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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.
- The exact cause of WM is unknown, although it is believed that genetics may play a role in disease development. The cancer occurs most commonly in people over age 60 years, is more frequently found in men than women, and is found in more Caucasians than African-Americans.
- 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) 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.

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 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 Leukemia & Lymphoma Society (LLS) booklet *Non-Hodgkin Lymphoma.*

About Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM), also called "lymphoplasmacytic lymphoma," 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 immunoglobulin (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 cells, which carry oxygen, the white 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 cells can lead to anemia, making people feel tired and weak; low numbers of white 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

Lymphoplasmacytic lymphoma (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.

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; less than 5 percent of other LPL cases are IgA-secreting, IgG-secreting, or nonsecreting 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 cancer. Currently, there is no known way to prevent this cancer, nor are the exact causes known. In WM, the following factors may raise a person's risk of developing the cancer, 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.
- 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.

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 chromosome defect is a deletion of part of chromosome 6. ("Deletion" is the term used when all or part of a chromosome is absent.) One of the genes associated with chromosome 6, known as *BLIMP 1*, is a tumor suppressor gene (gene that suppresses cancer formation). A partial or complete loss of this gene could result in a predisposition for the development of WM.
- Researchers have found that some WM patients have important changes or defects in other bone marrow cells, which may also cause the excess growth of cancer cells. Certain cells in the bone marrow called "dendritic cells" release a protein that changes the cell's normal function. The protein, called "interleukin-6" (IL-6), helps normal

plasma cells and plasmacytoid lymphocytes grow. The overproduction of IL-6 appears to be an important factor in the development of WM.

- A presentation at the 2011 American Society of Hematology annual meeting described research that suggests a mutation in the gene *MYD88* is associated with most cases of WM and may be a target for new therapies against the disease.

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

Cryoglobulinemia. Up to 20 percent of patients with WM may develop a condition called "cryoglobulinemia," although fewer than 5 percent of patients have symptoms. With this condition, 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).

Raynaud's syndrome (also called "Raynaud's 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.

Supportive therapy 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 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.

Disease Complications

Transformation. About 10 to 15 percent of 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.

Other rare complications. Other rare complications 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.

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 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 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. Many patients have elevated serum $beta_2$-microglobulin (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. The lymphocytes associated with WM are B cells and are also characterized by the cell markers (antigens on the surface of the cell) CD19, CD20, CD22, CD79 and FMC7. 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 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 booklet *Understanding Lab and Imaging Tests.*

Treatment Planning

Every patient's medical situation is different and should be evaluated individually by an 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 old)
- 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 fact sheet *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.

These 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. These drugs may be used alone as single agents or combined with other drugs or treatments.

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 chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab (Rituxan®) or a rituximab-containing regimen. 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.
- 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 myelodysplasia (a disease in which the bone marrow does not effectively produce blood cells).
- 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 alone or 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).
- 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.

- 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.

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 currently used in the treatment of WM patients include

- BDR: Bortezomib (Velcade), dexamethasone and rituximab (Rituxan)
- RCD: Cyclophosphamide (Cytoxan), dexamethasone and rituximab (Rituxan)
- R-CHOP: Cyclophosphamide (Cytoxan), doxorubicin (Adriamycin®), vincristine (Oncovin®), prednisone and rituximab (Rituxan)
- CPR: Cyclophosphamide (Cytoxan), prednisone, rituximab (Rituxan)
- VR: Bortezomib (Velcade) and rituximab (Rituxan)
- FR: Fludarabine (Fludara) and rituximab (Rituxan)
- TR: Thalidomide (Thalomid) 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 fact sheet *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 used infrequently 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 "nonmyeloblative 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 booklet *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 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 booklet *Understanding Drug Therapy and Managing Side Effects*.

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

- Fludarabine (Fludara®)
- Bortezomib (Velcade®)
- Alemtuzumab (Campath®)
- Bendamustine (Treanda®), either alone or in combination with rituximab (Rituxan®)
- Thalidomide (Thalomid®).

Treatments Undergoing Investigation

LLS invests research funds in WM and other blood cancers. LLS is funding research related to the development of new cell lines, allowing researchers to test the effectiveness of new drugs and new treatments while still in the laboratory.

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. Studies are also conducted to evaluate new indications for therapies that are already approved for other cancers or types of diseases. 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.

Some classes of novel therapies and drugs under investigation include

- Monoclonal antibodies. Alemtuzumab (Campath®) targets CD52 on the surface of WM cells, but CD52 is also present on normal T cells and, therefore, can make patients more sensitive to certain types of infections. Campath has shown promise in helping WM patients who no longer respond to other treatment options and is being investigated in combination with chemotherapy, followed by allogeneic stem cell transplantation. Ofatumumab (Arzerra®, also known as "HuMax-CD20") targets the CD20 molecule in the cell membrane of B cells and is being researched as single-agent treatment and in combination with Velcade® for relapsed patients. Arzerra is approved in the treatment of refractory chronic lymphocytic leukemia.
- Proteasome inhibitor. Bortezomib (Velcade) is approved for the treatment of myeloma. It is being studied in clinical trials for patients with previously untreated or relapsed WM. Carfilzomib (PR-171) is being studied in other NHLs and in myeloma in the relapsed and/or refractory setting.
- Immune-modulatory regulator. Thalidomide (Thalomid®) is approved for myeloma and myelodysplastic syndromes. It is being studied to treat WM alone or in combination with other drugs, such as rituximab (Rituxan®). Thalidomide may be a beneficial option for patients with refractory or relapsed WM, for patients who are not candidates for alkylating or nucleoside analogue therapy, or for patients with extremely low blood cell counts.
- Alkylating agent. Bendamustine (Treanda®) attacks cancer cells' DNA and disrupts the cell-division cycle. Treanda is being studied as both a single agent and in combination with other therapies, such as Rituxan, in both newly diagnosed and relapsed patients with WM.
- mTOR inhibitor. Everolimus (Afinitor®, Zortress®; also known as "RAD001") works by preventing cells from growing and dividing. It is being studied for safety and efficacy in both newly diagnosed and relapsed and/or refractory patients with WM.

- Vaccine. BiovaxID® is a personalized cancer vaccine whose goal is to extend disease-free survival. This treatment engages the immune system to fight malignant lymphoma B cells and is used following treatment with standard regimens such as chemotherapy and anti-CD20 monoclonal antibodies. It is being studied for use in WM.

Combination Therapies

- A combination therapy of dexamethasone, Rituxan and cyclophosphamide (Cytoxan®) has shown promising results in clinical trials as a well-tolerated treatment for symptomatic patients. Studies have indicated that besides achieving disease control, this combination does not produce severe blood count depletion, a common side effect of nucleoside analogues such as fludarabine (Fludara®) and cladribine (Leustatin®).

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 109 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 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.

Acknowledgement

LLS gratefully acknowledges

Guido J. Tricot, MD, PhD
Director, Myeloma Program
The University of Utah, Hematology Division
Salt Lake City, UT

for his review of *Waldenström Macroglobulinemia Facts* and his important contributions to the material presented in this publication.

LLS also gratefully acknowledges the Board of Trustees and staff of the **International Waldenström's Macroglobulinemia Foundation** for their important contributions to the material presented in this publication.

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 you, enter your ZIP code into "Find Your Chapter" at www.LLS.org, or contact

The Leukemia & Lymphoma Society
1311 Mamaroneck Ave.
White Plains, NY 10605
Information Specialists at (800) 955-4572
Email: infocenter@LLS.org

Callers may speak directly with an Information Specialist Monday through Friday, from 9 a.m. to 6 p.m. ET. You may also contact an Information Specialist between 10 a.m. and 5 p.m. ET by clicking on "Live Chat" at www.LLS.org or by sending an email. Information Specialists can answer general questions about diagnosis and treatment options, offer guidance and support and assist with clinical-trial searches for leukemia, lymphoma, myeloma, myelodysplastic syndromes and myeloproliferative neoplasms. The LLS website, www.LLS.org/clinicaltrials, has information about how to find a clinical trial, including a link to TrialCheck®, a clinical-trials search service.

LLS also provides fact sheets and booklets that can be ordered via the 800 number or through the "Free Education Materials" option at www.LLS.org/resourcecenter.

Other Resources

International Waldenstrom's Macroglobulinemia Foundation (IWMF)

(941) 927-4963
www.iwmf.com

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

The National Cancer Institute (NCI)

(800) 422-6237
www.cancer.gov

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 cancer.gov/clinicaltrials, where WM patients can look for clinical trials.

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