Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

Chemotherapy – Alkylating Agents and Nucleoside Analogs

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Introduction

Waldenstrom's macroglobulinemia (WM) is a lymphoma, or cancer of the lymphatic system. It occurs in a type of white blood cell called a B-lymphocyte or B-cell, which normally matures into a plasma cell that manufactures immunoglobulins (also called antibodies) to help the body fight infection. In WM, there is a malignant change to the B-cell in the late stages of maturing, and it continues to proliferate, forming a clone of identical cells, primarily in the bone marrow but also in the lymph nodes and other tissues and organs of the lymphatic system. These clonal cells over-produce an antibody of a specific class called IgM.

Under the microscope, WM cells have characteristics of both B-lymphocytes and plasma cells, and they are called lymphoplasmacytic cells. For that reason, WM is classified as a type of non-Hodgkin's lymphoma called lymphoplasmacytic lymphoma (LPL). About 95% of LPL cases are WM, but it is a very rare disease – only about 1,800 patients are diagnosed with WM each year in the US. WM is usually indolent (slow growing) and can be managed as a chronic disease for a number of years.

As a result of proliferation in the bone marrow and other sites, the lymphoplasmacytic cells of WM may interfere with normal function. In the bone marrow where blood cells are produced, the WM cells "crowd out" the normal blood cells and may lead to a reduction in normal blood counts; in the lymph nodes and other organs, the WM cells may lead to enlargement of these structures and other complications.

The over-production of IgM may also cause many of the symptoms associated with the disease. IgM is a large molecule and tends to make the blood thicker than normal, a condition called hyperviscosity. Unlike normal antibodies that fight infection, the IgM produced by WM cells has no useful function. Sometimes the IgM may incorrectly recognize the body's tissues as "foreign" and attach to them, causing inflammation and injury.

Despite continued remarkable advances in biochemical, genetic, and medical research, a cure for WM remains elusive. Multiple treatment options are available to the WM patient, and careful evaluation of all options in formal consultation with one or more knowledgeable physicians is essential before any treatment is undertaken. Treatment recommendations need to be tailored to the individual patient, depending on the characteristics of his or her disease.

This Treatment Options Guide is not intended to recommend any specific protocol. Such decisions must be made with your physician and with knowledge of current treatment recommendations. Its primary purpose is to provide you with some of the information necessary to discuss treatment options intelligently with your physician and to make these difficult choices more easily.

Unlike many cancers for which early detection and treatment are important to one's survival, WM often, although not always, offers the luxury of time: time to seek out competent physicians and time for a second opinion, which is always considered a good idea when one is unclear or undecided regarding a future course of action. A directory of international physicians who are experts in WM is maintained on the IWMF website at Directory of WM Physicians.

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Approach to Treatment

The goal of treatment for WM is to provide disease control and thereby improve quality of life. This Guide and others in our Treatment Options series focus on the drug therapies that are used for disease control. There is no single standard of therapy to treat WM; instead, there are many options available to WM patients, including the following:

- **Chemotherapy** with alkylating agents such as chlorambucil, cyclophosphamide, and bendamustine or with nucleoside analogs such as fludarabine and cladribine;
- **Corticosteroids**, including prednisone and dexamethasone;
- **Monoclonal antibodies** such as rituximab and ofatumumab;
- **Immunomodulators**, including thalidomide and lenalidomide;
- **Proteasome inhibitors** such as bortezomib and carfilzomib;
- **Targeted therapies/pathway inhibitors** to B-cell signaling, including ibrutinib and everolimus.

Some of these drugs may be used as single agents (monotherapy); however, combinations of drugs are much more frequently used, as demonstrated by improved overall responses to therapy, either for initial (also called first-line, induction, or primary) treatment or for salvage (after first relapse) therapy.

Treatment is only required when WM patients become symptomatic and should not be initiated on the basis of blood test results alone. This applies not only to consideration of first-line treatment but also to salvage therapy. Initiating treatment early in the course of the disease in an asymptomatic patient does not prolong survival and may carry with it a range of unpleasant or even serious side effects; therefore, treatment is delayed until the onset of symptomatic disease. Some patients may remain stable and continue to be asymptomatic for years.

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

- Hyperviscosity syndrome (excessive thickness of the blood due to high IgM).
- Anemia (low red blood cell count and low hemoglobin) due to infiltration of the bone marrow with WM cells. Anemia is the most frequent condition that leads to treatment for WM. Generally speaking, a hemoglobin level less than 10 g/dL may be used as an indication to begin therapy.
- A platelet count less than <100,000 (called thrombocytopenia) due to bone marrow infiltration.
- Constitutional symptoms – weakness, fatigue, night sweats, fever, or weight loss.

- Symptomatic cryoglobulinemia, cold agglutinin disease, and peripheral neuropathy. Systemic amyloidosis should be treated even when asymptomatic. More information about these conditions can be found on the IWMF website in the Signs and Symptoms section.
- Progressive, symptomatic enlargement of the lymph nodes, liver, or spleen.
- Kidney disease (nephropathy) related to WM.
- Masses of WM cells outside the bone marrow (extramedullary masses) – treatment may be initiated based on the location, size, and rate of growth of the masses.

Given that WM remains a very heterogeneous disease and no two patients are alike, patients and clinicians must decide which treatment to use based on the individual patient's situation and disease characteristics. These may include the presence of one or more cytopenias (decreased production of blood cells); the need for rapid control of aggressive disease vs. non-immediate need; age; co-morbidities (other chronic health conditions); overall health status; and candidacy for possible future autologous stem cell transplant.

Treatment can usually be administered in an outpatient setting or at home and may be oral, by intramuscular or subcutaneous injection, or by intravenous therapy. Some treatments require that certain medications be taken the day before or the day of treatment in order to minimize associated side effects. Traditionally, treatment has been done in cycles that may take several weeks to months, depending on the course of therapy chosen. It is not unusual to have a round of therapy and then wait a week or a month before another round of treatment. Some of the newer targeted therapies such as ibrutinib are oral and require regular daily or several times-a-week dosing instead, until relapse or significant toxicities develop.

Outside of clinical trials, the choice of salvage therapy after relapse is dependent on first-line therapy use, the quality and duration of response achieved during that therapy, and other variables such as age, tolerance of initial therapy, candidacy for stem cell transplant, etc. Reuse of a first-line single agent therapy or combination is reasonable if a patient achieved a response that lasted for at least 2 years; for patients who had shorter responses or resistance to first-line therapy, salvage therapy may consist of agents of a different class, either alone or in combination with other drugs.

At the biennial International Workshops on Waldenstrom's Macroglobulinemia (IWWM), a consensus panel of international WM experts is appointed to update recommendations for both first-line and salvage therapy in WM patients. These recommendations are developed after extensive review of published and ongoing clinical trials in WM. A similar set of clinical practice guidelines for treatment of WM/LPL is updated regularly by the National Comprehensive Cancer Network (NCCN®), a not-for-profit alliance of 27 of the world's leading cancer centers. The recommendations discussed in this Treatment Guide are based on both sets of guidelines.

The following is a review of the chemotherapy-type drug classes known as **alkylating agents** and **nucleoside analogs.** The other drug treatment options listed above are discussed in a series of Treatment Options Guides available on the IWMF website at Downloadable 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 hair loss.

Although alkylating agents such as chlorambucil (see below) have been used as single-agent therapy in the past, combinations with other agents such as monoclonal antibodies and/or corticosteroids are more typically used because they tend to be more effective and lead to longer treatment responses.

Chlorambucil (Leukeran)

Chlorambucil is one of the oldest alkylating agents used in the treatment of chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphomas (NHL) including WM, having been in use for more than fifty years. It is relatively inexpensive, is taken at home orally, has a low potential to cause nausea, and, although not curative, frequently results in sustained responses. Chlorambucil may be given daily or intermittently at six-week intervals until the patient reaches a plateau-state resolution of the IgM protein level. Therapy is then discontinued until relapse, at which time treatment with chlorambucil may be resumed or another agent may be used.

The response rate to chlorambucil is about 60%, but it is slow and is not appropriate for patients who require rapid disease reduction, such as those with symptomatic hyperviscosity.

Although it is no longer frequently used in WM patients, chlorambucil may be quite acceptable for frail elderly patients or those with co-morbidities severe enough to preclude the use of stronger agents. It provides long-term disease control and is generally safe, although it has produced myelodysplasia (ineffective production of blood cells) and acute myelogenous leukemia. It should be used sparingly in patients considered potential candidates for autologous stem cell transplant as it damages the stem cells. It is rarely used in patients younger than 65.

Cyclophosphamide (Cytoxan)

Like chlorambucil, cyclophosphamide has been a mainstay alkylating agent for many years, most frequently given as part of combination therapy. The drug may be administered either orally or intravenously, the latter being more common. Typically it is given in one cycle every three weeks for a total of six to eight cycles. Rarely, extended treatment may result in an increased risk of bladder cancer. Cyclophosphamide has a lower risk for producing myelodysplasia or acute leukemia than chlorambucil. 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 (DRC regimen) 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 4.1 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 (low neutrophil count) 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 fairly widely used as first-line and salvage therapy in the treatment of WM. It can be helpful in frail patients requiring combination therapy.

Cyclophosphamide combined with hydroxydoxorubicin, 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 salvage therapy. Because vincristine is associated with a high risk of peripheral neuropathy in WM patients, cyclophosphamide-based regimens without vincristine may be considered.

The combination of rituximab, fludarabine, and cyclophosphamide (called FCR) is effective as first-line therapy and salvage therapy in WM, with median progression-free survival exceeding 50 months. (Progression-free survival is the length of time during and after the treatment that a patient lives with the disease but it does not progress.) However, due to the potential toxicities of fludarabine (discussed below under **Nucleoside analogs used in WM**), first-line treatment use is not recommended, but salvage therapy is an option in patients with high-risk relapsed disease who are not candidates for autologous stem cell transplant.

Melphalan (Alkeran)

Melphalan is more commonly used for the treatment of some conditions related to WM such as multiple myeloma and AL amyloidosis. It has special use as a conditioning regimen for bone marrow stem cell transplantation. A conditioning regimen is one given to help eradicate the patient's disease just prior to the infusion of stem cells. In the context of stem cell transplantation, it has been used in WM patients. Melphalan can be administered orally or by IV and has toxicities similar to those of other alkylating agents.

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 recently 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 III study of 546 patients with indolent non-Hodgkin's lymphoma, including 41 WM patients. A similar overall survival (the length of time after diagnosis that a patient survives) 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 28.1 months). 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 3 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.

As a result of these and other studies (and including extensive clinical use of bendamustine by physicians treating WM patients), the use of bendamustine alone or in combination with an anti-CD20 monoclonal antibody (such as rituximab) is now recommended as a treatment option in both first-line and salvage therapy for WM. 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 cycles of Benda-R may be sufficient to achieve adequate response in most WM patients.

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

Purine nucleoside analogs, especially in combination therapy, provide patients with response rates of 60-95%, and the responses tend to be durable. Fludarabine and cladribine each has had its champions among respected clinicians, and there is no clear indication as to which may be superior in the treatment of WM. Most physicians lean toward the drug with which they are more familiar.

A marked reduction in white blood cells (particularly neutrophils and T-cells) 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 is similarly recommended in selected cases.

Recent reports have suggested an increased incidence of myelodysplasia and acute leukemia, as well as an increased incidence 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 younger 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, recent information on long-term toxicity of nucleoside analogs in the treatment of WM has resulted in an attempt to minimize the number of cycles received by the patient. Delayed 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.

Both fludarabine and rituximab (FR therapy), as well as fludarabine, cyclophosphamide, and rituximab (FCR) are effective in first-line and salvage therapy, with median progression-free survivals exceeding 50 months. Due to potential toxicities, however, first-line treatment use is usually not recommended. Fludarabine-based combinations can be considered in fit 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.

Cladribine (2CdA or Leustatin)

Cladribine is administered intravenously, usually on five consecutive days. 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. As is the case with fludarabine, 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 mission: to offer mutual support and encouragement to the Waldenstrom's macroglobulinemia community and others with an interest in the disease; to provide information and educational programs that address patients' concerns; and to promote and support research leading to better treatments and ultimately, a cure.

More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF and its affiliate organizations can be found on our website, www.iwmf.com.

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.