Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

Proteasome Inhibitors

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.

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. It is prescribed off-label for WM. Additional proteasome inhibitors have since been developed or are currently under development to improve potency and ease of administration and to reduce side effects.

The earliest clinical trial protocol of bortezomib for WM therapy administered it intravenously twice a week along with dexamethasone and rituximab (abbreviated BDR) in 23 previously untreated patients. 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 is the length of time during and after treatment that a patient has the disease but does not show signs or symptoms of disease progression.)

Subsequent studies of bortezomib combination therapy for first-line and relapsed/refractory WM patients administered bortezomib intravenously once a week, with response rates comparable to those seen with twice-weekly administration. Once-weekly bortezomib regimens have been associated with lower rates of serious peripheral neuropathy.

According to the NCCN® Guidelines, the combination of bortezomib, rituximab, and dexamethasone is one of the preferred treatment options for both first-line and relapsed/refractory WM. However, bortezomib regimens should be used with caution in WM patients who have pre-existing neuropathy. Bortezomib only, bortezomib with dexamethasone, or bortezomib with rituximab can be considered as alternatives for those who are intolerant to rituximab and/or dexamethasone.

Because neuropathy is a major concern with bortezomib treatment, subcutaneous (under the skin) administration of bortezomib once a week is now the preferred method of administration, based on study results in multiple myeloma patients that reported less neuropathy with this method. Subcutaneous bortezomib is currently being evaluated in trials of WM patients as a part of several combination regimens, including cyclophosphamide and rituximab or cyclophosphamide, dexamethasone, and rituximab.

Plasmapheresis followed by bortezomib therapy can be particularly helpful for rapid reduction of serum IgM levels in patients with symptomatic hyperviscosity, symptomatic cryoglobulinemia, symptomatic cold agglutinin disease, amyloidosis, and renal impairment. Another advantage of bortezomib is that it is not toxic to bone marrow 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 does not suggest a risk for secondary malignancies.

Bortezomib treatment is associated with a high rate of herpes zoster (shingles), and prophylactic treatment with an antiviral is strongly recommended during treatment. Bortezomib treatment can decrease normal levels of IgA and IgG, and these levels should be carefully monitored during therapy.

Carfilzomib (Kyprolis)

Carfilzomib is a second-generation proteasome inhibitor associated with a lower risk of neuropathy in multiple myeloma patients. It was evaluated in combination with rituximab and dexamethasone (CaRD regimen), in a Phase 2 trial of 31 previously untreated WM patients. The overall response rate was 87%, similar to response rates seen in bortezomib-based regimens and was not impacted by MYD88 L265P mutation status. IgM flare was reported in 23% of patients. No significant neuropathy was observed.

Carfilzomib is associated with an increased risk of cardiovascular events in multiple myeloma patients and should be used with caution in patients who have WM and cardiovascular disease, particularly if they are older than 65 years.

Carfilzomib was approved by the EMA (European Medicines Agency) in 2015 for the treatment of multiple myeloma. Within the US, CaRD therapy is not a preferred regimen for first-line use in the NCCN® Guidelines, but it is an alternate option in the first-line setting. Prophylactic treatment with an antiviral agent is strongly recommended during treatment to prevent shingles. Carfilzomib-based therapy can reduce IgA and IgG levels, necessitating the use of immunoglobulin therapy or discontinuation of CaRD treatment.

Ixazomib (Ninlaro)

Ixazomib is a newer proteasome inhibitor administered orally that has been approved by the FDA (Food and Drug Administration) for the treatment of relapsed/refractory multiple myeloma. Ixazomib combined with dexamethasone and rituximab (IDR regimen) was evaluated in a Phase 2 clinical trial of 26 previously untreated WM patients. All participants had the MYD88 L265P mutation, and 58% also had a CXCR4 mutation. The median time to response was longer in patients with CXCR4 mutations (12 weeks vs. 8 weeks). The overall response rate was 96%, which was unaffected by CXCR4 mutation status. There was no statistically significant difference in progression-free survival based on CXCR4 mutation status. The most common adverse events were mild gastrointestinal symptoms and rituximab-related infusion reactions.

IDR was also evaluated in a Phase 2 trial of 59 relapsed/refractory WM patients in The Netherlands, Belgium, and Greece. The first dose of rituximab was intravenous, with subsequent doses administered subcutaneously. The overall response rate was 71%. Serious adverse events occurred in 16 patients and were mainly infections. There was new onset or worsening of peripheral neuropathy in 16 patients, which was reversible in 10 of them. In this study, there was no statistically significant difference in progression-free survival based on CXCR4 mutation status, although there was a tendency for the patients with CXCR4 mutations to have shorter progression-free survival.

Ixazomib was approved by the EMA (European Medicines Agency) in 2016 for the treatment of multiple myeloma. IDR is not a preferred regimen for first-line use in the NCCN®Guidelines, but it is an alternate option in the first-line setting. As is true with other proteasome inhibitors, prophylaxis for shingles is strongly recommended, and reduction in IgA and IgG levels can occur.

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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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