LEUKEMIA & LYMPHOMA SOCIETY®

Waldenström Macroglobulinemia

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

Highlights

- Waldenström macroglobulinemia (WM) is a rare and typically slow-growing subtype of non-Hodgkin lymphoma (NHL) that affects white blood cells.
- A main characteristic of WM is the overproduction of a monoclonal protein called "immunoglobulin M" (IgM). This 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 (cancer) cells. The mutation turns on pathways that sustain the growth and survival of WM cells. About 30 to 40 percent of patients have a *CXCR4* gene mutation. WM cells with mutations in the *CXCR4* gene may be resistant to treatment and this can influence treatment approach.
- 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. Treatments that have shown promising results include a combination of chemotherapy, targeted therapies and immunomodulatory agents. 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 or with a combination regimen that may or may not include the same agents that were used during the first-line treatment. The choice of treatment agents will depend on how long the first response to treatment lasted.

Introduction

"Lymphoma" is the name for cancers that originate in the lymphatic system, the body's germ-fighting network. Lymphoma is divided into two major categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

A critical part of the lymphatic system is the white cells in the blood. There are three types of white blood cells, called "lymphocytes": B lymphocytes, T lymphocytes, and natural killer (NK) cells. B lymphocytes make antibodies to fight infection; T lymphocytes have many functions including helping B lymphocytes make the antibodies that fight infection; and natural killer (NK) cells attack cancer cells and viruses. Lymphocytes are created in the bone marrow and then move through the blood to the lymphatic system.

Lymphoma may arise in any of the three types of lymphocytes, but in general, lymphomas are more common in B lymphocytes than in T lymphocytes or natural killer (NK) cells. Lymphocytes go through several stages of development. The final stage of B lymphocyte development is a mature, immunoglobulin-producing plasma cell.

WM is classified by the World Health Organization (WHO) as a subtype of NHL and accounts for approximately 1 to 2 percent of blood (hematologic) 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*.

Visit www.LLS.org/booklets to view, download or order all free LLS publications.

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About Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM) is a cancer of the B lymphocytes 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 B cells and their more mature forms (plasma cells and 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 type responsible for producing its own class of antibodies. In WM, 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 lymphocyte clones, like all cancer cells, start crowding out the many different other types of healthy blood cells.

As a result, there are too many of the same kind of B lymphocytes in the bone marrow (along with the same kind of IgM immunoglobulin or macroglobulin produced by these 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, making it hard for the body to fight infection. The numbers of platelets (cells that help blood to clot) in the blood can also drop, leading to increased bleeding and bruising.

The WM cells only produce one type of antibody (IgM), called a monoclonal protein, or simply 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

Lymphoplasmacytic lymphoma (LPL) is a slow-growing type of NHL. It is usually found in the bone marrow but could also be present in the lymph nodes or spleen. Lymphoplasmacytic lymphoma cells can secrete immunoglobulins. It is when a monoclonal IgM protein is identified in the blood, along with LPL in the bone marrow, that the disease is referred to as WM.

Incidence, Causes and Risk Factors

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

There is no known way to prevent WM, nor have exact causes been determined. However, certain risk factors may play a role in the development of WM. 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 71 years.
- Sex—the incidence of WM appears to be higher in males than in females.
- Race—WM incidence is highest among whites and is rare in other population groups. The incidence of WM may also be higher for individuals of Ashkenazi Jewish descent.
- History of disease—MGUS (monoclonal gammopathy of undetermined significance) 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 IgM MGUS develop WM, another type of NHL, or myeloma. **See the free LLS publication *Monoclonal Gammopathy of Undetermined Significance (MGUS)* and the book *Myeloma* for more information.**
- 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 who has 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 (NHL) as a cancer associated with Agent Orange. For more information, see *We're Here to Help* on page 14.

Signs, Symptoms and Complications

At least 25 percent of people with WM have no symptoms (called "asymptomatic"). For these patients, the cancer is diagnosed when it shows up in blood test results that are commonly ordered as part of 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 like those of people with other types of non-Hodgkin lymphoma (NHL). The symptoms of WM are usually 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
- Weakness due to anemia

Other common signs and symptoms include:

- Fever
- Night sweats
- Weight loss
- Enlarged lymph nodes
- Enlarged spleen and liver
- Headaches
- Nosebleeds
- Slow, progressive reduction in kidney function (but acute kidney failure is rare)

Disorders Caused by Monoclonal IgM. In some but not all patients, monoclonal IgM may be present in the blood and tissues and may cause disorders such as those listed below.

Hyperviscosity Syndrome. This syndrome is caused by the accumulation of high amounts of IgM proteins in the blood. Viscosity means thickness; hyperviscosity is a condition in which blood can't flow freely through your arteries. The buildup of the IgM proteins thickens the blood, eventually impairing blood flow, especially in the smallest blood vessels. The resulting poor blood circulation to the brain can lead to problems like 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 the nose and gums; it may also strain the heart and cause congestive heart failure. Hyperviscosity syndrome occurs in about 10 to 30 percent of WM patients.

Symptoms of hyperviscosity are rare in patients with an IgM concentration of less than 4,000 mg/dL. 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. 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. An insoluble protein called amyloid can accumulate in organs such as the heart or kidneys, causing damage. If amyloid builds up in the heart muscle, it can make the heart weaker. In WM, this condition, called "amyloidosis," is usually caused by fragments of light chains produced by the LPL (lymphoplasmacytic lymphoma) cells.

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

Cryoglobulinemia. Some people with WM develop cold-sensitive antibodies called cryoglobulins ("cryo" means cold). The blood becomes thick and gel-like when exposed to cold temperatures, causing circulatory problems in body areas exposed directly to the cold, such as fingertips, ears, the nose, or toes. Exposed areas may turn blue or black and be painful. Up to 20 percent of patients with WM may develop this condition, although fewer than 5 percent of patients exhibit symptoms. The presence of cryoglobulins in the blood can interfere with blood IgM level measurements, causing the level of IgM to appear lower than it actually is. When low IgM is found, it may be necessary to retest the blood IgM level; it is recommended that future IgM measurements be done under warmer conditions.

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.

Peripheral Neuropathy. Sometimes the immune system makes antibodies that attack a person's own nerves, which leads to neuropathy. Antibodies that attack a person's own body are called "autoantibodies." Two examples of autoantibodies associated with neuropathy in WM are called "anti-MAG" and "anti-GM1." Autoantibodies can cause damage to peripheral nerves, resulting in pain and tingling ("pins and needles") and numbness in the feet, legs and hands. Levels can be measured with a blood test.

Bing-Neel Syndrome (BNS). This rare WM complication occurs when WM cells gain access to the central nervous system (CNS). The buildup of malignant cells in the CNS can cause headaches, weakness, nausea, vomiting and neurological deficits such as memory loss and seizures. Bing-Neel Syndrome (BNS) is seen in about 1 percent of patients. Treatment requires medications that can penetrate the CNS like **fludarabine, methotrexate** and **cytarabine**. The Bruton's tyrosine kinase (BTK) inhibitor **ibrutinib (Imbruvica®)** may also be effective in treating patients with WM and BNS (see page 7).

Supportive Therapy Options. The treatments listed below may help relieve some of the symptoms, complications, and problems associated with WM.

Plasmapheresis. Plasmapheresis reduces blood viscosity. It uses a machine that separates the liquid part of the blood called the "plasma" (which contains the abnormal IgM protein) from the blood cells. The blood 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 (called an "anticoagulant") is given through the patient's 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. People without symptoms of hyperviscosity but with a very high level of IgM (4,000 mg/dL or higher) may benefit from treatment with plasmapheresis before receiving drug therapy, especially if systemic therapy that includes **rituximab (Rituxan®)** is planned. Rituximab can cause a temporary increase in IgM, leading to hyperviscosity and potentially serious side effects, a phenomenon called "IgM flare."

Plasmapheresis may also be indicated for patients who have symptoms caused by IgM-related peripheral neuropathy. A course of 2 to 3 months of weekly plasmapheresis may be required before there is an improvement in symptoms.

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

Splenectomy. Rarely, WM patients require the surgical removal of the spleen ("splenectomy"). Splenectomy is indicated in some patients with WM who have painful enlargement of the spleen and for whom drug therapy is not helpful. Splenectomy may also benefit individuals who have an enlarged spleen and/or who develop severely low blood counts.

Common Genetic Mutations

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

- *MYD88 L265P*—In WM, the most common mutation occurs in the *MYD88 L265P* gene. Over 90 percent of patients carry this mutation in their WM cells. A mutation in *MYD88 L265P* turns on (stimulates) growth and survival pathways for the cancer, including Bruton tyrosine kinase (BTK) (see page 7); BTK is the target of **ibrutinib (Imbruvica®).**
- *CXCR4*—About 30 to 40 percent of WM patients carry a mutation called *CXCR4*, a gene that turns on (stimulates) growth and survival pathways for the cancer. More than 40 types of *CXCR4* mutations can be found in patients with WM. Patients with "nonsense mutations" of *CXCR4* can have higher serum IgM levels and bone marrow involvement. ("Nonsense mutations" are mutations that cause part of the protein

to be cut off, creating a shorter CXCR4 protein that lacks the segment that allows it to shut off.) WM cells with mutations of the *CXCR4* gene show resistance to **ibrutinib.**

The impact of *MYD88* and *CXCR4* mutations on treatment outcome has been studied in several clinical trials. Patients who have the *MYD88* mutation but do not have the *CXCR4* mutations have the best outcomes with ibrutinib therapy. People with both *MYD88* and *CXCR4* mutations may experience a delay of 4 to 5 months in obtaining a major response to treatment with **ibrutinib.**

- *ARID1A*—This is the third most common mutation in WM patients, occurring in 17 percent of all cases. Patients who have mutations of both the *ARID1A* and *MYD88 L265P* genes, compared with patients who do not have the *ARID1A* gene mutation, have greater bone marrow disease involvement and lower hemoglobin values and platelet counts.

New treatment approaches for WM under investigation include drugs targeting these genes and mutations.

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, a patient's doctor will order blood, bone marrow and other tests to determine:

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

Tests doctors use 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.

The amounts of all five types of immunoglobulins (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 cause the blood to thicken, leading to abnormal blood flow. Most patients with WM have an elevated serum viscosity level, higher than 1.8 cP (centipoise). Typically, patients become symptomatic at levels over 4.0 cP. For some patients, even a 3.0 cP viscosity level may cause changes in the retina of the eye(s) and bleeding that requires medical treatment.

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

- **Hemoglobin / Hematocrit**—Anemia (a decrease in red blood cells) is present in most patients at diagnosis of WM. 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 (a condition called "leukopenia") may be present at diagnosis. However, the number of lymphocytes (a type of white cell) is usually increased.
- **Beta-2 Microglobulin (B2M)**—Many patients have an elevated serum B2M level at diagnosis. This protein is found on the surface of many cells including lymphocytes; the level is a marker of how much cancer is in the body, called "tumor burden." The B2M level is also elevated in patients who have abnormal kidney function.
- **Lactate Dehydrogenase (LD or LDH)**—LDH is an enzyme found in the blood and other body tissues. An increased amount in the blood may be a sign of tissue damage and some types of cancers. Some WM patients have an elevated serum LDH level.
- **Immunoglobulins**—There may be a decrease in the number of uninvolved immunoglobulins (IgG, IgA, IgD and IgE) as well as an increase of IgM.

Bone Marrow Aspiration and Biopsy. The symptoms of WM can also be caused by noncancerous problems such as infections, or by other types of cancer, so a diagnosis of WM can only be confirmed by performing bone marrow tests. During a bone marrow aspiration and biopsy, a small amount of fluid (aspiration) and a small portion of bone (for biopsy) from the bone marrow are removed from the patient. These are examined under a microscope by a pathologist to see if lymphoma cells are present, to quantify the amount of the lymphoma, and for special testing such as cytogenetics or molecular testing. These marrow tests can be done at the doctor's office or at the hospital, and the patient can return home soon after the procedure is completed.

Lymph Node Biopsy. Rarely, a lymph node biopsy, in which tissue is removed from a lymph node, may be used to diagnose WM, although lymph node biopsy 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 specialized light. The test is often used to look at markers on the surface of a large number of cells or inside the lymphocytes. Flow cytometry has become increasingly important in helping doctors 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.
- **Urine Tests**—IgM can accumulate in both urine and blood. The patient's doctor may order:
  - An analysis of urine collected over 24 hours to detect elevated levels of protein in the urine.
  - A urine protein electrophoresis (UPEP) test to detect and identify excessive production of immunoglobulins in a urine sample.
  - A urine immunofixation electrophoresis (UIFE) test to identify the type of M protein being produced by myeloma cells.
- **Liver Function Tests**—Patients with WM, especially those affected by cryoglobulinemia, may have an underlying hepatitis C infection. In addition, if the patient has received **rituximab (Rituxan®),** it 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.
- **Eye Exam**—Hyperviscosity caused by WM can create eyesight problems such as double or blurry vision. If the level of IgM in the blood is 3.0 g/dL or higher, or if there are other symptoms of hyperviscosity, a retinal eye exam may be recommended to check for any abnormalities or bleeding.

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 to 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 myeloma, a similar plasma cell cancer. In contrast to myeloma, lytic bone lesions (holes in the bones where the tissue has been destroyed) are not typically seen in WM. A CT scan is usually obtained prior to treatment to look for enlarged lymph nodes (called "adenopathy"), and can be used for comparison later.

See the free LLS book *Understanding Lab and Imaging Tests* for more information.

Treatment Planning

Every patient's medical situation is different and should be evaluated individually by a hematologist-oncologist. The specialists who treat non-Hodgkin lymphoma (NHL) often treat WM because WM is a slow-growing subtype of NHL. Before patients begin treatment, they will discuss treatment options with the doctor. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. Patients can take an active role in this decision by considering all treatment options.

Treatment plans for 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
- The potential need for a stem cell transplant in the future
- The patient's gene mutation profile

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

Treatment

Several treatment options are available to prevent or control symptoms of WM and improve the quality of life of patients. Not all newly diagnosed WM patients need immediate treatment. Of all WM patients who seek treatment, 25 percent 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 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 treatment of asymptomatic WM patients provides any greater survival benefit than waiting for symptoms to appear and then starting treatment. Smoldering (asymptomatic, slow-growing) WM is associated with a 12 percent per year rate of progression to symptomatic WM, amyloidosis (see page 3) or lymphoma for the first five years, followed by 2 percent progression to symptomatic WM per year thereafter.

See the free LLS booklet *Watch and Wait* for more information.

According to The National Comprehensive Cancer Network® (NCCN) WM guidelines, treatment should be started when patients have the following symptoms and/or certain laboratory test results indicate that prompt treatment is required:

- Low blood cell counts (hemoglobin 10g/dL or less; platelets <100 x 10^9/L)
- Symptomatic enlargement of lymph nodes and organs, such as the liver and the spleen
- Severe peripheral neuropathy due to the IgM protein
- Systemic amyloidosis with organ damage related to the IgM protein
- Hyperviscosity syndrome
- Symptomatic cryoglobulinemia
- Symptomatic cold agglutinin disease
- Renal dysfunction
- Central nervous system (CNS) involvement
- Recurrent fever, night sweats, weight loss, and/or fatigue

Drug Therapy. Several different therapies are effective against WM, but no single or combination standard treatment 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 involvement in clinical trials.

Bruton Tyrosine Kinase (BTK) Inhibitor—This class of drugs targets BTK, a protein activated by the mutation of the *MYD88 L265P gene*. The BTK protein sends signals that help cancerous B cells stay alive and multiply. **Ibrutinib (Imbruvica®)** is FDA-approved for the treatment of symptomatic WM patients. Ibrutinib is taken by mouth and is also approved in combination with **rituximab (Rituxan®)** for the treatment of adult patients with WM. Ibrutinib works more effectively in people with the *MYD88* mutation. People with *CXCR4* mutations show lower response rates and delayed responses to ibrutinib.

Ibrutinib must be taken continuously to control WM. Stopping ibrutinib suddenly can cause WM to return and to progress quickly. Side effects associated with stopping ibrutinib include fever, body aches, night sweats, headaches, chills and an increase in blood IgM concentration. These symptoms and side effects improve rapidly after restarting ibrutinib.

Monoclonal Antibodies—Biological therapies are targeted therapies directed at specific proteins.

- **Rituximab (Rituxan®)** targets CD20, a protein found on the surface of B cells, including WM cells. Rituximab is approved by the FDA for use, either alone or in combination with other medications (including ibrutinib), to treat certain types of non-Hodgkin lymphoma (NHL). Rituximab is also considered an effective choice for treating patients who have IgM-related neuropathies. Rituximab is administered intravenously (IV) or subcutaneously. Medication may be given before administration to prevent an allergic reaction.

  Rituximab, when used as a single agent or in a combination, 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 by 25 percent or more, which can produce hyperviscosity, requiring urgent plasmapheresis therapy. Some WM patients may need plasmapheresis before starting treatment with rituximab to reduce the risk of symptomatic hyperviscosity.

- **Ofatumumab (Arzerra®)** targets the CD20 protein and is administered intravenously (IV). Ofatumumab is recommended as an alternative for patients who are intolerant of rituximab. Ofatumumab can also cause an IgM flare so patients need to be monitored for symptoms of hyperviscosity. If the IgM levels stay high while taking this medication, plasmapheresis may be needed to counteract the effects of IgM flare and prevent or reduce hyperviscosity. Ofatumumab is being studied in clinical trials.

Alkylating Agents—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—except for cyclophosphamide—because these drugs are likely to decrease the production of functioning red blood cells, white blood cells and platelets. In addition, alkylating agents may increase the incidence of disease transformation and the development of myelodysplastic syndromes (in which the bone marrow does not effectively produce blood cells), and also increase the incidence of acute myeloid leukemia (AML) in patients with WM.

- **Chlorambucil (Leukeran®)** is taken by mouth
- **Cyclophosphamide (Cytoxan®)** can be taken by mouth or intravenously (IV)
- **Bendamustine hydrochloride (Bendeka®),** given IV, is indicated for treatment of patients with indolent (slow-growing) B-cell NHL that has progressed either during or within 6 months of treatment with rituximab (Rituxan®) or a rituximab-containing regimen (WM is a subtype of NHL).

Antimetabolites or Nucleoside Analogues—This category of drugs includes **pentostatin (Nipent®), fludarabine (Fludara®)** and **cladribine (Leustatin®).** These medications are administered by IV injection or infusion. Pentostatin has been found to be effective for patients who are candidates for high-dose chemotherapy with autologous stem cell transplantation. These patients should not be treated with fludarabine or cladribine until an adequate number of stem cells has been collected. In addition, one study found that nucleoside analogue-based combinations may be associated with an increased risk of disease transformation or myelodysplastic syndromes; as a result, these agents are rarely used now.

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** can be administered by mouth or intravenously (IV) and **prednisone** is taken by mouth. Both medications can be useful in the treatment of WM, especially in patients who have extremely low blood cell counts but who are not candidates for treatment with drugs that affect normal blood cell production. Corticosteroids also help decrease the side effects of nausea and vomiting 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, taken by mouth, that have been shown to be effective in WM when combined with rituximab. Immunomodulators are not favored due to toxicity.

mTOR Inhibitors—These drugs inhibit the mTOR pathway that promotes the growth and survival of cells. **Everolimus (Affinitor®)** is a drug taken by mouth and is FDA-approved for treatment of other non-blood cancers; it has also shown responses in some patients with previously treated WM.

Proteasome Inhibitors—These drugs block the action of proteasomes (cellular complexes that break down proteins).

- **Bortezomib (Velcade®),** administered intravenously (IV) or by subcutaneous injection, 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, peripheral neuropathy is a major concern, and in people who already have neuropathy, bortezomib can make it worse.
- **Carfilzomib (Kyprolis®),** which has a low risk for neuropathy, has shown to be effective in treating WM patients when used in combination with rituximab and dexamethasone. Carfilzomib is administered intravenously (IV) and is approved by the FDA for the treatment of previously treated myeloma patients. Bortezomib and carfilzomib can reactivate the herpes zoster (shingles) virus. To reduce this risk, patients may need to receive the shingles vaccine and take an antiviral medication called acyclovir. Carfilzomib may also cause heart and lung damage, especially in elderly patients.
- **Ixazomib (Ninlaro®),** taken by mouth, is approved by the FDA for treating myeloma patients who have received prior therapy. It has shown promising results in some studies and is currently under investigation for WM treatment.

Combination Therapies. Based on the positive outcomes reported in recent studies, the use of combination therapy (treatment with two or more drugs) is increasingly recommended for both previously untreated patients and for those whose disease has relapsed.

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

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

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

Patients should discuss the benefits and risks of any treatment with their doctors. Alkylating agents and antimetabolite agents have been associated with certain long-term or late effects, such as transformation to a more aggressive lymphoma and/or development of a myelodysplastic syndrome or acute myeloid leukemia

See the free LLS booklet *Long-Term and Late Effects of Treatment* in Adults for more information.

Response to Treatment and Disease Monitoring. After initial treatment is over, the doctor will order tests to check treatment results. Tests may include a physical exam, plus blood and imaging tests, such as CT scans of the chest and abdomen/pelvis.

Response to treatment is based, in part, on the level of the IgM in the blood after treatment is finished. However, it is not the only factor used to determine if treatment is successful. See **Table 1** on this page for a description of the different response categories for WM treatment. According to the recommendations from the National Comprehensive Cancer Network (NCCN) panel for WM in its NCCN Guidelines, if the first-line treatment is successful, the IgM level should be measured:

- Every 3 months for 2 years
- Then every 4 to 6 months for an additional 3 years
- Then every 6 to 12 months thereafter

Table 1. Types of Response After WM Treatment

Response Type	Description	Indications
Complete response	• Normal range IgM • No sign of cancer in the bone marrow • Lymph nodes and organs return to normal size • No signs or symptoms of WM	• Watch and wait • Monitor IgM • Maintenance therapy with rituximab (Rituxan®)–optional
Very good partial response	• A very small amount of IgM remains • Lymph nodes and/or organs have reduced in size • No new signs or symptoms of WM	**If no symptoms:** • Watch and wait • Monitor IgM • Maintenance therapy with rituximab (Rituxan®)–optional **If symptoms:** • Switch to a different treatment regimen
Partial response	• IgM level reduced by more than half • Lymph nodes or organs have reduced in size • No new signs or symptoms of WM	
Minor response	• IgM level reduced by less than half • No new signs or symptoms of WM	
Stable disease	• IgM level stayed stable – no increase or decrease • Signs and symptoms of WM have stayed the same	Switch to a different treatment regimen
Pro-gressive disease	• IgM level went up 25 percent or more OR • Signs and symptoms of WM have gotten worse	

Table 1. Abbreviation: IgM = immunoglobulin M (monoclonal IgM protein). Adapted from National Comprehensive Cancer Network. *NCCN Guidelines for Patients* 2020. (see References.)

IgM Fluctuations. Some medications for WM can cause IgM levels to fluctuate, making it difficult to accurately measure the response to treatment. For instance, rituximab (Rituxan®) can cause IgM levels to go up for weeks or months. Other medications may take longer than others to lower IgM levels.

If the IgM level increases, it does not necessarily mean that treatment needs to be restarted. Besides monitoring IgM levels, the treatment team will check to see whether there are any new or worsening symptoms. More treatment is only needed if symptoms return.

Stem Cell Transplantation. This option is for patients whose disease is relapsed and/or refractory, 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 most often used to treat WM patients. This procedure uses the patient's own stem cells to restore blood cell production after intensive chemotherapy. Based on data from numerous 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 differs from autologous because it uses donor stem cells, rather than the patient's own stem cells. Allogeneic transplant has more risks and side effects than autologous. According to the recommendations from the National Comprehensive Cancer Network (NCCN) panel for WM in its NCCN Guidelines, this type of transplant should be considered only as part of a clinical trial.

Talk to your doctor about whether stem cell transplantation is a treatment option to consider. **See the free LLS book *Blood and Marrow Stem Cell Transplantation* for more information.**

Side Effects of Treatment

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

Treatment side effects may include fatigue, nausea, vomiting, mouth sores, fever, chills, dizziness, shortness of breath, confusion, constipation, temporary hair loss, increased risk of infection and other side effects.

Everyone reacts differently to treatment. Side effects depend on the type of medication given, the dose, and the length of treatment. Managing side effects is important. If there are any concerns about side effects, talk to your doctor to get help. Most side effects are temporary and resolve when treatment is completed. **See the free LLS series titled Side Effects Management by visiting www.LLS.org/booklets and filtering by Side Effect Management.**

Treatment for Relapsed and/or Refractory Patients

Because WM is not curable, and the disease grows slowly, virtually all patients experience relapse (return of the cancer) and/or refractory WM (the cancer resists treatment) after initial therapy, and 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 2021, administering the same first-line treatment again is acceptable for relapsed disease if a patient achieved a response that lasted at least 24 months or longer. 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. In patients who are candidates for autologous stem cell transplantation, it is important to avoid using stem cell-damaging agents such as alkylators or antimetabolites. Therapies that are not toxic to stem cells must be offered, especially if stem cells have not been previously obtained.

See the section *Drug Therapy* on page 7 and *Combination Therapies* on page 9 for some of the treatments available for these patients.

In several studies, ibrutinib has been found to be an effective treatment option for patients whose disease did not respond to rituximab therapy. Autologous stem cell transplantation is an option for the treatment of relapsed WM in selected patients.

Disease Transformation

Rarely, WM patients have disease that transforms to diffuse large B-cell lymphoma (DLBCL, also 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), 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 disease transformation.

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

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

Treatments Under Investigation

Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians and researchers as well as patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time treatment is discussed with the doctor. Patient participation in past clinical trials has resulted in the therapies we have today. Patients interested in participating in a clinical trial for WM are encouraged to talk with their hematologist-oncologist about whether a clinical trial would be appropriate for them.

When patients speak to their hematologist-oncologists to discuss a clinical trial as a potential treatment option, it may be helpful to:

- Have a list of questions to ask concerning risks versus benefits (visit www.LLS.org/WhatToAsk for lists of suggested questions)
- Ask a family member, friend, or another advocate to come to appointments—both for support and to take notes

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. **Visit www.LLS.org/CTSC for more information. Also, see the free LLS book *Understanding Clinical Trials for Blood Cancers* for more information.**

Examples of the types of therapy currently under study in clinical trials are:

- **Monoclonal Antibodies**—A type of targeted therapy directed at specific proteins.
  - Ulocuplumab targets *CXCR4.* It is being studied in combination with ibrutinib for symptomatic WM patients who have the *CXCR4* gene mutation.
  - Various monoclonal antibodies, to be used in combination with other agents such as ibrutinib (Imbruvica®), are being evaluated in trials.
- **BTK Inhibitors**—Drugs that target BTK, a protein activated by the mutation of the *MYD88 L265P* gene. Tirabrutinib hydrochloride (Velexbru®) has received supplemental approval in Japan for use in WM and LPL patients. It is being studied in US trials as a single agent for treating WM patients who have received prior therapy. Acalabrutinib (Calquence®) and zanubrutinib (Brukinsa®) are other BTK inhibitors being studied in combination with many different agents, to treat relapsed and refractory WM patients.
- **Proteasome Inhibitors**—Drugs that block the action of proteasomes (cellular complexes that break down proteins). Ixazomib (Ninlaro®), taken by mouth, has shown activity in relapsed/ refractory myeloma patients without producing significant neuropathy, and it is being studied in WM. The combination of ixazomib, dexamethasone and rituximab (Rituxan®) called IDR is currently under investigation in symptomatic untreated WM patients. Ixazomib is also being studied in combination with ibrutinib (Imbruvica®) for relapsed and refractory WM.
- **PI3K Inhibitors**—Drugs that block an enzyme which transmits signals in cells and that help control cell growth. Idelalisib (Zydelig®) is currently under study for treatment as a single agent and in combination with obinutuzumab (Gazyva®) for the treatment of patients with either relapsed and/or refractory WM.
- **BCL-2 Inhibitors**—Drugs that target BCL-2, a protein that helps control whether a cell lives or dies. Venetoclax (Venclexta®) 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.
- ***CXCR4* Antagonists**—Drugs that target the *CXCR4* mutations present in some WM cells. Mavorixafor, taken by mouth, is currently under study when used in combination with ibrutinib (Imbruvica®) for treating relapsed WM.

- **Chimeric Antigen Receptor (CAR) T-cell Therapy**—Treatment that uses a patient's T cells and modifies them in the laboratory so they will attack cancer cells. This therapy has shown promising results in several B-cell malignancies. CAR T-cell therapy that targets CD20 has shown preclinical activity against WM cells, and several trials are being conducted for patients who have relapsed or who have not responded to therapy. **See the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy* for more information.**

Treatment Outcomes

The prognosis for patients with WM depends on several 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.

The 2019 International Prognostic Scoring System for Waldenström Macroglobulinemia (IPSS-WM) is internationally accepted as a predictive model for long-term outcomes in newly diagnosed patients. The IPSS-WM, see **Table 2**, uses several factors to estimate survival. The five criteria are not weighted equally. Age has the greatest impact on prognosis. According to the IPSS-WM, patients older than 65 years cannot be in a low-risk category. Also, although IgM protein levels are important for making a prognosis, they do not enter into the staging system until the IgM exceeds 7,000 mg/dL. Except for age, each of the factors that help estimate survival is worth one point. The points are added to calculate a score. The score assigns WM patients into one of three risk groups.

The risk groups of the IPSS-WM 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. According to the IPSS-WM, the estimated median survival for WM is, in the higher-risk category, approximately 4 years; it is 8 years in the intermediate-risk category; and 12 years in the lower-risk category. The years refer to the time after the start of treatment.

Table 2. International Prognostic Scoring System for WM (IPSS-WM)

Factors Associated With Prognosis
• 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 • Beta-2 microglobulin (B2M) greater than 3 milligrams per liter (mg/L) • Serum monoclonal protein (IgM) concentration greater than 7,000 milligrams per deciliter (mg/dL) Except for age, each of these factors is worth a single point. The points are added to make a score.
Risk Groups
Based on their score, WM patients fall into one of the following three risk groups: • **Low risk**—includes patients younger than 65 years who have no more than 1 point • **Intermediate risk**—includes patients who are at least 65 years of age and/or have 2 points • **High risk**—includes patients who have at least 3 points

Table 2. Adapted from Gertz M. *American Journal of Hematology.* 2021. (See References)

Keep in mind that the most recent survival statistics for WM may almost certainly underestimate survival, because these data do not fully 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.

Acknowledgement

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Glossary

Antigen. Any substance that causes an immune response in the body. For example, an antigen can be bacteria, a virus, or a toxin.

Beta-2 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 B2M 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 liquid 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 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 (thickness) of a fluid. The viscosity of blood serum may be elevated in Waldenström macroglobulinemia. Normal blood serum viscosity is 1.4 to 1.8 cP. Water viscosity is 1.0 cP. See Viscosity.

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

Lymphoplasmacytic cells. Cells that have characteristics of both lymphocytes and plasma cells; this is the usual description of WM cells.

Plasmapheresis. The process of separating certain cells from the plasma in the blood using a machine. After the separation, only the cells, not the plasma, are returned to the patient’s body. Plasmapheresis can be used to remove excess antibodies from the blood. In WM treatment, it removes excess IgM monoclonal antibody.

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

Questions to Ask the Doctor

It may be helpful to prepare some questions to ask the treatment team at the 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. After initial treatment ends, how will I be monitored? How often will I need to see my treatment team? What type of tests will be required?
10. 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 website at www.LLS.org/chapterfind or contact:

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

Contact 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 that are available. Use this information to learn more, to ask questions, and to make the most of the healthcare team.

Consult with an Information Specialist. Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date disease, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information.

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm ET)
- Email and Live Chat: www.LLS.org/InformationSpecialists

Clinical Trials Support Center (CTSC). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

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.

Free Mobile Apps

- LLS Coloring For Kids™ – Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.
- LLS Health Manager™ – Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.

Financial Assistance. LLS offers financial support including insurance premium and medication co-pay assistance, as well as travel and other needs, to eligible individuals with blood cancer. For more information, please:

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

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. Patients can share their 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 provided by a registered dietitian who has experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or 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. *The Bloodline* with LLS is here to remind patients that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects,

doctor-patient communication and other important survivorship topics. 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), local support groups, and other great resources. For more information about these programs or to contact the 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 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 a patient's mood does not improve over time—for example, if they 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

Other Resources

International Waldenström's Macroglobulinemia Foundation (IWMF)
www.iwmf.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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