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Waldenström Macroglobulinemia Facts

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

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Highlights

- Waldenström macroglobulinemia (WM) is an indolent (slow-growing) subtype of non-Hodgkin lymphoma that affects small lymphocytes (white blood cells). WM is rare, with an incidence rate of about 6 cases per million people per year in the United States.
- WM probably begins with one or more acquired changes (mutations) to the DNA of a single B lymphocyte. The cancer causes the overproduction of a monoclonal protein called "immunoglobulin M" (IgM), which can result in a thickening of the blood known as "hyperviscosity." This monoclonal IgM protein may lead to many symptoms, including fatigue, unexplained weight loss, enlarged lymph nodes or spleen, weakness and unexplained bleeding.
- 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.
- Over 30 percent of WM patients have a mutation in the *CXCR4* gene, which promotes the WM cells to return to the bone marrow.
- The exact cause of WM is unknown, although it is believed that genetics may play a role in disease development. Many patients with WM have a family member with WM or a closely related lymphoma, chronic lymphocytic leukemia (CLL), or multiple myeloma. The cancer occurs most commonly in people over age 60 years, is more frequently found in men than women, and is found in more whites than blacks. WM is also found in a high frequency of individuals of Ashkenazi Jewish descent.
- 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 "watchful waiting." 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 biological agents (treatment that stimulates the immune system to fight cancer), signaling inhibitors (drugs that block progrowth and survival signals), and chemotherapy have provided promising results. The safety and effectiveness of potential new therapies for WM patients, including the use of new drugs and drug combinations, are being researched in clinical trials. Recently ibrutinib (Imbruvica®) became the first ever drug approved for the treatment of symptomatic patients with WM.

Introduction

"Lymphoma" is the name for many different types of cancer that arise in the 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 attack cancer cells and viruses.

Lymphocytes go through several stages of development. The final stage of B-lymphocyte development is a mature, immunoglobulin-producing plasma cell. Lymphoma may arise in any of these types of lymphocytes. 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 as a subtype of NHL. WM 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, please see the free The Leukemia & Lymphoma Society (LLS) publication *Non-Hodgkin Lymphoma*.

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About Waldenström Macroglobulinemia

WM, also called "lymphoplasmacytic lymphoma (LPL)," is a rare, indolent (slow-growing) blood cancer that is treatable with available therapies but is not curable. Large amounts of an abnormal monoclonal protein called "immunoglobulin M" (IgM or "macroglobulin") are produced. Immunoglobulins, sometimes called "gamma globulins," are proteins that help the body fight infection. The major classes of immunoglobulins (Ig) are IgG, IgA, IgM, IgD and IgE. Low Ig levels may cause repeated infections in some patients.

WM probably begins with one or more changes (mutations) to the DNA of a B lymphocyte (B cell), which then multiplies uncontrollably. These mutations occur during the cell's maturation stage so that it continues to reproduce more malignant (cancer) cells. The result is the overproduction of IgM antibody by the malignant B cells.

The abnormal WM cells grow mainly in the bone marrow. As a result, the healthy red blood cells, which carry oxygen; the white blood cells, which fight infection; and the platelets, which help with blood clotting, are crowded out and normal blood production is disrupted. Low levels of red blood cells can lead to anemia, making people feel tired and weak; low numbers of white blood cells make it hard for the body to fight infection; and a low platelet count can result in increased bleeding and bruising.

At the time of diagnosis, WM most commonly involves the blood and bone marrow; however, WM can start almost anywhere and spread to almost any part of the body, affecting the lymph nodes, liver or spleen as well as the stomach, intestines or lungs. WM rarely involves the skin or thyroid gland.

Lymphoplasmacytic Lymphoma (LPL)

LPL and WM are closely related, slow-growing types of lymphoma that originate in a B-lymphocyte precursor.

In LPL, the lymph nodes are typically more involved than in WM. Both disorders show malignant lymphoplasmacytic cells. LPL is usually diagnosed by lymph node biopsy and often does not have a measurable level of serum IgM monoclonal protein; if the protein is present, it is present in low quantities. WM is diagnosed by marrow examination, and an IgM protein is almost always present and usually at higher levels.

Incidence, Causes and Risk Factors

WM is rare, with an incidence rate of about 6 cases per million people per year in the United States. About 1,000 to 1,500 people are diagnosed with WM each year in the United States. WM results from the accumulation, mainly in the bone marrow, of clonal lymphocytes, lymphoplasmacytic cells and plasma cells that secrete a monoclonal IgM protein. Most cases of LPL are WM, with less than 5 percent of cases made up of IgA-secreting, IgG-secreting or non-secreting LPL. WM accounts for approximately 1 to 2 percent of all hematologic (blood) cancers.

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. Currently, there is no known way to prevent this cancer, nor are the exact causes known.

The following factors may raise a person's risk of developing WM, although 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 63 years.
- Gender—Men are more likely than women to develop the cancer.
- Race—WM incidence is highest among Caucasians and is rare in other population groups.
- Monoclonal gammopathy of undetermined significance (MGUS)—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 publications *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 degree of familial clustering of WM or another type of lymphoma in about 20 percent of the cases examined.
- 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 the *We're Here to Help* section on page 9.

Additional risk factors being studied:

- Scientists have recently made progress in the understanding of how certain changes in DNA 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 IgM, a key reason for many symptoms of WM.
- In WM, the most common mutation occurs in *MYD88* gene. Over 90 percent of patients carry this mutation in the WM cells. MYD88 L265P mutation turns on growth and survival pathways including Bruton tyrosine kinase (BTK), the target of ibrutinib.

- About a third of WM patients also carry a mutation in the gene *CXCR4* that turns on growth and survival pathways. Over thirty different types on mutations occur in WM patients, and the particular type of mutation of the *CXCR4* gene can impact disease presentation at diagnosis. 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 CXCR4 protein to be cut off, thereby a shorter protein exists which lacks the segment that allows it to be shut off.) WM cells with mutations of the *CXCR4* gene also show resistance to ibrutinib.

Symptoms and Complications

At least 25 percent of people with 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 exam.

Some patients are symptomatic (have signs and symptoms). The signs and symptoms may be similar to those of people with other types of NHL. WM symptoms are mostly associated with the effects of

- WM cells in the marrow
- Monoclonal IgM in the blood.

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

- Fever
- Night sweats
- Weight loss
- Enlarged lymph nodes
- Enlarged spleen and liver
- Peripheral neuropathy (numbness or a painful "pins and needles" sensation in the feet, legs and hands).

Slow and progressive reduction in kidney function may occur with WM. However, acute kidney failure is rare.

The following are several distinguishing features of WM found in some but not all patients.

Hyperviscosity syndrome is the large accumulation of IgM proteins in the blood. These proteins thicken the blood and impair blood flow. When the blood gets too thick, it has trouble traveling through the smallest blood vessels. This causes poor circulation to the brain, which can lead to problems similar to a stroke, including slurred speech and weakness on one side of the body. It can 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. Symptoms of hyperviscosity syndrome typically do not develop unless the patient's serum viscosity is especially elevated. Therefore, patients need to be tested periodically for evidence of hyperviscosity syndrome progression.

Problems associated with hyperviscosity syndrome include

- Clotting and bleeding abnormalities that may result from the interaction of IgM with coagulation factors in the blood
- Bleeding that may result when monoclonal IgM coats the platelets, interfering with their function.

Some of the most common symptoms associated with hyperviscosity syndrome include

- Abnormal bleeding, especially from the nose, gums and the lining of the gastrointestinal tract
- Fatigue
- Headache
- Infections
- Vertigo
- Visual impairment (blurred vision)
- Changes in mental status (ranging from impaired thinking to dementia)
- Shortness of breath.

Symptomatic hyperviscosity syndrome is considered a medical emergency and requires treatment with plasmapheresis, which rapidly reduces the concentration of IgM proteins in the blood. Appropriate treatment for WM may also be required to reduce the number of cells making these abnormal proteins. If the syndrome is not treated, the proteins will accumulate at high levels again and the symptoms will recur.

Cold agglutinin disease is when monoclonal IgM destroys red cells when a patient is in an environment with a low temperature. About 10 percent of WM patients have this acquired hemolytic anemia.

Cryoglobulinemia is when monoclonal IgM in the blood becomes thick and gel-like when exposed to cold temperatures, causing circulatory problems in areas exposed directly to the cold, such as fingertips, ears and nose; joint pain; kidney problems; skin lesions; and purpura (purplish or red-brown discoloration of the skin). Up to 20 percent of patients with WM may develop this condition although fewer than 5 percent of patients have symptoms.

Raynaud's syndrome (also called "Raynaud phenomenon") is associated with both cold agglutinin disease and cryoglobulinemia. This syndrome is characterized by signs of poor red 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 are supportive therapy options that may be used to help manage WM:

Plasmapheresis is used when IgM levels get very high and the blood becomes very thick. Plasmapheresis reduces the viscosity (thickness) of the blood using a machine that separates the plasma (the liquid part of the blood) that contains the abnormal protein from the blood cells. The cells are returned to the person undergoing treatment, 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. Impaired kidney function can generally be reversed and hyperviscosity symptoms can be alleviated by removal of the abnormal protein through plasmapheresis. 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 to treat anemia may benefit patients with WM. However, patients may also have reduced capillary blood flow following transfusions because of hyperviscosity. Therefore, patients should not be transfused unless treatment for hyperviscosity has been implemented first to reduce 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.

Diagnosis

A diagnosis of WM may be suspected if blood test results show low blood counts or unusually high protein levels. To determine the presence and amount of IgM monoclonal proteins, an additional test called "serum protein electrophoresis" (SPEP) will be performed. SPEP 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 serum. This test is typically ordered to detect and identify excessive production of specific proteins (immunoglobulins). All five types of immunoglobulin (IgG, IgA, IgM, IgE, or IgD) are measured by this test. An excessive production of a monoclonal immunoglobulin may be shown on lab results as a spike on a graph. Generally, IgM protein levels greater than 3 grams per deciliter (g/dL) are an indication of WM.

Other typical findings from blood tests may include

- Red blood cells
  - Anemia (low levels of red 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, although 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 cell count (leukopenia) may be present at diagnosis. However, the number of lymphocytes (a type of white cell) is usually increased.
- $Beta_2$-microglobulin (B_2M). Many patients have elevated serum B_2M at diagnosis. B_2M is a protein found on the surface of many cells including lymphocytes and is a marker of tumor burden. Its level is also increased in patients with abnormal kidney function.
- Immunoglobulins. There may be a decrease in the number of uninvolved immunoglobulins (IgG, IgA, IgD and IgE).

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 a bone marrow aspiration and bone marrow biopsy, in which a small amount of bone and marrow are removed and examined under a microscope by a pathologist (a doctor specializing in evaluating cells, tissues and organs to diagnose disease) to see if lymphoma cells are present. A bone marrow biopsy can be done at the doctor's office or at the hospital, and the patient can usually go home soon after the procedure. 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 other types of lymphoma.

Other laboratory tests used in the diagnosis of WM include

- 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 FMC7. CD stands for cluster of differentiation, which 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.
- An analysis of urine collected over 24 hours—This test is used to detect elevated levels of protein in the urine.

Imaging Tests

Imaging tests may include computed tomography (CT or CAT) scan, which may 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 a similar plasma cell cancer called "myeloma." In contrast to myeloma, in WM no lytic bone lesions are seen. Magnetic resonance imaging (MRI) and/or positron emission tomography (PET) may be useful in determining where the lymphoma is located throughout the body.

For additional information about laboratory and imaging tests, please see the free LLS publication *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 NHL. It is important for you and members of your medical team to discuss all treatment options, including treatments being studied in clinical trials.

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 and eligibility for stem cell transplantation (typically, a stem cell transplant is reserved for patients younger than 70 years)
- The patient's overall health and quality of life
- 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 publication *Choosing a Blood Cancer Specialist or Treatment Center.*

Treatment

There are several treatment options available to prevent or control symptoms of 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 50 percent of those patients will not require therapy within three years.

Asymptomatic patients are medically observed in an approach called "watchful waiting" or "watch and wait." Active treatment for these patients only begins if symptoms develop. In the past, increases in IgM levels were used as the benchmark to begin treatment. However, it was determined that the IgM level alone does not accurately reflect the tumor burden or prognosis in WM. To date, there is no evidence suggesting that treatment of asymptomatic WM patients provides a greater survival benefit than treatment of patients who begin therapy once symptoms appear.

To identify symptomatic patients who need immediate therapy, the Second International Workshop on Waldenström's Macroglobulinemia has determined that starting treatment is appropriate when patients have the following symptoms:

- Recurrent fever
- Night sweats
- Fatigue due to anemia with a hemoglobin value of 10 grams per deciliter (g/dL) or lower; or a platelet count lower than 100 grams per liter (g/L) due to marrow infiltration; or fatigue due to weight loss
- Severe peripheral neuropathy due to the IgM protein
- Impaired kidney function due to the abnormal IgM protein
- Systemic amyloidosis with organ damage related to the IgM protein.

The following complications may also be indications for therapy:

- Hyperviscosity syndrome
- Symptomatic cryoglobulinemia
- Symptomatic cold agglutinin disease
- Symptomatic adenopathy (enlargement of the lymph nodes) and/or hepatosplenomegaly (simultaneous enlargement of both the liver and the spleen).

There are a number of therapies that are effective against WM, but few studies have compared different treatments to determine if one is better than another. Currently, 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.

Treatment for previously untreated WM patients includes alkylating and other chemotherapy agents, purine nucleoside

analogues, monoclonal antibodies, corticosteroids, immunomodulatory agents and proteasome inhibitors. The Bruton tyrosine kinase inhibitor, ibrutinib (Imbruvica®) was recently approved by the US FDA for the treatment of patients with symptomatic WM.

Specific treatments include

Drug Therapy

- **Alkylating agents**—This class of chemotherapy drugs includes chlorambucil (Leukeran®), cyclophosphamide (Cytoxan®), melphalan (Alkeran®) and bendamustine (Treanda®). Treanda is FDA approved to treat CLL and indolent non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab (Rituxan®) or a rituximab-containing regimen and this drug is active in WM. A trial comparing Treanda with Rituxan against R-CHOP (rituximab [Rituxan] plus cyclophosphamide, doxorubicin [hydroxydoxorubicin], Oncovin® [vincristine], prednisone) showed superior progression-free survival for the WM patients being treated with Treanda and Rituxan. These drugs directly damage the DNA 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 cells, white cells and platelets.

- **Biological therapy (monoclonal antibodies)**—Biological therapies are a type of targeted therapy directed at specific proteins. Rituximab (Rituxan) targets a protein called "CD20" that is found on the surface of B cells, including WM cells; it is FDA approved for use alone or in combination with other medications to treat certain types of NHL. Rituxan is also considered a very effective choice for treating patients with IgM-related neuropathies. Alemtuzumab (Campath®) targets a different protein, called "CD52," on the membrane of lymphoma cells. Campath is FDA approved to treat CLL, but it has also been found to help some patients with WM and is currently being studied in clinical trials (see *Treatments Undergoing Investigation* on page 8).

- **Bruton tyrosine kinase (BTK) inhibitor**—This class of drugs targets BTK which is activated by the MYD88 L265P mutation. The FDA approved ibrutinib (Imbruvica®), taken by mouth, for the treatment of symptomatic WM patients. Mutations in the *CXCR4* gene may impact response to ibrutinib.

- **Corticosteroids**—Steroids such as dexamethasone and prednisone as well as other glucocorticoids can be useful in the treatment of WM, especially in patients with severely low blood cell counts who are not candidates for treatments with drugs that affect normal blood cell production. Corticosteroids also help decrease the nausea and vomiting that other chemotherapy agents may cause.

- **Immunomodulating agents**—Thalidomide (Thalomid®) is a drug approved in the treatment of myeloma and has been shown to be effective in some patients with WM, although it is still under clinical-trial investigation. The best results with thalidomide in WM patients have occurred when it was used in combination with other drugs, such as Rituxan or dexamethasone.

- **mTOR inhibitors**—This class of drugs inhibits the mammalian target of rapamycin (mTOR) pathway that promotes growth and survival of cells. Everolimus (Affinitor®) is a drug taken by mouth that is approved for other nonblood cancers but is in clinical trials for 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. Velcade induces apoptosis (cell death) of primary WM lymphoplasmacytic cells. Neuropathy is a major concern for the use of Velcade in WM patients, and weekly (instead of twice weekly) administration has been investigated to decrease risk of neuropathy. 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 US FDA for the treatment of previously treated myeloma patients.

- **Purine 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. Fludarabine is FDA approved to treat CLL in patients who have not responded to at least one standard alkylating agent-containing regimen or whose disease has progressed during treatment with such a regimen. Patients who are candidates for stem cell transplantation should not be treated with fludarabine or cladribine until an adequate number of stem cells have been collected. In addition, a report has indicated that nucleoside analogue-based combinations may be associated with an increased risk of disease transformation or myelodysplastic syndrome (a disease in which the bone marrow does not effectively produce blood cells).

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 with relapsed WM.

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

- BDR: Bortezomib (Velcade), dexamethasone and rituximab (Rituxan)
- VR: Bortezomib (Velcade) and rituximab (Rituxan)
- CaRD: Carfilzomib (Kyprolis), rituximab (Rituxan), dexamethasone.
- RCD: Cyclophosphamide (Cytoxan), dexamethasone and rituximab (Rituxan)
- Benda-R: Bendamustine(Treanda) and rituximab (Rituxan).
- FR: Fludarabine (Fludara) 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 purine nucleoside analogues, such as transformation to a more aggressive WM and development of a myelodysplastic syndrome or acute myeloid leukemia. Patients should speak to their doctors about the benefits and risks of any treatment. See the free LLS publication *Long-Term and Late Effects of Treatment in Adults* for additional information about potential long-term effects of these and other drug treatments.

Radiation Therapy

Radiation therapy is not frequently used to treat WM patients because of the toxic effects of this treatment on older patients. It may be used in the rare occurrence of bony lesions.

Stem Cell Transplantation

Stem cell transplantation is being studied in clinical trials for the treatment of WM. This therapy is rarely used for newly diagnosed patients, unless they have multiple high-risk features, but high-dose chemotherapy with stem cell transplantation is an option for some relapsed and/or refractory patients, especially younger patients who have had multiple relapses or who have primary refractory disease. There are two main types of stem cell transplantation: autologous and allogeneic.

Autologous stem cell transplantation is the type 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 is usually reserved for younger patients with advanced disease who have failed to respond, or no longer respond, to other treatment options.

A newer approach to allogeneic stem cell transplantation, called "reduced-intensity transplantation" or "nonmyeloablative transplantation," uses lower doses of chemotherapy or radiation therapy. This type of transplant may be an option for older and sicker patients who are not responding to other treatments.

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 publication *Blood and Marrow Stem Cell Transplantation*.

Side Effects of Treatment for Patients with 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 your 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 publication *Understanding Side Effects of Drug Therapy.*

Treatment for Patients With Relapsed and/or Refractory WM

Because 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, requiring 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 with 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.

Recommendations for relapsed and/or refractory treatment from the Fourth International Workshop on Waldenström's Macroglobulinemia include reusing therapies if the patient achieved a response that lasted for at least 12 months. For WM patients who experienced a short remission or resistance to initial therapy, the recommendation is to use different classes of drugs either alone or in combination.

Some therapies to use alone or in combination include

- Ibrutinib (Imbruvica)
- Fludarabine (Fludara)
- Bortezomib (Velcade)
- Alemtuzumab (Campath)
- Bendamustine (Treanda), either alone or in combination with rituximab (Rituxan)
- Everolimus (Affinitor).

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 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 WM and may provide patients with additional treatment options. Patients interested in participating in clinical trials are encouraged to talk to their doctors about whether a clinical trial would be appropriate for them. For more information about clinical trials, see the free LLS publication *Understanding Clinical Trials for Blood Cancers* or visit www.LLS.org/clinicaltrials.

These are some classes of novel therapies and drugs currently under investigation.

- There are several promising novel therapies under study in WM that target both MYD88- and non-MYD88-related signaling in WM. One example is an upcoming clinical trial of ibrutinib in symptomatic, previously untreated WM patients. This study will clarify the role of the MYD88 pathway in the frontline treatment of WM.

- In a prospective study of idelalisib, which included previously treated patients with various indolent B-cell malignancies, a 70 percent overall response rate was observed among the WM patients included in this series. Idelalisib has received approval by the FDA for other malignant B-cell indications, and a prospective study to more clearly define the role of this agent in previously treated WM patients will be beginning.

- ABT-199, the B-cell lymphoma 2 (BCL-2) inhibitor, induces cell death in WM cells treated with either ibrutinib or idelalisib. In a prospective clinical study that included previously treated patients with various indolent B-cell malignancies, three of four WM patients demonstrated a response including one complete response. A prospective study to evaluate ABT-199 in WM patients with previously treated disease is being considered, and future studies examining ABT-199 in combination with other active agents in WM including ibrutinib or idelalisib will also be of interest.

- The *CXCR4* gene is mutated in 30 to 35 percent of patients, and can be resistant to many therapies, including ibrutinib and idelalisib. The use of CXCR4-blocking agents (plerixafor, BMS536964) stopped that drug resistance. A clinical trial examining the combination of ibrutinib with a CXCR4-blocking agent in *CXCR4*-mutated WM patients is being planned.

- Due to the high prevalence of treatment-related neuropathy with bortezomib in WM, studies are being planned to develop a drug that does not cause neuropathy. Oprozomib, taken by mouth, is an epoxyketone proteasome inhibitor that is similar to carfilzomib. In a phase II study of previously treated WM patients, there was an overall response rate of 59 percent. Phase I and II studies have shown oprozomib does not cause neuropathy, though GI intolerance was common. Ixazomib, is a novel, oral proteasome inhibitor, which has shown activity in relapsed/refractory myeloma patients, without significant neuropathy, though rash is common. Clinical trials examining the combination of ixazomib, dexamethasone and rituximab (IDR) in symptomatic untreated WM patients in the United States, and in previously treated WM patients (in Europe) have been started.

- Chimeric antigen receptor (CAR) modified T-cell therapy has shown promising results in several B-cell malignancies. A second-generation CAR has shown robust preclinical activity against WM cells, and a clinical trial for patients with relapsed or refractory WM, in which chemotherapy preconditioning is followed by a single dose of 19-28z CAR modified autologous T cells, is under way.

Disease Complications

Transformation. Rarely, WM patients have disease that transforms to aggressive 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. Prior use of nucleoside analogue drugs, such as fludarabine or cladribine, has been reported as an association with transformation.

Other rare complications. These may include skin lesions (including hives, ulcers and flesh-colored bumps called "papules"), kidney complications, bone involvement and the development of WM cell masses outside the bone marrow. High amounts of an abnormal nonsoluble monoclonal protein (amyloid) can accumulate in the tissues and organs, causing damage. If amyloid builds up in the heart muscle (a condition called "primary amyloidosis"), it can make the heart weaker. In addition, research is showing a potential risk for secondary cancers in WM patients.

Treatment Outcomes

The prognosis for patients with WM depends on a number of factors, including patient age, rate of disease progression and response to therapy. Some patients may have 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's Macroglobulinemia (IPSSWM) is internationally accepted as a predictive model for long-term outcomes in newly diagnosed patients.

According to the IPSSWM, factors that estimate survival include

- Age greater than 65 years
- Hemoglobin level less than 11.5 grams per deciliter (g/dL)
- Platelet count of less than 100 x 10^9 per liter (L)
- $Beta_2$-microglobulin greater than 3 milligrams per liter (mg/L)
- Serum monoclonal protein concentration greater than 70 g/L (7 g/dL)
- Elevated serum lactate dehydrogenase (LDH). A typical normal range is 104-333 international units per liter (IU/L).

IgM levels, according to most studies, 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— Includes patients younger than 65 years who have no more than one point
- Intermediate—Includes patients who are at least 65 years of age and/or have two points.
- High—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 WM[1] 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.

[1]The estimated median survival for WM ranges from 5 years (higher risk) to 12 years (lower risk) after treatment begins.

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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 country and in Canada. To find the chapter nearest to you, visit our website at www.LLS.org 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 lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team's knowledge and skills.

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, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists

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

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

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

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

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

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can provide support and help cancer patients to reach out to others in similar circumstances, and share information. For more information, please visit www.LLS.org/chat or www.LLS.org/discussionboard.

LLS Chapters. LLS offers community 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

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
- Visit: www.LLS.org/clinicaltrials

Advocacy. LLS enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please:

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

Other Resources

International Waldenström's Macroglobulinemia Foundation (IWMF)
www.iwmf.com
(941) 927-4963

Provides support, information, resources and a community network for individuals with 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.

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

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