

Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

**Corticosteroids and
Immunomodulators**



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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. The WM cells may lead to enlargement of the lymph nodes, liver and spleen producing localized symptoms.

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.

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 and duration of life. This Guide and others in our Treatment Options series focus on 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, ofatumumab, and obinutuzumab;
- **Immunomodulators**, including thalidomide and lenalidomide;
- **Proteasome inhibitors** such as bortezomib, carfilzomib, and ixazomib;
- **Targeted therapies/pathway inhibitors** to B-cell signaling, including ibrutinib, everolimus, acalabrutinib, zanubrutinib, and venetoclax.

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.
- Symptomatic cryoglobulinemia, cold agglutinin disease or severe 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.

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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; age; co-morbidities (other chronic health conditions); overall health status; and candidacy for a possible 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. 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 many of the leading US cancer centers. The recommendations discussed in this Treatment Guide are based on both sets of guidelines.

The following is a review of the drug classes known as **corticosteroids** and **immunomodulators**. The other drug treatment options listed above are discussed in a series of Treatment Options Guides available on the IWMF website at [Publications & Videos](#).

Corticosteroids used in WM

Corticosteroids are a group of natural and synthetic analogs of hormones secreted by the adrenal glands. Corticosteroids are implicated in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation.

Corticosteroids are rarely used as single agents in treating WM. They are administered frequently in combination with other therapies or as pre-treatments to help prevent allergic-type reactions that may occur in some patients during the administration of monoclonal antibodies such as rituximab. Steroids alone or in combination therapy may be beneficial in patients who develop WM-associated hematologic complications such as cryoglobulinemia, cold agglutinin disease, and thrombocytopenia.

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Side effects are common and are proportional to the dosage and duration of therapy. These can include excitatory effects on the central nervous system such as euphoria, psychosis, and insomnia; steroid-induced osteoporosis; glaucoma; cataracts, muscle wasting; an increased susceptibility to infection; and appetite stimulation with weight gain. Despite the potential side effects of long-term steroid therapy, the use of steroids in combination with other anti-cancer agents for WM is widespread, given that they are administered during a (usually) short course of therapy and have a noted synergistic action with other drugs.

The most common corticosteroids used in WM treatment are prednisone, prednisolone, and dexamethasone. Prednisone and prednisolone are equally effective. Prednisone is activated by the liver into prednisolone. For this reason and because it is more easily absorbed, prednisolone may be preferred if liver disease is present. Dexamethasone is approximately 10 times more potent than prednisone and typically has a longer duration of action.

Immunomodulators (IMiDs) used in WM

Immunomodulators (IMiDs) appear to kill cancer cells by four described mechanisms of action: they starve the cancer cells from the blood supply that feeds them; they enhance the cancer-killing properties of the body's own immune cells such as T-cells and natural killer cells; they block some of the interactions between cancer cells and other cells in the bone marrow environment, and they seem to directly kill cancer cells by a mechanism not yet fully understood.

The immunomodulators used in cancer therapy are based on thalidomide and its derivatives, and all are oral medications. Immunomodulators are currently still included as treatment options in guidelines published by the IWWM consensus panels but have been removed from the lists of preferred and other recommended regimens in the NCCN[®] Guidelines.

Thalidomide (Thalomid)

Originally developed and marketed in Europe as a sedative in the late 1950s, thalidomide was taken off the market when it was implicated in birth defects during use by pregnant women. It was subsequently discovered to be effective in the treatment of leprosy, and in the late 1990s, was found to have significant activity in the treatment of multiple myeloma.

Thalidomide is an active agent in WM but infrequently used. It enhances the efficacy of rituximab in combination, has been used as first-line or salvage therapy in WM patients who have significant bone marrow suppression, and is non-toxic to stem cells. An overall response rate of 70% with a 3-year progression-free survival has been observed in WM patients. (Progression-free survival is the length of time during and after treatment that a patient lives with the disease but does not show signs or symptoms of disease progression.) Side effects include constipation, sleepiness, and notably, peripheral neuropathy. Lower doses of thalidomide (50-100 mg/day) decrease the risk of neuropathy.

Lenalidomide (Revlimid)

Lenalidomide was developed in 2004 and is used primarily for the treatment of multiple myeloma, mantle cell lymphoma, and myelodysplasia (ineffective production of blood cells).

In a Phase I/II clinical trial, single agent lenalidomide was used at low dose (starting at 15 mg) in 17 previously treated WM patients. At the highest dose tested, 20 mg, dose-limiting toxicities occurred; thus, the dose of lenalidomide chosen for further testing was 15 mg/day for 21 days out of 28. Fifty percent of patients completed one year of treatment, and the overall response rate was 29%, with all responses obtained from cycles 9-12. An IgM “flare” effect, which is a transient increase in IgM, was observed in three patients. The most frequent adverse events at grade 3 or greater (severe) were anemia in 14% and neutropenia (low neutrophil count) in 43%.

The combination of lenalidomide (25 mg/day for 21 days followed by 7 days off) and rituximab was studied in 16 WM patients, 12 of whom were previously untreated. The overall response rate was 50%, and only one case of neuropathy was observed. However, abrupt decreases in hematocrit were observed in 88% of patients and occurred despite reduction of lenalidomide to 5 mg/day. IgM flare was also observed and necessitated plasmapheresis in some patients.

Pomalidomide (Actimid or Pomalyst)

Pomalidomide was approved in 2013 for the treatment of relapsed/refractory multiple myeloma.

The combination of pomalidomide, dexamethasone, and rituximab (PDR therapy) was explored in previously treated WM patients in a small, dose-escalating Phase I clinical trial. Among the 7 patients enrolled, three (43%) attained a major response. The median time to response was 2.1 months. Three patients required plasmapheresis for an IgM flare, and this led to discontinuation of the protocol therapy. The median response duration was 15.1 months.

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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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