Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Waldenström Macroglobulinemia

Lymphoma Research Foundation

Waldenström macroglobulinemia (WM) is a type of *indolent* (slow-growing) B-cell lymphoma. WM is rare and represents only 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 may 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 look like a mixture of B cells and plasma cells (a type of white blood cell). Lymphoplasmacytic cells can survive longer and multiply faster than normal B-cells (Figure 1). High numbers of these abnormal cells in the bone marrow can slow down its function and reduce the number of healthy blood cells and platelets. This can result in anemia (low levels of red blood cells), *neutropenia* (low levels of white blood cells called neutrophils), and *thrombocytopenia* (low levels of platelets). In some cases, increased number of the abnormal cells can also be found in lymph nodes (small bean-shaped structures that help the body fight disease) or the spleen, which might appear enlarged on a computed tomography (CT) scan (uses a computer linked to an x-ray machine to make pictures of areas inside the body).

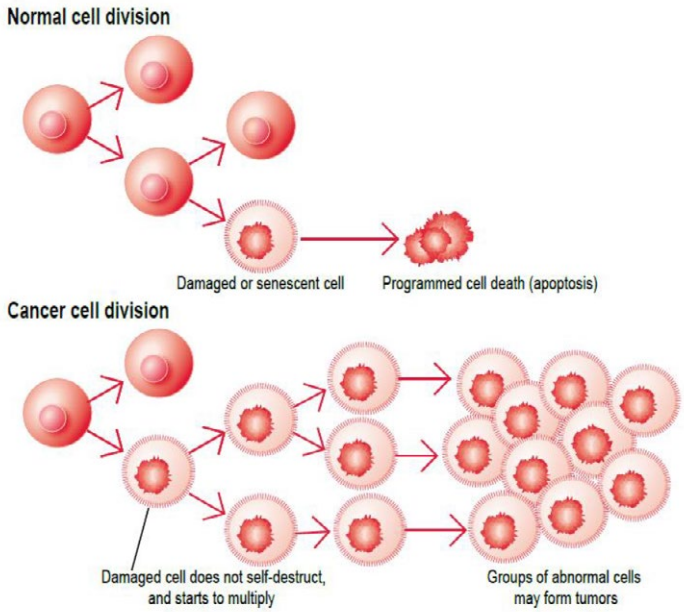

Figure 1: Normal and cancer cell division. In normal cell division, damaged (with mutations that lead to cancer) or senescent (old) cells are destroyed by apoptosis (a type of cell death the body uses to get rid of abnormal cells). In cancer, abnormal cells multiply uncontrollably.

Patients with WM have an increased level of a protein called immunoglobulin M (IgM) in their blood, which is produced by the abnormal lymphoplasmacytic cells. 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 or hearing problems, heart complications, and nervous system issues. In some cases, the IgM in the blood can cause other issues, such as autoimmune hemolytic anemia (a condition where the body attacks and destroys it's own red blood cells) or neuropathy (tingling, numbness or pain caused by damage to the nerves).

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 Foundations website (visit lymphoma.org/lymphoma).

Treatment is indicated (recommended) for patients with symptoms, evidence of weakened bone marrow function (low levels of blood cells and platelets, caused by the presence of lymphoplasmacytic, or lymphoma cells), and symptoms related with the excess of IgM protein, such as hyperviscosity syndrome, and autoimmune complications (when the body's immune system attacks its own healthy cells), such as autoimmune hemolytic anemia.

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.
- Disease burden (includes how the cancer affects the patient clinically and in other areas of life, such as financial).
- 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.

Patients with very high IgM and symptoms related to hyperviscosity 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 thickened plasma is replaced with a fluid containing albumin (a natural component of plasma) before returning the blood to the patient, now thinner and clearer of IgM protein. Physicians often follow plasmapheresis with other treatments, such as immunotherapy (drugs that help the body's immune system fight cancer) or chemotherapy.

Treatment options for patients with WM include:

- *Targeted therapy* (drugs that work by blocking molecules that cancers cells use to grow or spread) with Bruton's thyrosine kinase (BTK) inhibitors like ibrutinib (Imbruvica) and zanubrutinib (Brukinsa). Acalabrutinib (Calquence) is also a BTK inhibitor that can be used to treat WM in some patients, even though it is not FDA approved for this use.
- *Immunotherapy* (drugs that help the patient's immune system fight cancer) with a monoclonal antibody (a protein made in the laboratory that binds to cancer cells and helps the immune system destroy them) called rituximab (Rituxan). Rituximab binds to a protein called CD20 located at the surface of WM cells and can be used in combination with ibrutinib (Imbruvica).

There are also many other drugs that can be used to manage WM, alone and/or in various combinations such as 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 4 in some cases), patients will stop treatment and be monitored over time for disease progression (when cancer continues to grow or spread).

For patients whose disease relapses (disease returns after treatment) or becomes refractory (does not respond to treatment), changing therapies may help in providing additional *remissions* (disappearance of signs and symptoms). Some of the previously described therapies can be used or reused depending on a patient's age, how long they have been in remission, 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 the Foundation's website (visit **lymphoma.org/lymphoma**).

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:

Table 2: Treatments Under Investigations for Waldenstrom's Macroglobulinemia in Phase 2 or 3 Clinical Trials

Agent (drug)	Class (type of treatment)
MB-106	CAR T-Cell Therapy; Anti CD20
Iopofosine I 131	Phospholipid Drug Conjugate
Pirtobrutinib (Loxo-305)	Targeted therapy; BTK inhibitor
Nemtabrutinib (MK-1026)	Targeted therapy; BTK inhibitor
Obinutuzumab (Gazyva)	Immunotherapy monoclonal antibody; Anti-CD20
Sonrotoclax (BGB-11417)	Targeted therapy; BCL-2 inhibitor
Loncastuximab Tesirine (Zynlonta)	Immunotherapy antibody-drug conjugate; anti-CD19

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

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 Lymphoma Research Foundation for any treatment updates that may have recently appeared.

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 the Foundation's website (visit **lymphoma.org/publications**) and the *Clinical Trials Search Request Form* at lymphoma.org, talk to their physician, or contact the Foundation's 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, CT scans, 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 side effects (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 was the treatment given).
- Frequency of treatment (how often was the treatment administered).
- Type of treatment given.
- Age and gender of the patient.
- Patient 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 care partners are encouraged to keep copies of all medical records. These include test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrence. The Foundation's award-winning *Focus On Lymphoma* mobile app (**lymphoma.org/mobileapp**) and *Lymphoma Care Plan* (**lymphoma.org/publications**) can help patients manage this documentation.

Lymphoma Care Plan

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. The Foundation's Lymphoma Care Plan document 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 document can be accessed by visiting **lymphoma.org/publications**.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

Helpline

The Foundation's 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. The Foundation 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 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**).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently 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 Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

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