LYMPHOMA RESEARCH • FOUNDATION

Understanding Lymphoma: Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM) is a type of indolent (slow-growing) B-cell lymphoma. WM is rare and represents nearly 2% of all blood cancers. There are about 1,000 to 1,500 new cases of WM diagnosed each year in the United States. The disease usually affects older adults and is mainly found in the bone marrow (the spongy tissue inside the bones), although lymph nodes and the spleen may be involved.

WM is a cancer that starts in B-cells (a type of white blood cell that helps the body fight infection). In WM, some B-cells have a mutation (permanent change) in their DNA (deoxyribonucleic acid, the molecule that carries genetic information inside the cells). This mutation produces abnormal cells (called lymphoplasmacytic cells), which multiply faster than normal B-cells (Figure 1). High numbers of these abnormal cells in the body can slow down the bone marrow function and reduce the number of healthy blood cells and platelets. This can result in anemia (a low level of red blood cells), neutropenia (a low level of a certain type of white blood cell called neutrophils), and thrombocytopenia (a low level of platelets).

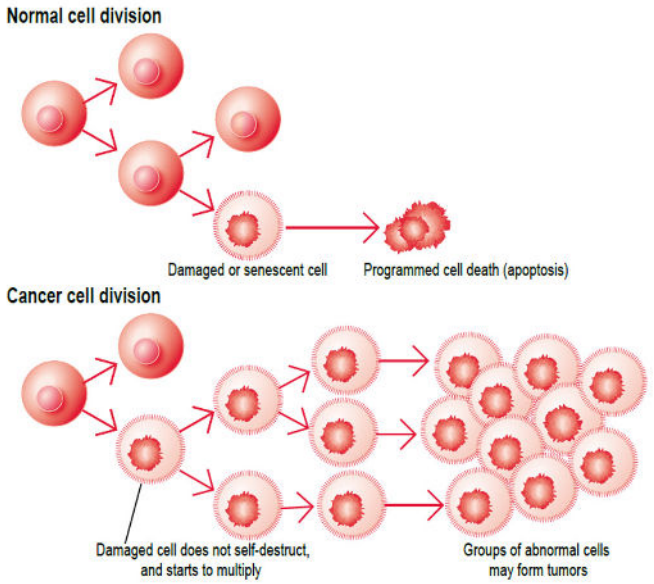

Figure 1. Normal and cancer cell division. In normal cell division, damaged (with mutations that lead to cancer) or senescent (old) cells are destroyed by apoptosis (a type of cell death the body uses to get rid of abnormal cells). In cancer, abnormal cells multiply uncontrollably.

Patients with WM have an increased level of a protein called immunoglobulin M (IgM) in their blood. Very high levels of IgM can cause blood hyperviscosity (thickening of the blood). Thickened blood cannot flow easily through the body, which may lead to excess bleeding, vision problems, heart complications, and nervous system issues.

Other common symptoms in patients with WM are:

- Bleeding (particularly from the nostrils and gums)
- Headaches
- Dizziness
- Double vision
- Fatigue (extreme tiredness)
- Night sweats
- Pain or tingling in the extremities

However, some patients with hyperviscosity do not experience any symptoms. To diagnose WM, blood tests and a bone marrow biopsy are usually performed. During the biopsy, a needle is inserted into a bone (usually the pelvic bone) to collect a small sample of the bone marrow. This sample is then examined to search for signs of cancer in the bones.

TREATMENT OPTIONS

Although WM is an incurable disease, it is treatable, and many patients have a long-term remission (reduction or disappearance of signs and symptoms of cancer for a long period of time) to treatment.

When patients have stable disease (cancer is neither decreasing nor increasing in size or severity) or show no or few symptoms, doctors may decide to monitor them without treating the disease. This approach is called active surveillance, or watchful waiting. In this case, patients' overall health and disease are monitored through regular check-up visits that may include laboratory tests (like a complete blood cell count) and physical examinations (like checking for any lymph node swelling). Active surveillance can last for many years for some patients. For more information on active surveillance, view the *Active Surveillance* fact sheet on the Lymphoma Research Foundation (LRF)'s website (visit **lymphoma.org/publications**).

Treatment would be indicated (recommended) for patients with evidence of weakened bone marrow function (low levels of blood cells and platelets caused by the presense of lymphoplasmacytic or lymphoma cells), symptoms related to the excess of IgM protein, such as hyperviscosity syndrome, and autoimmune complications, like autoimmune hemolytic anemia (red blood cells are destroyed faster than they can be replaced).

For patients who require treatment, many factors help determine the best type of treatment, such as:

- The type and severity of the symptoms
- The level of IgM in the blood
- The disease burden (including how the cancer affects the patient clinically and in other areas of life, such as financially)
- The genetic characteristics of the disease
- The patient's age and overall health

Treatment choice is based on an individual patient's needs, as well as considerations for short-term (**caused by** treatment and usually goes away after treatment ends) and long-term (occurs **during** treatment and continues for months or years) side effects.

Some patients undergo a procedure called plasmapheresis to temporarily reverse or prevent the symptoms associated with the excess of IgM protein. This procedure involves passing the patient's blood through a machine that separates the plasma (the liquid part of the blood that contains the IgM protein) from the blood cells. The blood cells are then mixed with a liquid that replaces the thickened plasma before returning the blood to the patient, now thinner and clearer of IgM protein. Physicians often combine plasmapheresis with other treatments, such as immunotherapy (drugs that help the body's immune system fight cancer) or chemotherapy.

In 2015, ibrutinib (Imbruvica; Bruton's tyrosine kinase [BTK] inhibitor) was the first therapy approved by the U.S. Food and Drug Administration (FDA) specifically for patients with WM. The combination of ibrutinib (Imbruvica) and rituximab (Rituxan) was subsequently approved by the FDA. Rituximab (Rituxan) is a monoclonal antibody administered intravenously (through a vein) that targets the CD20 protein, which is present at the surface of WM cells.

In 2021, zanubrutinib (Brukinsa), another BTK inhibitor, was approved for the treatment of adult WM patients. Acalabrutinib (Calquence), although not FDA approved for WM, is another BTK inhibitor option. These therapies are used as continuous oral therapy and only discontinued if a patient experiences side effects or the disease stops responding to treatment.

There are also many other drugs that can be used to manage WM, alone and/or in various combinations (e.g., chemoimmunotherapy, a combination of chemotherapy with immunotherapy), including the following:

- Rituximab (Rituxan)
- Bendamustine (Treanda)
- Cyclophosphamide (Cytoxan)
- Bortezomib (Velcade)
- Carfilzomib (Kyprolis)
- Ixazomib (Ninlaro)
- Cladribine (Leustatin)
- Fludarabine (Fludara)
- Corticosteroids

The standard (proper treatment that is widely used by healthcare professionals and accepted by medical experts) immunotherapy or chemoimmunotherapy combinations are used for a set period of time. Once the desired number of cycles are administered (usually 6, and in some cases, 4), patients will stop treatment and be monitored over time for disease progression (when cancer continues to grow or spread).

For patients whose disease relapses (returns after treatment) or becomes refractory (does not respond to treatment), changing therapies may help in providing additional remission (disappearance of signs and symptoms). Some of the previously described therapies can be used or reused depending on a patient's age, remission length, other medical problems, and previous experience of side effects. Additional therapies to treat relapsed/refractory WM include:

- Everolimus (Afinitor)
- Venetoclax (Venclexta)
- Autologous (patient receives own stem cells) stem cell transplant (SCT), following high-dose chemotherapy

For more information on stem cell transplantation, view the *Understanding Cellular Therapy* guide on LRF's website (visit **lymphoma.org/publications**).

TREATMENTS UNDER INVESTIGATION

Several promising new drugs and drug combinations are being studied in clinical trials for the treatment of patients with WM (some for relapsed/refractory disease), including:

It is critical to remember that today's scientific research is always evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with the LRF for any treatment updates that may have recently appeared.

Table 1. Treatments Under Investigation for Waldenström's Macroglobulinemia in Phase 2 or 3 Clinical Trials

Agents (Drugs)	Class (Type of Treatment)
Brexucabtagene autoleucel	CAR T-cell therapy; anti-CD19
Pirtobrutinib (Loxo-305)	Targeted therapy; BTK inhibitor
Nemtabrutinib (MK-1026)	Targeted therapy; BTK inhibitor
Obinutuzumab (Gazyva)	Immunotherapy monoclonal antibody; anti-CD20
Idelalisib (Zydelig)	Targeted therapy; PI3K Inhibitor
Pembrolizumab (Keytruda)	Immunotherapy, immune checkpoint inhibitor; anti-PD-1
Ulocuplumab (BMS-936564)	Immunotherapy monoclonal antibody; anti-CXCR4

BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CXCR4, chemokine receptor 4; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and the best treatment doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF's website (visit **lymphoma.org/publications**) and the *Clinical Trials Search Request Form* at **lymphoma.org**, talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling (800) 500-9976 or emailing helpline@lymphoma.org.

FOLLOW-UP

Patients with WM should have regular visits with their physician. During these visits, medical tests such as blood tests, computed tomography (CT) scans [uses a computer linked to an x-ray machine to make pictures of areas inside the body], positron emission tomography (PET) scans [uses a special dye that is injected into the patient to provide images of the body], and biopsies, may be required to evaluate the need for additional treatment.

Some treatments can cause side effects that are long-term or late (appear only months, years or decades **after** treatment has ended). These side effects can vary depending on the following factors:

- Duration of treatment (how long the treatment lasted)
- Frequency of treatment (how often the treatment was administered)
- Type of treatment given
- Age and gender of the patient
- Patient's overall health at the time of treatment

A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the patient stays in remission.

Patients and their caregivers are encouraged to keep copies of all medical records. These include test results as well as information on the type, amount, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrence. LRF's award-winning *Focus on Lymphoma* mobile app (**lymphoma.org/mobileapp**) and the *Lymphoma Care Plan* fact sheet (**lymphoma.org/publications**) can help patients manage this documentation.

LYMPHOMA CARE PLAN AND PATIENT EDUCATION PROGRAMS

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. LRF's *Lymphoma Care Plan* fact sheet organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The *Lymphoma Care Plan* fact sheet can be accessed by visiting **lymphoma.org/publications**. LRF also offers a variety of educational activities, including live meetings and webinars, for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

LRF Helpline

The LRF Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. LRF also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at **lymphoma.org**, or contact the LRF Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Para información en Español, por favor visite **lymphoma.org/es**. (For Information in Spanish, please visit **lymphoma.org/es**).

LRF FOCUS ON LYMPHOMA MOBILE APP

Focus on Lymphoma is the first app to provide patients and their caregivers with tailored content based on lymphoma subtype and actionable tools to better manage diagnosis and treatment. It provides convenient and comprehensive lymphoma management in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at **lymphoma.org/mobileapp**, or contact the LRF Helpline at **800-500-9976** or **helpline@lymphoma.org**.

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Supported through grants from: Bristol Myers Squibb · Genentech | Biogen · BeiGene

Last updated 2023