

Detailed Guide: Waldenstrom's Macroglobulinemia

What Is Waldenstrom Macroglobulinemia?

Waldenstrom macroglobulinemia is a type of non-Hodgkin lymphoma (see the American Cancer Society document on [non-Hodgkin lymphoma](#)) that produces large amounts of an abnormal protein (called a macroglobulin). Having too much of this abnormal protein causes many of the symptoms associated with this condition.

The lymphoma cells grow mainly in the bone marrow but can grow in other organs such as the liver and the spleen. The lymphoma cells can crowd out the normal blood-producing cells of the bone marrow. This can cause other symptoms, due to low blood counts. Waldenstrom macroglobulinemia is named after Jan Waldenstrom, the Swedish doctor who first recognized this condition in 1944. Although this is a type of lymphoma, most doctors call it Waldenstrom macroglobulinemia.

Lymphoid Tissue and the Immune System

Lymphoid tissue is formed by several types of immune system cells that work together to resist infections. Lymphoid tissue also reacts to transplanted tissues (such as blood transfusions or organ transplants) from other people and is involved in fighting some types of cancer.

Lymphoid tissue is found in *lymph nodes*, which are pea-sized collections of immune system cells found in the underarm area, in the groin, on the sides of the neck, inside the chest, and inside the abdomen. Lymphoid tissue is found in the bone marrow, as well as other organs such as the thymus (found behind the chest bone and in front of the heart), the spleen (on the left side of the abdomen next to the stomach), and the tonsils and adenoids. Lymphoid tissue is also scattered throughout the body within other systems such as the digestive system and respiratory system.

Waldenstrom macroglobulinemia is a cancer of the B lymphocytes (lymph cells). *Lymphocytes* (lymph cells) are the main cell type of the immune system and of lymphoid tissue. There are 2 types of lymphocytes: *T cells* and *B cells*. When B cells respond to an infection, they mature and change from round-shaped lymphocytes into oval-shaped plasma cells. As this change occurs, the cells begin to produce and release proteins called *immunoglobins* (antibodies) to attack and help kill disease-causing germs such as bacteria. T cells mainly help direct the immune response but also can directly kill invading infections.

Cells Responsible for Waldenstrom Macroglobulinemia

The cancer cells in people with Waldenstrom macroglobulinemia have some similarities to those of 2 other types of cancer: multiple myeloma and non-Hodgkin lymphoma. Multiple myeloma is considered a cancer of plasma cells and non-Hodgkin lymphoma is a cancer of lymphocytes. The cells of Waldenstrom macroglobulinemia are often described as lymphoplasmacytoid, meaning that they have features of both plasma cells and lymphocytes. These cells produce large amounts of an abnormal type of antibody protein (immunoglobulin M, or IgM) that causes most of the symptoms of Waldenstrom macroglobulinemia, including excessive bleeding, problems with vision, and nervous system problems.

Revised: 03/01/2004

What Are the Key Statistics About Waldenstrom Macroglobulinemia?

There are no exact statistics about this disease. It is estimated that about 1,000 to 1,500 people are diagnosed with Waldenstrom macroglobulinemia each year in the United States. There is no firm evidence that this number has either increased or decreased in the last few years.

The chance of developing this disease increases with age. In one large group of patients, half were over the age of 67. It is exceptionally rare in people under age 50, but Waldenstrom macroglobulinemia has been seen in patients as young as 27. White males develop this cancer twice as often as black males or white or black females.

The average survival of people with Waldenstrom macroglobulinemia is about 7 to 9 years according to various experts. Younger patients generally live longer. In one study the average survival of those under age 65 was over 14 years. Those over 65 had an average survival of 7 years. Survival is shorter if there is extensive disease. It is important to know that these numbers come from patients treated many years ago. Newer treatments have been developed and the survival rate may be better now.

Revised: 03/01/2004

What Are The Risk Factors For Waldenstrom Macroglobulinemia?

A *risk factor* is anything that increases a person's chance of getting a disease. Different cancers have different risk factors. For example, unprotected exposure to strong sunlight is a risk factor for skin cancer. Smoking is a risk factor for cancers of the lung, mouth, larynx, bladder, kidney, and several other organs.

Researchers have found few risk factors that make a person more likely to develop Waldenstrom macroglobulinemia. However, most people with these risk factors never develop the disease. Even if a patient with Waldenstrom macroglobulinemia does have one or more risk factors, it is impossible to know for sure how much that risk factor contributed to causing the cancer.

Monoclonal Gammopathy of Undetermined Significance (MGUS): Monoclonal gammopathy of undetermined significance (MGUS), which is found with a special blood test, is an abnormality of antibody-producing cells that is related to multiple myeloma and Waldenstrom macroglobulinemia. In MGUS, there is also too much production of an antibody protein (immunoglobulin) by abnormal plasma cells, or "lymphoplasmacytoid" cells. However, these abnormal cells do not form an actual tumor or mass and do not cause any symptoms. MGUS usually has no impact on a person's health. But, about 20% of people with MGUS will develop multiple myeloma or non-Hodgkin lymphoma within 20 years. Most of these cases of non-Hodgkin lymphoma involve cancer cells with "lymphoplasmacytoid" features.

Aging: Age is among the most significant risk factor. This disease is rare among people younger than 50 years old.

Race: Waldenstrom macroglobulinemia is more common among whites than among African Americans. This is the opposite of the situation for multiple myeloma, which is about twice as common among African Americans as white Americans. The reasons for these differences are not known.

Sex: Men are more likely to develop this disease than are women.

Heredity: Genetic factors may play a role. In one study, about 20% of patients with Waldenstrom macroglobulinemia had a close relative with another type of lymphoma or Waldenstrom macroglobulinemia.

Revised: 03/01/2004

How Is Waldenstrom Macroglobulinemia Staged?

There is no standard staging system for Waldenstrom macroglobulinemia as there is for most other cancers. This means that the usual staging studies such as imaging tests are not as important in this disease. The diagnosis of Waldenstrom macroglobulinemia is made by finding the abnormal protein in the blood and the typical lymphoplasmacytoid lymphoma cells in the bone marrow. Doctors look at the degree of anemia, the amount of immunoglobulin in the blood and, most importantly, a protein in the blood called beta-2-macroglobulin. People with a level of beta-2-macroglobulin below 3 mg/L (milligrams per liter) live 2 to 3 times longer than those whose level is above 3. Patients with Waldenstrom macroglobulinemia who are anemic or have a low blood platelet count also have a shorter survival. Being older also leads to a poorer outlook.

In one study, people with none of these unfavorable signs had an average survival of 14 years. People with all of them lived, on average, only about 4 years.

Revised: 03/01/2004

How Is Waldenstrom Macroglobulinemia Treated?

This information represents the views of the doctors and nurses serving on the American Cancer Society's Cancer Information Database Editorial Board. These views are based on their interpretation of studies published in medical journals, as well as their own professional experience.

The treatment information in this document is not official policy of the Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your doctor.

Your doctor may have reasons for suggesting a treatment plan different from these general treatment options. Don't hesitate to ask him or her questions about your treatment options.

In recent years, some progress has been made in treating people with Waldenstrom macroglobulinemia. It is important to understand all treatment options. It is often a good idea to seek a second opinion, since it can provide additional information and help the patient feel more confident about the treatment plan that is chosen.

Revised: 03/01/2004

Systemic Chemotherapy

Chemotherapy uses anticancer drugs that are injected into a vein or a muscle, or are taken by mouth. These drugs enter the bloodstream and reach all areas of the body (that is why it is called "systemic"), making this treatment very useful for lymphoma.

There are many drugs that are useful in the treatment of patients with lymphoma and Waldenstrom macroglobulinemia. The most commonly used drugs have been chlorambucil (Leukeran) and prednisone, given together. Other chemotherapy drugs are cyclophosphamide (Cytoxan) and doxorubicin (Adriamycin). Recently, doctors have begun to favor the drugs fludarabine (Fludara) and cladribine (Leustatin). These are given intravenously for several days at a time. Sometimes, several drugs are combined. Most of these chemotherapy treatments are given on an outpatient basis (in the doctor's office or clinic or hospital outpatient department), but some require hospital admission. Sometimes a patient may take one chemotherapy combination for several cycles and later be switched to a different one if the first treatment combination does not seem to be working effectively. This is usually determined after retesting blood samples for IgM levels, by physical examination (for example, if an enlarged lymph node hasn't shrunk), or by imaging tests (for example, CT or MRI scans indicate that internal organs or lymph nodes inside the body have not shrunk).

Chemotherapy drugs are intended to kill lymphoma cells but they can also damage normal cells. For this reason, some side effects occur. Side effects depend on the type and dose of drugs given and the length of time they are taken. Drugs used in cancer chemotherapy specifically attack cells that are rapidly dividing. These drugs are useful because cancer cells spend more of their time dividing and reproducing than normal cells do. There are some normal tissues such as the bone marrow, the lining of the mouth and intestines, and the hair follicles that also grow rapidly to replace cells that wear out. These rapidly growing normal cells are the ones most likely to be adversely affected by chemotherapy. As a result, a patient may have hair loss, mouth sores, lowered resistance to infection due to low white blood cell counts, and easy bruising and bleeding due to low platelet counts. Loss of appetite, nausea, and vomiting result in part from damage to intestinal cells. The effects of certain drugs on areas of the brain controlling appetite also contribute to these problems.

The doctor will try to avoid them with special drugs that are designed to overcome some of these side effects. For example, drugs can be given along with the chemotherapy to prevent or reduce nausea and vomiting. He or she will also discuss what the patient can do to lessen the side effects. These side effects are temporary and go away after treatment is finished.

Some chemotherapy drugs also have side effects that are not related to their effects on rapidly dividing cells. Organs that could be directly damaged by these chemotherapy drugs include the kidneys, liver, testes, ovaries, brain, heart, and lungs. With careful monitoring, such side effects are rare. If serious side effects occur, the chemotherapy may have to be reduced or stopped, at least temporarily. Careful monitoring and adjustment of drug doses is important because some side effects to organs are permanent.

One of the most serious late complications of successful chemotherapy is the possibility of developing leukemia. This affects a small percentage of patients.

Revised: 03/01/2004

Biological Therapy or Immunotherapy

Biological therapies use naturally occurring substances produced by the immune system. These substances may kill lymphoma cells, slow their growth, or may activate the patient's immune system to more effectively fight the lymphoma.

Interferon: Interferon is a hormone-like protein naturally produced by white blood cells to help the immune system fight infections. Some studies have suggested that interferon can cause tumors of some lymphomas to shrink. Side effects of this treatment include moderate to severe fatigue, fever, chills, headaches, muscle and joint aches, and mood changes. It is still not certain whether interferon is the best treatment for some patients who have non-Hodgkin lymphoma with Waldenstrom macroglobulinemia. It is usually used only in patients who continue to get sicker after treatment with standard chemotherapy drugs.

Immunotherapy with monoclonal antibodies: Antibodies are normally produced by the immune system to help fight infections. Similar antibodies called *monoclonal antibodies* can be made in the laboratory. Instead of attacking germs as usual antibodies do, some monoclonal antibodies can be designed to attack lymphoma cells. After years of laboratory research, several monoclonal antibodies are now being tested in clinical trials as treatments for non-Hodgkin lymphoma.

The most widely used monoclonal antibody is rituximab (Rituxan). Rituximab specifically recognizes and attaches to a substance called CD20 that is found on the surface of the lymphoma cells responsible for Waldenstrom macroglobulinemia. This attachment seems to cause the

lymphoma cell to die. Patients receive intravenous (in a vein) infusions once a week for 4 treatments. The treatments can be given in the oncologist's office or clinic. Common side effects include chills, fever, nausea, rashes, fatigue, and headaches. Although more serious side effects rarely occur, side effects similar to those seen during chemotherapy do not occur. This treatment has generally been used for patients whose lymphoma either has not responded to chemotherapy or has come back. Many doctors are now using monoclonal antibodies together with chemotherapy for the initial treatment of people with Waldenstrom macroglobulinemia.

A second monoclonal antibody, called alemtuzumab (Campath), has also helped patients with Waldenstrom macroglobulinemia when they stopped responding to other treatments.

Thalidomide: Thalidomide is a drug that has been useful in treating multiple myeloma. A small number of patients with Waldenstrom macroglobulinemia have improved with thalidomide treatment. Many have stopped the drug because of its side effects of drowsiness, fatigue, severe constipation, and sometimes, nerve damage. New drugs that work like thalidomide but without the side effects are being developed.

Bortezomib (Velcade): This newly approved drug has also been useful in people whose disease has stopped responding to other drugs.

The cost of the biological medicines is very high, even with a good insurance company. Changes in recent laws require that patients pay for 20% of their medicine as copayment. If your medicine costs thousands of dollars, this becomes quite expensive, unless you have health insurance that fully covers the cost. Be sure to check with your health insurance company before deciding to take these kinds of treatments.

Revised: 03/01/2004

Plasmapheresis

This treatment is used to lower the viscosity ("thickness") of the blood. Blood is removed from a vein and the *plasma* (liquid part of the blood) is separated from the blood cells. The blood cells are mixed with salt solution and given back to the patient. The plasma containing the abnormal protein is discarded. Often this is done continuously with a cell separator device, but if the blood is too viscous, it may need to be done manually by removing a single pint of blood at a time. Each plasmapheresis treatment takes a few hours.

Plasmapheresis is very helpful in relieving symptoms of newly diagnosed patients (while chemotherapy is starting to work) and for those whose Waldenstrom macroglobulinemia is not controlled by chemotherapy, biological therapy, or other treatments. When patients have symptoms from elevated IgM, they need to have plasmapheresis right away to prevent complications.

Revised: 03/01/2004

Stem Cell Transplantation (SCT)

This is a treatment that is still being studied and should be done as part of a clinical trial.

There are 2 main methods of SCT: *allogeneic* and *autologous*. In an *allogeneic stem cell transplant*, the donor and patient are matched by certain basic cell characteristics that are inherited. Usually the donor is a brother or sister. If there is no sibling that can be matched, an unrelated donor may also be matched. The blood-forming stem cells can be taken from several bone marrow aspirates or they can be separated from the peripheral (circulating) blood by a method known as *apheresis*. Recent studies have shown that there may be an advantage to using blood-forming stem cells obtained by apheresis instead of bone marrow aspiration. This has

become the usual way to obtain these. Allogeneic transplantation has limited usefulness due to the need for a matched donor. Another limitation is that side effects of this treatment are too severe for most people older than 50 years old.

In an *autologous stem cell transplant*, a patient's own blood-forming stem cells are removed from his bloodstream. This is usually done after the patient has received treatment that destroys as much as possible of the Waldenstrom macroglobulinemia cells.

Blood-forming stem cells collected from a donor or the patient are carefully frozen and stored. The patient then receives high-dose chemotherapy and sometimes whole body radiation treatment as well. This destroys remaining cancer cells, but it also kills all or most normal cells in the bone marrow. After therapy, the frozen stem cells are thawed and returned to the body in a blood transfusion.

A radiation oncologist will see the patient before the stem cell transplant is done and will take measurements of the patient so that radiation shields can be built to protect the lungs, heart, and kidneys from damage during high-dose, whole body radiation therapy.

The patient having a stem cell transplant may be admitted to the hospital transplant unit or receive treatment as an outpatient depending on a variety of factors. If done as an outpatient, patients and families need to be able to identify early complications requiring their doctor's attention. Unless they live close to the transplant center, they will be asked to stay in a nearby hotel. After the patient and family are educated about the process and complications, the patient starts high-dose chemotherapy and may be given high-dose whole body radiation.

Next, the patient's own stem cells (autologous), or a matched donor's stem cells (allogeneic), are given through a vein or venous access line. Even though the cells are given into a vein, they will eventually settle into the bone marrow where they will begin to grow. Then the waiting period begins.

Patients who receive a donor's stem cells are given antirejection drugs (such as prednisone or cyclosporine). For the next 3 to 4 weeks the patient is given as much supportive therapy as needed. This can include intravenous nutrition, antibacterial, antiviral, and antifungal antibiotics, red blood cell transfusions, platelet transfusions, or other medications as needed.

Usually around 14 to 21 days after the stem cells have been infused, they begin producing white blood cells. This is followed by the production of platelets and, several weeks later, red blood cells. Patients are kept in protective isolation until their white blood cell count rises above 500. They can usually leave the hospital when their white blood cell count nears 1,000. The patient is then examined in the outpatient clinic almost every day for several weeks.

Patients typically make regular visits to the outpatient transplantation clinic for about 6 months, after which time their care is continued by their oncologist or internist. At this point they only come back to the bone marrow transplant clinic for their annual exam. If they have symptoms, these should be brought to the attention of their doctor.

Bone marrow or peripheral blood stem cell transplant is still a complex treatment. If the doctors think the patient may benefit from transplantation, the best place to have it done is at a nationally recognized cancer center where the staff has experience with the procedure and with managing the recovery period. Patients should not hesitate to ask the doctor about the number of times he or she has done this procedure and how patients responded to the treatment. Experience and knowledge are key factors in providing the best care.

Bone marrow transplantation is very expensive (more than \$100,000) and can require a lengthy hospital stay. Some insurance companies view this procedure as experimental and may not pay for it. Because there are fewer complications with autologous (stem cells from the patient) transplants than with allogeneic (stem cells from a matched donor), they are usually less expensive.

Side effects from a stem cell transplant are generally divided into early and long-term effects. The early complications and side effects are basically the same as those caused by any other type of high-dose chemotherapy. They are caused by damage to the bone marrow and other rapidly growing tissues of the body. Complications and side effects that can persist for a long time or not occur until years after the transplant include:

- Radiation damage to the lungs, causing shortness of breath
- Graft-versus-host disease, which occurs only in allogeneic (donor) transplants (see below)
- Damage to the ovaries that can cause infertility and loss of menstrual periods
- Damage to the thyroid gland that can cause problems with metabolism
- Cataracts (damage to the lens of the eye that can affect vision)
- Bone damage called aseptic necrosis. If damage is severe, the patient will need to have part of the affected bone and the joint replaced.
- Leukemia that can develop because of damage to bone marrow cells

Graft-versus-host disease is the major complication of allogeneic (donor) stem cell transplants. It occurs after an allogeneic transplant because the immune system of the patient is taken over by that of the donor. The donor immune system then begins reacting against the patient. The most disabling symptoms are severe rashes with itching and severe diarrhea. The liver and lungs may also be damaged. The patient may develop fatigue and muscle aching. Sometimes the graft-versus-host disease becomes chronic and disabling. If it is severe enough, it can be fatal. Usually drugs can control most of the symptoms of graft-versus-host disease.

On the positive side, the graft-versus-host disease also leads to graft-versus-lymphoma activity. Lymphoma cells remaining after the chemotherapy and radiation therapy will often be killed by immune reactions of the donor cells. (For information about bone marrow and stem cell transplants, please refer to the American Cancer Society document, "[Bone Marrow and Peripheral Blood Stem Cell Transplants.](#)")

Revised: 03/01/2004

Copyright 2007 © American Cancer Society, Inc.

All content and works posted on this website are owned and copyrighted by the American Cancer Society, Inc. All rights reserved.