

Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

Monoclonal Antibodies



Monoclonal Antibodies

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Introduction

Waldenstrom's macroglobulinemia (WM) is a lymphoma, or cancer of the lymphatic system. It occurs in a type of white blood cell called a B-lymphocyte or B-cell, which normally matures into a plasma cell that manufactures immunoglobulins (also called antibodies) to help the body fight infection. In WM, there is a malignant change to the B-cell in the late stages of maturing, and it continues to proliferate, forming a clone of identical cells, primarily in the bone marrow but also in the lymph nodes and other tissues and organs of the lymphatic system. These clonal cells over-produce an antibody of a specific class called IgM.

Under the microscope, WM cells have characteristics of both B-lymphocytes and plasma cells, and they are called lymphoplasmacytic cells. For that reason, WM is classified as a type of non-Hodgkin's lymphoma called lymphoplasmacytic lymphoma (LPL). About 95% of LPL cases are WM, but it is a very rare disease – only about 1,800 patients are diagnosed with WM each year in the US. WM is usually indolent (slow growing) and can be managed as a chronic disease for a number of years.

As a result of proliferation in the bone marrow and other sites, the lymphoplasmacytic cells of WM may interfere with normal function. In the bone marrow where blood cells are produced, the WM cells “crowd out” the normal blood cells and may lead to a reduction in normal blood counts; in the lymph nodes and other organs, the WM cells may lead to enlargement of these structures and other complications.

The over-production of IgM may also cause many of the symptoms associated with the disease. IgM is a large molecule and tends to make the blood thicker than normal, a condition called hyperviscosity. Unlike normal antibodies that fight infection, the IgM produced by WM cells has no useful function. Sometimes the IgM may incorrectly recognize the body's tissues as “foreign” and attach to them, causing inflammation and injury.

Despite continued remarkable advances in biochemical, genetic, and medical research, a cure for WM remains elusive. Multiple treatment options are available to the WM patient, and careful evaluation of all options in formal consultation with one or more knowledgeable physicians is essential before any treatment is undertaken. Treatment recommendations need to be tailored to the individual patient, depending on the characteristics of his or her disease.

This Treatment Options Guide is not intended to recommend any specific protocol. Such decisions must be made with your physician and with knowledge of current treatment recommendations. Its primary purpose is to provide you with some of the information necessary to discuss treatment options intelligently with your physician and to make these difficult choices more easily.

Unlike many cancers for which early detection and treatment are important to one's survival, WM often, although not always, offers the luxury of time: time to seek out competent physicians and time for a second opinion, which is always considered a good idea when one is unclear or undecided regarding a future course of action. A directory of international physicians who are experts in WM is maintained on the IWMF website at [Directory of WM Physicians](#).

Approach to Treatment

The goal of treatment for WM is to provide disease control and thereby improve quality of life. This Guide and others in our Treatment Options series focus on the drug therapies that are used for disease control. There is no single standard of therapy to treat WM; instead, there are many options available to WM patients, including the following:

- **Chemotherapy** with alkylating agents such as chlorambucil, cyclophosphamide, and bendamustine or with nucleoside analogs such as fludarabine and cladribine;
- **Corticosteroids**, including prednisone and dexamethasone;
- **Monoclonal antibodies** such as rituximab and ofatumumab;
- **Immunomodulators**, including thalidomide and lenalidomide;
- **Proteasome inhibitors** such as bortezomib and carfilzomib;
- **Targeted therapies/pathway inhibitors** to B-cell signaling, including ibrutinib and everolimus.

Some of these drugs may be used as single agents (monotherapy); however, combinations of drugs are much more frequently used, as demonstrated by improved overall responses to therapy, either for initial (also called first-line, induction, or primary) treatment or for salvage (after first relapse) therapy.

Treatment is only required when WM patients become symptomatic and should not be initiated on the basis of blood test results alone. This applies not only to consideration of first-line treatment but also to salvage therapy. Initiating treatment early in the course of the disease in an asymptomatic patient does not prolong survival and may carry with it a range of unpleasant or even serious side effects; therefore, treatment is delayed until the onset of symptomatic disease. Some patients may remain stable and continue to be asymptomatic for years.

The following symptoms and conditions are considered appropriate reasons to begin treatment:

- Hyperviscosity syndrome (excessive thickness of the blood due to high IgM).
- Anemia (low red blood cell count and low hemoglobin) due to infiltration of the bone marrow with WM cells. Anemia is the most frequent condition that leads to treatment for WM. Generally speaking, a hemoglobin level less than 10 g/dL may be used as an indication to begin therapy.
- A platelet count less than <100,000 (called thrombocytopenia) due to bone marrow infiltration.
- Constitutional symptoms – weakness, fatigue, night sweats, fever, or weight loss.

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- Symptomatic cryoglobulinemia, cold agglutinin disease, and peripheral neuropathy. Systemic amyloidosis should be treated even when asymptomatic. More information about these conditions can be found on the IWMF website in the [Signs and Symptoms](#) section.
- Progressive, symptomatic enlargement of the lymph nodes, liver, or spleen.
- Kidney disease (nephropathy) related to WM.
- Masses of WM cells outside the bone marrow (extramedullary masses) – treatment may be initiated based on the location, size, and rate of growth of the masses.

Given that WM remains a very heterogeneous disease and no two patients are alike, patients and clinicians must decide which treatment to use based on the individual patient's situation and disease characteristics. These may include the presence of one or more cytopenias (decreased production of blood cells); the need for rapid control of aggressive disease vs. non-immediate need; age; co-morbidities (other chronic health conditions); overall health status; and candidacy for possible future autologous stem cell transplant.

Treatment can usually be administered in an outpatient setting or at home and may be oral, by intramuscular or subcutaneous injection, or by intravenous therapy. Some treatments require that certain medications be taken the day before or the day of treatment in order to minimize associated side effects. Traditionally, treatment has been done in cycles that may take several weeks to months, depending on the course of therapy chosen. It is not unusual to have a round of therapy and then wait a week or a month before another round of treatment. Some of the newer targeted therapies such as ibrutinib are oral and require regular daily or several times-a-week dosing instead, until relapse or significant toxicities develop.

Outside of clinical trials, the choice of salvage therapy after relapse is dependent on first-line therapy use, the quality and duration of response achieved during that therapy, and other variables such as age, tolerance of initial therapy, candidacy for stem cell transplant, etc. Reuse of a first-line single agent therapy or combination is reasonable if a patient achieved a response that lasted for at least 2 years; for patients who had shorter responses or resistance to first-line therapy, salvage therapy may consist of agents of a different class, either alone or in combination with other drugs.

At the biennial International Workshops on Waldenstrom's Macroglobulinemia (IWWM), a consensus panel of international WM experts is appointed to update recommendations for both first-line and salvage therapy in WM patients. These recommendations are developed after extensive review of published and ongoing clinical trials in WM. A similar set of clinical practice guidelines for treatment of WM/LPL is updated regularly by the National Comprehensive Cancer Network (NCCN[®]), a not-for-profit alliance of 27 of the world's leading cancer centers. The recommendations discussed in this Treatment Guide are based on both sets of guidelines.

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The following is a review of the drug class known as **monoclonal antibodies**. The other drug treatment options listed above are discussed in a series of Treatment Options Guides available on the IWMF website at [Downloadable Publications](#).

Monoclonal antibodies used in WM

Monoclonal antibodies are a relatively new innovation in cancer treatment. A monoclonal antibody is a laboratory-produced molecule that is carefully engineered to attach to a specific receptor on the surface of cells. Monoclonal antibodies mimic the antibodies your body naturally produces as part of your immune system's response to germs, vaccines and other invaders. When a monoclonal antibody attaches to a cell, it can make the cell more “visible” to the body’s own immune system and thus enables the immune system to kill the cell. Monoclonal antibodies can also be combined with radioactive particles, chemotherapy molecules, or toxins in order to deliver these cell-killing substances directly to cancer cells, while decreasing damage to normal healthy cells that are not targeted by the monoclonal antibodies.

The first monoclonal antibodies were developed from mice, but these were short-lived and not very compatible with human immune systems. Monoclonal antibodies in use today are chimeric (a combination of mouse and human antibodies that is approximately 65% human), humanized (a combination that is 95% human), and fully human. All monoclonal antibody therapies are of the IgG type.

Most monoclonal antibodies are administered intravenously. In general, monoclonal antibodies cause fewer side effects than traditional chemotherapy drugs because they are more targeted to cancer cells. Typically the most common side effects occur during intravenous infusion when the drugs are administered for the first time, with subsequent infusions usually better tolerated. Infusion reaction symptoms may include headache, fever, chills, flushing, nausea, and dizziness. More severe allergic symptoms include hives, chest tightness, trouble breathing, and swelling of the face, lips, tongue, or throat. In order to minimize reactions, pre-medication with acetaminophen, antihistamine, and sometimes a corticosteroid, is standard. If a reaction is noted during the infusion, the rate of administration can be adjusted and more of the pre-medication drugs can be given to relieve symptoms.

Rituximab (Rituxan or Mabthera)

Rituximab was the first monoclonal antibody to receive FDA approval, which was for the treatment of relapsed non-Hodgkin’s lymphoma in 1998. It is now commonly used as single agent therapy as well as in combination therapies and, more recently, as maintenance therapy for both first-line and relapsed/refractory treatment. Rituximab targets the CD20 surface antigen on B-cells.

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Rituximab is widely used in WM and is an important part of therapy for many patients. Two schedules for single agent rituximab have been studied: the standard one, in which one weekly infusion of 375 mg/m² is administered for 4 weeks; and the extended one, in which responding patients receive 4 more weekly infusions during weeks 12-16. With the standard schedule, the reported overall response rate was 30-60%, with a duration of response of 8-11 months in both first-line and relapsed/refractory patients. With the extended schedule, the overall response rate was 35-45%, with a duration of response of 16-29 months.

Rituximab is usually well tolerated, although about 50% of WM patients experience a transient increase in serum IgM levels – the IgM “flare” phenomenon. This flare occurs mostly during the first months of treatment but may persist for several months; it is not associated with a higher risk of treatment failure, and physicians should be cautious not to interpret flare as a lack of response or even disease progression. Patients with baseline high serum IgM levels (4,000 mg/dL or greater) may consider plasmapheresis prior to treatment, or rituximab should be avoided during the first one or two cycles until IgM declines to a safer level.

Late-onset neutropenia (low neutrophil count) has been observed with rituximab, mostly when combined with chemotherapy. The underlying mechanism is not well understood. Reactivation of hepatitis B virus has also been observed, and screening for prior hepatitis B exposure is recommended. Hepatitis B carriers should be closely monitored for clinical and laboratory signs and symptoms of active infection during therapy and for several months afterward.

A patient’s genetic make-up can significantly influence response rates to single-agent rituximab therapy. This involves the Fc receptor site on a person’s immune cells that attaches to the rituximab molecule. One can think of this attachment as similar to fitting a key to a lock – a better fit is more effective. Sequences of amino acids make up the genes that code for this Fc site, and the sequences can vary somewhat from one individual to another. It has been demonstrated that one part of the Fc site, called FcRIIIa, can have either the amino acid valine or phenylalanine in position 158 of its gene sequence. Since a person receives one gene from his father and one from his mother, a person who has two valine amino acids at this position has a better response to rituximab than a person who has two phenylalanines – a person with one of each typically has an intermediate response. The valine seems to confer a better binding site or “locking” mechanism for the immune cell to rituximab.

Because of the relatively lower rate of response in WM patients with high IgM levels and the risk of IgM flare, single-agent rituximab should be avoided in patients with high IgM levels but should be considered for WM patients with disorders secondary to WM, such as neuropathy, or in frail patients less likely to tolerate chemotherapy. Rituximab has been combined with alkylating agents, nucleoside analogs, proteasome inhibitors, and immunomodulators. Therefore, virtually all combination therapies for WM include rituximab, resulting in higher response rates than single-agent rituximab.

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There has been controversy as to the exact role of rituximab maintenance therapy in WM. Maintenance therapy is prolonged treatment given after the initial treatment course (usually combination rituximab therapy) has taken effect and reduced the disease burden. The goal of maintenance therapy is to prolong the amount of time before disease progression occurs and re-treatment becomes necessary. Maintenance therapy has been more thoroughly researched for the common indolent lymphoma called follicular lymphoma.

The use of maintenance rituximab was recently reported in a study that examined the outcome of 248 rituximab-naïve WM patients who responded to rituximab-containing regimens, 35% of whom received maintenance. The median number of infusions over a 2-year period of maintenance rituximab was 8. Responses improved in 10% of patients overall. Both progression-free survival and overall survival were longer in patients on maintenance. (Progression-free survival is the length of time during and after the treatment that a patient lives with the disease but it does not get progress, while overall survival is the length of time after diagnosis that a patient survives.) An increased number of infections was observed, along with depletion of IgA and IgG. A prospective randomized clinical trial aimed at clarifying the role of rituximab as maintenance therapy in WM patients is currently underway in Germany and is evaluating the impact of 2 years of rituximab maintenance vs. observation alone after initial therapy with rituximab and bendamustine.

Maintenance rituximab therapy is considered an option in WM patients, although more studies are needed to address the optimal dose, schedule, and duration of maintenance. The typical maintenance rituximab dosing schedule in WM thus far has been a single infusion every 3 months for 2 years.

Ofatumumab (Arzerra)

Ofatumumab is a fully human monoclonal antibody that targets a different region on the CD20 surface antigen than rituximab, and in cells expressing low levels of CD20, it is more potent.

Two studies have looked at the role of ofatumumab in WM patients, including those who were intolerant to rituximab. These studies demonstrated that ofatumumab could be successfully administered as either a single-agent or as combination therapy, although infusion reactions similar to those from rituximab have occurred. A test dose of ofatumumab with appropriate pre-medication should be considered in patients with rituximab intolerance. There is a risk of IgM flare with ofatumumab, and precautions similar to those used for rituximab should be considered in patients who have evidence of hyperviscosity or who have significantly elevated IgM levels.

Alemtuzumab (Campath)

Alemtuzumab is a humanized monoclonal antibody that targets CD52 on B-cells and mast cells. In a multicenter Phase II clinical trial, the activity of alemtuzumab was examined in 28 patients with symptomatic WM/LPL (lymphoplasmacytic lymphoma), 23 of whom were previously treated. The overall response rate was 76%, with major responses in 32% and a median time to progression of 14.5 months. Hematologic and infectious complications, including cytomegalovirus reactivation, were more common in the previously treated patients and were associated with 3 deaths. Long-term follow-up revealed late-onset autoimmune thrombocytopenia in 4 patients, contributing to the death of one.



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Treatment protocols vary, although dosing is usually more frequent than with rituximab, and a subcutaneous form of alemtuzumab is available.

Alemtuzumab is infrequently used in the treatment of WM, although it remains an option for salvage therapy.

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About the IWMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer-led, nonprofit 501(c)(3) organization with an important mission: to offer mutual support and encouragement to the Waldenstrom's macroglobulinemia community and others with an interest in the disease; to provide information and educational programs that address patients' concerns; and to promote and support research leading to better treatments and ultimately, a cure.

More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF and its affiliate organizations can be found on our website, www.iwmf.com.

The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a Business Office at 6144 Clark Center, Ave., Sarasota, FL 34238. The Office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.

The information presented here is intended for educational purposes only. It is not meant to be a substitute for professional medical advice. Patients should use the information provided in full consultation with, and under the care of, a professional medical specialist with experience in the treatment of WM. We discourage the use by a patient of any information contained here without disclosure to his or her medical specialist.

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