Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

Biologic Therapy – Monoclonal Antibodies

IWMF
International Waldenstrom's Macroglobulinemia Foundation

Introduction

Waldenstrom's macroglobulinemia (WM) is a lymphoma, or cancer of the lymphatic system. WM develops in a type of white blood cell called a B-lymphocyte or B-cell. B-lymphocytes typically develop into plasma cells whose job it is to manufacture immunoglobulins (antibodies) to help the body fight infection. In WM, there is a malignant change during the later stages of B-cell maturation that results in the development of a clone of cells. This clone primarily resides in the bone marrow but is often also present in the lymph nodes and spleen. These clonal cells overproduce an antibody of a specific class called IgM.

Under the microscope, the malignant cells in WM have characteristics of both B-lymphocytes and plasma cells and 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. The remaining 5% do not secrete IgM and consequently are not classified as WM, but often have a similar disease course and are managed in much the same way as WM. WM is a very rare disease – only about 1,500 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. Unfortunately, with our currently available therapies it is not yet curable.

As a result of proliferation in the bone marrow, the lymphoplasmacytic cells of WM may interfere with normal blood cell production as the WM cells "crowd out" the healthy blood cells. This may lead to a reduction in normal blood counts. Additionally, in the lymph nodes and other organs, the WM cells may lead to lymph node enlargement or may prevent normal function of other organs.

The over-production of IgM may also cause many of the symptoms associated with the disease. IgM is a large antibody that, unlike other types of antibodies, can bind together and form a pentamer (a group of five IgM antibodies bound together). This pentamer can make the blood thicker than normal, a condition called hyperviscosity. Additionally, sometimes the IgM may incorrectly recognize the body's tissues as "foreign" and attach to them, causing inflammation and injury. For example, in some patients the IgM may bind to nerves and cause damage (peripheral neuropathy) or bind to red blood cells and cause red blood cell destruction in cold temperatures (cold agglutinin).

Although a cure for WM remains elusive, continuing research has resulted in multiple treatment options 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, as well as the patient's baseline medical health issues.

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 physicians from around the world 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 cyclophosphamide and bendamustine, or with nucleoside analogs, such as fludarabine and cladribine;
- **Biologic therapy** with monoclonal antibodies such as rituximab and ofatumumab;
- **Proteasome inhibitors** such as bortezomib, carfilzomib, and ixazomib;
- **Targeted therapies** to the B-cell signaling pathways, including BTK inhibitors such as ibrutinib and zanubrutinib.

Newer targeted therapies being tested (including the BCL-2 inhibitor venetoclax and the second generation BTK inhibitors acalabrutinib, pirtobrutinib, and tirabrutinib) and combinations of these drugs with older therapies are being added to the treatment arsenal.

Some of these drugs may be used as single agents (monotherapy); however, combinations of drugs are frequently used, and many lead to improved overall responses to therapy, either for initial (also called first-line, induction, or primary) treatment or for therapy after previously treated (relapsed) WM.

Treatment is typically required when patients with WM become symptomatic and should not be initiated based on blood test results alone. This applies not only to consideration of first-line treatment but also to treatment for relapsed WM. Initiating treatment early in the course of the disease in most asymptomatic patients does not prolong survival and may result in a range of unpleasant or even serious side effects. Some patients may remain stable and continue to be asymptomatic for years without treatment.

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

- Hyperviscosity syndrome (symptoms related to 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 or destruction of red blood cells due to the abnormal IgM. 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.
- Thrombocytopenia (platelet count less than <100,000) due to bone marrow infiltration.
- Constitutional symptoms – weakness, fatigue, night sweats, fever, or weight loss.
- Systemic light-chain (AL) amyloidosis, symptomatic cryoglobulinemia, cold agglutinin disease, or moderate to severe peripheral neuropathy. (Explanations about these conditions can be found on the IWMF website in the Symptoms of WM section.)
- Bing-Neel syndrome (infiltration of WM cells into the brain, lining around the brain and/or spinal cord, or fluid surrounding the spinal cord and brain).
- Progressive, symptomatic enlargement of the lymph nodes, liver, or spleen.
- Kidney disease (nephropathy) related to WM.
- Masses of WM cells outside the bone marrow or pleural effusions (fluid in the chest) – treatment is initiated based on the location, size, and rate of cell growth.

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.

When immediate IgM reduction is required (such as for hyperviscosity syndrome, symptomatic cryoglobulinemia, severe hemolysis due to cold agglutinin disease, etc.), the most rapidly acting therapy is plasmapheresis, which is a procedure to withdraw plasma containing excess IgM from the blood. After plasmapheresis, IgM levels can be reduced significantly, but the effect is only transient, and systemic drug therapy is required for disease control. In some cases, a surgical procedure may be needed to place a central catheter for plasmapheresis. More information about plasmapheresis can be found in a separate Fact Sheet on the IWMF website at IWMF & Affiliate Publications.

Drug treatment can usually be administered in an outpatient setting or at home. The treatment may be given orally, by intramuscular or subcutaneous injection, or by intravenous therapy depending on the specific therapy chosen. 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 may take months to complete, depending on the course of therapy chosen. Newer targeted therapies such as ibrutinib are oral and require regular daily dosing until relapse or significant toxicities develop.

Outside of clinical trials, the choice of 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 durable or long-lasting response; for patients who had short responses or resistance to first-line therapy, relapse 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 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 **targeted therapies known to affect 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 IWMF & Affiliate Publications.

Monoclonal antibodies used in WM

Monoclonal antibody therapy is based on a laboratory-produced biologic molecule that is carefully engineered to attach to a specific receptor on the surface of cells, for instance, cancer cells. Monoclonal antibodies mimic the antibodies your body naturally produces as part of your immune system's response to infection from bacteria, viruses, and parasites and to vaccination.

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), or fully human. All monoclonal antibody therapies are of the IgG type.

Most monoclonal antibodies are administered intravenously, although a few are now being administered subcutaneously (under the skin). In general, monoclonal antibodies cause fewer side effects than traditional chemotherapy drugs because they are more targeted. Typically, the most common side effects occur during intravenous infusion when the monoclonal antibody is 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 prescribed off-label for WM and is now commonly used as single agent therapy as well as in combination therapies and as maintenance therapy for both first- line and relapsed/refractory treatment. Rituximab targets the CD20 surface antigen on B-cells.

Two schedules for single agent rituximab have been studied in WM: the standard one, in which one weekly infusion of 375 mg/m^2 is administered for four weeks; and the extended one, in which responding patients receive four more weekly infusions during weeks 12-16. Reported response rates vary between 25-45%.

Recently, subcutaneous administration of rituximab was FDA approved for several blood cancers and may also be prescribed off-label for WM, although it has not been specifically studied in WM patients. The subcutaneous formulation is called Rituxan Hycela and is given by injection in 5-7 minutes rather than the typical several hours needed for intravenous infusion. The approval stipulates that the subcutaneous option can be used only after patients have received at least one treatment of rituximab intravenously. In clinical trials the effectiveness of the subcutaneous formulation was equivalent to that of intravenous rituximab, and the side effects of subcutaneous administration, in addition to those seen with intravenous administration, include skin issues such as rash, blistering, and peeling.

About 50% of WM patients treated with rituximab experience a transient increase (greater than 25%) in serum IgM levels—referred to as the IgM "flare" phenomenon. This flare may lead to symptomatic hyperviscosity, as well as worsening of other IgM-related conditions. Flare occurs mostly during the first 2-4 months of treatment; it is not associated with a higher risk of treatment failure, and one should be cautious not to interpret flare as a lack of response or even disease progression.

To avoid complications from flare, patients with symptomatic hyperviscosity or with serum IgM concentrations

greater than 4,000 mg/dL should avoid single agent rituximab when possible. If serious IgM flare during single agent or combination treatment is considered a possibility, plasmapheresis prior to therapy should be considered to reduce the IgM level, or rituximab should be avoided during the first one or two cycles of combination therapy until the IgM declines to a safer level.

Rarely, patients may be intolerant to rituximab, meaning that they have worsening infusion reactions that result in the therapy becoming unsafe. For such patients, slow infusion rates should be tried, or other drugs considered.

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.

Rituximab has been combined with alkylating agents, nucleoside analogs, proteasome inhibitors, and targeted therapies to B-cell signaling pathways. It is a part of almost every combination regimen for both first-line and relapsed/refractory WM.

Biosimilars for rituximab have been approved in Europe and the US. A biosimilar is a biological product that is highly similar to and has no clinically meaningful difference from an existing approved reference product. As patent protections for rituximab and similar drugs are expiring, biosimilars are being developed to provide more treatment options, increase access to medications, and potentially lower health care costs through competition. Although rituximab biosimilars are considered equivalent to the original product and may be prescribed off-label for WM, they have not been specifically studied in WM patients.

While rituximab maintenance therapy has been studied extensively in other blood cancers, there has been controversy about its role in WM. Maintenance therapy is prolonged treatment given after the initial treatment course (typically combination therapy including rituximab) has resulted in a response. The rationale for its use has been to prolong the amount of time before disease progression occurs.

There is no standardized rituximab maintenance dosing schedule for WM; in clinical practice, it has varied from one weekly infusion every two or three months to four weekly infusions every six months. The duration of maintenance is typically two years.

A randomized Phase 3 trial of maintenance rituximab in 218 WM patients used bendamustine and rituximab as front-line therapy. Participants who achieved at least a partial response to treatment were randomly assigned to either two years of maintenance rituximab given every two months or to observation (no maintenance). The median progression-free survival in the maintenance arm of the study was 101 months and in the observation arm was 83 months; however, this difference was not statistically significant. The median overall survival had not yet been reached in either arm. The current IWWM consensus panel opinion is that maintenance rituximab should not be recommended for WM patients who have achieved a partial response or better after chemoimmunotherapy. This is based on the risk vs benefit of long-term rituximab use, which can lead to an increased risk of infection for continuous B-cell depletion due to maintenance.

Ofatumumab (Arzerra)

Ofatumumab is a fully human monoclonal antibody that targets a different region on the CD20 surface antigen

than rituximab. It is suggested for use in patients who are intolerant to rituximab, 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 significantly elevated IgM levels.

Obinutuzumab (Gazyva)

Obinutuzumab is a humanized anti-CD20 monoclonal antibody approved for the treatment of chronic lymphocytic leukemia and follicular lymphoma. It has not been extensively studied in 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 vision, "A World Without WM," and a mission to "Support and educate everyone affected by WM while advancing the search for 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.

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