Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

Chemotherapy and Proteasome Inhibitors

IWMF
International Waldenstrom's Macroglobulinemia Foundation

Chemotherapy and Proteasome Inhibitors
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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. WM may also cause enlargement or abnormal function of other organs, such as the liver, spleen, and lymph nodes.

The overproduction 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 with other IgM molecules to form a pentamer (a group of five IgM antibodies bound together). This pentamer, especially in the setting of high IgM levels, 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 agglutinins).

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 other medical issues.

This Treatment Options Guide is not intended to recommend any specific treatment. 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, although there is the hope that drugs in clinical trials now or in the future may eventually provide a cure. There is no single standard of therapy to treat WM; instead, there are a number of treatment options currently recommended or in clinical trials for people with WM. They include the following:

- **Chemotherapy** with alkylating agents, such as bendamustine or cyclophosphamide; or with nucleoside analogs, such as fludarabine and cladribine.
- **Immunotherapy** with monoclonal antibodies such as rituximab; or with drugs in newer therapy classes, such as bispecific T cell engagers, antibody-drug conjugates, and CAR-T cell therapy.
- **Proteasome inhibitors** such as bortezomib, carfilzomib, and ixazomib.
- **Targeted therapies** to the B cell signaling pathways, including BTK inhibitors, such as ibrutinib, zanubrutinib, acalabrutinib, and pirtobrutinib; BCL-2 inhibitors, such as venetoclax; and the relatively newer class of drugs called BTK degraders.

Several of the drug classes listed above are used in combination therapies; however, most of the targeted therapy drugs are currently used as single agents (monotherapy), although this is beginning to change. Drugs can be recommended for initial (also called first-line, induction, or primary) treatment or for therapy in previously treated (relapsed or refractory) disease. Relapsed disease is one that has responded to a therapy with improvement in signs and symptoms for a period of time but has become active again, while refractory disease is one that has not responded to a therapy.

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 therapy for previously treated 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 from high IgM).
- Anemia (low red blood cell count and low hemoglobin) from infiltration of the bone marrow with WM cells or from destruction of red blood cells by 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) from bone marrow infiltration.
- Constitutional symptoms – weakness, fatigue, night sweats, fever, and weight loss.
- Systemic light-chain (AL) amyloidosis, symptomatic cryoglobulinemia, symptomatic 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, the lining around the brain and/or spinal cord, or the fluid surrounding the brain and spinal cord).
- Progressive, symptomatic enlargement of the lymph nodes, liver, or spleen.
- Kidney disease (nephropathy) related to WM.

- Masses of cells outside the bone marrow or pleural effusions (fluid in the chest) – treatment is initiated based on symptoms, location, size, and rate of cell growth.

Given that WM is a disease affecting patients in many different ways, 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); the need for deep responses in certain situations, such as peripheral neuropathy or amyloidosis; and overall health status.

When immediate IgM reduction is required (such as for hyperviscosity syndrome, symptomatic cryoglobulinemia, severe anemia from 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 temporary, and drug therapy is required for disease control. More information about plasmapheresis can be found in a Fact Sheet on the IWMF website at IWMF & Global Partner Publications.

Drug treatment can usually be administered in an outpatient setting or at home. The treatment may be given orally, by subcutaneous injection, or by intravenous infusion, depending on the specific therapy chosen. Some treatments require that certain medications be taken the day before or the day of treatment to minimize side effects. Traditionally, older treatments with chemotherapy or proteasome inhibitors take a few months to complete, depending on the course of therapy chosen. Then patients discontinue treatment until the disease relapses and symptoms require treatment again. Targeted therapies, such as the BTK inhibitors, BTK degraders, and BCL-2 inhibitors, often require regular daily oral dosing indefinitely, until relapse or significant side effects develop. Researchers are now investigating combinations of two or more different targeted therapies or combinations of targeted therapies with more traditional therapies to provide improved time-limited treatments, rather than indefinite treatments.

How a patient's disease reacts to treatment is called a "response." A response and how long it lasts vary widely in WM. Currently, there is no way to accurately predict how good or how long a response will be for an individual patient. However, it is a goal of WM researchers to make more accurate predictions as they continue to refine their understanding of WM biology and discover new and better treatments. The different categories of response to treatment for WM are defined below:

- Complete response – the absence of monoclonal IgM protein, a normal serum IgM level, and no evidence of disease in the bone marrow or other organs.
- Very good partial response – a 90% reduction or greater in serum IgM level or a serum IgM level within normal range.
- Partial response – from a 50% reduction to less than a 90% reduction in serum IgM level.
- Minor response – from a 25% reduction to less than a 50% reduction in serum IgM level.
- Stable disease – from less than a 25% reduction to less than a 25% increase in serum IgM level.
- Progressive disease – a 25% increase or greater in serum IgM level with a minimum increase of 500 mg/dL from the lowest point and with confirmation required by two subsequent measurements.

When WM clinical trial results are reported, the terms overall response rate, major response rate, and deep response rate are used. An overall response rate is the percentage of all responses that are minor and better. A major response rate is the percentage of partial, very good partial, and complete responses, while a deep response rate is the percentage of very good partial and complete responses. Clinical trial reports also typically use terms like progression-free survival, overall survival, progression-free survival rate, and overall survival

rate. Progression-free survival is the length of time after treatment that patients live with a disease but it does not get worse, and overall survival is the length of time after diagnosis or treatment that patients with a disease remain alive. The progression-free survival rate is the percentage of participants whose disease does not get worse over a designated period of time after treatment (such as five years), while the overall survival rate is the percentage of participants who remain alive for a designated period of time after diagnosis or treatment.

Outside of clinical trials, the choice of therapy after previous treatment is dependent on several factors: how quickly the disease and its signs and symptoms are progressing; the previous therapy used; the quality and duration of response achieved during that therapy as well as the side effects experienced from it; and other variables such as age, overall health status, etc. Reuse of a therapy is reasonable if a patient achieved a durable or long-lasting response and it was well-tolerated, although cumulative harm to the healthy cells in the bone marrow from repeat chemotherapy should be considered in the treatment decision. For patients who had short responses or who developed resistance to previous therapy or were intolerant to it, subsequent therapy may consist of agents of a different class, either alone or in combination with other drugs.

WM patients are encouraged to join clinical trials when they are considering treatment. Clinical trial participation is essential to develop safer and more effective therapies for WM. Any patient with WM should consider clinical trial participation at any stage of their disease.

At each biennial International Workshop on Waldenstrom's Macroglobulinemia (IWWM), a consensus panel of international WM experts is appointed to update recommendations for both first-line and previously treated therapy in WM patients. These recommendations are developed after an 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 treatment recommendations and response definitions discussed in this Treatment Guide are based on both sets of guidelines.

The following is a review of **chemotherapy and proteasome inhibitors used or being considered for WM**. The other drug treatment options listed above are discussed in a series of Treatment Options Guides available on the IWMF website at IWMF & Global Partner Publications.

Chemotherapy

Chemotherapy owes its origin to the mustard gas of World War I, followed by an air raid in World War II involving mustard gas that produced a marked reduction of white blood cells in those exposed. This led to the use of nitrogen mustard in the treatment of leukemias and lymphomas. Chemotherapy drugs target fast-growing cells throughout the body. Thus, they not only affect many cancer cells but also the rapidly dividing cells of the bone marrow, stomach lining, and hair follicles, often causing neutropenia (low neutrophil count), nausea and mouth sores, and hair loss. Chemotherapy drugs are rarely used alone; in WM, one or more chemotherapy drugs may be combined with an immunotherapy like the monoclonal antibody rituximab, and/or with corticosteroids such as prednisone or dexamethasone. When combined with an immunotherapy, chemotherapy-based regimens are commonly referred to as "chemoimmunotherapy." Two common types of chemotherapy regimens used for WM are alkylating agents and nucleoside analogs.

Even in the age of targeted therapies, chemoimmunotherapy represents an established and historically effective treatment approach for WM. Targeted therapies and chemoimmunotherapy both result in deep and long-lasting responses. Chemoimmunotherapy is a fixed-duration treatment strategy, in contrast to targeted therapies, such as the BTK inhibitors ibrutinib, acalabrutinib, and zanubrutinib, that require constant daily use until resistance

to treatment or intolerable side effects occur. Patients receiving chemoimmunotherapy should be aware of its potential for both short-term and long-term side effects. Short-term concerns include low blood counts and increased risk for infections. In contrast, long-term risks include stem cell damage, which potentially contributes to the development of secondary myeloid blood cancers like leukemia. These risks are especially important to consider for younger patients with WM, given their extended life expectancy. Targeted therapies, on the other hand, do not appear to cause stem cell damage. However, the BTK inhibitors, in particular, have their own set of side effects to consider, including the potential to develop high blood pressure, heart arrhythmias such as atrial fibrillation, and bleeding.

Alkylating Agents

Alkylating agents are compounds that work by adding a chemical molecule called an alkyl group to the DNA molecule, preventing the strands of the DNA double helix structure from linking as they should. This causes breakage of the DNA strands, affecting the ability of the cancer cell to multiply. Eventually, the cancer cell dies.

Alkylating agents were one of the first drug classes to be used against cancer. The following are the most common alkylating agents now used in WM and appearing in treatment guidelines.

Bendamustine (Bendeka, Treanda, Belrapso, Vivimusta, or Levact)

Bendamustine was developed in the 1960s in what was formerly East Germany. It was not until the 1990s that it was formally studied in patients. The US Food and Drug Administration (FDA) approved bendamustine in late 2008 for the treatment of patients with indolent (slow-growing) B cell non-Hodgkin's lymphoma, of which WM is one example. It was subsequently approved in Europe, Canada, Australia, and China for the same use.

Bendamustine is an intravenous medication. A rapid-infusion (10-minute) formulation of bendamustine called Bendeka was also approved for use. In WM patients, bendamustine has been primarily used in combination with rituximab (a chemoimmunotherapy regimen referred to as Benda-R or B-R). Bendamustine has been studied in two dosing strengths for WM, either 90 mg/m^2 or 70 mg/m^2. Prospective clinical trials have used protocols with six cycles of bendamustine at the 90 mg/m^2 dose, while lower dosing and fewer cycles have been evaluated only in retrospective studies (those that examine health outcomes in the past). Treatment is usually well tolerated, but the lower dose of bendamustine may be appropriate for older and frail patients to reduce side effects, as well as for those with renal (kidney) impairment. Four to six cycles of Benda-R are usually sufficient to achieve an adequate response in most WM patients.

The Benda-R combination was compared to CHOP-R (the combination of cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab, also called R-CHOP) in a Phase 3 study of 546 patients with indolent non-Hodgkin's lymphoma, including 41 WM patients. A similar overall survival but a longer progression-free survival was reported for the Benda-R arm of the study (a median of 69.5 months) vs. CHOP-R (a median of 28 months). Side effects, including neutropenia, infections, peripheral neuropathy, and hair loss, were less for the Benda-R patients than for the CHOP-R patients.

The outcome of 30 WM patients with relapsed/refractory disease who received bendamustine alone or combined with an anti-CD20 monoclonal antibody (such as rituximab) was also examined. An overall response rate of 83% and a median progression-free survival of 13 months were reported.

Another study looked at Benda-R in 71 previously treated WM patients. The overall response rate was 80%, and the major side effect was moderate to severe neutropenia in 13% of patients. The median progression-free

survival was not reached after a median follow-up of 19 months. Among responders, the median time to 50% reduction in monoclonal IgM was three months, and no IgM flare (temporary increase in IgM) was observed. No patients developed an aggressive lymphoma or another blood cancer called myelodysplasia, but in three cases, a solid tissue cancer was observed.

As a result of these and other studies (and including extensive clinical use of bendamustine by physicians treating WM patients), the NCCN® Guidelines document lists bendamustine in combination with rituximab as one of the "Preferred Regimens" in both first-line and previously treated therapy. For patients who cannot tolerate rituximab, bendamustine alone is included in the category of "Other Recommended Regimens" for first-line therapy and in the category of "Useful in Certain Circumstances" for previously treated patients.

A prophylactic antibiotic to prevent *Pneumocystis* pneumonia should be considered for patients on Benda-R, and the use of bendamustine in any regimen can cause reduction of IgA and IgG levels, resulting in increased risk of infections. Other frequently reported side effects include nausea and vomiting, constipation, diarrhea, fatigue, rash, and low blood counts. Patients have reported redness, pain, and swelling at the intravenous infusion site because of bendamustine and should be monitored for this side effect during and after each infusion. Suggestions for reducing this side effect include using a port for the period of treatment or diluting the bendamustine with additional saline. Although there are no clear long-term data indicating stem cell toxicity or high risk of transformation to aggressive lymphoma with bendamustine, it should be used with caution in younger patients and in patients who have been previously heavily treated.

Cyclophosphamide (Cytoxan)

Cyclophosphamide is an alkylating agent that has been used for many years, most frequently given as part of combination therapy. The drug may be administered either orally or intravenously. Typically, it is given in one cycle every three weeks for a total of six to eight cycles. The use of cyclophosphamide in any regimen can cause reduction of IgA and IgG levels, thereby increasing the risk of infections. Rarely, extended treatment may result in an increased risk of bladder cancer. Cyclophosphamide does not appear to harm stem cell collection and can therefore be used in patients who may be candidates for autologous stem cell transplant.

The combination of the corticosteroid dexamethasone along with rituximab and cyclophosphamide (referred to as DRC, CDR, or RCD) was evaluated as a first-line therapy in a study of 72 WM patients. An overall response rate of 83% was observed. The median time to response was long, about four months, which suggests that this combination is not the best to use if rapid control of disease is necessary. This study was updated after longer follow-up, showing a time to disease relapse of 35 months. Side effects with DRC are usually mild or moderate and include loss of appetite, nausea, hair loss, and low blood counts, especially neutropenia. The majority of relapsing patients were still sensitive to other rituximab-based therapies. Long-term toxicities, including transformation to aggressive lymphoma or to myelodysplasia, were low. DRC is considered especially helpful for frail patients.

In the NCCN® Guidelines, DRC, or DRC with the proteasome inhibitor bortezomib (Velcade) added, are "Other Recommended Regimens" for first-line WM treatment, and DRC is a "Preferred Regimen" for previously treated patients. Cyclophosphamide combined with rituximab and the corticosteroid prednisone (rather than the more potent dexamethasone) is included in the list of "Other Recommended Regimens" for both first-line and previously treated WM patients.

CHOP-R is included in the NCCN® Guidelines as "Useful in Certain Circumstances" for previously treated WM. Because vincristine is associated with a high risk of peripheral neuropathy, cyclophosphamide-based regimens without vincristine may be preferred in patients who have an already-existing neuropathy.

The combination of the nucleoside analog fludarabine, cyclophosphamide, and rituximab, (called FCR) is effective in WM, with rapid response rates. However, because of the potential toxicities of fludarabine in this combination (discussed below under the heading **Nucleoside Analogs**), FCR is listed as "Useful in Certain Circumstances" for previously treated WM in the NCCN® Guidelines. Prophylaxis to prevent *Pneumocystis* pneumonia and herpes zoster (shingles) should be seriously considered for patients on FCR.

Nucleoside Analogs

Purine nucleoside analogs mimic several of the normal building blocks of DNA and, when incorporated into the DNA of rapidly dividing cancer cells, will stop their reproduction. The nucleoside analogs used to treat WM are listed below.

Purine nucleoside analogs, especially combined with rituximab, have provided WM patients in clinical trials with response rates of 60-95%, and the responses tend to be durable. However, a marked reduction in white blood cells (particularly neutrophils and T-cells) and reduction of IgA and IgG levels following nucleoside analog therapy may result in increased susceptibility to infections. Shingles infections are common; it is therefore strongly recommended to use antiviral therapy during, and for an extended period of time after, nucleoside analog therapy. Antibiotic therapy to prevent bacterial infections, especially *Pneumocystis* pneumonia, is similarly recommended.

Studies have reported an increased incidence of myelodysplasia and acute leukemia, as well as an increased frequency of disease transformation to aggressive lymphoma, in WM patients treated with nucleoside analogs. Limiting the exposure of these agents in WM patients is strongly recommended.

Fludarabine (Fludara)

Fludarabine is typically administered intravenously for four or five consecutive days in three- or four-week cycles. Fludarabine may also be given orally, more commonly in countries outside the US. The number of cycles is determined by the patient's response; but, as mentioned, information on the long-term toxicity of nucleoside analogs has resulted in an attempt to minimize the number of cycles administered. Delayed maximum treatment responses are quite common with fludarabine; it is not unusual to see a patient's IgM continue to drop for 6-12 months following the end of therapy.

Fludarabine alone, fludarabine with rituximab (FR), or fludarabine with cyclophosphamide and rituximab (FCR) are considered "Useful in Certain Circumstances" for previously treated WM in the NCCN® Guidelines. In patients who are eligible for autologous stem cell transplant, stem cells should be collected before fludarabine administration.

Cladribine (2CdA or Leustatin)

Cladribine is administered intravenously, usually on five consecutive days, and can be used alone or in combination with rituximab to treat WM. It has also been given as a seven-day treatment through a continuous pump worn by the patient. The usual treatment consists of two to four or more such cycles, spaced four weeks apart. Side effects are similar to those from fludarabine, and current practice favors limiting the number of cycles

to the fewest required by the individual patient. Cladribine alone or cladribine with rituximab (CR) are listed in the category of "Useful in Certain Circumstances" for previously treated WM in the NCCN® Guidelines.

Proteasome Inhibitors

The mechanism by which proteasome inhibitors work is different from that of chemotherapy. 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.

Following are the proteasome inhibitors used to treat WM.

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 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 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 treatment naive patients. The overall response rate and major response rate were 96% and 83%, respectively. Sixty percent of patients discontinued treatment after four cycles because of treatment-related peripheral neuropathy. The median progression-free survival was 66 months.

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 "Other Recommended Regimens" for both first-line and previously treated WM. Bortezomib can be added to the chemotherapy regimen of cyclophosphamide, dexamethasone, and rituximab, and this combination is also in the "Other Recommended Regimens" list for first-line WM treatment.

Bortezomib is being actively studied in clinical trials that include combining it with rituximab and either bendamustine or BTK inhibitors such as ibrutinib, acalabrutinib, and zanubrutinib. However, bortezomib regimens should be used with caution in WM patients who have pre-existing neuropathy.

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 that have reported a lower risk of neuropathy with this method.

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.

Bortezomib treatment is associated with a high rate of 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 treatment naïve 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.

In the NCCN® Guidelines, CaRD therapy is a treatment option under "Other Recommended Regimens" for first-line therapy in WM. Prophylactic treatment with an antiviral agent is strongly recommended during treatment to prevent shingles. Carfilzomib-based therapy can reduce IgA and IgG levels, possibly necessitating the use of replacement immunoglobulin therapy or discontinuation of CaRD treatment.

Carfilzomib is an intravenous medication. It should be used with caution because it can potentially cause cardiac and lung toxicity, especially in older patients.

Ixazomib (Ninlaro)

Ixazomib is a newer proteasome inhibitor administered orally and has been approved by the FDA and by the European Medicines Agency (EMA) for the treatment of multiple myeloma. Rates of peripheral neuropathy are lower for ixazomib compared to bortezomib.

Ixazomib combined with dexamethasone and rituximab (IDR regimen) was evaluated in a Phase 2 clinical trial of 26 treatment naïve 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); however, 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 ten of them.

IDR is one of the "Other Recommended Regimens" for both first-line and relapsed or refractory WM patients in the NCCN® Guidelines. As is true with other proteasome inhibitors, prophylaxis for shingles is strongly recommended, and reductions in IgA and IgG levels can occur.

Ixazomib is being investigated in clinical trials that include combinations with BTK inhibitors such as ibrutinib and zanubrutinib.

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About IWMF

International Waldenstrom's Macroglobulinemia Foundation (IWMF), the only international organization dedicated solely to WM, is a patient-founded and patient-driven nonprofit with a simple but compelling vision, "A world without WM," and mission, "Support and educate everyone affected by WM to improve patient outcomes while advancing the search for a cure."

IWMF relies on donor contributions to fulfill its mission, and we welcome your support. You can contribute to the organization by visiting our website at www.iwmf.com or by mailing a check to International Waldenstrom's Macroglobulinemia Foundation, 6144 Clark Center Ave., Sarasota, FL 34238. Our office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.