About Waldenstrom Macroglobulinemia

Overview and Types

If you have been diagnosed with Waldenstrom macroglobulinemia or are worried about it, you likely have a lot of questions. Learning some basics is a good place to start.

- **What Is Waldenstrom Macroglobulinemia?**

Research and Statistics

See the latest estimates for new cases of Waldenstrom macroglobulinemia in the US and what research is currently being done.

- **What Are the Key Statistics About Waldenstrom Macroglobulinemia?**
- **What’s New in Waldenstrom Macroglobulinemia Research and Treatment?**

**What Is Waldenstrom Macroglobulinemia?**

Waldenstrom macroglobulinemia (WM) is a type of non-Hodgkin lymphoma (NHL). The cancer cells make large amounts of an abnormal protein (called a *macroglobulin*). Another name for WM is *lymphoplasmacytic lymphoma*. This condition used to be called *Waldenstrom’s macroglobulinemia*, so some people refer to it as *Waldenstrom’s*.

To understand WM, it helps to know about the functions of lymphoid tissue in the body.

**Lymphoid tissue and the immune system**

Lymphoid tissue is made up several types of immune system cells that work together to
help the body resist infections. Lymphoid tissue is found in many places in the body:

- Lymph nodes, which are pea-sized collections of immune system cells throughout the body, including in the underarm area, in the groin, on the sides of the neck, and inside the chest and abdomen
- Bone marrow, the soft inner part of certain bones where new blood cells are made
- The thymus, a small organ behind the chest bone and in front of the heart
- The spleen, an organ on the left side of the abdomen next to the stomach
- The tonsils and adenoids in the throat
- Throughout body systems like the digestive system and respiratory system

Lymphocytes (lymph cells) are the main cells of lymphoid tissue. There are 2 main types of lymphocytes:

- **B lymphocytes (B cells)** respond to an infection by changing into a different type of cell called a *plasma cell*. Plasma cells make proteins called *antibodies* (also called *immunoglobulins*) that help the body attack and kill disease-causing germs like bacteria.
- **T lymphocytes (T cells)** help direct immune responses, but they also can kill invading germs directly.

**Waldenstrom macroglobulinemia**

WM is a cancer that starts in B cells. The cancer cells in people with WM are similar 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. WM cells have features of both plasma cells and lymphocytes and are called *lymphoplasmacytoid*.

WM cells make large amounts of a certain type of antibody (immunoglobulin M, or IgM), which is known as a *macroglobulin*. Each antibody (protein) made by the WM cells is the same, so it is called a *monoclonal protein*, or just an *M protein*. The buildup of this M protein in the body can lead to many of the *symptoms* of WM, including excess bleeding, problems with vision, and nervous system problems.

The WM cells grow mainly in the bone marrow, where they can crowd out the normal cells that make the different types of blood cells. This can lead to low levels of red blood cells (called *anemia*), which can make people feel tired and weak. It can also cause low numbers of white blood cells, which makes it hard for the body to fight infection. The numbers of platelets in the blood can also drop, leading to increased bleeding and
Lymphoma cells can also grow in organs like the liver and spleen, causing these organs to swell and leading to abdominal pain. (For more on the symptoms of WM, see Signs and Symptoms of Waldenstrom Macroglobulinemia.)
What's New in Waldenstrom Macroglobulinemia Research and Treatment?

Research into the causes, prevention, and treatment of Waldenstrom macroglobulinemia (WM) is being done in many medical centers throughout the world.

Genetics

As noted in Do We Know What Causes Waldenstrom Macroglobulinemia? scientists are making great progress in understanding how changes in DNA can cause normal lymphocytes to develop into WM cells.

For example, in most people with WM, the cancer cells have been found to have changes in the MYD88 gene. More recently, a smaller percentage of WM cells have been found to have changes in the CXCR4 gene. Changes in these genes have been linked with a greater chance of WM causing symptoms and requiring treatment, and seem to affect survival as well.

Researchers are now looking to develop drugs that can target cells with these gene changes. Some of these drugs are now in early clinical trials.

Chemotherapy and targeted therapies

Clinical trials are studying many new drugs to treat WM, as well as ways to use drugs already known to be effective by combining them in new ways, using different doses, or different sequences of drugs, one after another.

Some of the newer types of drugs that have shown promise or are being tested against WM include:

- mTOR inhibitors, such as everolimus (Afinitor) and temsirolimus (Torisel)
- Proteasome inhibitors, such as bortezomib (Velcade), carfilzomib (Kyprolis), and
oprozomib

- Histone deacetylase (HDAC) inhibitors, such as panobinostat, romidepsin (Istodax), and belinostat (Beleodaq)
- Bruton tyrosine kinase (BTK) inhibitors, such as ibrutinib (Imbruvica), ACP-196, and AVL-292
- PI3K inhibitors, such as idelalisib (Zydelig) and buparlisib (BKM120)
- Aurora kinase inhibitors, such as alisertib

**Biological therapy**

Another newer approach to WM treatment is the use of biological response modifiers that stimulate the patient’s immune system to attack and destroy the lymphoma cells.

For example, it has recently been found that the bone marrow support tissues (stromal cells) make a substance called *interleukin 6* (IL-6). IL-6 is a strong growth factor for multiple myeloma cells. IL-6 also helps cause the bone destruction seen in myeloma. Some current research efforts are focused on trying to develop ways to block these functions of IL-6, which might lead to new treatments for WM.

**Bone marrow and peripheral blood stem cell transplant**

Researchers are continually improving bone marrow and peripheral blood stem cell transplant methods, as well as trying to determine how helpful this type of treatment can be for people with WM.

**Vaccines**

Doctors know it is possible for people with cancer to develop immune responses to their cancer. In rare instances, people’s immune systems have rejected their cancers, and they have been cured. Scientists are now studying ways to boost this immune reaction by using vaccines.

Unlike vaccines used to prevent infections, these vaccines create an immune reaction against the lymphoma cells in patients who have very early disease or whose disease is in remission but could come back or relapse. This is a major area of research in treating lymphomas (including WM), but it is still being tested in clinical trials. You might want to consider enrolling in one of these studies.
Waldenstrom Macroglobulinemia Causes, Risk Factors, and Prevention

Risk Factors

A risk factor is anything that affects your chance of getting a disease such as cancer. Learn more about the risk factors for Waldenstrom macroglobulinemia.

- What Are the Risk Factors for Waldenstrom Macroglobulinemia?
- Do We Know What Causes Waldenstrom Macroglobulinemia?

Prevention

At this time there is not a way to protect against this cancer. Learn more about what is known.

- Can Waldenstrom Macroglobulinemia Be Prevented?

What Are the Risk Factors for Waldenstrom Macroglobulinemia?

A risk factor is anything that affects your chance of getting a disease such as cancer. Different cancers have different risk factors. Some cancer risk factors, like smoking, can be changed. Others, like a person’s age or family history, can’t be changed.

Researchers have found a few risk factors that make a person more likely to develop Waldenstrom macroglobulinemia (WM). But most people with these risk factors never develop WM.
Monoclonal gammopathy of undetermined significance

Monoclonal gammopathy of undetermined significance (MGUS) is an abnormality of antibody-making cells that is related to multiple myeloma and WM. In MGUS, like WM and multiple myeloma, abnormal cells in the bone marrow make large amounts of one particular antibody. This antibody is called a monoclonal (or M) protein, and the condition is called a monoclonal gammopathy.

As long as the patient has no symptoms from the abnormal cells or the M protein they make, the abnormal cells make up less than 10% of the bone marrow, and the amount of abnormal M protein in the blood is not very high (less than 3 g/dl), this condition is called MGUS.

MGUS itself does not cause health problems, but each year about 1% to 2% of people with MGUS go on to develop a related cancer (like multiple myeloma, WM, or lymphoma) or another serious health problem (like amyloidosis).

Age

The risk of WM goes up with age. It is rare among people younger than 50 years old.

Race

WM is more common among whites than among African Americans. In contrast, multiple myeloma is about twice as common among African Americans as white Americans. The reasons for these differences are not known.

Sex

Men are more likely than women to develop this disease. The reason for this is not known.

Heredity

Inherited genes seem to play a role in at least some people who get WM. About 1 in 5 people with WM has a close relative with WM or with a related B-cell disease, such as
MGUS or certain types of lymphoma or leukemia.

**Hepatitis C**

Hepatitis C is caused by infection with a virus (known as the *hepatitis C virus*, or HCV). Some studies have found that people with chronic hepatitis C infection might be more likely to develop WM than people without the virus. But not all studies have found such a link.

**Certain autoimmune diseases**

Some research has suggested that people with certain types of autoimmune disease, such as Sjögren (Sjogren) syndrome, might be at higher risk for WM.

- References
  See all references for Waldenstrom Macroglobulinemia

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**Do We Know What Causes Waldenstrom Macroglobulinemia?**

Some risk factors can make a person more likely to get Waldenstrom macroglobulinemia (WM), but often it's not clear exactly how these factors might increase risk.

Scientists have learned how certain changes in the DNA inside normal lymphocytes can make them become lymphoma or multiple myeloma cells. Changes in the DNA of some lymphoma cells can also cause them to make high levels of IgM, which leads to most of the symptoms of WM.

The DNA inside our cells makes up our genes – the instructions for how our cells
function. We tend to look like our parents because they are the source of our DNA. But DNA affects more than how we look.

Some genes control when cells grow, divide to make new cells, and die at the right time. Certain genes that help cells grow, divide, or live longer are called oncogenes. Others that slow down cell division or make cells die at the right time are called tumor suppressor genes. Cancers can be caused by DNA changes that turn on oncogenes or turn off tumor suppressor genes.

Some people inherit DNA changes from a parent that increase their risk for certain types of cancer. Researchers are studying families that have many cases of WM to try to find the genes that might cause this disorder in some people.

The DNA changes found in WM cells are usually acquired after birth (not passed on from a parent). Some of these acquired changes may have outside causes, but often they occur for no apparent reason. They seem to happen more often as we age, which might help explain why WM usually occurs in older people.

Recent research has found that about 9 times out of 10, WM cells have a mutation (change) in a gene known as MYD88, which normally helps immune system cells signal each other and helps keep them alive. The DNA change in this gene might make it stay turned on all the time, which might help the WM cells survive longer than they should.

Sometimes, WM cells have other kinds of DNA changes. In each human cell, the DNA is packaged in 23 pairs of chromosomes. In some WM cells, a piece of a chromosome is missing. This is called a deletion. The most common chromosome defect seen in WM is a deletion of part of chromosome 6. It’s not clear exactly which genes this might affect. Another type of chromosome defect in WM is called a translocation. In a translocation, a piece of one chromosome becomes attached to a different chromosome. Chromosome changes like these can cause oncogenes to be turned on or tumor suppressor genes turned off.

Researchers have found that some patients with WM have important changes or defects in other bone marrow cells. These changes might also help cancer cells grow. Certain cells in the bone marrow called dendritic cells release a hormone called interleukin-6 (IL-6) that helps normal plasma cells and plasmacytoid lymphocytes grow. Excess IL-6 production by these cells appears to be an important factor in the development of WM.

Scientists are learning about the exact gene changes that cause WM. But even though they have found some of these gene changes, they still do not know why these changes occur.
Can Waldenstrom Macroglobulinemia Be Prevented?

Most of the risk factors for Waldenstrom macroglobulinemia (WM), such as older age or monoclonal gammopathy of undetermined significance (MGUS), can’t be changed or controlled, so there is no way to prevent cancers that might be related to these risk factors.

Some research suggests that people with hepatitis C might be more likely to develop WM. There is currently no vaccine to prevent hepatitis C, but there are ways to lower your risk of getting it, such as avoiding known risk factors like injection drug use or unprotected sex with many partners. Hepatitis C can also be treated effectively in many cases, although it’s not known how this might affect a person’s risk of WM.
Waldenstrom Macroglobulinemia Early Detection, Diagnosis, and Staging

Detection and Diagnosis

Catching cancer early often allows for more treatment options. Some early cancers may have signs and symptoms that can be noticed, but that is not always the case.

- [Can Waldenstrom Macroglobulinemia Be Found Early?](#)
- [Signs and Symptoms of Waldenstrom Macroglobulinemia](#)
- [How Is Waldenstrom Macroglobulinemia Diagnosed?](#)

Stages and Outlook (Prognosis)

After a cancer diagnosis, staging provides important information about the extent of cancer in the body and anticipated response to treatment.

- [How Is Waldenstrom Macroglobulinemia Staged?](#)
- [Survival Rates for Waldenstrom Macroglobulinemia](#)

Questions to Ask About Waldenstrom Macroglobulinemia

Here are some questions you can ask your cancer care team to help you better understand your cancer diagnosis and treatment options.

- [What Should You Ask Your Doctor About Waldenstrom Macroglobulinemia?](#)

Can Waldenstrom Macroglobulinemia Be Found Early?
Waldenstrom macroglobulinemia (WM) is not common, and at this time there are no widely recommended screening tests to look for this disease in people without symptoms.

Still, many cases of WM are found early, either when people go to the doctor because of symptoms they are having, or when they have blood tests done for other reasons. The best way to find this cancer early is to see your doctor if you have signs or symptoms that might be caused by this disease.

- References

See all references for Waldenstrom Macroglobulinemia

Signs and Symptoms of Waldenstrom Macroglobulinemia

Sometimes, Waldenstrom macroglobulinemia (WM) isn’t causing any symptoms when it’s first found. Instead, it’s found when the person has blood tests done for some other reason. WM found this way is sometimes called asymptomatic or smoldering WM.

When WM does cause symptoms, some of them can be like those seen with other types of non-Hodgkin lymphoma (NHL). For example, weight loss, fever, night sweats, and swollen lymph nodes can be seen in many types of NHL.

Other WM symptoms are caused by the large amounts of abnormal IgM antibody (M protein) made by the cancer cells:

- In hyperviscosity syndrome, too much of the M protein in the blood can cause it to become too “thick.” (This is not the kind of thickness that can be treated with drugs known as blood thinners.) When the blood gets too thick, it has trouble moving through blood vessels. This can cause problems such as poor circulation to the brain, which can lead to symptoms like those from a stroke.
  - If the M protein only thickens the blood in cooler parts of the body (like in the tip of
the nose, ears, fingers, and toes), it is called a cryoglobulin. Cryoglobulins can cause pain or other problems in these areas if a person is exposed to cooler temperatures.

- A condition called amyloidosis can occur when a part of the IgM antibody (called the light chain) builds up in organs like the heart and kidneys. This buildup can lead to heart and kidney problems.

Not all people with WM develop hyperviscosity, cryoglobulins, or amyloidosis.

**Common symptoms of WM**

**Weakness:** This is one of the most common symptoms of WM. It can be caused by anemia (too few red blood cells), which can happen when the WM cells crowd out normal cells in the bone marrow. Some people also feel weak when the blood thickens from the buildup of the abnormal protein.

**Loss of appetite:** Some people with WM lose their appetite.

**Fever, sweats, weight loss:** WM, like other lymphomas, can cause fevers (without an infection), drenching night sweats, and weight loss (without trying). Together, these are called B symptoms.

**Neuropathy:** In some people with WM, the abnormal antibody can attack and damage nerves outside the brain. This can lead to numbness or a painful “pins and needles” sensation in the feet and legs, which is called neuropathy.

**Other problems**

**Enlarged lymph nodes:** These usually appear as lumps under the skin around the neck, in the groin, or in the armpits. Enlarged lymph nodes are usually about 1 or 2 inches across. They are seen less often in WM than in most other lymphomas.

**Swollen abdomen (belly):** WM can sometimes make the spleen or liver bigger, making the belly look swollen. In the upper part of the abdomen, the liver is on the right and the spleen on the left. When the spleen gets larger, it can press on the stomach, which makes people feel full when they eat even a small amount.

**Nervous system symptoms:** In hyperviscosity syndrome, the thickened blood causes poor brain circulation, leading to problems like headache, confusion, and dizziness. It can also cause symptoms like those seen with a stroke, including slurred speech and weakness on one side of the body. Patients with these symptoms should contact their
Abnormal bleeding: High levels of abnormal antibody can damage blood vessels, which can lead to problems like nosebleeds and bleeding gums.

Vision problems: Bleeding around the small blood vessels inside the eyes or poor circulation in these vessels caused by thickened blood might lead to blurred vision or blind spots.

Kidney problems: High levels of the M protein can damage the kidneys directly or through the development of amyloidosis. When the kidneys don’t work well, excess salt, fluid, and body waste products stay in the blood. This can cause symptoms like weakness, trouble breathing, and fluid buildup in body tissues.

Heart problems: High levels of the M protein can damage heart tissue directly or through the development of amyloidosis, in which the protein builds up in the heart muscle. This weakens the heart, affecting its ability to pump blood. In addition, because the blood of people with WM is thicker than normal, their hearts have to work harder to pump blood throughout the body. This strain can wear down the heart muscle, leading to a condition called congestive heart failure. Symptoms can include heart palpitations, feeling tired and weak, cough, shortness of breath, rapid weight gain, and swelling in the feet and legs.

Infections: The high levels of abnormal antibody in WM can slow the body’s normal antibody production. This makes it harder for the body to resist infections.

Digestive symptoms: In some people with WM, the buildup of the M protein in the intestines can lead to problems such as diarrhea, poor absorption of vitamins, or gastrointestinal bleeding (seen as blood in the stools or dark stools).

Sensitivity to cold: In people with cryoglobulins, exposure to cold temperatures can lead to pain, itching, a bluish color, or even sores on the tip of the nose, ears, fingers, or toes due to reduced blood flow to these areas.

- References
  See all references for Waldenstrom Macroglobulinemia

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How Is Waldenstrom Macroglobulinemia Diagnosed?

Waldenstrom macroglobulinemia (WM) is often found when a person goes to see their doctor because of symptoms they are having, or because they just don’t feel well and go in for a checkup. Sometimes it’s found in people without symptoms when they have blood tests done for some other reason.

If signs or symptoms suggest that a person might have WM, exams and tests will be done to be sure. The most important ones will look for abnormal proteins in the blood and abnormal cells in the bone marrow.

This document is about WM, but it will sometimes discuss ways to diagnose non-Hodgkin lymphoma (NHL). This is because WM is a type of lymphoma. Like other lymphomas, WM can invade the bone marrow, lymph nodes, and other organs.

Medical history and physical exam

If you have signs or symptoms that suggest you might have WM (or another type of lymphoma), your doctor will want to get a thorough medical history, including information about your symptoms, possible risk factors, family history, and other medical conditions.

Next, the doctor will examine you, paying special attention to your lymph nodes and other areas of your body that might be involved, including the eyes, nerves, spleen, and liver. The doctor might also look for signs of infection, which can cause many of the same symptoms.

If the doctor suspects that WM (or another type of lymphoma) might be causing your symptoms, he or she will probably order blood tests as the next step. You might also be referred to a hematologist, a doctor who specializes in diseases of the blood.

Lab tests

WM might be suspected if your doctor finds you have low blood cell counts or unusual
protein levels on blood tests. If so, your doctor may order a blood test called serum protein electrophoresis to find out what the abnormal proteins are. It is usually only after these tests are done that a biopsy of either the bone marrow or a lymph node is considered.

**Blood cell counts**

The complete blood count (CBC) is a test that measures the levels of red blood cells, white blood cells, and platelets. If lymphoma cells occupy too much of the bone marrow, these levels will be low.

**Quantitative immunoglobulins**

This test measures the levels of the different antibodies (immunoglobulins) in the blood – IgA, IgE, IgG, and IgM – to see if any are abnormally high or low. In WM the level of IgM is high but the IgG level is often low.

**Electrophoresis**

The abnormal immunoglobulin made in WM is an IgM antibody. This antibody is monoclonal, meaning that it is many copies of the exact same antibody. Serum protein electrophoresis (SPEP) is a test that measures the total amount of immunoglobulins in the blood and finds any monoclonal immunoglobulin. Another test, such as immunofixation or immunoelectrophoresis, is then used to determine the type of antibody that is abnormal (IgM or some other type).

Finding a monoclonal IgM antibody in the blood is needed to diagnose WM. This abnormal protein in WM is known by many different names, including monoclonal immunoglobulin M, IgM protein, IgM spike, IgM paraprotein, M protein, and M-spike. High levels of other types of monoclonal immunoglobulins, like IgA or IgG, are seen in different disorders (like multiple myeloma and some other lymphomas).

Sometimes pieces of the IgM protein are excreted by the kidneys into the urine. These proteins can be detected with a test called urine protein electrophoresis (or UPEP).

**Viscosity**

Viscosity is a measure of how thick the blood is. If the IgM level is too high, the blood will become thick (viscous) and can’t flow freely (think about pouring honey compared to pouring water).
Cryocrit

This test measures the blood levels of cryoglobulins (proteins that clump together in cool temperatures and can block blood vessels).

Cold agglutinins

Cold agglutinins are antibodies that attack and kill red blood cells, especially at cooler temperatures. These dead cells can then build up and block blood vessels. A blood test can be used to detect these antibodies.

Beta-2 microglobulin (2M)

This test measures another protein made by the cancer cells in WM. This protein itself doesn’t cause any problems, but it’s a useful indicator of a patient’s prognosis (outlook). High levels of 2M are linked with a worse outlook.

Biopsies

The symptoms of WM and NHL are not distinctive enough for a doctor to know for certain if a person has one of them, based on symptoms alone. Most symptoms can also be caused by non-cancerous problems like infections or by other kinds of cancers. Blood tests can help point to the correct diagnosis, but a biopsy (removing samples of affected tissue to look at under a microscope) is the only way to be sure. Several types of biopsies might be used.

Bone marrow aspiration and biopsy

This is the most important type of biopsy for WM, and is needed to confirm the diagnosis. It can be done at the doctor’s office or at the hospital.

The bone marrow aspiration and biopsy are usually done at the same time. The samples are taken from the back of the pelvic (hip) bone, although in some cases they may be taken from the sternum (breast bone) or other bones.

In bone marrow aspiration, you lie on a table (either on your side or on your belly). The doctor cleans the skin over the hip and then numbs the area and the surface of the bone by injecting a local anesthetic. This may briefly sting or burn. A thin, hollow needle is then inserted into the bone, and a syringe is used to suck out a small amount of liquid
bone marrow. Even with the anesthetic, most patients still have some brief pain when the marrow is removed.

A bone marrow biopsy is usually done just after the aspiration. A small piece of bone and marrow is removed with a slightly larger needle that is pushed down into the bone. This may also cause some brief pain.

Once the biopsy is done, pressure is applied to the site to help stop any bleeding. There will be some soreness in the biopsy area when the numbing medicine wears off. Most patients can go home right after the procedure.

The bone marrow samples are then sent to a lab, where they are tested to see if they have lymphoma cells (see below). For a diagnosis of WM, at least 10% of the cells in the bone marrow must be lymphoplasmacytoid lymphoma cells.

**Fine needle aspiration (FNA) biopsy**

In an FNA biopsy, the doctor uses a very thin, hollow needle with a syringe to withdraw a small amount of tissue from a tumor or lymph node. This type of biopsy is useful for sampling lymph nodes to see if they are enlarged because of cancer or another cause such as infection. FNA can help diagnose some lymphomas, but WM is usually diagnosed with a bone marrow biopsy instead.

For an FNA on an enlarged node near the surface of the body, the doctor can aim the needle while feeling the node. If the enlarged node (or tumor) is deep inside the body, the needle can be guided while it is seen on a computed tomography (CT) scan or ultrasound (see the descriptions of imaging tests later in this section).

The main advantage of FNA is that it does not require surgery and can often be done in a doctor’s office. The main drawback is that in some cases it might not get enough tissue to make a definite diagnosis of lymphoma. However, advances in lab tests (discussed later in this section) and the growing experience of many doctors with FNA have improved the accuracy of this procedure.

**Excisional or incisional biopsy**

For these types of biopsies, a surgeon cuts through the skin to remove an entire lymph node or tumor (excisional biopsy) or a just a small part of a large tumor or lymph node (incisional biopsy). These biopsies are rarely needed in people with WM because the diagnosis is usually made with a bone marrow biopsy. They are used more often for other types of lymphoma.
If the area to be biopsied is near the skin surface, this can be done using local anesthesia (numbing medicine). If the area is inside the chest or abdomen, general anesthesia or deep sedation is used (where the patient is asleep). These types of biopsies almost always provide enough tissue to diagnose the exact type of lymphoma.

**Fat pad fine needle aspiration**

This type of biopsy may be used in some people with WM to check for amyloid. In this procedure, a thin, hollow needle with a syringe attached is inserted into an area of fat (usually under the skin of the abdomen/belly). A small amount of fat is removed and sent to the lab for testing.

**Lab tests on biopsy specimens**

All biopsy specimens are looked at under a microscope by a pathologist—a doctor with special training in using lab tests to diagnose diseases. In some cases, a hematopathologist, a doctor with further training in diagnosing blood and lymph node diseases, might also look at the biopsy. The doctors look at the size and shape of the cells and how the cells are arranged. Sometimes just looking at the cells doesn't provide a clear answer, so other lab tests are needed.

**Immunohistochemistry**

In this test, a part of the biopsy sample is treated with special man-made antibodies that attach to cells only if they contain specific molecules. These antibodies cause color changes, which can be seen under a microscope. This test may help tell different types of lymphoma from one another and from other diseases.

**Flow cytometry**

In this test, cells are treated with special man-made antibodies. Each antibody sticks only to certain types of cells. The cells are then passed in front of a laser beam. If the cells now have antibodies attached to them, the laser will make them give off light, which is measured and analyzed by a computer.

This is the most common test for immunophenotyping—classifying lymphoma cells according to the substances (antigens) on their surfaces. Different types of lymphocytes have different antigens on their surface. These antigens also change as each cell matures.
This test can help show whether a lymph node is swollen because of lymphoma, some other cancer, or a non-cancerous disease. It has become very important in helping doctors determine the exact type of lymphoma so they can select the best treatment.

**Cytogenetics**

Doctors use this technique to look at the chromosomes (long strands of DNA) inside lymphoma cells. Cells (usually from the bone marrow) are first grown in the lab. Then the chromosomes are stained and looked at under a microscope. Because it takes time for the cells to start dividing, this test can take weeks.

In some lymphomas, the cells may have too many chromosomes, too few chromosomes, missing parts of chromosomes (called deletions), or other abnormalities. These changes can help identify the type of lymphoma. In WM, deletions are the most common type of chromosome change.

**Molecular genetic tests**

Molecular tests such as fluorescent in situ hybridization (FISH) and polymerase chain reaction (PCR) are not usually needed to diagnose WM, but they are sometimes used to diagnose other types of NHL. These tests look at the cells’ DNA without having to grow the cells in the lab first. The tests can give results in less time than cytogenetics and can be done on cells from different sources (like lymph nodes, blood, and bone marrow). They are generally used to look for specific chromosome or gene changes, not just any change.

**More testing information**

See our document Testing Biopsy and Cytology Specimens for Cancer to learn more about different types of biopsies and lab tests used to diagnose cancer and what the results can tell you.

**Imaging tests**

Imaging tests use x-rays, magnetic fields, sound waves, or radioactive particles to produce pictures of the inside of the body. These tests are not needed to diagnose WM, but one or more of them might be done to help show the extent of the disease in the body.
**Chest x-ray**

An x-ray might be done to look at the chest for enlarged lymph nodes.

**Computed tomography (CT) scan**

The CT scan uses x-rays to make detailed cross-sectional images of your body. Unlike a regular x-ray, CT scans can show the detail in soft tissues (such as internal organs). This scan can help show if any lymph nodes or organs in your body are enlarged. CT scans are useful for looking for signs of lymphoma in the chest, abdomen, and pelvis.

Before the test, you may be asked to drink a contrast solution and/or get an intravenous (IV) injection of a contrast dye to better outline abnormal areas in the body. You might need an IV line through which the contrast dye is injected. The injection can cause some flushing (a feeling of warmth, especially in the face). Some people are allergic to the dye and get hives or a flushed feeling or, rarely, have more serious reactions like trouble breathing and low blood pressure. Be sure to tell the doctor if you have any allergies (especially iodine or shellfish) or have ever had a reaction to any contrast material used for x-rays. Medication can be given to help prevent and treat allergic reactions.

A CT scanner has been described as a large donut, with a narrow table that slides in and out of the middle opening. You need to lie still on the table while the scan is being done. CT scans take longer than regular x-rays, and some people might feel a bit confined by the ring while the pictures are being taken.

**CT-guided needle biopsy:** CT scans can also be used to guide a biopsy needle into a suspicious area. For this procedure, the patient lies on the CT scanning table while the doctor moves a biopsy needle through the skin and toward the area. CT scans are repeated until the needle is in the right place. A biopsy sample is then removed and sent to the lab to be looked at under a microscope.

**Magnetic resonance imaging (MRI) scan**

Like CT scans, MRI scans make detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays. This test is rarely used in WM, but if your doctor is concerned about the brain or spinal cord, MRI is very useful for looking at these areas.

Sometimes a contrast material is injected into a vein to make some structures clearer. This contrast is not the same as the contrast used for CT scans, but allergic reactions
can still occur. Again, medicine can be given to prevent and treat allergic reactions.

MRI scans take longer than CT scans – often up to an hour. You may have to lie inside a narrow tube, which is confining and can upset some people. Newer, more open MRI machines might be another option. The machine makes loud buzzing and clicking noises that some people find disturbing. Some places provide headphones or earplugs to help block this noise out.

**Ultrasound**

Ultrasound uses sound waves and their echoes to make pictures of internal organs or masses.

Ultrasound can be used to look at lymph nodes near the surface of the body or to look inside your abdomen for enlarged lymph nodes or organs such as the liver, spleen, and kidneys. (It can’t be used to look at organs or lymph nodes in the chest because the ribs block the sound waves.) It is sometimes used to help guide a biopsy needle into an enlarged lymph node.

For this test, a small, microphone-like instrument called a *transducer* is placed on the skin (which is first lubricated with a gel). It gives off sound waves and picks up the echoes as they bounce off the organs. A computer then converts the echoes into a black and white image on a screen.

This is an easy test to have, and it uses no radiation. For most ultrasounds, you simply lie on a table, and a technician moves the transducer over the part of your body being looked at.

**Positron emission tomography (PET) scan**

For a PET scan, a radioactive sugar (known as *FDG*) is injected into the blood. (The amount of radioactivity used is very low and will pass out of the body in a day or so.) Because cancer cells in the body grow quickly, they absorb large amounts of the sugar. You then lie on a table in the PET scanner for about 30 minutes while a special camera creates a picture of areas of radioactivity. The picture is not detailed like a CT or MRI scan, but it can provide helpful information about your whole body.

PET scans can help tell if an enlarged lymph node contains lymphoma or not. It can also help spot small areas that might be lymphoma, even if the area looks normal on a CT scan. These tests can be used to tell if a lymphoma is responding to treatment. They can also be used after treatment to help decide whether an enlarged lymph node still
contains lymphoma or is merely scar tissue.

Many medical centers now use a machine that combines the PET scan with a CT scan (PET/CT scan). This lets the doctor compare areas of higher radioactivity on the PET scan with the more detailed appearance of that area on the CT scan.

- References

See all references for Waldenstrom Macroglobulinemia

How Is Waldenstrom Macroglobulinemia Staged?

For most types of cancer, determining the stage of the cancer is very important. The stage of a cancer is a summary of how far it has spread. This can be helpful in predicting outcomes and in deciding on treatment.

There is no standard staging system for Waldenstrom macroglobulinemia (WM) based on the extent of the disease in the body because this hasn’t been shown to be important when looking at outcomes or deciding on treatment.

Instead, doctors look at other factors, such as age, blood cell counts, the amount of immunoglobulin (IgM) in the blood, and the level of another protein in the blood called beta-2 microglobulin (2M). People with lower levels of IgM and 2M tend to do better than those with higher levels. People with WM who are older, are anemic (based on a low blood hemoglobin level), or have a low blood platelet count tend to have a poorer outlook.

Experts have used these factors to develop a system that helps predict prognosis (outlook) for patients with WM. It is called the International Prognostic Scoring System for Waldenstrom Macroglobulinemia (ISSWM). This system takes into account the factors that seem to predict a poorer outcome, such as:
• Age more than 65 years old
• Blood hemoglobin level 11.5 g/dL or less
• Platelet count 100,000/mcL or less
• Beta-2 microglobulin more than 3 mg/L
• Monoclonal IgM level more than 7 g/dL

Except for age, each of these factors is worth a single point. The points are added to make a score, which is used to divide patients into 3 risk groups:

• The low-risk group includes patients 65 or younger who have no more than 1 point.
• The intermediate-risk group includes those who are older than 65 with 2 or fewer points, and those younger than 65 who have 2 points.
• The high-risk group includes those of any age who have at least 3 points.

These groups can be used to help predict survival (discussed in more detail in Survival Rates for Waldenstrom Macroglobulinemia).

• References
See all references for Waldenstrom Macroglobulinemia

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Survival Rates for Waldenstrom Macroglobulinemia

Survival rates are often used by doctors as a standard way of discussing a person’s prognosis (outlook).

The 5-year survival rate refers to the percentage of patients who live at least 5 years after their cancer is diagnosed. Of course, many people live much longer than 5 years.

Five-year relative survival rates assume that some people with WM will die of other causes and compare the observed survival with that expected for people without WM. This is a better way to see the impact of the cancer on survival.
To get 5-year survival rates, doctors have to look at people who were treated at least 5 years ago. There have been many improvements in the treatment of WM in recent years, so people now being diagnosed with WM may have a better outlook than would be expected based on the numbers below.

According to the National Cancer Institute’s SEER database (based on people diagnosed between 2001 and 2010), the overall relative 5-year survival of people with WM is about 78%.

The group that created the International Prognostic Scoring System for Waldenstrom Macroglobulinemia (ISSWM) used data from about 600 patients with WM who were diagnosed and treated before January 2002 to develop their risk groups:

<table>
<thead>
<tr>
<th>ISSWM risk group</th>
<th>5-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>87%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>68%</td>
</tr>
<tr>
<td>High</td>
<td>36%</td>
</tr>
</tbody>
</table>

**Median survival**

Median survival is another way to look at survival. It is the length of time at which half of the patients in a group are still alive, and half have died. By definition, half of the patients live longer than the median survival. The group that developed the ISSWM used data from WM patients diagnosed and treated before January 2002 and found the following:

<table>
<thead>
<tr>
<th>ISSWM risk group</th>
<th>Median survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>12 years</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8 years</td>
</tr>
<tr>
<td>High</td>
<td>3.5 years</td>
</tr>
</tbody>
</table>

*Median survival is measured from the point that treatment is started.

Survival rates are based on previous outcomes of large numbers of people who had the disease, but they can’t predict what will happen with any particular person. They don’t take into account all of the factors that can affect a person’s outlook, such as how well the cancer responds to treatment. Your doctor knows your situation best and can tell you how the numbers above might apply to you.
What Should You Ask Your Doctor About Waldenstrom Macroglobulinemia?

As you deal with Waldenstrom macroglobulinemia (WM) and the process of treatment, you need to have honest, open discussions with your cancer care team. You should ask about anything you don’t understand or want to know more about. Among the questions you might want to ask are:

- How sure are you about my diagnosis?
- Do I need any other tests before we can decide on treatment?
- Do I need to see any other doctors?
- How much experience do you have treating this disease?
- Should I get a second opinion before starting treatment? Can you suggest someone?
- What treatment options do I have?
- Are there clinical trials I should consider?
- Do you recommend starting treatment now or waiting until later on?
- What would be the goal of treatment (to reduce symptoms, lower IgM levels, etc.)?
- Which drugs do you recommend? How would you compare their effectiveness and side effects to others?
- Is a stem cell transplant an option in my situation? What are the pros and cons of this treatment?
- What should I do to be ready for treatment?
- How long will treatment last? What will it be like? Where will it be done?
- What side effects might I expect from treatment?
- How long will it take me to recover from treatment?
- When can I go back to work or resume other activities after treatment?
- What would we do if the treatment doesn’t work or if the cancer comes back?
- What is my outlook for survival?
- What type of follow-up will I need after treatment?

You will no doubt have other questions. Be sure and write them down so you remember to ask them during each visit with your cancer care team. Keep in mind, too, that doctors are not the only ones who can give you information. Other health care professionals, such as nurses and social workers, might be able to answer some of your questions. You can find out more about speaking with your health care team in The Doctor-Patient Relationship.

- References

See all references for Waldenstrom Macroglobulinemia

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Treating Waldenstrom Macroglobulinemia

Once Waldenstrom macroglobulinemia (WM) has been diagnosed, your cancer care team will discuss your treatment options with you. Your options may be affected by factors such as your age and general health and the type of symptoms you are having.

Not everyone with WM needs to be treated right away. People who don’t have serious or bothersome symptoms can often be watched closely, and then treated later if needed (see “When to treat people with Waldenstrom macroglobulinemia”).

If treatment is needed for WM, several types can be used:

- Chemotherapy
- Targeted drugs
- Biological therapy (immunotherapy)
- Plasmapheresis (plasma exchange)
- High-dose chemotherapy and stem cell transplant
- Radiation therapy

The 2 main ways to treat WM are chemotherapy and different types of biological therapy (immunotherapy). Based on the situation, one or both of these types of treatments might be used. See

In recent years, much progress has been made in treating people with WM. A number of newer drugs have been found to work against WM, but few studies have compared them to see which ones are best. Because of this, there is no single standard treatment for all patients.

In choosing a treatment plan, consider your health, your symptoms, and what you hope to get from treatment. Be sure that you understand all the risks and side effects of your treatment options before making a decision.
Based on your treatment options, you might have different types of doctors on your treatment team:

- A hematologist: a doctor who treats disorders of the blood, including lymphomas such as WM
- A medical oncologist: a doctor who treats cancer with chemotherapy and other medicines
- A radiation oncologist: a doctor who treats cancer with radiation therapy

Many other specialists might be part of your treatment team as well, including physician assistants (PAs), nurse practitioners (NPs), nurses, nutrition specialists, social workers, and other health professionals. See Health Professionals Associated With Cancer Care for more on this.

**Making treatment decisions**

It’s important to discuss all treatment options, including their goals and possible side effects, so you can make the decision that best fits your needs. You may feel that you need to make a decision quickly, but it’s important to give yourself time to absorb the information you have learned. Ask your cancer care team questions. You can find some good questions to ask in Questions to Ask Your Doctor About Waldenstrom Macroglobulinemia.

**Getting a second opinion**

You may want to get a second opinion. This can give you more information and help you feel more certain about the treatment plan you choose. If you aren’t sure where to go for a second opinion, ask your doctor for help.

**Thinking about taking part in a clinical trial**

Clinical trials are carefully controlled research studies that are done to get a closer look at promising new treatments or procedures. Clinical trials are one way to get state-of-the-art cancer treatment. In some cases they may be the only way to get access to newer treatments. They are also the best way for doctors to learn better methods to treat cancer. Still, they’re not right for everyone.

If you would like to learn more about clinical trials that might be right for you, start by asking your doctor if your clinic or hospital conducts clinical trials. See Clinical Trials to learn more.
Considering complementary and alternative methods

You may hear about alternative or complementary methods that your doctor hasn’t mentioned to treat your cancer or relieve symptoms. These methods can include vitamins, herbs, and special diets, or other methods such as acupuncture or massage, to name a few.

Complementary methods refer to treatments that are used along with your regular medical care. Alternative treatments are used instead of a doctor’s medical treatment. Although some of these methods might be helpful in relieving symptoms or helping you feel better, many have not been proven to work. Some might even be dangerous.

Be sure to talk to your cancer care team about any method you are thinking about using. They can help you learn what is known (or not known) about the method, which can help you make an informed decision. See Complementary and Alternative Medicine to learn more.

Choosing to stop treatment or choosing no treatment at all

For some people, when treatments have been tried and are no longer controlling the cancer, it could be time to weigh the benefits and risks of continuing to try new treatments. Whether or not you continue treatment, there are still things you can do to help maintain or improve your quality of life. Learn more in If Cancer Treatments Stop Working.

Some people, especially if the cancer is advanced, might not want to be treated at all. There are many reasons you might decide not to get cancer treatment, but it’s important to talk to your doctors and you make that decision. Remember that even if you choose not to treat the cancer, you can still get supportive care to help with pain or other symptoms?

Help getting through cancer treatment

Your cancer care team will be your first source of information and support, but there are other resources for help when you need it. Hospital- or clinic-based support services are an important part of your care. These might include nursing or social work services, financial aid, nutritional advice, rehab, or spiritual help.

The American Cancer Society also has programs and services – including rides to treatment, lodging, and more – to help you get through treatment. Call our National
Cancer Information Center at 1-800-227-2345 and speak with one of our trained specialists.

The treatment information given here is not official policy of the American Cancer 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.

Chemotherapy for Waldenstrom Macroglobulinemia

Chemotherapy (chemo) uses anti-cancer drugs that are taken by mouth, or injected into a vein, a muscle, or under the skin. These drugs enter the bloodstream and reach all areas of the body, making this treatment very useful for Waldenstrom macroglobulinemia (WM).

Doctors give chemo in cycles, in which a period of treatment is followed by a rest period to allow the body time to recover. Each chemo cycle generally lasts for several weeks. Most chemo treatments are given on an outpatient basis (in the doctor’s office, clinic, or hospital outpatient department).

Many types of chemo drugs can be used to treat patients with WM:

**Alkylating agents**

- Cyclophosphamide (Cytoxan®)
- Chlorambucil
- Bendamustine (Treanda®)

**Purine analogs**

- Fludarabine (Fludara®)
- Cladribine (2-CdA, Leustatin®)

**Corticosteroids**

- Prednisone
- Dexamethasone (Decadron®)
Other chemo drugs

- Vincristine (Oncovin®)
- Doxorubicin (Adriamycin®)

Chemo drugs may be used alone or combined with other drugs, such as targeted drugs or immunotherapy drugs. (For a list of some common combinations used in WM, see When to Treat People With Waldenstrom Macroglobulinemia.)

Chemo side effects

Chemo drugs attack cells that are dividing quickly, which is why they work against WM cells. But other cells in the body, such as those in the bone marrow (where new blood cells are made), the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to certain side effects.

The side effects of chemo depend on which drugs are used, the doses, and the length of time they are taken. Common side effects include:

- Nausea and vomiting
- Loss of appetite
- Hair loss
- Mouth sores
- Diarrhea or constipation
- Increased risk of infections (from having too few white blood cells)
- Problems with bleeding or bruising (from having too few blood platelets)
- Fatigue (tiredness) and shortness of breath (from having too few red blood cells)

Other side effects can be seen with certain drugs. For example, doxorubicin can damage the heart. Corticosteroid drugs can cause problems sleeping and an increased appetite.

If you have side effects, your cancer care team can suggest steps to ease them. For example, medicines can be taken to help prevent and control nausea and vomiting. Most side effects are temporary and go away after treatment is finished. If you have serious side effects, the chemo may have to be reduced or stopped, at least temporarily.

Long-term side effects of chemotherapy

Some chemo drugs cause long-term side effects that can affect almost any part of the
body. One of the most serious complications with certain chemo drugs is the possibility of developing leukemia later on. It affects a very small percentage of patients, but it is more common in patients who take fludarabine or alkylating agents.

For more about chemotherapy, see the Chemotherapy.

- References
See all references for Waldenstrom Macroglobulinemia

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Targeted Drugs for Waldenstrom Macroglobulinemia

As researchers have learned more about the changes inside cells that cause cancer, they have developed newer drugs that target these changes. They are often referred to as targeted therapy. These drugs work differently from standard chemotherapy (chemo) drugs. They sometimes work when chemo drugs don’t, and they often have different (and less severe) side effects.

Proteasome inhibitors

These drugs stop enzyme complexes (proteasomes) inside cells from breaking down proteins that normally help keep cell division under control.

Bortezomib (Velcade®) is often used to treat multiple myeloma and some types of lymphoma. It has also been found to be helpful in some cases of WM. This drug is given as an infusion into a vein (IV) or an injection under the skin (sub-q).

Other proteasome inhibitors, such as carfilzomib (Kyprolis®), are now being studied to see if they can help treat WM as well.

Although these drugs work in a slightly different way from most chemo drugs, they can still cause many of the same types of side effects, including low blood counts, nausea,
and loss of appetite. They can also damage nerves, causing pain in the feet and legs. The nerve damage usually gets better after the drug is stopped, but it might not go away completely.

**mTOR inhibitors**

These drugs block a cell protein known as mTOR, which normally helps cells grow and divide into new cells.

**Everolimus (Afinitor®)** is used more often to treat some other types of cancer, but it has also been shown to be useful in treating WM after other treatments have been tried. This drug is taken daily as a pill. Common side effects include fatigue (tiredness), mouth pain, rash, diarrhea, and infections.

Other mTOR inhibitors, such as **temsirolimus (Torisel®)**, are now being studied to see if they can help treat WM as well.

**Bruton tyrosine kinase (BTK) inhibitors**

**Ibrutinib (Imbruvica®)** blocks a protein called **Bruton tyrosine kinase (BTK)** inside lymphoma cells, which normally helps the cells grow and survive. This drug can be used to treat some types of lymphoma, including WM. Ibrutinib is taken by mouth, once a day. Common side effects include diarrhea or constipation, nausea and vomiting, fatigue, swelling, decreased appetite, and low blood counts.

Other drugs that block BTK or other kinases in lymphoma cells are also being studied for use against WM (see [What's New in Waldenstrom Macroglobulinemia Research and Treatment?](#)).

- **References**
  
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**Biological Therapy or Immunotherapy**
for Waldenstrom Macroglobulinemia

Biological therapies help the body’s immune system fight the cancer or use man-made versions of substances normally made by the immune system. These substances can kill Waldenstrom macroglobulinemia (WM) cells or slow their growth.

Monoclonal antibodies

Antibodies are proteins made by the immune system to help fight infections. Man-made versions, called monoclonal antibodies, can be designed to attack a specific target, such as a substance on the surface of lymphocytes (the cells in which WM starts).

Rituximab (Rituxan®) is the most widely used monoclonal antibody for WM. It attaches to a protein on the surface of lymphoma cells called CD20. This attachment tells the lymphoma cell to die. Patients get rituximab by infusion into a vein (IV) at the doctor’s office or clinic. Rituximab can be given alone or with chemotherapy (or other drugs) as a part of treatment.

This drug has to be given carefully in patients with WM because sometimes it can actually raise the level of IgM in the blood at first, which can lead to problems with hyperviscosity (thickened blood). Side effects during the infusion are common, and can include chills, fever, nausea, rashes, fatigue, and headaches. Unlike regular chemotherapy, rituximab does not cause low blood counts or hair loss.

Ofatumumab (Arzerra®) is another antibody that targets the CD20 antigen. It can be used in people who have trouble taking rituximab. Side effects are similar to those seen with rituximab, including an increased risk of IgM levels going up when the drug is first given.

Alemtuzumab (Campath®) is directed at a different protein on lymphoma cells called CD52. This drug is more commonly used to treat patients with chronic lymphocytic leukemia, but it also helps some patients with WM. It is given by infusion into a vein (IV) or under the skin, usually 3 times a week. A serious side effect of alemtuzumab is a large drop in blood cell counts that can last weeks or even months. People on this drug can develop life-threatening infections that are hard to treat while their white blood cells are low.

Immunomodulating drugs

Immunomodulating drugs (IMiDs) are thought to work against certain cancers by
boosting parts of your immune system, although exactly how they work is not clear. These drugs are most often used to treat multiple myeloma, but they might also be helpful in treating WM.

**Thalidomide (Thalomid®)** is the IMiD with the most evidence showing it can help some patients with WM. But many patients have trouble tolerating some of the side effects of this drug. These include drowsiness, fatigue (tiredness), severe constipation, and neuropathy (painful nerve damage). The neuropathy might not go away after the drug is stopped. There is also an increased risk of serious blood clots that start in the leg and can travel to the lungs. The best results with thalidomide in WM have been seen when it is given along with other drugs, such as rituximab or dexamethasone.

**Lenalidomide (Revlimid®) and pomalidomide (Pomalyst®)** are newer IMiDs that generally cause less severe side effects than thalidomide. These drugs are used mainly to treat multiple myeloma, but studies are now looking at whether they can help treat WM as well.

Because of concerns these drugs can cause severe birth defects if taken during pregnancy, they can only be obtained through special programs run by the drug company that makes them.

**Cytokines**

Cytokines are hormone-like proteins normally made by white blood cells to help your immune system fight infections.

**Interferon** is a cytokine that can be made in the lab and given to patients. Some studies have suggested that interferon can make some lymphoma tumors 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 a good option for patients with WM. It is most often used only in patients who continue to get sicker after treatment with other drugs.

For more on biologic treatments and immunotherapies for cancer, see [Cancer Immunotherapy](#).

- [References](#)
  See all references for Waldenstrom Macroglobulinemia

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Plasmapheresis (Plasma Exchange) for Waldenstrom Macroglobulinemia

If the level of the abnormal IgM protein in the blood gets very high in a patient with Waldenstrom macroglobulinemia (WM), the blood becomes very thick (viscous). This is called hyperviscosity syndrome and can lead to brain damage (like a stroke) and bleeding problems. When this happens, the level of IgM needs to be lowered right away.

Plasmapheresis (also known as plasma exchange) does this using a machine that separates the plasma (the liquid part of the blood) that contains the abnormal IgM protein from the blood cells. The plasma containing the abnormal protein is discarded, while the blood cells are mixed with salt solution and plasma from a donor and given back to the patient.

Plasmapheresis is done over a few hours while the person lies in a bed or sits in a reclining chair. The blood is removed through an IV line (usually in a vein in the arm), goes through the machine where the plasma is replaced, and then is returned to the body through another IV line. Sometimes, minor surgery is done before the procedure to put a single large catheter in a large vein just below the neck or under the collar bone instead of using IV lines in the arms. This type of catheter, called a central line or central venous catheter (CVC), has both IVs built in.

Plasmapheresis is not painful (aside from the IV lines being put in), but it can be hard to stay sitting or lying down in the same place for 2 or 3 hours. Calcium levels can drop in some people during treatment, causing numbness and tingling (especially in the hands and feet and around the mouth) and muscle spasms, which can sometimes be painful. This can be treated by giving the patient calcium.

Plasmapheresis works quickly to bring down the IgM level. However, it does not treat the cause of the high IgM level (the cancer cells themselves), so it will go back up again without further treatment (like chemotherapy). Plasmapheresis is usually given to help the patient until chemotherapy or other drugs have a chance to work. It can also be used in people whose WM is not controlled by chemotherapy, targeted therapy, biological therapy, or other treatments.
Stem Cell Transplant for Waldenstrom Macroglobulinemia

The doses of chemotherapy (chemo) drugs (and radiation) doctors can give are limited by the side effects they can cause. Higher doses can’t be used, even if they might kill more cancer cells, because they would severely damage the bone marrow, where new blood cells are made. This could lead to life-threatening infections, bleeding, and other problems due to low blood cell counts. Doctors can try to get around this problem by giving an infusion of blood-forming stem cells after treatment. These stem cells settle in the bone marrow, where they can create new blood cells.

A stem cell transplant (SCT) is not a common treatment for Waldenstrom macroglobulinemia (WM), but it might be an option in younger patients for whom other treatments are no longer working.

Blood-forming stem cells used for a transplant come either from the blood or from the bone marrow. Bone marrow transplants were more common in the past, but they have largely been replaced by stem cells taken from the blood.

The blood-forming stem cells can come either from the patient (called an autologous SCT) or from a donor (called an allogeneic SCT).

**Autologous stem cell transplant**

This is the type of transplant used most often in WM. In an autologous SCT, a patient’s own blood-forming stem cells are removed from his bloodstream and stored to use later. Then high doses of chemo (and sometimes radiation) are given to kill the WM cells. The high doses of chemo kill the normal bone marrow cells as well as the cancer cells. After chemo, the frozen stem cells are thawed and returned to the body (like a blood
transfusion).

Autologous transplants can help some people with WM, but doctors are still trying to figure out which patients will benefit the most.

**Allogeneic stem cell transplant**

This is a treatment that is still being studied for WM, and experts recommend it be done only as part of a clinical trial.

In an allogeneic SCT, the stem cells for the transplant come from someone else (a donor). The donor’s tissue type (also known as the HLA type) needs to match the patient’s tissue type as closely as possible to help prevent the risk of major problems with the transplant. Usually this donor is a brother or sister if they have the same tissue type as the patient. If there are no siblings with a good match, the cells may come from an HLA-matched, unrelated donor – a stranger who has volunteered to donate their cells.

The stem cells for an allogeneic SCT are usually collected from a donor’s bone marrow or blood on several occasions. Regardless of the source, the stem cells are then frozen and stored until they are needed for the transplant.

Allogeneic transplants have more risks and side effects than autologous transplants, so patients typically need to be younger and relatively healthy to be good candidates. Another challenge is that it can sometimes be difficult to find a matched donor.

One of the most serious complications of allogeneic SCTs is known as *graft-versus-host disease* (GVHD). It happens when the patient’s immune system is taken over by that of the donor. When this happens, the donor immune system may consider the patient’s own body tissues to be foreign and attacks them.

Symptoms can include severe skin rashes, itching, mouth sores (which can affect eating), nausea, and severe diarrhea. Liver damage can cause yellowing of the skin and eyes (jaundice). The lungs can also be damaged. The patient may also become easily fatigued and develop muscle aches. Sometimes GVHD can become disabling, and if it is severe enough, it can be life-threatening.

**Non-myeloablative transplant:** In this newer approach to allogeneic SCT (also called a mini-transplant), lower doses of chemo or radiation therapy are used than in a traditional allogeneic SCT. Patients are given drugs to suppress their immune system. This allows the donor cells to grow and partly take over the patient’s immune system.
The donor cells then begin attacking the WM cells (known as a *graft-versus-lymphoma* effect).

This type of transplant may be an option for some patients who couldn’t tolerate a regular allogeneic transplant because it would be too toxic. Most of the side effects with this type of transplant are less severe than with a standard allogeneic transplant. But this type of transplant can still cause graft-versus-host disease (GVHD), which can make patients very sick.

Doctors are trying to refine this treatment to work against the WM cells without affecting the normal cells.

**Practical points**

A stem cell transplant is a complex treatment that can cause life-threatening side effects because of the high doses of chemotherapy used. Be sure you understand the possible benefits and risks. If the doctors think you might benefit from a transplant, it should be done at a hospital where the staff has experience with the procedure and with managing the recovery phase. Some stem cell transplant programs might not have experience in certain types of transplants, especially transplants from unrelated donors.

SCTs often require a long hospital stay and can be very expensive (costing well over $100,000). Because some insurance companies might view it as an experimental treatment, they might not pay for it. Even if the transplant is covered by your insurance, your co-pays or other costs could easily amount to tens of thousands of dollars. Find out what your insurer will cover before deciding on a transplant so you will have an idea of what you might have to pay.

**Possible side effects**

Side effects from a stem cell transplant are generally divided into early and long-term effects.

**Early or short-term effects:** The early complications and side effects are basically the same as those caused by any other type chemotherapy (see [Chemotherapy for Waldenstrom Macroglobulinemia](https://www.cancer.gov/types/waldenstrom-macroglobulinemia/treatment#tab-side-effects)), but they tend to be more severe.

One of the most common and serious short-term effects is the increased risk of infection. Antibiotics are often given to try to keep this from happening. Other side effects, like low red blood cell and platelet counts, may require blood product transfusions or other treatments.
A possible side effect of allogeneic transplants is graft-versus-host disease, which is described above.

**Long-term side effects:** Some complications and side effects can remain for a long time or might not occur until months or years after the transplant. These include:

- Loss of fertility
- Damage to the thyroid gland
- Cataracts (damage to the lens of the eye)
- Damage to the lungs, causing shortness of breath
- Bone damage called aseptic necrosis (If damage is severe, the patient might need to have part of the affected bone and the joint replaced.)
- Development of another cancer (such as leukemia) years later

For more about stem cell transplants, see [Stem Cell Transplant for Cancer](#).

**References**

- See all references for Waldenstrom Macroglobulinemia

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## Radiation Therapy for Waldenstrom Macroglobulinemia

Radiation therapy uses high-energy rays to kill cancer cells. This type of treatment is not used often to treat Waldenstrom macroglobulinemia (WM). Rarely, it is used to shrink an enlarged spleen or lymph nodes if they are causing symptoms.

The type of radiation therapy used to treat WM is called *external beam radiation*. The treatment is much like getting an x-ray, but the radiation is much stronger. The procedure itself is painless. Before the treatments start, the radiation team takes careful measurements to determine the correct angles for aiming the radiation beams and the proper dose of radiation. Each treatment lasts only a few minutes, although the setup time — getting you into place for treatment — usually takes longer. Most often, radiation
treatments are given 5 days a week for a few weeks.

**Possible side effects**

Immediate side effects of radiation therapy can include sunburn-like skin problems, fatigue, and low blood cell counts. Other side effects depend on the area being treated. Radiation of the abdomen may cause nausea, vomiting, or diarrhea. Radiation to the head and neck area can lead to mouth sores and trouble swallowing. Often these effects go away a short while after treatment is finished.

A rare long-term side effect of radiation is a new cancer developing in the treated area.

To learn more about radiation therapy, visit A Guide to Radiation Therapy.

- References
  See all references for Waldenstrom Macroglobulinemia

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**When to Treat People With Waldenstrom Macroglobulinemia**

While Waldenstrom macroglobulinemia (WM) is generally not considered to be curable, it is treatable. Many different medicines can help keep WM under control, often for long periods of time.

Not everyone with WM needs treatment right away. In fact, some people are diagnosed with WM before they even have symptoms from it. Most experts recommend that people with WM should not usually be treated until the disease is causing problems. This lets people avoid the side effects of chemotherapy (chemo), targeted therapy, or immunotherapy drugs until they really need these medicines. In fact, studies suggest that patients who delay treatment until their WM is causing problems do not live any less time than those who start treatment as soon as they are diagnosed.
Doctors agree that hyperviscosity syndrome is a reason to treat right away, because it can be life threatening. Other reasons to start treatment include problems from amyloidosis or cryoglobulins, as well as anemia (too few red blood cells), kidney or heart problems, nerve damage, or any severe symptom from the WM.

Once a decision has been made to start treatment, there are several options, depending on the patient’s age, general health, and symptoms. Treatment is also based on whether or not the patient might have a stem cell transplant in the future.

Patients with serious symptoms caused by hyperviscosity or with very high levels of IgM protein in the blood might need to be treated with plasmapheresis first to bring the IgM level down. Then treatment with chemotherapy or other drugs can be used to target the cancer cells themselves.

The drugs used to treat WM can be given in a variety of combinations and schedules depending on the situation. Some doctors like to combine drugs (often some type of chemotherapy plus rituximab), while others prefer to start with a single drug. The patient’s age, overall health, and symptoms can also affect which treatments are recommended.

In general, rituximab is not usually given when the IgM level is very high because it can make the IgM level temporarily go up even higher. Plasmapheresis may be used first to lower the IgM level before starting rituximab.

If a stem cell transplant might be used later on, many experts recommend not giving certain chemo drugs (chlorambucil, bendamustine, cladribine, or fludarabine) because they might affect the stem cells in the body.

Some of the drugs and combinations that might be used as the first treatment for WM include:

- Bendamustine, with or without rituximab
- Bortezomib, with or without dexamethasone and/or rituximab
- Chlorambucil
- Cladribine, with or without rituximab
- Cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R)
- Cyclophosphamide, prednisone, and rituximab (CPR)
- Fludarabine, with or without rituximab
- Fludarabine, cyclophosphamide, and rituximab (FCR)
- Rituximab
- Rituximab, cyclophosphamide, and dexamethasone (RCD)
• Thalidomide, with or without rituximab
Other drugs and drug combinations can also be used. Talk to your doctor about which regimen might be best for you based on your situation.

During treatment, you’ll have regular visits with your doctor, who will ask you about your symptoms, do physical exams, and test your blood to see how well the treatment is working. In most people with WM, the disease will respond to treatment (IgM levels will go down and symptoms will get better) within a few months, although this may take longer in people getting rituximab alone. If a response is achieved, options include close monitoring for signs of disease progression or giving rituximab on a regular schedule to help keep the disease in check.

**If initial treatment doesn’t work or if the disease comes back after treatment**

No single treatment for WM works for all patients. If the first drug or set of drugs doesn’t work, other drugs may be helpful.

Most people with WM will require treatment with different drugs at some point. Often, a certain drug or combination will work at first, but over time it might stop working. Or a person might stop treatment if the WM is under control, only to have it come back some time later. If the WM remained under control for at least a year after the first treatment, then giving the same drug(s) again can often help bring the cancer back under control.

If the cancer comes back sooner, or if the initial treatment was not effective, then switching to another drug or combination is likely to be a better option. Many of the same drugs and combinations listed above as first-line treatments might be helpful here. Other drugs that might also be tried include alemtuzumab (Campath), ofatumumab (Arzerra), ibrutinib (Imbruvica), or everolimus (Afinitor). **High-dose chemotherapy with stem cell transplant** might also be an option for some patients.

If chemotherapy or other drugs are no longer slowing the growth of the WM, some patients can still get relief from symptoms by getting plasmapheresis at regular intervals to lower the levels of the abnormal IgM protein in their blood.

Sometimes WM can turn into an aggressive lymphoma. When this happens, the cancer grows much more quickly and causes symptoms that can soon become life threatening. These lymphomas are usually treated with a combination of several chemo drugs like those used for patients who are first diagnosed with an aggressive non-Hodgkin lymphoma (see the treatment section of **Non-Hodgkin Lymphoma**). If combination
chemo is not successful, high-dose chemo with a stem cell transplant may be an option.

- References

See all references for Waldenstrom Macroglobulinemia

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After Treatment for Waldenstrom Macroglobulinemia

Living as a Cancer Survivor

For many people, cancer treatment often raises questions about next steps as a survivor.

- What Happens After Treatment for Waldenstrom Macroglobulinemia?
- Lifestyle Changes With Waldenstrom Macroglobulinemia
- How Might Having Waldenstrom Macroglobulinemia Affect Your Emotional Health?

Cancer Concerns After Treatment

Treatment may remove or destroy the cancer, but it is very common to have questions about cancer coming back or treatment no longer working.

- If Treatment for Waldenstrom Macroglobulinemia Stops Working

What Happens After Treatment for Waldenstrom Macroglobulinemia?

Current treatments for Waldenstrom macroglobulinemia (WM) are not likely to result in a cure. Most people with WM are treated for some time, followed by a break, and then treated again when the disease comes back. Learning to live with cancer that does not go away can be difficult and very stressful. Managing Cancer as a Chronic Illness has more about this.

Follow-up care
Even during treatment breaks, your doctors will still want to watch you closely. It is very important to go to all of your follow-up appointments. During these visits, your doctors will ask questions about any problems you are having, and may examine you and get lab tests or imaging tests (such as CT scans) to look for signs of cancer or treatment side effects.

Almost any cancer treatment can have side effects. Some may last for only a short time, but others can last longer, possibly even for the rest of your life. Tell your cancer care team about any changes or problems you notice and about any concerns you have.

Follow-up visits usually include a careful physical exam. The doctor will also check how you are feeling. Be sure to report any new or ongoing symptoms. Your blood cell counts, IgM, and beta-2 microglobulin levels will be checked. Blood chemistry tests and other tests may also be done to see whether the abnormal IgM is damaging the kidneys, liver, or other organs. The choice of tests depends on your symptoms and what treatment (if any) you have received.

It is very important to keep your health insurance during this time. Tests and doctor visits cost a lot, and even though no one wants to think of their cancer coming back or getting worse, this could happen.

Should your cancer come back, Coping with Cancer Recurrence can give you information on how to manage and cope with this phase of your treatment.

**Seeing a new doctor**

At some point after your cancer diagnosis and treatment, you may find yourself seeing a new doctor who does not know your medical history. It is important that you be able to give your new doctor the details of your diagnosis and treatment. Gathering these details soon after treatment may be easier than trying to get them at some point in the future. Make sure you have this information handy (and always keep copies for yourself):

- A copy of your pathology report(s) from any biopsies or surgeries
- Copies of imaging tests (CT or MRI scans, etc.), which can usually be stored digitally (on a DVD, etc.)
- If you had surgery, a copy of your operative report(s)
- If you stayed in the hospital, a copy of the discharge summary that the doctor wrote when you were sent home
- If you had radiation therapy, a copy of the treatment summary
Lifestyle Changes With Waldenstrom Macroglobulinemia

You can’t change the fact that you have had cancer. What you can change is how you live the rest of your life – making choices to help you stay healthy and feel as well as you can. This can be a time to look at your life in new ways. Maybe you are thinking about how to improve your health over the long term. Some people even start during cancer treatment.

Making healthier choices

For many people, a diagnosis of cancer helps them focus on their health in ways they may not have thought much about in the past. Are there things you could do that might make you healthier? Maybe you could try to eat better or get more exercise. Maybe you could cut down on alcohol, or give up tobacco. Even things like keeping your stress level under control may help. Now is a good time to think about making changes that can have positive effects for the rest of your life. You will feel better and you will also be healthier.

You can start by working on those things that worry you most. Get help with those that are harder for you. For instance, if you are thinking about quitting smoking and need help, call the American Cancer Society at 1-800-227-2345 for information and support.

Eating better
Eating right can be hard for anyone, but it can get even tougher during and after cancer treatment. Treatment may change your sense of taste. Nausea can be a problem. You may not feel like eating and lose weight when you don’t want to. Or you may have gained weight that you can’t seem to lose. All of these things can be very frustrating.

If treatment causes weight changes or eating or taste problems, do the best you can and keep in mind that these problems usually get better over time. You may find it helps to eat small portions every 2 to 3 hours until you feel better. You might also want to ask your cancer team about seeing a dietitian, an expert in nutrition who can give you ideas on how to deal with these treatment side effects.

One of the best things you can do after cancer treatment is practice healthy eating habits. You may be surprised at the long-term benefits of some simple changes, like increasing the variety of healthy foods you eat. Getting to and staying at a healthy weight, eating a healthy diet, and limiting your alcohol can lower your risk for a number of types of cancer, as well as having many other health benefits.

To learn more, see our document Nutrition and Physical Activity During and After Cancer Treatment: Frequently Asked Questions.

Rest, fatigue, and exercise

Extreme tiredness, called fatigue, is very common in people treated for cancer. This is not a normal tiredness, but a bone-weary exhaustion that often doesn’t get better with rest. For some people, fatigue lasts a long time after treatment, and can make it hard for them to exercise and do other things they want to do. But exercise can help reduce fatigue. Studies have shown that patients who follow an exercise program tailored to their personal needs feel better physically and emotionally and can cope better, too.

If you were sick and not very active during treatment, it’s normal for your fitness, endurance, and muscle strength to decline. Any plan for physical activity should fit your own situation. A person who has never exercised will not be able to take on the same amount of exercise as someone who plays tennis twice a week. If you haven’t been active in a few years, you will have to start slowly – maybe just by taking short walks.

Talk with your health care team before starting anything. Get their opinion about your exercise plans. Then, try to find an exercise buddy so you’re not doing it alone. Having family or friends involved when starting a new activity program can give you that extra boost of support to keep you going when the push just isn’t there.

If you are very tired, you will need to learn to balance activity with rest. It’s OK to rest
when you need to. Sometimes it’s really hard for people to allow themselves to rest when they are used to working all day or taking care of a household, but this is not the time to push yourself too hard. Listen to your body and rest when you need to. (For more information on dealing with fatigue, see Cancer-related Fatigue. Keep in mind exercise can improve your physical and emotional health.

- It improves your cardiovascular (heart and circulation) fitness.
- Along with a good diet, it will help you get to and stay at a healthy weight.
- It makes your muscles stronger.
- It reduces fatigue and helps you have more energy.
- It can help lower anxiety and depression.
- It can make you feel happier.
- It helps you feel better about yourself.

And long term, we know that getting regular physical activity plays a role in helping to lower the risk of some cancers, as well as having other health benefits.

Can I lower my risk of Waldenstrom macroglobulinemia progressing?

Most people want to know if there are specific lifestyle changes they can make to reduce their risk of cancer progressing or coming back. Unfortunately, for most cancers there isn’t much solid evidence to guide people. This doesn’t mean that nothing will help — it’s just that for the most part this is an area that hasn’t been well studied. Most studies have looked at lifestyle changes as ways of preventing cancer in the first place, not slowing it down or preventing it from coming back.

At this time, not enough is known about Waldenstrom macroglobulinemia (WM) to say for sure if there are things you can do that will be helpful. Adopting healthy behaviors such as not smoking, eating well, and staying at a healthy weight might help, but no one knows for sure. However, we do know that these types of changes can have positive effects on your health that can extend beyond your risk of WM or other cancers.

So far, no dietary supplements of any kind have been shown to clearly help lower the risk of WM progressing. Again, this doesn’t necessarily mean that none will help, but it’s important to understand that none have been proven to do so.

- References

See all references for Waldenstrom Macroglobulinemia

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How Might Having Waldenstrom Macroglobulinemia Affect Your Emotional Health?

During and after treatment, you may find yourself overcome with many different emotions. This happens to a lot of people.

You may find yourself thinking about death and dying. Or maybe you’re more aware of the effect the cancer has on your family, friends, and career. You may take a new look at your relationships with those around you. Unexpected issues may also cause concern. For instance, you might be stressed by the costs of your treatment. You might also see your health care team less often and have more time on your hands. These changes can make some people anxious.

Almost everyone who is going through or has been through cancer can benefit from getting some type of support. You need people you can turn to for strength and comfort. Support can come in many forms: family, friends, cancer support groups, religious or spiritual groups, online support communities, or one-on-one counselors. What’s best for you depends on your situation and personality. Some people feel safe in peer-support groups or education groups. Others may feel more at ease talking one-on-one with a trusted friend or counselor. Whatever your source of strength or comfort, make sure you have a place to go with your concerns.

The cancer journey can feel very lonely. It’s not necessary or good for you to try to deal with everything on your own. And your friends and family may feel shut out if you don’t include them. Let them in, and let in anyone else who you feel may help. If you aren’t sure who can help, call your American Cancer Society at 1-800-227-2345 and we can put you in touch with a group or resource that may work for you. You may also want to see Coping with Cancer for more information.

- References
See all references for Waldenstrom Macroglobulinemia

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If Treatment for Waldenstrom Macroglobulinemia Stops Working

If Waldenstrom macroglobulinemia (WM) keeps growing or comes back after one kind of treatment, other treatments can often still be helpful. Clinical trials also might offer chances to try newer treatments that could be helpful.

But when a person has tried many different treatments and the WM is no longer getting better, even newer treatments may no longer be helpful. If this happens, it’s important to weigh the possible limited benefits of trying a new treatment against the possible downsides, including treatment side effects. Everyone has their own way of looking at this.

This is likely to be the hardest part of your battle with cancer — when you have been through many treatments and nothing’s working anymore. Your doctor might offer you new options, but at some point you may need to consider that treatment is not likely to improve your health or change your outcome or survival.

If you want to continue to get treatment for as long as you can, you need to think about the odds of treatment having any benefit and how this compares to the possible risks and side effects. Your doctor can estimate how likely it is the cancer will respond to treatments you’re considering. For instance, the doctor may say that more treatment might have about a 1 in 100 chance of working. Some people are still tempted to try this. But it’s important to have realistic expectations if you do choose this plan.

**Palliative care**

No matter what you decide to do, it’s important that you feel as good as you can. Make sure you are asking for and getting treatment for any symptoms you might have, such as nausea or pain. This type of treatment is called palliative care.

Palliative care helps relieve symptoms, but it is not expected to cure the disease. It can be given along with cancer treatment, or can even be cancer treatment. The difference is its purpose — the main goal of palliative care is to improve the quality of your life, or
help you feel as good as you can for as long as you can. Sometimes this means using drugs to help with symptoms like pain or nausea. Sometimes, though, the treatments used to control your symptoms are the same as those used to treat cancer. For instance, radiation might be used to help relieve pain caused by a large tumor. Or chemo might be used to help shrink a tumor and keep it from blocking the bowels. But this is not the same as treatment to try to cure the cancer.

**Hospice care**

At some point, you may benefit from hospice care. This is special care that treats the person rather than the disease; it focuses on quality rather than length of life. Most of the time, it is given at home. Your cancer may be causing problems that need to be managed, and hospice focuses on your comfort. You should know that while getting hospice care often means the end of treatments such as chemo and radiation, it doesn't mean you can't have treatment for the problems caused by the cancer or other health conditions. In hospice the focus of your care is on living life as fully as possible and feeling as well as you can at this difficult time. You can learn more about hospice in Hospice Care.

Staying hopeful is important, too. Your hope for a cure may not be as bright, but there is still hope for good times with family and friends — times that are filled with happiness and meaning. Pausing at this time in your cancer treatment gives you a chance to refocus on the most important things in your life. Now is the time to do some things you've always wanted to do and to stop doing the things you no longer want to do. Though the cancer may be beyond your control, there are still choices you can make.

You can learn more about the changes that occur when treatment stops working, and about planning ahead for yourself and your family, in Advance Directives and Nearing the End of Life.

- **References**

See all references for Waldenstrom Macroglobulinemia

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