ongoing. Patients can learn about clinical-trials and how to access them. For more information, please call (800) 955-4572 to speak with our LLS Information Specialists who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

Free Information Booklets. LLS offers free education and support booklets that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

Financial Assistance. LLS offers financial assistance to individuals with blood cancer. Visit www.LLS.org/finances for more information.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

- Call: (877) 557-2672
- Visit: www.LLS.org/copay.

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit www.LLS.org/community to join.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations by a registered dietitian with experience in oncology nutrition. Dietitians assist callers about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition for more information.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients to reach out and share information. Please visit www.LLS.org/chat for more information.

Podcast. Listen in as experts and patients guide listeners in understanding diagnosis and treatment, and suggest resources available to blood cancer patients. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Visit www.LLS.org/TheBloodline for more information and to subscribe.

LLS Chapters. LLS offers support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. Please visit www.LLS.org/resourcedirectory for more information.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

Information for Veterans. Veterans with WM who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/agentorange.

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes.

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a 2-week period. For more information, please

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter “depression” in the search box.

Feedback. To give suggestions about this booklet, visit www.LLS.org/PublicationFeedback.

Other Resources

International Waldenström’s Macroglobulinemia Foundation (IWMMF)

www.iwmmf.com

(941) 927-4963

Provides support, information, resources and a community network for individuals who have Waldenström macroglobulinemia.

The National Cancer Institute (NCI)

www.cancer.gov

(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including Waldenström macroglobulinemia (WM). The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where WM patients can look for clinical trials.

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