Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

Chemotherapy – Alkylating Agents and Nucleoside Analogs

International Waldenstrom's Macroglobulinemia Foundation

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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. 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.

Alkylating agents used in WM

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 low-grade lymphomas. Chemicals in this category are known as alkylating agents. These are cell-cycle non-specific drugs which target fast-growing cells throughout the body. Thus, they not only affect many malignant 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.

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 dexamethasone, rituximab, and cyclophosphamide (referred to as DRC, CDR, or RCD) was evaluated in a study of 72 previously untreated 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. Toxicities with DRC were mild, with the only moderate to severe toxicity being neutropenia in 9% of patients. This study was recently updated, showing a time to disease relapse of 35 months. The majority of relapsing patients were still sensitive to rituximab-based therapies. Long-term toxicities, including transformation to aggressive disease or to myelodysplasia, were low. This particular combination has become widely used as first-line and relapse therapy in the treatment of WM and is one of the preferred regimens in both settings, according to the NCCN® Guidelines and the IWWM Consensus Panel Treatment Recommendations. It can be helpful in frail patients requiring combination therapy.

Cyclophosphamide combined with hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone is called CHOP, and if rituximab is added, referred to as CHOP-R or R-CHOP. It can be used as first-line and relapse therapy but is not a preferred regimen in the NCCN® Guidelines or the IWWM Consensus Panel Treatment Recommendations. Because vincristine is associated with a high risk of peripheral neuropathy, cyclophosphamide-based regimens without vincristine may be preferred.

The combination of rituximab, fludarabine, and cyclophosphamide (called FCR) is effective in WM, with rapid response rates. However, due to the potential toxicities of fludarabine in this combination (discussed below under **Nucleoside analogs used in WM**), FCR is not a preferred regimen in the NCCN® Guidelines or the IWWM Consensus Panel Treatment Recommendations in either first-line or relapse settings, although it can be used as an alternate option in patients with high-risk disease who are not candidates for autologous stem cell transplant. Prophylaxis to prevent *Pneumocystis* pneumonia and herpes zoster (shingles) should be seriously considered for patients on FCR.

Bendamustine (Bendeka, Treanda, 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 B-cell non-Hodgkin's lymphoma.

Bendamustine is an intravenous medication. A rapid-infusion (10-minute) formulation of bendamustine called Bendeka was also approved for use. Bendamustine has been used as single agent therapy or in combination with other agents, including rituximab (a regimen referred to as Benda-R).

The Benda-R combination was compared to CHOP-R 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). Progression-free survival is the length of time during and after treatment that a patient lives with the disease but does not show signs or symptoms of disease progression, whereas overall survival is the length of time after diagnosis that a patient survives. Toxicities, including neutropenia, infections, peripheral neuropathy, and hair loss, were less for the Benda-R patients.

The outcome of 30 WM patients with relapsed/refractory disease who received bendamustine alone or 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 toxicity 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 aggressive lymphoma or myelodysplasia, but in three cases, a solid cancer was observed.

No randomized clinical trials have directly compared cyclophosphamide, rituximab, and dexamethasone to bendamustine and rituximab. However, two retrospective studies have suggested a higher activity rate, but also higher toxicity, associated with bendamustine and rituximab.

As a result of these and other studies (and including extensive clinical use of bendamustine by physicians treating WM patients), the NCCN® Guidelines and the IWWM Consensus Panel Treatment Recommendations list bendamustine in combination with rituximab as one of the preferred treatment regimens in both first-line and relapse therapy, with bendamustine alone as a recommended option in both settings for patients who are intolerant or refractory to rituximab. Treatment is well tolerated even in elderly patients, but the dose of bendamustine may need to be lowered for these patients, as well as for those with renal impairment. Four to six cycles of Benda-R are usually sufficient to achieve adequate response in most WM patients.

Prophylaxis 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. Patients have reported redness, pain, and swelling at the intravenous site due to bendamustine and should be monitored for this side effect during and after each infusion. 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 patients where stem cell harvest is being considered for autologous transplant and in patients who have been previously heavily treated.

Nucleoside analogs used in WM

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 most commonly used purine nucleoside analogs for WM have been fludarabine and cladribine. Purine nucleoside analogs are also used in varying combinations with other drugs, such as monoclonal antibodies.

Purine nucleoside analogs, especially in combination therapy, have provided patients in clinical trials with response rates of 60-95%, and the responses tend to be durable. There is no clear indication as to which, fludarabine or cladribine, is superior to the other in the treatment of WM, but most physicians lean toward the drug with which they are more familiar.

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. Outbreaks of herpes zoster (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. Because the risk is upwards of 8-15%, limiting the exposure of these agents in WM patients is strongly recommended. They are not preferred regimens for either first-line or relapse therapy in the NCCN® Guidelines or the IWWM Consensus Panel Treatment Recommendations.

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 long-term toxicity of nucleoside analogs has resulted in an attempt to minimize the number of cycles received by the patient. 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 and rituximab (FR therapy), and fludarabine in combination with cyclophosphamide, and rituximab (FCR therapy) are effective in first-line and relapse therapy, with high response rates and median progression-free survivals in some studies exceeding 50 months. Fludarabine-based treatments can be considered in fit, older WM patients with previously treated disease who have failed other, less toxic treatments. In patients who are eligible for autologous stem cell transplant, stem cells should be collected before fludarabine administration. More information about stem cell transplantation can be found in a separate Fact Sheet on the IWMF website at IWMF & Affiliate Publications.

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. Toxicities are similar to those of fludarabine, and current practice favors limiting the number of cycles to the fewest required by the individual patient.

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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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