

# Waldenström Macroglobulinemia

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

## Highlights

- Waldenström macroglobulinemia (WM) is an uncommon blood cancer. It is a subtype of non-Hodgkin lymphoma.
- WM begins with one or more acquired changes (mutations) to the DNA of a single B lymphocyte. The disease starts as an indolent (slow-growing) disease that is treatable but not curable.
- Common symptoms include fatigue, weakness, unexpected weight loss and bleeding that cannot be explained by other causes.
- Patients with symptoms usually need treatment. Treatment may include drug therapy and/or immunotherapy, red cell transfusions and plasmapheresis; in some cases, splenectomy and/or stem cell transplantation may be part of the treatment.
- Some individuals with WM do not have symptoms at diagnosis and may not require treatment for years. It is important for patients without symptoms to have regular follow-up medical appointments to be checked for signs of disease progression.
- About 10 to 30 percent of WM patients develop hyperviscosity syndrome. Untreated, long-standing hyperviscosity syndrome can cause life-threatening complications. Patients need to be tested periodically for evidence of this condition. Other complications of WM may also occur.
- The safety and effectiveness of new therapies for WM patients, including the use of new drugs and drug combinations, are being researched in clinical trials.

## Introduction

Waldenström macroglobulinemia (WM) is an uncommon blood cancer that is classified by the World Health Organization as a subtype of non-Hodgkin lymphoma. WM is also referred to as a “B-cell lymphoproliferative disease” and accounts for approximately 6 percent of all B-cell lymphoproliferative diseases (disorders where B lymphocytes become cancerous and reproduce abnormally). For additional information about non-Hodgkin lymphoma, please see the free Leukemia & Lymphoma Society (LLS) booklet *Non-Hodgkin Lymphoma*.

This fact sheet provides specific information about the diagnosis, treatment, expected outcomes as well as additional information and support resources for WM. The research exploring more effective therapies for WM is ongoing and examples of new treatment studies are discussed in the clinical trials section of this fact sheet on page 8.

## About Waldenström Macroglobulinemia

WM starts as an indolent (slow growing) disease that is treatable, but not curable, with available therapies. It is a clonal disorder, which means that it begins with one or more changes (mutations) to the DNA of a single cell that multiplies uncontrollably. In WM the change takes place in a type of cell called a B lymphocyte.

**A lymphocyte** is a type of white cell that is part of the body's immune system. There are three major types of lymphocytes: B lymphocytes, which produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes, which have several functions, including assisting B lymphocytes to make antibodies; and natural killer cells, which can attack virus-infected cells or tumor cells. Lymphocytes go through several stages of development. The final stage of B-lymphocyte development is a mature, immunoglobulin-producing plasma cell.

**Immunoglobulins**, sometimes called “gamma globulins,” are proteins that help the body fight infection. The major classes of immunoglobulins (abbreviated as “Ig”) are IgG, IgA, IgM, IgD and IgE. Low Ig levels may cause repeated infections in some patients.

B lymphocytes can become cancerous at any stage of their development. With WM, the cancerous transformation takes place just before the B lymphocyte becomes a mature, immunoglobulin-producing plasma cell.

The WM cells

- Produce an abnormal protein known as “monoclonal immunoglobulin” (also called “monoclonal IgM” or “M protein”); monoclonal IgM accumulation in various tissues throughout the body can cause symptoms including fatigue, weakness and unexplained bleeding
- Accumulate in the bone marrow and in other organs, crowding out normal healthy cells and interfering with the production of sufficient numbers of healthy blood cells.

## Incidence, Causes and Risk Factors

WM is estimated to affect approximately 1,500 people in the United States each year and accounts for about 1 to 2 percent of all blood cancers. The median age at diagnosis is 65 years and less than 3 percent of patients are younger than 40 years. WM is more common in people of European descent than in those of African descent and it is somewhat more prevalent in men.

The reason(s) for the cancerous change that leads to the development of WM is not yet understood and is under study. Some possible causes are listed here:

- Genetic factors may play a role in the development of this disease for some patients. Various blood cell chromosomal abnormalities have been observed in many WM patients. Although no one particular chromosomal abnormality has been identified in most WM patients, the deletion of the long arm of chromosome 6 has been observed with some frequency. One of the genes associated with chromosome 6, known as *BLIMP-1*, is a tumor-suppressor gene and a regulator of B-cell development. This gene aids in the transition from the mature B-cell stage to the plasma cell stage. A partial or complete loss of this gene could result in a predisposition for the development of WM.
- WM sometimes occurs in multiple family members. Researchers are investigating genetic factors that may predispose certain individuals to developing these disorders. For more information about studies of families with two or more members diagnosed with WM or other B-cell lymphoproliferative disorders please go to [www.LLS.org](http://www.LLS.org) and click on “Treatment & Clinical Trials” in the “Disease Information” section on the left side of the page. Then, click on “Other Disease Studies.”
- Studies exploring a possible link between uncontrolled hepatitis C infection and the development of WM have led to mixed conclusions about this potential association.

Although a few cases of patients developing WM years after radiation therapy have been reported, scientists have not noted a significant increase in the incidence of this disorder as a result of exposure to radiation and/or other environmental toxins.

## Diagnosis

WM may be diagnosed when blood test results show an elevated level of protein. Some WM patients do not have any symptoms, so the blood test may have been ordered as part of a periodic physical exam or as part of a checkup for another condition. A diagnosis can be confirmed if additional tests show that monoclonal IgM is present in the blood and there are signs of monoclonal B lymphocytes in the marrow.

Generally, the tests used in the diagnosis of WM include

- Blood tests that can detect the presence of monoclonal IgM
- Immunophenotyping (a method used to identify a specific type of cell in a sample of blood or marrow cells) is used to determine if the changed 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 and CD79.
- Bone marrow aspiration and biopsy to check for the presence of abnormal B lymphocytes in the marrow.

Other typical findings from blood tests may include

Red cells	<ul style="list-style-type: none"> <li>• Anemia (low levels of red cells) is present in most patients at diagnosis.</li> <li>• 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).</li> </ul>
White cells	A reduction in the total white cell count (leucopenia) may be present at diagnosis. However, the number of lymphocytes (a type of white cell) is increased.
Beta 2-microglobulin	Many patients have elevated serum beta 2-microglobulin ( $\beta$ 2-M) at diagnosis. $\beta$ 2-M is a protein found on the surface of many cells including lymphocytes.
Immunoglobulins	There may be a decrease in the number of uninvolved immunoglobulins (IgG, IgA, IgD and IgE).

Other diagnostic tests for WM may include

- X-rays and/or CT scans of the abdomen and pelvis to detect the enlargement of the spleen, liver and lymph nodes
- An analysis of urine collected over 24 hours—to detect elevated levels of protein in the urine.

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

The term “IgM monoclonal gammopathy of undetermined significance” (IgM MGUS) is used to describe patients without symptoms who have monoclonal IgM in the blood and cancerous cells in the bone marrow. Patients with either slow-growing WM or IgM MGUS do not need treatment but should have their IgM levels monitored every couple of months. Generally, increasing IgM levels predict the eventual transformation from IgM MGUS to symptomatic WM.

### Symptoms and Complications of Waldenström Macroglobulinemia

Symptoms are mostly associated with the effects of

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

There does not appear to be a correlation between the amount of IgM in the blood and the degree of symptoms. Patients with similar laboratory test results may show very different types of symptoms and degree of symptoms.

For patients with symptoms, the most common early symptoms of WM are fatigue and weakness due to anemia. Other common symptoms include

- Weight loss
- Enlarged lymph nodes
- Enlarged spleen and liver
- Peripheral neuropathy (damage to the network of nerves that transmits information from the central nervous system to other parts of the body).

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

*Hyperviscosity syndrome.* This circulatory condition is caused by the concentration of the monoclonal IgM, which can thicken the blood and impair blood flow. It 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
- Monoclonal IgM that can coat platelets and by interfering with their function cause bleeding problems.

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
- Headache
- Vertigo
- Visual impairment (blurred vision)
- Changes in mental status (ranging from impaired thinking to full-blown dementia).
- Shortness of breath.

*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.* Twenty 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 known as "Raynaud's syndrome," and symptoms of 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 a condition 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, and discoloration of the affected areas.

*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.

*Rare complications.* Pulmonary complications, cardiac manifestations, skin lesions (including hives, ulcers and flesh-colored bumps called "papules"), kidney complications, bone involvement and secondary amyloidosis (a condition in which certain proteins accumulate in tissues of the body) are rare but possible.

## Treatment

The goal of treatment for WM is to improve the quality of life of patients by relieving any symptoms caused by the disease. Patients without symptoms are generally observed (watch and wait) and do not need treatment until symptoms or complications develop. Some patients may not need treatment for years. However, patients in watch and wait need to have regular medical follow-up visits and lab tests to check for disease progression.

Factors influencing treatment include the

- Nature and extent of symptoms
- Need for rapid disease control
- Eligibility for stem cell transplantation
- Patient's overall health and quality of life.

Generally, it is appropriate to begin treatment for patients with symptoms of recurrent fever, night sweats, fatigue due to anemia, hemoglobin values of 100 grams per liter (g/L) or less, and severe thrombocytopenia (low platelet counts).

Additional reasons to begin treatment for WM include

- Clearly enlarged lymph nodes, an enlarged spleen or an enlarged liver
- Complications including symptomatic hyperviscosity, severe peripheral neuropathy, impaired kidney function, symptomatic cryoglobulinemia, cold agglutinin disease or amyloidosis.

The quantity of the IgM protein is not an indication for therapy.

Treatment for previously untreated WM patients includes alkylating agents, purine nucleoside analogues, monoclonal antibodies, proteasome inhibitors and immunomodulatory drugs, given either as single agents or in combination.

Currently, no specific single or combination drug therapy is recommended because there is limited data from studies comparing the effectiveness of various therapies. Patients are advised to discuss with their physicians the most appropriate treatment for their situation.

### **Drug Therapy**

**Alkylating agents** such as chlorambucil (Leukeran<sup>®</sup>), cyclophosphamide (Cytoxan<sup>®</sup>), and melphalan (Alkeran<sup>®</sup>) have been used as the standard therapy for WM patients who have not had previous treatment. 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** have typically been given to individuals who do not respond to therapy with alkylating drugs. However, these drugs, particularly fludarabine (Fludara<sup>®</sup>) and cladribine (Leustatin<sup>®</sup>) are now often used for patients who have not been previously treated. Pentostatin (Nipent<sup>®</sup>) has been found to be effective for patients who are candidates for high-dose chemotherapy with autologous stem cell transplantation. Patients who are candidates for stem cell transplantation should not be treated with fludarabine or cladribine until an adequate number of stem cells have been collected.

**Rituximab** (Rituxan<sup>®</sup>) is a type of drug called a “monoclonal antibody” that targets CD20 on the surface of WM cells. Rituximab is being used increasingly in the management of WM patients because of its positive treatment responses, limited toxicity and because it does not inhibit normal blood cell production. Rituximab is also considered a very effective choice for treating patients with IgM-related neuropathies.

**Prednisone** or 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. Prednisone is also being studied in clinical trials to test its effectiveness when used in combination with other anti-cancer drugs.

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 persons or those with relapsed WM.

Examples of combination therapies currently used in the treatment of WM patients include

- The M-2 protocol, consisting of carmustine (BiCNU<sup>®</sup>), cyclophosphamide (Cytoxan), vincristine (Oncovin<sup>®</sup>), melphalan (Alkeran) and prednisone
- Cladribine (Leustatin) and cyclophosphamide (Cytoxan) in combination with rituximab (Rituxan)
- Pentostatin (Nipent) and cyclophosphamide (Cytoxan) in combination with rituximab (Rituxan)
- CHOP-R combination therapy (cyclophosphamide (Cytoxan), doxorubicin [Adriamycin<sup>®</sup>], vincristine [Oncovin], prednisone) in combination with 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.

Please see the free LLS booklet *Understanding Drug Therapy and Managing Side Effects* for additional information about potential side effects of these and other drug treatments.

Certain long-term or late effects have been associated with the use of alkylating agents and purine nucleoside analogues, such as the development of a myelodysplastic syndrome or acute myeloid leukemia. Patients should speak to their physicians about the benefits and risks of any treatment. Please see the free LLS fact sheet *Long-Term and Late Effects of Treatment for Adults* for additional information about potential long-term effects of these and other drug treatments.

## Supportive Treatment

### *Plasmapheresis*

Plasmapheresis is a process that uses a device to separate plasma (the liquid portion of the blood) from blood cells. The plasma is removed and replaced with plasma that does not contain the monoclonal IgM. 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. This procedure may also be helpful for patients who do not tolerate or have not benefited from chemotherapy treatment.

### *Red Cell Transfusions*

Patients with WM may benefit from periodic transfusions of packed red cells to treat anemia. However, patients may also have reduced capillary blood flow following transfusions due to hyperviscosity. As a result, patients should not be transfused unless treatment for hyperviscosity has been implemented first to reduce serum IgM levels.

### *Splenectomy*

The need for the surgical removal of the spleen (splenectomy) in WM patients 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.

### *Radiation Therapy*

Radiation therapy is used infrequently to treat WM patients because of the toxic effects of this treatment on older-age patients. It may be used in the rare occurrence of bony lesions.

## Clinical Trials

Patient participation in clinical trials is important in order to develop new and better treatments. Patients are encouraged to talk to their physicians about whether to consider taking part in a clinical trial.

Examples of therapies currently under study to achieve longer-lasting remissions for WM patients are

**Alemtuzumab (Campath®).** Like rituximab (Rituxan), this agent is a type of monoclonal antibody. It targets CD52 on the surface of WM cells. Alemtuzumab has shown promise in helping WM patients who no longer respond to other treatment options. Other research studies are investigating the use of alemtuzumab in combination with chemotherapy, followed by allogeneic stem cell transplantation.

**Epratuzumab (LymphoCide®).** This is another type of monoclonal antibody. It targets CD22 on the surface of WM cells. In clinical trials, this drug is showing promising results in the treatment of some patients who do not respond to chemotherapy.

**Bortezomib (Velcade®).** This agent is a drug-type called a “proteasome inhibitor” and is approved for the treatment of myeloma. It is being studied in clinical trials for patients with previously untreated or relapsed WM.

**Perifosine.** This is one of a class of new agents called “Akt inhibitors.” Perifosine is under study as a treatment for WM either as a single agent or in combination with other drug therapies such as bortezomib (Velcade) and rituximab (Rituxan). Perifosine may be active in cells that are resistant to other forms of anticancer therapy without causing excessive toxicity.

**Thalidomide (Thalomid®) and lenalidomide (Revlimid®).** These are two immunomodulatory regulator drugs that are approved for myeloma and myelodysplastic syndromes, respectively. Each is being studied to treat WM alone or in combination with other drugs, such as rituximab (Rituxan). These drugs may be beneficial options for patients with refractory WM, for patients who have relapsed WM and are not candidates for alkylating or nucleoside analogue therapy, or for patients with extremely low blood cell counts.

**Sildenafil citrate (Viagra®).** This is a drug that is used to treat certain noncancerous conditions such as erectile dysfunction. It is being studied in the treatment of WM patients with slow-progressing disease. Research has shown that it may produce a significant decrease in IgM levels and may help some patients to achieve complete remissions.

A combination therapy consisting of **dexamethasone (Decadron®), rituximab (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).

**Stem cell transplantation.** Various types of stem cell transplantation are being studied in the treatment of WM.

Both autologous stem cell infusion (using the patient’s own stem cells, which are collected prior to high-dose chemotherapy) and allogeneic stem cell transplantation (using stem cells from either a related or unrelated, matched donor) have been used in treating WM patients. Results of small studies employing high-dose chemotherapy followed by autologous stem cell transplantation have indicated promising results in achieving partial and complete remissions, even in patients who have not responded to standard therapy.

Fewer cases of patients treated with allogeneic stem cell transplantation have been reported. Allogeneic stem cell transplantation is associated with high mortality risks. Because the median age of WM patients at diagnosis is nearly 65 years, most patients may not be eligible for this therapy. Generally, allogeneic stem cell transplants are considered for younger patients with advanced disease who have failed to respond to or no longer respond to other treatment options.

For older and sicker patients, reduced-intensity allogeneic stem cell transplantation (also known as “nonmyeloablative allogeneic stem cell transplantation”) may be an option for patients who do not respond to other treatments. Patients being conditioned for a reduced-intensity transplant receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. Immunosuppressive drugs are used to prevent rejection of the graft, and the engraftment of donor immune cells may allow these cells to attack the disease (graft-versus-cancer effect). The theory being tested with a reduced-intensity transplant is that by undergoing less-toxic procedures prior to the transplant, the body is better able to withstand the transplant. However, full donor engraftment still takes place, and the desired graft-versus-tumor effect still occurs.

Patients who are being considered for stem cell transplantation are not treated with purine nucleoside analogues or alkylating agents as these drugs may decrease the normal production of white cells, red cells and platelets. Other drugs, including rituximab (Rituxan), may be good alternatives for these patients. For additional information on stem cell transplantation, please see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

### **Outcomes for Patients with Waldenström Macroglobulinemia**

All patients are advised to discuss survival information with their physicians. Outcome data can show how other people with WM responded to treatment, but cannot tell how any one person will respond.

In general, the outlook for WM patients is variable. There are many factors that influence patient outcome. IgM levels, according to most studies, have no value in predicting patient outcomes.

Factors that may indicate a more favorable outcome include

- Hemoglobin concentration not falling below 100 grams per liter (g/L)
- Age less than 65 at diagnosis
- No related weight loss or cryoglobulinemia
- A low degree of cytopenia (lower than normal blood cell counts)
- Limited presence of WM cells in the bone marrow
- Absence of an increase in serum  $\beta$ 2-microglobulin levels
- Absence of an increase in serum LDH levels.

The median survival of individuals diagnosed with WM ranges from 5 to 10 years after the initiation of treatment. However, the most recent survival statistics may underestimate survival to a small degree since these data do not incorporate outcomes of current treatment options.

## 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, visit our Web site, [www.LLS.org](http://www.LLS.org), or contact

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

1311 Mamaroneck Ave.  
White Plains, NY 10605

### **Information Resource Center (IRC): (800) 955-4572**

Email: [infocenter@LLS.org](mailto:infocenter@LLS.org)

Callers to the Information Resource Center may speak directly with an information specialist, Monday to Friday, 9 a.m. to 6 p.m., ET. You may also contact an information specialist by clicking on Live Help (10 a.m. to 5 p.m., ET) at [www.LLS.org](http://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 diseases. The LLS Web site has information about how to find a clinical trial, including a link to TrialCheck®, a clinical trials search service provided by LLS.

LLS also provides fact sheets and booklets that can be ordered via the 800 number or through the Free Materials on the Web site.

## Other Resources

### **International Waldenstrom's Macroglobulinemia Foundation**

**(941) 927-4963**

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

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

### **The National Cancer Institute (NCI)**

**(800) 422-6237 or (800) 4-CANCER**

**[www.cancer.gov](http://www.cancer.gov)**

Part of the National Institutes of Health, NCI functions as a national resource center for information and education about all forms of cancer, including Waldenström macroglobulinemia.

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