

# Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

**Targeted Therapies/  
Pathway Inhibitors**



### 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.

## Targeted Therapies/ Pathway Inhibitors

### A Guide to Treatment Options

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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.

## Targeted Therapies/ Pathway Inhibitors A Guide to Treatment Options

The following is a review of the drug class known as **targeted therapies/pathway inhibitors to B-cell signaling pathways**. The other drug treatment options listed above are discussed in a series of Treatment Options Guides available on the IWMF website at [Downloadable Publications](#).

### Targeted therapies/pathway inhibitors used in WM

To live and multiply, B-cells rely on a very complex series of molecular signals via proteins on their surfaces that in turn initiate a series of reactions to enable the cells to carry out their normal functions. This signaling cascade is also an essential requirement for the survival of malignant B-cells, and in many cases, several of these signals are enhanced, suppressed, or turned on and off by malignant B-cells so that they can survive and grow. As researchers have learned more about genes and their protein expression in WM, we are beginning to understand the complicated pathways involved in the disease and develop treatments that are targeted to and affect specific portions of these pathways, thereby interfering with survival and growth of WM cells.

While the early clinical trials of these drugs have assessed them as single-agent therapies, it is highly likely that combinations of one or more of these agents or combinations of these agents with more traditional therapies will result in better and longer responses.

These treatments are different from traditional therapies in several ways, and these differences have important implications for patients. They are more specific for tumor cells than chemotherapy, which often damages normal cells. Almost all of them are oral medications administered daily or several times a week, which means that they can be taken at home. This makes them more convenient, but it also means that patients must be compliant about when and how to take their medication. These treatments do not damage stem cells in the bone marrow, although they all have side effects that may lead patients to discontinue their use. They can result in dramatic improvements in disease status, but they appear to slow or arrest tumor cell growth rather than completely eliminate the cancer. This means that, once patients begin these treatments, they may need to continue until the treatments no longer work or until side effects become intolerable. This represents a significant change from the older therapies which are typically administered cyclically for a period of time and then discontinued after a patient achieves a response.

The novel oral agents are very expensive, and not all insurers pay for them. Federal and state regulations are being changed so that Medicare, Medicaid, and private insurers may eventually be required to cover their cost to the same extent that they cover intravenous and injectable drugs (so-called "oral parity" laws), but for now this remains an ongoing issue for many cancer patients.

#### Ibrutinib (Imbruvica)

Ibrutinib is an inhibitor of an enzyme in the B-cell signaling pathway called Bruton's tyrosine kinase (BTK). There was a strong rationale to begin testing this drug in WM patients because BTK is activated by MYD88 L265P, a gene mutation found in approximately 90-95% of WM patients. Activated BTK enhances the survival of WM cells by subsequent activation of an important protein called NF kappa-B in the B-cells.

## Targeted Therapies/ Pathway Inhibitors

### A Guide to Treatment Options

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Ibrutinib was approved for WM in 2015 by the US Food and Drug Administration, the only drug so far to receive specific approval for WM treatment. It has subsequently been approved by Health Canada and by the European Medicines Agency for WM patients who are not candidates for chemotherapy.

The clinical trial that led to approval was a Phase II study of ibrutinib in 63 symptomatic WM patients who had received at least one prior treatment. The median time to response was 4 weeks. The overall response rate was 91%, with a major response rate of 73%. Treatment-related side effects of grade 2 (moderate) or higher included neutropenia (low neutrophil count) at 22%; thrombocytopenia (low platelet count) at 14%; post-procedural bleeding at 3%; nosebleeds associated with the use of fish-oil supplements at 3%; and atrial fibrillation associated with a history of arrhythmia (5%). Similar results have been observed in other studies.

Overall, treatment with ibrutinib is well tolerated in WM patients. An off-target effect on platelet aggregation with bleeding complications has been described in trials of chronic lymphocytic leukemia patients on the drug. The use of ibrutinib in patients requiring anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and care should be taken if anticoagulant therapy is used. In case of surgery, ibrutinib should be discontinued at least 3-7 days pre- and post-surgery, depending on the type of surgery and the risk of bleeding. Acquired von Willebrand disease is a bleeding disorder and may occur with a high IgM level. It is recommended that testing for von Willebrand activity in WM patients with a history of bleeding be considered before starting ibrutinib.

In a series of 112 WM patients on ibrutinib, the cumulative risk of atrial fibrillation at 1, 2, and 3 years was 5.4%, 7.1%, and 8.9%, respectively. Patients with a prior history of atrial fibrillation had a shorter time to recurrence compared to those without such a history. Nearly all patients who developed atrial fibrillation were able to continue ibrutinib following cardiac intervention and/or ibrutinib dose reduction. In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to ibrutinib should be considered.

Ibrutinib also produces a mild decrease in QT interval (a part of the electrical cycle of the heartbeat). The underlying mechanism and safety relevance of this finding are not understood. Clinicians should use judgment when assessing whether to prescribe ibrutinib for patients at risk from further shortening of their QT interval.

Both MYD88 and CXCR4 mutations can impact overall and major responses to ibrutinib. WM patients who have unmutated MYD88 may have a lower overall response rate. Its efficacy may also be impacted by CXCR4 mutations, with both a lower overall response rate and fewer major responses, as well as delayed responses. It is recommended that testing of bone marrow for the MYD88 L265P mutation by AS-PCR (allele specific polymerase chain reaction) should be an essential part of the workup of newly diagnosed patients and that patients who were previously diagnosed be tested for the mutation prior to ibrutinib therapy. It is also recommended that, in addition to testing for the MYD88 L265P mutation, CXCR4 mutational status should be investigated in the context of clinical trials to clarify its impact on treatment outcomes.

## Targeted Therapies/ Pathway Inhibitors

### A Guide to Treatment Options

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Ibrutinib should not be discontinued, except temporarily for surgical procedures, unless toxicity or disease progression is suspected. Increases in serum IgM and reductions in hemoglobin can occur if ibrutinib is temporarily withheld and should not necessarily be regarded as treatment failure. The optimal use of ibrutinib, for instance as first-line vs. salvage therapy or as single-agent vs. combination therapy, continues to be a subject for study.

In chronic lymphocytic leukemia, resistance to ibrutinib has been described in a few patients and remains under investigation. Newer BTK inhibitors are in clinical development and may offer choices to overcome resistance. Combinations of BTK inhibitors with other new agents or with more traditional therapies are being studied in clinical trials.

#### **Everolimus (RAD001 or Afinitor)**

Everolimus blocks mTOR, a protein in the PI3K/AKT pathway that promotes cell growth and survival. Used to treat advanced kidney cancer as well as advanced breast cancer, among others, everolimus may also stop tumors from developing new blood vessels, which helps to limit their growth.

A Phase II trial of everolimus in 60 relapsed/refractory WM patients reported a partial response rate of 50% and a major response rate of 23%. The median time to response was 2 months, and the median progression-free survival was 21 months. Toxicity was hematologic, with grade 3-4 (severe) anemia at 27% and thrombocytopenia at 20%. Pulmonary toxicity such as pneumonitis was also reported. Among previously untreated, symptomatic WM patients, the overall and major response rates were 72% and 60%, respectively. A discordance (lack of agreement) between serum IgM levels and bone marrow response were common and made response assessment difficult. Mouth sores frequently occurred, and an oral dexamethasone swish and spit solution was helpful.

A Phase I/II study of everolimus in combination with rituximab, and with or without bortezomib, in 46 WM patients reported an overall response rate of 89% and a median progression-free survival of 21 months in the 36 patients who received full dose therapy.

Everolimus is currently recommended as an option for salvage therapy in WM, although owing to the toxicities associated with it, everolimus may be best considered in patients who are unresponsive or have progressed after multiple lines of other, better-tolerated therapies. Serial bone marrow biopsies may help to clarify the disease response to everolimus. The drug is currently accessible in the US as an off-label indication for WM; however, it is not available for WM in many other countries.

#### **Other targeted therapies/pathway inhibitors in development**

There are several other pathway inhibitors in pre-clinical development and in clinical trials for B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia, and some are being assessed specifically for WM as well. It remains to be seen how safe and effective they will prove to be and whether they will receive FDA approval or off-label indication for WM treatment. Some of the most promising ones at this point include the following: acalabrutinib (BTK inhibitor), ONO-4059 (BTK inhibitor), idelalisib (PI3K inhibitor), and duvelisib (PI3K inhibitor), among others.



# Targeted Therapies/ Pathway Inhibitors

## A Guide to Treatment Options

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### About the IWMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteered, 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](http://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](mailto: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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