

Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

Proteasome Inhibitors



Proteasome Inhibitors

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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 **proteasome inhibitors**. The other drug treatment options listed above are discussed in a series of Treatment Options Guides available on the IWMF website at [Downloadable Publications](#).

Proteasome inhibitors used in WM

A proteasome is a large protein complex found inside almost all cells, and its main function is to degrade unneeded or damaged proteins by chemically breaking them down with enzymes. Degradation of such proteins is a normal, necessary, and orderly cellular process. The structure of the most common proteasome resembles a barrel with a core of four protein rings stacked around a central opening referred to as the central pore. The core is “capped” on each end by additional proteins. When unneeded or damaged proteins enter the central pore of the proteasome, they are broken down into peptides and amino acids, the basic building blocks of proteins. These amino acids can be recycled and used to make new proteins.

If you think of a proteasome as the cell’s “garbage disposal,” a disruption of this normal process with a proteasome inhibitor will cause the unneeded or damaged protein “garbage” to accumulate and “clog” the cell, to the point where this can interfere with cell reproduction and other functions and lead to cell death. Studies have shown that because cancer cells tend to accumulate proteins more quickly, they are more susceptible to the action of proteasome inhibitors than normal cells.

Bortezomib (Velcade)

Bortezomib (Velcade) was the first proteasome inhibitor, developed in 1995 and approved by the FDA in 2003 for the treatment of refractory multiple myeloma. It has since been approved for relapsed mantle cell lymphoma and as first-line therapy for multiple myeloma.

The Waldenstrom’s Macroglobulinemia Clinical Trials Groups studied intravenous bortezomib, dexamethasone, and rituximab (abbreviated BDR) in 23 previously untreated patients, with administration of intravenous bortezomib at 1.3 mg/m² and dexamethasone at 40 mg twice a week on days 1, 4, 8, 11, along with rituximab at 375 mg/m² on day 11 for 4 cycles as first-line treatment and for 4 more cycles after 3 months as maintenance treatment. The overall response rate and major response rate were 96% and 83%, respectively. Sixty percent of patients discontinued treatment after 4 cycles because of treatment-related peripheral neuropathy. The median progression-free survival was 66 months, progression-free survival being the length of time during and after the treatment that a patient lives with the disease but it does not get worse.

Treatment with once a week intravenous bortezomib has also been investigated, with patients receiving 1.6 mg/m² on days 1, 8, and 15 during 6 cycles, and rituximab at 375 mg/m² at each cycle during 4 cycles. Eighty-eight percent of patients obtained a response, including 65% with major responses. No grade 3-4 (severe) treatment-related neuropathy was reported, but grade 3-4 neutropenia (low neutrophil count) was observed in 12% of patients. Among previously treated patients with this regimen, the overall response rate was 85%, with a 51% major response rate. Grade 3 neutropenia developed in 16%, and grade 3 neuropathy occurred in 5% of patients.

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Another study of first-line therapy in 59 WM patients used intravenous bortezomib only (1.3 mg/m² on days 1, 4, 8, 11) during the first cycle to avoid IgM “flare,” which is a transient increase in IgM that has been observed following certain therapies, especially those including rituximab. This was followed by four cycles of weekly bortezomib (1.6 mg/m² for 4 weeks) with rituximab and dexamethasone in cycles 2 and 5. Peripheral neuropathy was observed in 46% of the patients, but only 8% discontinued treatment due to neuropathy.

For patients who are intolerant to rituximab, bortezomib with dexamethasone can be considered as an alternate option. Bortezomib is particularly helpful for rapid reduction of serum IgM levels and is recommended for patients with symptomatic cryoglobulinemia, symptomatic cold agglutinin disease, amyloidosis, and renal impairment. Treatment responses are prompt, with partial responses occurring at a median of 1.4 months in one study. Another advantage of bortezomib is that it is not toxic to hematopoietic stem cells and therefore can be used as treatment for patients who are considering autologous stem cell transplantation as a future option. Long-term follow-up in multiple myeloma patients also does not suggest a risk for secondary malignancies.

Because nerve toxicity is a major concern with bortezomib treatment, weekly dosing and subcutaneous administration (as observed in multiple myeloma patients) reduces the rate and severity of neuropathy, and these options are continuing to be studied in randomized clinical trials. In cases where urgent reduction of IgM level is needed, bortezomib can be started at a dose of twice a week for one or two cycles and then changed to once weekly or subcutaneous dosing in order to reduce the risk of neurotoxicity.

Bortezomib treatment is associated with a high rate of herpes zoster (shingles), and prophylactic treatment with an antiviral is strongly recommended during treatment.

Carfilzomib (Kyprolis)

Carfilzomib is a second-generation proteasome inhibitor associated with a lower risk of nerve toxicity in multiply myeloma patients. It was evaluated in combination with rituximab and dexamethasone (CaRD regimen), mainly in previously untreated WM patients, in a schedule of dosing on days 1, 2, 8, and 9 and in maintenance therapy on days 1 and 2 every 8 weeks for 8 cycles (reduced from typical myeloma dosing). The overall response rate was 87%, and no grade 3 or greater neuropathy was observed.

Cardiac toxicity has been reported in 3-4% of multiple myeloma patients and could be an issue in elderly WM patients with pre-existing cardiac conditions. Other open issues include the optimal dose and optimal schedule of administration.

Carfilzomib is accessible in the US as an off-label indication for WM; however, it is not currently available for WM in many other countries.

As with bortezomib, prophylactic treatment with an antiviral is strongly recommended during carfilzomib treatment to prevent shingles. Carfilzomib-based therapy can rapidly deplete IgA and IgG levels, and serial serum levels of these antibodies should be carefully monitored.



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Ixazomib (Ninlaro)

This is a newer proteasome inhibitor administered orally that has been approved for treatment of relapsed/refractory multiple myeloma. Ixazomib combined with dexamethasone and rituximab (IDR regimen) is currently being evaluated in a clinical trial for previously untreated WM patients.

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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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