TREATMENT OPTIONS

Mission Statement:
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.

To promote and support research leading to better treatments, and ultimately, a cure.

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PREFACE

The IWMF booklet *Waldenstrom’s Macroglobulinemia - Treatment Options* was initially conceived for Waldenstrom’s macroglobulinemia (WM) patients and their caregivers who wish to undertake the study necessary to help them engage with their physicians in determining the best course of action for their particular circumstances. It has become increasingly apparent in the past few years that many physicians, be they hematologist-oncologists or primary care physicians, are using this booklet and other IWMF publications as ready references for themselves and as educational tools for their WM patients.

The patient who intends to fully participate in complex (and sometimes overwhelming) discussions about this disease with his or her physicians and to read and understand relevant medical literature must become somewhat familiar with terms used by the medical profession. In the discussion that follows, no attempt has been made to simplify the medical terminology within the body of this booklet. Words likely to be unfamiliar to the lay reader are defined in the Glossary. Italics are used to indicate terms included in the Glossary when they are used for the first time.

Cancer research continues to expand at an ever increasing pace; treatments that were in preliminary studies a few short years ago are now becoming mainstream options, and, as always, treatments unknown today may be announced tomorrow. *Treatment Options*, written in the spring of 2004, revised in the fall of 2009, and now revised again in the spring of 2013, must always be regarded as a work in progress. The IWMF will publish periodic revisions, ensuring that WM patients have ready access to new information.

Each person’s body, disease characteristics, and response to treatment are different, and no one should undertake a course of medical treatment described in this booklet without formal consultation with his or her physicians.
The assistance of the many physicians involved in providing information used in this booklet is gratefully acknowledged. Special thanks to Robert Kyle, MD, Morie Gertz, MD, and Steven Treon, MD; indeed, I wish to acknowledge and thank Dr. Treon for his review of this latest edition. Many thanks as well to all members of the IWMF Board of Trustees, the IWMF Scientific Advisory Committee, and all the dedicated physicians and researchers who continue to work assiduously for the benefit and well being of WM patients worldwide. Thanks also go to my frequent collaborators, Sue Herms, Alice Riginos, and Sara McKinnie, for their assistance in the completion of this booklet.

Much of the updated information contained in this booklet results from the IWMF-sponsored Seventh International Workshop on Waldenström’s Macroglobulinemia, held August 23-26, 2012, in Newport, Rhode Island, USA. For the first time in the publication of this booklet, I have included relevant information and recommendations from the National Comprehensive Cancer Network (NCCN) Guidelines®, Version 2.2013 in WM/LPL. This booklet, as was the case with the earlier editions of Treatment Options, is meant for an international audience, and not every treatment option may be available in all countries to all WM patients.

The other sister IWMF publications, Waldenstrom’s Macroglobulinemia - Questions and Answers, Blood Tests, Waldenstrom’s Macroglobulinemia - Medical Tests, and Waldenstrom’s Macroglobulinemia - Basic Immunology in Waldenstrom’s Macroglobulinemia, may also be very helpful to the interested lay reader. For physicians, the publication Waldenström’s Macroglobulinemia - Review of Therapy is recommended. The IWMF website at www.iwmf.com contains a wealth of resources. Suggested readings of notable importance, as well as selected references from scientific journals, have been included at the end of this booklet.

Guy Sherwood, MD
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2 - Waldenström’s Macroglobulinemia - Treatment Options
# Table of Contents

- Introduction ................................................................. 4
- About Waldenstrom's Macroglobulinemia ....................... 6
- Watchful Waiting (Watch and Wait) ................................. 9
- Treatment Options – Supportive/Palliative Treatments .... 11
  - Plasmapheresis ............................................................ 11
  - Growth Factors .......................................................... 12
- Treatment Options – Chemotherapy/Disease Modifying Agents ......................................................... 14
  - Alkylating Agents .......................................................... 15
  - Nucleoside (or Purine) Analogs ..................................... 17
  - Monoclonal Antibodies .................................................. 20
  - Proteasome Inhibitors .................................................... 25
  - Immunomodulators/Immunosuppressants ....................... 26
  - Targeted Therapies/Pathway Inhibitors ......................... 28
  - Combination Therapies .................................................. 29
  - Stem Cell Transplantation .............................................. 31
  - Emerging Therapies ...................................................... 34
  - Radioimmunotherapy ..................................................... 35
  - Vaccine Therapy ........................................................ 36
- Treatment Recommendations ........................................... 38
- Appendices 1-6 ............................................................... 42
- Suggested Readings ....................................................... 47
- References ...................................................................... 49
- Glossary ......................................................................... 57
INTRODUCTION

Waldenstrom’s macroglobulinemia (WM) was initially described in 1944 by Dr. Jan Gosta Waldenström. Despite continued remarkable advances in biochemical, genetic, and medical research, a cure remains elusive. Multiple treatment options are now 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. There is no “gold standard” in the treatment of WM. It is now clear that treatment recommendations need to be tailored to the individual patient, depending on the characteristics of his or her disease.

The questions most commonly posed by WM patients probably have to do with treatment options: When should treatment begin? Which treatment is most effective? What about newer treatments? These questions reflect uncertainty in the minds of patients, and choosing a particular treatment is certainly a daunting task for most WM patients. Clearly there continues to be a need for an understandable patient-friendly document that will anticipate and answer many of these questions.

In the following pages the most up to date information is described regarding treatments for WM recommended by international experts in the disease. Newer treatments and emerging therapies currently undergoing clinical trials are also discussed.

This booklet will not answer all of your questions, and the intent is certainly not to recommend any specific protocol. Such decisions must be made with your physicians. The primary purpose of the booklet is to provide the information necessary to discuss treatment options intelligently and to make these difficult choices more confidently.

Unlike many cancers for which early detection and treatment are important to one’s survival, WM often, but not always, offers the luxury of time: time to seek out competent and compatible
physicians and time for a second opinion, which is certainly always considered a good idea when one is unclear or undecided regarding diagnosis and future course of action. Perhaps the most important decision a patient can make in his or her journey with WM is the choosing of the primary treating physician. Your treating physician should be board-certified in hematology-oncology and preferably have had experience in treating a number of patients with WM. Given the relative rarity of WM, few oncologists have such experience; nonetheless, you will receive the best advice from a physician with extensive clinical knowledge of lymphoma, multiple myeloma, plasma cell disorders, and possibly leukemia.

Beyond this consideration lies the necessity for the physician and patient to share a common attitude toward treatment. Some physicians are more aggressive and are willing to take risks for the possibility of better outcomes. Others may be more conservative in their approach and be inclined to recommend older, better known treatments. Obviously, your attitude toward your illness and your willingness to take certain risks must be matched by your physician’s comfort level with your choices.

With more than 100 types of cancer, it is unreasonable to expect every hematologist-oncologist to be equally familiar with all of them. In fact, given the rarity of WM, it is not at all unusual to find physicians who have never treated the disease. Many simply do not have the time to do the necessary research, owing to busy clinical responsibilities. The IWMF office and the IWMF website keep a list of major cancer centers around the world that have WM experts on clinical staff. Many patients feel it is well worth the time and effort to travel hundreds of miles for an expert second opinion. After receiving a second opinion, WM patients are frequently treated in their regional area by a local oncologist who agrees to follow the recommendations of the expert who was consulted.
ABOUT WALDENSTROM’S MACROGLOBULINEMIA

Description

In 1944 Dr. Jan Gosta Waldenström, a Swedish physician, described a malignancy of the white blood cell \textit{B-lymphocytes (or B-cells)} that features the secretion of excessive amounts of an \textit{immunoglobulin (antibody)} called \textit{IgM}. When these cancerous cells multiply out of control and produce unregulated amounts of IgM, the result is an elevated IgM level in the blood, which can often be accompanied by an elevated \textit{serum viscosity (SV)}. When these cells proliferate in the \textit{bone marrow}, the production of red blood cells may be impaired, resulting in \textit{anemia}.

Although WM bears some similarities to the much more common hematological malignancies multiple myeloma and \textit{chronic lymphocytic leukemia}, it has been separately classified by the World Health Organization as a form of \textit{lymphoplasmacytic lymphoma (LPL)}, a low-grade, or \textit{indolent}, type of \textit{non-Hodgkin’s lymphoma (NHL)}.

Signs and Symptoms

Many patients at the time of diagnosis are \textit{asymptomatic}, but others may have clinical \textit{signs} and \textit{symptoms} commonly found in many, but not all, patients with WM: fatigue, weakness, headaches, night sweats, an enlarged \textit{spleen} and/or liver, neurological symptoms such as \textit{peripheral neuropathy}, unexplained weight loss, as well as nosebleeds and visual disturbances caused by \textit{hyperviscosity syndrome}. Clinical examination of the patient and diagnostic tests, including \textit{bone marrow biopsies} and \textit{CT/MRI scans}, may reveal abnormal blood counts, enlarged \textit{lymph nodes} and/or spleen, bone marrow involvement, and abnormal \textit{funduscopic exams}.
Diagnosis

Delegates to the Second International Workshop on Waldenström’s Macroglobulinemia in Athens, Greece, in September 2002, adopted the following diagnostic criteria: “... the definition of WM should be confined to those patients with bone marrow infiltration by lymphoplasmacytic lymphomas who have a demonstrable IgM paraprotein.” The NCCN Guidelines® for WM/LPL offer a more robust diagnostic definition: “key to the diagnosis of WM/LPL is the demonstration of bone marrow infiltration by a lymphoplasmacytic cell population manifested by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation.”

The bone marrow infiltration should be supported by immunophenotypic studies (flow cytometry and/or immunohistochemistry) showing the following profile: sIgM+, CD19+, CD20+, CD22+. According to the current WHO classification, the lymphocytes in WM are typically negative for CD5, CD10, and CD23. However, this should not exclude diagnosis as exceptions occur. About 10-20% of cases may express CD5, CD10, or CD23.

WM is sometimes initially confused with multiple myeloma or chronic lymphocytic leukemia, both of which are also B-cell malignancies that may, albeit rarely, express an elevated IgM protein. There are challenges as well from a histopathological perspective as WM may closely mimic marginal zone lymphoma and others. Simply put, the diagnosis must be confirmed by a bone marrow biopsy, and, if needed, further sophisticated tests (flow cytometry and immunochemistry) may be necessary to clearly establish the diagnosis.

Prognosis

Like the other hematological malignancies to which it is most closely related, WM is considered treatable but currently remains incurable. Although WM is viewed as an indolent non-
Hodgkin’s lymphoma, an individual’s disease characteristics can vary greatly from one patient to another – some may not require any interventions or therapy for a number of years following diagnosis. It is for this reason that *prognosis* and *median survival* rates are difficult to establish. Clearly, however, survival in WM has been steadily increasing: initially cited as five years from time of diagnosis, it is now felt to be at least twelve years +, with many patients living well beyond twenty years. A recent study published in 2006 noted a median disease specific survival of 11.2 years in 337 patients with symptomatic WM. This was a relatively old study (given today’s rapid rate of novel treatment development) using even older data; newly diagnosed WM patients can take comfort in the thought that as newer, safer, and more effective treatments emerge, the survival rates are expected to continue to increase. Not only must WM patients and their clinicians consider efficacious treatments, but the safety of these treatments, particularly the long-term side effects that may present themselves years after therapy, need to be considered carefully.

Fortunately, when therapy is needed, WM is generally responsive to many if not most chemotherapy/immunotherapy agents. Given the heterogeneity of the disease among WM patients, some patients may require more aggressive treatment than others, and, similarly, remissions (or the preferred term “responses”) may be short-lived in some patients, necessitating more frequent treatments.

A great deal of research has been devoted to develop a prognostic model that may be able to predict the degree of response to a treatment, length of response/remission, and overall survival. A large study of 587 WM patients, published in 2009, identified five prognostic factors (also called adverse characteristics) that seemingly impacted response to treatment and ultimately survival: age > 65 years, β2-microglobulin > 3g/L, M-protein > 70 g/L, hemoglobin < 11.5 g/dL, and platelets < 100 x 109/L.
International Prognostic Scoring System for WM (IPSSWM) is a work in progress. When initially developed, there was a paucity of data on WM patients who had been exposed to many of the newer targeted agents. Nonetheless, the IPSSWM has identified three types of patients: low risk (≤1 adverse characteristic and age ≤65), intermediate risk (2 adverse characteristics or > 65 years) and high risk (> 2 adverse characteristics). Low risk patients (27% of total patients) had an 87% 5-yr survival rate; intermediate risk patients (38% of patients) had a 68% 5-yr survival rate; high risk patients (35% of patients) had a 36% 5-yr survival rate. The stratification of patients into three different risk categories will permit clinicians to individualize therapy in order to neutralize adverse factors while minimizing excessive exposure to toxic agents.

**WATCHFUL WAITING (WATCH AND WAIT)**

A diagnosis of WM frequently results from a routine physical exam of a patient who is asymptomatic; the patient in question feels quite normal even though tests may reveal the presence of anemia, an abnormally high serum IgM level, and elevated serum viscosity. In this case your oncologist may advise against the need for immediate treatment in favor of a period of watchful waiting, during which time your health and disease status are monitored regularly until such time as treatment is warranted.

The primary advantage of watchful waiting is that, by deliberately postponing treatment, one temporarily avoids any potential treatment-related side effects. In addition, unlike many cancers, early treatment of asymptomatic patients does not seem to affect prognosis and life expectancy. In fact, a long-term study of smoldering WM patients showed a median time from diagnosis to required treatment of 4.6 years, a risk of progression of 12% per year for first 5 years, and then 2% risk of progression per year for the next 5 years thereafter.⁹
On the other hand, even though you may not have any noticeable symptoms, the anemia that often results from WM may gradually worsen and can sap your energy. It is important during the waiting period to monitor blood counts regularly and have regular office visits, not only with your hematologist-oncologist but also with your family physician/internist.

To “do nothing” while knowing that your body is harboring a malignancy can be very frustrating to many patients who often are eager to do something – anything at all – to alleviate the feelings of helplessness that may accompany a period of watchful waiting. Some patients turn to forms of alternative medicine and unproven remedies available at health food stores, few of which have yet to demonstrate any effectiveness in slowing the progress of cancer, much less in curing it. Use of any substance, including mega-vitamins and over-the-counter medications, should always be discussed routinely with your physician(s).

One of the most important things patients can do is to follow recognized guidelines for optimum health. These include following a healthy balanced diet, high in fruits and vegetables and low in red meat and other fatty foods; adopting a regular exercise regimen (after consultation with your physician); and recognizing your increased susceptibility to infection and avoiding exposure to germs and infectious diseases. Many patients report increased feelings of well-being through the use of recognized integrative complementary modalities such as tai chi, qigong, yoga, and meditation or prayer.
PLASMAPHERESIS

Plasmapheresis (PP), also known as plasma exchange, is a well-established treatment that can be useful in the management of WM, particularly for rapid control of the symptoms of hyperviscosity syndrome.\textsuperscript{10,11} The primary aim of plasmapheresis in WM is the removal of IgM from the patient’s circulation.

Plasmapheresis is a medical procedure in which whole blood is separated into its primary components, usually by a centrifuge or a membrane method, in a closed-loop system. The desired plasma component which includes IgM can be removed from the circulation, and the blood cells returned to the patient. Blood is continuously removed (and returned), usually from veins in both arms using large-bore IV needles. As the blood enters the centrifuge from one arm, it is separated into its primary components, plasma and red and white blood cells. Once the plasma component containing the IgM has been separated by centrifuge, the rest of the blood, including red and white cells along with the necessary replacement saline and albumin, is returned to the patient in the other arm.

This procedure can be done as often as required until the desired result (lowered serum IgM levels) is achieved. It is generally a safe procedure when done in an experienced medical center by experienced technicians. Semi-permanent catheters (also known as central lines) are often used when the patient is expected to require multiple plasmapheresis procedures or if the peripheral arm veins are not of sufficient size to accommodate the needles required for this treatment. There can be bleeding on rare occasions at the site of placement of the catheters in the large veins. Proper care of the catheters and strict hygiene are a must.

Patients can occasionally experience light-headedness and nausea during or just after a procedure. There may be tingling of the
lips and mild muscle cramps at times during the procedure; the administration of extra calcium rapidly relieves these symptoms. The patient’s blood pressure is continuously monitored during the procedure in order to minimize any episodes of low blood pressure that may occur.

Plasmapheresis is efficient in removing IgM from the circulation; thus it is effective in lowering the blood viscosity and alleviating the symptoms of hyperviscosity. Since it does not affect the production of the IgM by the WM cells in the bone marrow, its effects are only temporary in nature. Eventually more aggressive therapy will probably be required, although some patients have used plasmapheresis as sole treatment for their disease for many years. Plasmapheresis is used by patients who have not yet received chemotherapy as well as by patients who are receiving chemotherapy. Plasmapheresis is now used frequently as a precautionary measure for patients with high IgM levels (usually above 3000-4000 mg/dL) who are to receive rituximab monoclonal antibody therapy in order to mitigate any potential “IgM flare” phenomena (rapid increase in serum IgM following rituximab treatment which can markedly increase serum viscosity).12,13

GROWTH FACTORS

A frequent clinical consequence of WM is a decrease in the bone marrow’s ability to produce adequate amounts of blood cells, leading to anemia (suppressed red blood cells) and resulting in increasing fatigue, leukopenia or neutropenia (suppressed white blood cells, leading in turn to increased susceptibility to infection) or thrombocytopenia (suppressed platelets, leading to increased susceptibility to bleeding). These conditions may also be caused by certain chemotherapeutic regimens.

To combat anemia, synthetic forms of DNA-recombinant erythropoietin are often used. The most commonly prescribed drugs for anemia are Procrit (epoetin alfa) and Aranesp (darbepoetin alfa). Similarly, to reverse neutropenia the granulocyte-colony
stimulating factors (G-CSF) Neupogen (filgrastim) and Neulasta (pegfilgrastim) are used. These agents are not typically prescribed for long-term use although they may be used for years in certain cases. In the case of chemotherapy-induced myelosuppression, these agents help the body achieve and maintain appropriate levels of the blood components affected.

**Erythropoietin**

Procrit and Aranesp are used to fight the anemia associated with cancer by stimulating the production of red blood cells. They are often used as well in patients with kidney failure who are on dialysis. In the case of WM, the anemia is frequently caused either by infiltration of the bone marrow by tumor cells or by chemotherapy. Thus Procrit and Aranesp may be used as palliative measures to forestall chemotherapy or to restore the red blood cells destroyed by chemotherapy. Procrit and Aranesp are administered by subcutaneous injection, usually weekly, bi-weekly, or monthly, and can often be done at home by the trained patient or caregiver. They are generally well tolerated with minimal discomfort from injection. Recently there has been much debate regarding the use of these agents for palliative purposes in patients who have not received chemotherapy, and some physicians, institutions, or health insurance companies may not be willing to provide this drug.

**Granulocyte-Colony Stimulating Factor (G-CSF)**

Neupogen and Neulasta are used to treat neutropenia, a decrease in the number of neutrophils (white blood cells used for fighting infection), which often results from chemotherapy. They are also used in virtually all bone marrow and stem cell transplant protocols, including peripheral blood stem cell collection, and occasionally for neutropenia resulting from bone marrow infiltration by malignant cells (another controversial issue). These biological agents may be given at the doctor’s office, clinic, or hospital but can also be administered subcutaneously by the trained patient or caregiver at home. Blood counts are monitored regularly to maintain proper
levels. Both Neupogen and Neulasta are generally well tolerated; side effects are usually minor and transient but may include mild discomfort from injection and bone pain.

**TREATMENT OPTIONS – CHEMOTHERAPY/DISEASE MODIFYING AGENTS**

Although there are a number of available treatments for WM, none stands out as a clear choice. To date there have been few studies pitting one treatment against another in Phase III clinical trials. As noted earlier, initiation of therapy should not be based on serum IgM levels alone, and early treatment of asymptomatic patients does not appear to influence prognosis and life expectancy. Nonetheless, previously asymptomatic patients should be considered for immediate therapy if they start developing one or more of these conditions: disease-related cytopenias (such as anemia with a hemoglobin level < 10 g/dL), bulky adenopathy or organomegaly, hyperviscosity syndrome, severe progressive peripheral neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease, or evidence of disease transformation.14

Perhaps the most important consideration when deciding which treatment to use is based on the individual patient’s disease characteristics: the presence of particular cytopenias, the need for rapid disease control, age and overall health status, and candidacy for possible future autologous transplantation.

Finally, before the patient and treating physician(s) select a treatment plan, the therapeutic outcomes of the proposed treatment should be evaluated using the updated response criteria from the Sixth International Workshop on Waldenstrom’s Macroglobulinemia.15 These newly revised response criteria have also been adopted by the NCCN Guidelines® Version 2.2013 (See Appendix 1).
ALKYLATING AGENTS

Chemotherapy owes its origin to the mustard gases of World War I when nitrogen mustard was shown to have a toxic effect on white blood cells and therefore of potential use in treating leukemia and related diseases, giving rise to a category of chemicals 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, nausea, and hair loss.

Although alkylating agents have been used as single-agent therapy in the past, combinations with other agents are more popular and much more effective. Designated drug combinations with the acronyms CHOP, R-CHOP, R-CVP, R-CD, R-FC (to name a few) are described later in this booklet.

**Chlorambucil (Leukeran)**

Chlorambucil is one of the oldest and most commonly used alkylating agents in the treatment of chronic lymphocytic leukemia (CLL), non-Hodgkin’s lymphomas (NHL), and WM, having been in use for more than forty years. It is relatively inexpensive, is taken at home in pill form, 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 symptoms and stabilization 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. Response to chlorambucil is slow and may not be appropriate for patients who require rapid disease reduction, such as the patient with symptomatic hyperviscosity. Patients are usually treated for at least six months before therapy is discontinued.16

For some WM patients, particularly the frail elderly, chlorambucil may be quite acceptable for long-term disease control over a period
of many years. While chlorambucil is generally a safe treatment, in rare cases it has resulted in the development of acute leukemia and/or myelodysplasia.\textsuperscript{17} It should also be used sparingly with patients considered potential candidates for autologous stem cell transplant as it may damage the stem cells. Chlorambucil is therefore rarely used in patients younger than 65.

**Cyclophosphamide (Cytoxan)**

Like chlorambucil, cyclophosphamide has been a mainstay as an alkylating agent for many years, most frequently given as part of combination therapy.\textsuperscript{18,19} This drug may be given 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 increased risk of bladder cancer. Cyclophosphamide appears to confer a lower risk for developing acute leukemia and/or myelodysplasia than does chlorambucil. Cyclophosphamide does not appear to harm stem cells and can therefore be used in patients who may require stem cell harvesting in anticipation of a bone marrow transplant.

**Bendamustine (Treanda or Levact)**

Bendamustine is a drug developed in the 1960s in the former East Germany. It was not until the 1990s that it was formally studied in patients. Bendamustine’s unique chemical structure gives it properties of an alkylating agent, such as cyclophosphamide, as well as properties of a nucleoside analog, such as fludarabine. Although formally classified as an alkylating agent, one can think of this drug as a potent combination of alkylating agent and nucleoside analog.

The U.S. Food and Drug Administration (FDA) approved bendamustine in late 2008 for the treatment of patients with indolent B-cell non-Hodgkin’s lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Bendamustine has been used both as sole therapy and in combination with other agents including rituximab, prednisone, and fludarabine. A landmark study published in 2008 evaluated bendamustine plus rituximab (BR) versus CHOP-R in previously untreated patients with indolent non-Hodgkin’s lymphoma: 42 patients with WM were included in this study. The overall response rate with BR in this study was similar to CHOP-R (96% vs. 94%). Relapse was seen in only 2 of 23 patients treated with BR, as opposed to 7 of 17 patients treated with CHOP-R. The patients who received BR experienced far fewer side effects.20

The use of bendamustine alone, or bendamustine plus rituximab (or ofatumumab in rituximab-intolerant patients) was studied in 30 relapsed/refractory WM patients and reported in 2011.21 This study convincingly demonstrated that bendamustine, alone or in combination with an anti-CD-20 monoclonal antibody, was well tolerated and produced very good and durable responses in previously treated WM patients.

As a result of the two above-mentioned studies (and including other studies and observations as well as extensive clinical use of bendamustine by physicians treating WM patients), the use of bendamustine alone or in combination with an anti-CD-20 monoclonal antibody is now recommended as a treatment option in both primary and salvage therapy for WM. It remains unclear whether bendamustine causes stem cell toxicity and/or risk of transformation, and as a result bendamustine-containing regimens should be used with caution in patients where stem cell harvest is being considered and in patients who have been heavily pre-treated.

**NUCLEOSIDE (OR PURINE) ANALOGS**

Nucleoside analogs are part of a larger class of anticancer drugs termed *antimetabolites*. While alkylating agents can be destructive to any fast-growing cell, purine analogs act specifically on proliferating cells. Two purine analogs, fludarabine phosphate
(Fludara) and cladribine, also known as 2CdA (Leustatin), came into frequent use in the 1990s as alternatives to alkylating agents in the treatment of WM.

Fludarabine and cladribine are often used in combination with other agents in the treatment of WM.\textsuperscript{22,23} Monotherapy (single-agent therapy) with nucleoside analogs is used infrequently at present.\textsuperscript{24,25}

Fludarabine was initially approved for use in the treatment of chronic lymphocytic leukemia, and cladribine was approved for use in the treatment of hairy cell leukemia. Both of these drugs have subsequently been shown to be active in the treatment of WM. Each of these drugs has its champions among respected researchers, 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. Other considerations such as ease of use, convenient dosing schedules, and length of treatment may enter into the treatment decision.

Nucleoside analogs are generally well tolerated, but they have been implicated in the development of hematologic and \textit{immunosuppressive} complications.\textsuperscript{26,27} The potential for hematological stem cell toxicity is well documented, and careful patient selection is required as future harvesting of stem cells for possible future autologous transplant may be difficult or impossible. The marked reduction in white blood cells (particularly neutrophils and \textit{CD-4+ 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 \textit{prophylaxis} during and for an extended period of time after nucleoside analog therapy. Antibiotic prophylaxis to prevent bacterial infections is similarly recommended in selected cases. Recent reports have suggested an increased incidence in the development of myelodysplasia
and acute leukemia, as well as an increased incidence of disease transformation in WM patients treated with nucleoside analogs. Because the risk is upwards of 15%, limiting the exposure of these agents in younger WM patients is now recommended. There has also been some observation of a low but nonetheless increased risk of secondary cancers in patients who have been treated with nucleoside analogs.

**Fludarabine (Fludara)**

Fludarabine is typically administered intravenously for four or five consecutive days in three or four week cycles. Fludarabine may also be given in pill form – more commonly in countries outside the U.S. The number of cycles is determined by the patient’s response; typically four to six cycles have been used, but 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 cessation of therapy. Patience is therefore an important consideration when assessing fludarabine efficacy.

**Cladribine (2CdA or Leustatin)**

Cladribine is typically administered intravenously, usually on five consecutive days, each treatment requiring about two hours. It may also be 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. Cladribine usually results in a faster overall decline in IgM than fludarabine.
MONOCLONAL ANTIBODIES

Antibodies are an integral part of the body’s immune system. They circulate in the bloodstream and attach themselves to surface molecules *(antigens)* found on bacteria and other foreign substances. Monoclonal antibodies (MAbs) are identical antibodies that are produced in large amounts in the laboratory from a single cell clone. These antibodies recognize and attach themselves to specific antigens found on the target cell’s surface. The monoclonal antibody rituximab (Rituxan) is designed to recognize and attach itself to the CD-20 antigen found on B-cells. Once the rituximab has latched on to the CD-20 receptor found on WM B-cells, it can either directly destroy the targeted cell or activate the immune system to kill it.

Although there is currently no standard treatment for first-line management of WM, most clinicians and investigators believe that anti-CD-20 directed therapy should comprise part of the regimen. Other MAbs that target similar or different antigens on the B-cell are described below. There is a significant number of newer MAbs that are currently being investigated in clinical trials and showing promise in the treatment of lymphoma.

**Rituximab (Rituxan or Mabthera)**

Rituximab was the first monoclonal antibody to receive FDA approval for treatment of cancer. Approved for relapsed non-Hodgkin’s lymphoma in 1998, rituximab has become commonly used as a first-line monotherapy as well as in combination therapies and, recently, in maintenance therapy.28,29

Treatment protocols for rituximab immunotherapy vary. The more common protocol, consisting of four weekly rituximab infusions, has a reported overall response rate of 20-30%. An extended-dose rituximab protocol, consisting of four weekly infusions followed by four more weekly infusions eight weeks later, has a reported overall response rate of 40-50%.30
A patient’s genetic make-up can significantly influence response rates to single-agent rituximab therapy. Patients with the preferred FcγRIIIA-158 polymorphism can experience up to four-fold higher rates of response than those patients with an unfavorable genetic profile.\textsuperscript{31} Testing for this advantageous genetic polymorphism is now FDA approved and will likely be used with greater frequency in the near future.

Virtually all therapies for WM using rituximab in combination with other agents confer higher response rates than rituximab monotherapy. A number of these combination therapies will be described later in the booklet.

The most common side effects of rituximab are infusion-related. It is quite common for a patient to develop chills, fevers, and tremors during the very first rituximab treatment. In order to minimize these side effects, medications are administered prior to all rituximab infusions. Typically an antipyretic such as acetaminophen, antihistamines, and possibly corticosteroids, including prednisone, are used. Subsequent rituximab infusions are generally much better tolerated.

Rituximab therapy of WM patients with high serum IgM may cause a rituximab-mediated IgM flare.\textsuperscript{32,33} Patients can experience a marked increase in their IgM levels following rituximab infusion, leading to an increase in serum viscosity and subsequent hyperviscosity syndrome and to a worsening of IgM-related neuropathy, cryoglobulinemia, and other IgM-related complications. The “Rituxan flare,” as it is more commonly known, is a phenomenon that is unpredictable and therefore needs to be monitored closely by the treating physician. The flare may last for a few weeks to a few months and does not suggest treatment failure.\textsuperscript{34} The reported occurrence rate is 40-50% when rituximab is used as monotherapy. In combination therapy the flare phenomenon seems to be less prevalent but remains unpredictable. Many clinicians advocate using plasmapheresis to reduce IgM levels prior to rituximab therapy in selected high-risk patients.
Rituximab causes less overall myelosuppression than either alkylating agents or nucleoside analogs. Although generally considered to be one of the least toxic of WM treatments, it can result in significant, albeit transient, depletion of normal B-cells.

**Rituximab Maintenance Therapy**

Currently no cure exists for WM. Many patients may experience long durable responses following treatment with a particular therapy, but re-treatment is invariably required at some future point in time for most. Researchers continue to work on improving current approaches by trying new drugs, as well as new combinations of drugs. As responses to newer treatments continue to improve and become more durable and long-lasting, the question of maintenance therapy, particularly maintenance rituximab (MR) therapy, appears to be gaining momentum. MR is prolonged treatment given after the initial chemotherapy course (usually combination rituximab therapy) has taken effect and reduced the disease burden. The goal of maintenance therapy is to prolong the amount of time before re-treatment becomes necessary.

There is some controversy as to the exact role of maintenance therapy with rituximab in WM. It was recently added in the NCCN Guidelines* for WM/LPL as a reasonable option to be considered for patients responding to rituximab-based therapy. Despite widespread use and very encouraging results, the lack of formal clinical trials has hampered the proper evaluation of the role of maintenance therapy in WM. MR has been thoroughly researched in the much more common indolent lymphoma called follicular lymphoma and in some studies has been found to essentially reduce the risk of relapse after three years by 40-65%. A convincing published study in one of the leading cancer journals has demonstrated that two years of maintenance therapy with rituximab dramatically improves the chances of survival for patients suffering from indolent non-Hodgkin’s lymphoma.35 This
study confirmed that rituximab maintenance therapy was highly beneficial for all patients, including those who had already received rituximab as part of their initial therapy. Rituximab maintenance therapy was applied as a single infusion every three months over a period of two years. The results showed a three-fold increase in median \textit{progression-free survival} for the rituximab-treated patients over patients not receiving maintenance therapy. There was a 60% reduction in risk of progression.

A retrospective analysis of 248 WM patients who had received rituximab + chemotherapy, and of whom 35% went on to receive maintenance rituximab, demonstrated a significant improvement in the median progression-free survival of 56.3 months in the maintenance group vs. 28.6 months in those who did not receive maintenance.\textsuperscript{36} Lower serum IgM levels as well as improved durability of responses were noted in the maintenance group. The most common side effects seen in MR for WM patients are lower than normal immunoglobulin levels and more frequent respiratory infections. Many WM experts now feel that WM patients who respond to an initial course of single agent rituximab or rituximab combination therapy should be considered for maintenance rituximab.

In WM, the most commonly used rituximab maintenance protocol is a single infusion of rituximab every two or three months for a period of two years. Other MR schedules are being investigated, and in one study bortezomib and dexamethasone were added every three months to rituximab in patients who responded to the initial combination of bortezomib, dexamethasone, and rituximab (BDR).

\textbf{Ofatumumab (HuMax-CD20 or Arzerra)}

Ofatumumab is a human anti-CD-20 monoclonal antibody with greater \textit{complement} activity than rituximab. Approved in the United States for patients with refractory chronic lymphocytic leukemia, it is now being used in other diseases such as WM, particularly in instances when a patient may not tolerate rituximab infusions.
A Phase II clinical trial demonstrated that ofatumumab could be successfully administered in patients with WM, including those who were intolerant to rituximab. The study demonstrated that ofatumumab is clinically active in WM patients and has an acceptable toxicity profile. IgM flare can occur with this drug as it does with rituximab. The overall response rate was 59%, including a 50% overall response rate in patients with IgM ≥ 4.0 g/dL. As a result of this and other studies, ofatumumab has been added to the NCCN Guidelines® for WM/LPL as a recommendation for salvage therapy for patients who are intolerant to rituximab. Further studies are ongoing with ofatumumab in combination with bortezomib (Velcade) that will help evaluate efficacy and safety in WM patients.

**Alemtuzumab (Campath)**

Alemtuzumab is a monoclonal antibody that targets the CD-52 antigen on B-cells (and *mast cells*) rather than the CD-20 antigen targeted by rituximab. As is the case with all MAbs, its effectiveness will depend on the extent to which the malignant cell expresses this specific antigen. Initially developed as a treatment for chronic lymphocytic leukemia, for WM it has produced an overall response rate of 76% in a clinical trial. Alemtuzumab also has an affinity for the CD-52 receptor on bone marrow mast cells, which are increased in WM patients and offer support to the malignant WM cells. Combination therapy with rituximab is currently being considered by clinical investigators. The treatment protocols are varied, although dosing is usually more frequent than with rituximab. Infusion-related side effect patterns are similar to those of rituximab. A subcutaneous form of alemtuzumab is available which reduces infusion-related reactions. Alemtuzumab can cause important hematological toxicity and atypical infections and thus is not considered first-line therapy in WM. *Cytomegalovirus* reactivation in treated patients is a concern.
PROTEASOME INHIBITORS

Bortezomib (Velcade)

Bortezomib is the first of a new class of drugs called proteasome inhibitors. Proteasomes are large protein complexes present in all cells that help regulate cell growth and death. When proteasomes are inhibited with bortezomib, many types of cancer cells, including those common to lymphoma and multiple myeloma, undergo apoptosis (cell death). Normal non-cancerous cells appear able to tolerate bortezomib without significant difficulties.

In a landmark Phase II clinical trial in WM, bortezomib was given as an IV injection on days 1, 4, 8, and 11 every 21 days for up to eight cycles. Rapid decreases in serum IgM were noted, and the overall response rate was 85%.³⁹ Of importance is the occasionally observed discordance between a drop in serum IgM levels and a reduction in actual tumor cells in the bone marrow. Patients receiving bortezomib alone or in combination may need more frequent bone marrow biopsies in order to properly assess response to therapy. Significant side effects such as peripheral neuropathy have resulted in reduction of doses and modification of subsequent dosing schedules in trials and clinical practice.⁴⁰ Less frequent side effects include autonomic nervous system dysfunction (blood pressure fluctuation, cardiac rhythm disturbances) as well as reduced blood counts (cytopenias). Dosing adjustments (including weekly vs. twice a week administration) have greatly reduced the subsequent incidence of peripheral neuropathy and other side effects. There is no data on use of subcutaneous bortezomib in WM patients, although in myeloma patients it has been used with a lower incidence of neuropathy compared to intravenous use. Bortezomib is now primarily used in varied combinations with rituximab and other agents and appears to attenuate the rituximab flare phenomenon.
Carfilzomib

Carfilzomib is a newer proteasome inhibitor currently being evaluated in combination with rituximab and dexamethasone in a Phase II clinical trial in WM patients. Combinations with rituximab, dexamethasone, and proteasome inhibitors like carfilzomib show high levels of activity in WM patients. Similar in action to bortezomib, carfilzomib is, however, an irreversible proteasome inhibitor and appears therefore to be more effective. Preliminary results thus far indicate that the treatment appears well tolerated, is associated with fewer side effects from peripheral neuropathy, improves low red blood cell counts (anemia), and rapidly reduces IgM levels. Preliminary results of a study using carfilzomib + rituximab + dexamethasone showed an overall response rate of 75% with no severe neuropathy reported. Although not at present officially approved for the treatment of WM in primary or salvage therapy, one can anticipate the recommendation of carfilzomib for treatment of WM in the relatively near future.

IMMUNOMODULATORS/ IMMUNOSUPPRESSANTS

Immunomodulators (IMiDs)

Originally developed and marketed in Europe as a sedative in the 1960s, thalidomide (Thalomid) was taken off the market when it was implicated in birth defects if used by pregnant women. It was subsequently discovered to be effective in the treatment of leprosy, and in the late 1990s thalidomide was found to have significant activity in the treatment of multiple myeloma.

The immunomodulatory thalidomide derivatives (IMiDs), including lenalidomide (Revlimid) and pomalidomide (Actimid), kill tumor cells by four described mechanisms of action: IMiDs starve the tumor cells from the blood supply that feeds them (anti-angiogenic effect); IMiDs enhance the tumor killing properties of T-lymphocytes and natural killer cells; IMiDs block some of the interactions between tumor cells and other (stromal) cells in the...
bone marrow microenvironment; and finally IMiDs seem to directly kill tumor cells by a mechanism not yet fully understood.

Thalidomide has been shown to be an active agent in WM but not as successfully as when used for multiple myeloma. Thalidomide enhances the efficacy of rituximab when used in combination. The combination of thalidomide and rituximab may be quite useful in WM patients who have significant myelosuppression but do not require immediate disease control. An overall response rate of 70% bolstered by a 3-year median progression-free survival has been observed. Side effects, particularly peripheral neuropathy, constipation, and sedation, are noted mostly at higher dosage levels.

The use of the second generation IMiD lenalidomide in WM is discouraged due to the development of a marked acute and persistent anemia seen in many WM patients.

The newer third generation IMiD pomalidomide is currently being investigated in the laboratory and in clinical trials for use in WM. Pomalidomide has efficacy as a single agent and with dexamethasone for the treatment of relapsed/refractory multiple myeloma and is noted to have fewer neuropathy-related side effects. A Phase I study of pomalidomide in patients with relapsed and/or refractory WM has suggested that pomalidomide is well tolerated. Pomalidomide may also stimulate the immune system to fight the cancer cells and possibly improve the effectiveness of dexamethasone and rituximab. As a result, a clinical trial is currently evaluating the combination of pomalidomide, dexamethasone, and rituximab in WM.

Corticosteroids (Steroids)

Corticosteroids are a group of natural and synthetic analogs of hormones secreted by the pituitary gland. Corticosteroids are implicated in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation.

The immunosuppressive effects of corticosteroids ("steroids") such as prednisone and dexamethasone are poorly understood.
Although rarely used as single agents in treating WM, they are administered frequently in combination with other therapies. Dexamethasone is approximately ten times more potent than prednisone and typically has a longer duration of action. Steroids alone or in combination therapy may be beneficial in patients who develop WM-associated hematologic complications such as cryoglobulinemia, cold agglutinin disease, and thrombocytopenia.

Side effects are common and are proportional to dosage and duration of therapy. These can include excitatory effects on the central nervous system such as euphoria, psychosis, and insomnia; steroid-induced osteoporosis; glaucoma; cataracts; muscle wasting; an increased susceptibility to infection; and finally weight gain and appetite stimulation. Despite the potential side effects of long-term steroid therapy, the use of steroids in combination with monoclonal antibodies or other chemotherapy agents is widespread, given the usual short duration of therapy (and reduced side effects) as well as the noted synergistic action of steroids when used in combination therapy for WM.

**TARGETED THERAPIES/PATHWAY INHIBITORS**

**Everolimus (RAD001 or Afinitor)**

Everolimus is a type of targeted therapy that blocks mTOR, a protein that normally promotes cell growth and survival. Used to treat advanced kidney cancer as well as advanced breast cancer, among others, everolimus may also stop tumors from developing new blood vessels (angiogenesis), which would help limit their growth. A Phase II trial in WM has shown that everolimus has high single-agent activity with an overall response rate of 70% and manageable toxicity in patients with relapsed WM. Side effects may include cytopenias and pulmonary toxicity. IgM discordance to underlying bone marrow involvement is common, wherein decreases in IgM do not accompany improvements in underlying disease. Bone marrow biopsies may be required to clarify response.
The NCCN Guidelines® for WM/LPL recently added everolimus to the recommended treatment regimens for salvage therapy in WM patients. Newer everolimus-containing combination treatments are being considered for study in WM clinical trials in the near future.

COMBINATION THERAPIES

Combinations of rituximab with other agents have been shown to result in responses equally as good as or better than monotherapy with any of the single agents. Overall response rates of greater than 90% are common, and median time to response and median duration of response are significantly improved. As a result, combination therapy is used more often in the treatment of WM than monotherapy. There are many different combinations of drugs used in the treatment of WM; primary and salvage combination therapy regimens are listed in Appendices 4 and 5.

The choice of appropriate therapy should take into account several important factors: the need for immediate or non-immediate disease control, the International Prognostic Scoring System for WM (IPSSWM) risk category, the specifics of the individual WM patient’s disease characteristics (hyperviscosity syndrome, neuropathy, anemia, cryoglobulinemia, etc.), and finally, the candidacy of a patient for autologous stem cell transplant, since prolonged use of both alkylating agents and nucleoside analogs can deplete hematopoietic stem cells.

Acronyms are often used when describing combinations of single agents. The more commonly used abbreviations for single agents are described in Appendix 6.

It is important to note that one of the most popular and effective combination therapies for lymphomas and WM in the recent past has been R-CHOP.\textsuperscript{46} Recently the value of the more toxic agents doxorubicin (H) and vincristine (O) in R-CHOP therapy for WM has been questioned. In fact, two recent studies have demonstrated equal effectiveness of either R-CD or CP-R to R-CHOP;
Furthermore, treatment-related side effects and complications were greatly reduced when doxorubicin and vincristine were omitted from the combination therapy.\textsuperscript{47}

One of the more commonly used combination treatments is cyclophosphamide + rituximab + prednisone (or dexamethasone). The use of this combination may be advantageous in younger WM patients for whom a transplant is a future potential option. With overall response rates at 80% and favorable progression-free survival metrics,\textsuperscript{48} this tried and true combination is a favorite of many WM treating clinicians worldwide.

Bendamustine + rituximab has certainly made quite an impact in the treatment of WM. Newer combinations of bendamustine and rituximab plus another agent or two are sure to be developed and evaluated in the future.

For many older patients, the combination of a nucleoside analog such as fludarabine and rituximab (+/- steroid or cyclophosphamide) remains an important option. These “older” agents are still proving to be very effective in the properly selected patient. Stem cell harvest concerns need to be addressed when choosing these particular combinations.

Bortezomib (Velcade) combinations are becoming increasingly popular with clinical investigators and bear mention. Although bortezomib is a relatively new treatment for WM, a recently completed clinical trial demonstrated very favorable response rates with the combination of bortezomib + dexamethasone + rituximab (BDR).\textsuperscript{49} Peripheral neuropathy is a major concern, but reduced dosing or subcutaneous dosing schedules of bortezomib, as well the anticipated increased use of the second-generation proteasome inhibitor carfilzomib, should reduce this painful complication of therapy.
STEM CELL TRANSPLANTATION

Among those treatments considered controversial until recently for WM is stem cell transplantation (SCT - also known as “high-dose chemotherapy with stem cell rescue” or simply “bone marrow transplant”). Two principal types of SCTs exist: autologous stem cell transplantation (ASCT), in which the patient serves as his or her own donor of hematopoietic stem cells; and allogeneic transplantation, in which the donor of the stem cells is another individual, preferably a relative (usually a brother or sister), but in some cases an unrelated individual.

Stem cells are primitive cells capable of both self-renewal and differentiation into some other tissue. In this case, the cells are capable of differentiating into bone marrow and immune system cells. Normally, these stem cells live in the bone marrow and travel in very small numbers into the blood. For many years they were obtained from the bone marrow; hence, the term “bone marrow transplant.” While this technique is effective and is still sometimes painfully performed, it has been largely replaced by peripheral blood stem cell harvest.

In peripheral ASCT the source of stem cells is the patient’s own blood. The cells that reside in the bone marrow are induced to migrate into the blood by means of a biological chemical called a growth factor or cytokine (see the section on Granulocyte-Colony Stimulating Factor). After approximately five to ten days of subcutaneous injection of the growth factor, the stem cells are collected from the donor by means of a technique called apheresis, a procedure easily performed that is somewhat similar to plasmapheresis. Collected stem cells can be frozen in liquid nitrogen up to 20+ years.

The goal of autologous transplantation is to kill the WM cells by administering a “conditioning” or preparative regimen involving high doses of chemotherapy ± radiation therapy, minimizing injury to other tissues, and subsequently replacing, or “rescuing”, the bone marrow with stem cells previously collected from the...
patient. Following stem cell infusion, colonization of the infused stem cells (engraftment) in the bone marrow is rapid, usually within 10 days. It may take approximately two to four weeks for the bacterial fighting capabilities of the immune system to redevelop and a somewhat longer time for the anti-viral and anti-fungal elements of the immune system to function adequately. Recently transplanted patients need to be very careful not to be exposed to infectious diseases for a period of months and are monitored carefully by the clinical transplant team.

In allogeneic stem cell transplantation, the stem cells are donated by an individual (donor) whose tissue type (HLA) matches that of the patient (recipient). Allogeneic transplant donors may be related (usually a closely HLA matched sibling), syngeneic (an identical twin of the patient – a perfect match), or unrelated (a donor who though not related is found to have a very close degree of HLA matching). Allogeneic transplants are also now being performed using umbilical cord blood as the source of stem cells, although this technique has seen its share of difficulties and remains rather rarely used.

In traditional allogeneic transplantation the patient receives aggressive chemotherapy, and possibly radiation therapy, to eradicate the patient’s disease. In the case of WM, the bone marrow is ablated (myeloablation) with chemotherapy doses that cause minimal injury to other tissues, and then the patient subsequently receives an infusion of healthy donor cells. The conditioning regimen not only eradicates the disease but also has an immunosuppressive effect that prevents rejection of the donor’s stem cells by the recipient’s immune system. The post-transplant prognosis often includes acute and chronic graft vs. host disease (GVHD), which may be life threatening and necessitates the use of powerful immunosuppressive medications. In the case of WM (and other leukemias and lymphomas), GVHD can coincide with protection against cancer relapse owing to the graft vs. tumor effect. In this instance, the donated stem cells not only reconstitute the
recipient’s immune system but also may recognize any residual WM cells and destroy them. This is potentially an enormously powerful and beneficial “side effect” and is considered to be one of the best hopes for a potentially curative therapy in WM.

Historically, standard allogeneic transplantation has been considered far too dangerous for most patients with WM. A new and exciting modification, however, is non-myeloablative stem cell transplantation, or mini-allo transplantation, whereby a reduced-intensity conditioning regimen is used that is considerably less toxic to the patient. In these non-myeloablative transplants, the reduced-intensity conditioning regimen serves not to completely eradicate the patient’s disease but rather to prepare the patient’s immune system to receive the stem cells from the donor. The donor cells themselves constitute the primary focus of this therapy. The patient receives a lower dose of chemotherapy, which may be coupled with radiation therapy, to cause an immunosuppressive effect on the remaining bone marrow cells followed by an infusion of matched donor stem cells. After a period of several weeks, the donor stem cells replace the patient’s immune system and ideally begin to attack the WM cells (graft vs. tumor effect) and replace them with healthy normal cells. The aim of this newer experimental type of transplant is to provide complete response as well as to reduce the serious side effects and toxicity of standard allogeneic transplants.50

Stem cell transplants have been shown to be effective in the treatment of WM for younger patients with relapsed or refractory disease, usually to several lines of therapy.51 Autologous stem cell transplants are considered appropriate salvage therapy for selected patients, are associated with a very low treatment-related mortality, and can offer long-term disease control. Whereas allogeneic transplants have high treatment-related mortality rates (greatly reduced in mini-allo transplants), the potential for complete and durable long-lasting responses is increased. Nonetheless, allogeneic transplants are currently recommended only in the context of clinical trials.
EMERGING THERAPIES

Ibrutinib

To live and multiply, WM B-cells rely on a complex series of molecular signals via proteins (B-cell receptors) on the surface of the cell. An intact B-cell receptor (BCR) signaling cascade is an essential requirement for the survival of B-cell malignancies like WM. A specific molecule, Bruton's tyrosine kinase (BTK), is critical in the BCR signaling pathway. Ibrutinib (previously known as PCI-32765) is an oral small molecule BTK inhibitor that inhibits BCR signaling in human B-cells and leads to apoptosis (cell death). A Phase II clinical trial to determine response in 16 WM patients with relapsed or refractory disease demonstrated rapid reduction in IgM levels and a corresponding increase in the patients' hemoglobin levels. At the time of this booklet's publication, ibrutinib had just received Breakthrough Therapy Designation from the FDA for the treatment of WM and relapsed mantle cell lymphoma. Breakthrough Therapy Designation is intended to expedite the development and review time for potential new medicines that can treat a serious or life-threatening disease and that demonstrate substantial improvement over existing therapies.

Perifosine and Enzastaurin

The PI3K/Akt/mTOR and NF-κB pathways are complex biochemical cellular pathways implicated in the regulation of cell death (apoptosis), cell division, tumor blood vessel growth, and tumor proliferation in WM. Perifosine is a Akt inhibitor, enzastaurin is a PI3/Akt inhibitor, and everolimus is a mTOR inhibitor (see the discussion of everolimus under Targeted Therapies/Pathway Inhibitors). These biological agents are currently the focus of active clinical research in a number of clinical trials. The newer agents perifosine, everolimus, and enzastaurin provide overall response rates of 35-70%. Most of these agents are well tolerated, although some WM patients have reported serious
side effects that warranted discontinuation of the drug in question. The use of these novel biological agents has measurably advanced the understanding of the biology and therapy of WM as well as mechanisms of drug resistance. Cellular pathways are complex and often redundant; therefore we can expect to see in the near future combination therapies with two or more of these newer agents coupled with more commonly used agents such as rituximab and dexamethasone.

**RADIOIMMUNOTHERAPY**

Radioimmunotherapy (RIT) combines the cell targeting ability of a monoclonal antibody like rituximab with a radioactive particle, or radioisotope. With RIT, the antibody binds to a specific antigen present on cancer cells, delivering a dose of radiation directly to the targeted cell. The targeted cell is thus destroyed; however, not only the targeted cell is affected but so are surrounding cells. In order to minimize the immunosuppression from this “crossfire effect,” patients who have greater than 25% disease in the bone marrow are excluded from treatment, and this likely includes many WM patients. Strategies are currently being developed to resolve this issue. Two RIT drugs, Zevalin and Bexxar, have received FDA approval for the treatment of non-Hodgkin’s lymphoma and clinical trials are ongoing.  

The side effects reported with Zevalin and Bexxar are similar to those associated with rituximab: mild flu-like symptoms that are controlled by medications such as Benadryl and Tylenol. The radiation does not penetrate outside the body, although a small amount may be present in body fluids such as blood and urine for about a week after treatment. Patients are advised to avoid people for a short period of time in order to limit possible radiation exposure.
**Ibritumomab (Zevalin)**

Zevalin binds to the CD-20 antigen found on the surface of normal and malignant B-cells, allowing radiation from the attached yttrium-90 isotope to kill them. Various protocols exist for administration, but the most common regimen takes 7-9 days, with two administrations of Zevalin using two different radioisotopes, indium-111 and yttrium-90. Each dose is preceded by a reduced dose of rituximab in order to pre-deplete B-lymphocytes and minimize secondary myelosuppression. The first intravenous infusion dose of Zevalin uses indium-111 (this emits gamma radiation that can be picked up by a scan) to ensure that no excess amounts go to the marrow, liver, etc. If the gamma scan is satisfactory, a second dose of Zevalin is given, using yttrium-90 as the actual treatment. Yttrium-90 emits cell-killing beta radiation.

**Tositumomab (Bexxar)**

Bexxar is similar to Zevalin but uses the CD-20 monoclonal antibody tositumomab and the radioisotope iodine-131(I-131). I-131 has a long track record of clinical experience and an excellent safety profile in the treatment of thyroid conditions. In addition, I-131 can be used for both imaging and treatment by virtue of the fact that I-131 has dual emissions (both beta and gamma particles). The usual Bexxar therapeutic regimen is given in two steps. First, patients receive a *dosimetric* dose to establish the patient-specific therapeutic dose. Second, a single therapeutic dose is administered. With appropriate instructions, the patient can generally be treated on an outpatient basis.

As of the publication date of this booklet, radioimmunotherapy is not officially recommended for the treatment of WM.

**VACCINE THERAPY**

The vaccines most of us are familiar with are those designed to prevent diseases such as tetanus, polio, measles, etc. This form of passive immunization is used to prevent disease in large populations.
The vaccines currently being developed for lymphomas differ from the more common passive vaccines in that they are designed to treat an established disease rather than preventing it. Vaccines for the treatment of lymphomas are called active, or therapeutic, vaccines. This personalized form of immunotherapy uses vaccines that are individually made from the patient’s own tumor cells. It is hoped that the vaccine will stimulate the patient’s immune system cells not only to destroy the cancer cells but also to provide long-lasting protection against the recurrence of the disease.

A lymphoma vaccine is created specifically for an individual patient from the patient’s own tumor cells. The vaccine is targeted at a specific antigen, or *idiotype*, found only on the surface of the cancer cells, thus sparing normal healthy cells. The specific targeting mechanism of the vaccine should result in fewer side effects than other cancer treatments such as chemotherapy, which destroys both cancer cells and normal cells. The vaccine is typically administered following conventional treatment with rituximab, chemotherapy, or a combination rituximab + chemotherapy. Once the tumor burden has been significantly reduced and the patient is in remission, the vaccine is administered together with an immune system booster like Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) monthly for up to six months. Side effects are minor, involving soreness at the site of the injection and sometimes development of a low-grade fever, bone or joint pain, or flu-like symptoms, which typically disappear within a few days.

Clinical trials with indolent or low-grade lymphomas are currently underway, and results so far have given rise to cautious optimism that vaccines will prove to be an effective treatment for lymphomas, including WM. The IWMF has funded a vaccine research project for WM, and it is hoped that a clinical trial for vaccine therapy in WM will be undertaken in the near future.
TREATMENT RECOMMENDATIONS

At the Seventh International Workshop on Waldenstrom’s Macroglobulinemia held in Newport, Rhode Island, USA, in August 2012, a consensus panel of international WM experts updated recommendations for both primary (first-line) and salvage therapy (after first relapse). These recommendations were developed after extensive review and debate of published and ongoing clinical trials in WM. As noted above, these updated recommendations have also been adopted by the NCCN Guidelines® Version 2.2013 (See Appendices 2, 3, 4, and 5).

Drug categories currently available include: alkylating agents, nucleoside analogs, monoclonal antibodies, proteasome inhibitors, immunomodulatory agents, as well as the newer targeted pathway inhibitors. Some of these drugs may be used as single agents for initial first-line therapy; however, combinations are now virtually always used, as demonstrated by improved overall responses to treatment, particularly in salvage therapy.

As was noted above, treatment is only required when WM patients become symptomatic. WM patients are considered symptomatic if they start developing hyperviscosity syndrome, severe progressive neuropathy, symptomatic adenopathy or organomegaly, amyloidosis, cryoglobulinemia, cold agglutinin disease, cytopenias (particularly anemia), or evidence of disease transformation. Given that WM remains a very heterogeneous disease and no two patients appear alike, patients and clinicians must decide which treatment to use based on the individual patient’s disease characteristics. These may include the particular cytopenia in question; the need for rapid control of aggressive disease vs. non-immediate need; age, co-morbidities and overall health status; and candidacy for possible future autologous transplantation.

What follows is a quick and succinct review of treatment options for the WM patient who exhibits certain key characteristics.
Appendices 2, 3, 4, and 5 are additional ready references. Once again, competent clinicians and a trusting patient-physician relationship are paramount to any successful treatment plan.

Many WM patients undergoing primary therapy will likely be considered for treatment first with single agent rituximab or a rituximab-containing regimen. Attention must be paid to the possibility of the rituximab IgM flare phenomenon, and plasmapheresis should be used when appropriate before the rituximab-containing therapy or during the treatment, if necessary. On occasion one can see a flare in a susceptible patient's neuropathy, cryoglobulinemia, or other IgM-related symptoms. Judicious use of plasmapheresis may be able to mitigate these undesirable complications.

Neuropathy can be a serious side-effect of bortezomib-containing treatment regimens. Careful evaluation of patients for the development or worsening of neuropathy, including autonomic neuropathy, is therefore emphasized. Patients at risk for neuropathy complications may wish to consider cyclophosphamide- or bendamustine-based therapy as these combinations have proven to be very effective.

Cyclophosphamide-based therapy remains a commonly utilized regimen for WM. It is very effective, stem cell-sparing, and has the advantage of being very familiar to many treating hematologist-oncologists. Recent studies have cast doubt on the importance of doxorubicin and vincristine in R-CHOP; the slight improvement in overall response rates may not be worth the added side effects of these two agents. Many clinicians will now opt for R-CD therapy (rituximab/cyclophosphamide/dexamethasone) or R-CP therapy (rituximab/cyclophosphamide/prednisone), as either is effective and stem cell-sparing as well.

Thalidomide has remained an option for WM patients who wish to avoid stem cell damage. The risk of neuropathy is present, but reduction in doses can alleviate this common side effect of therapy.
The above-mentioned treatment options are all considered safe for patients who may be candidates for stem cell harvest and possible autologous stem cell transplant in the future. Many WM patients are increasingly harvesting their stem cells for potential future use.

The nucleoside analogs fludarabine and cladribine are very effective for rapid disease control when used in combination with rituximab and other agents. However, reports of prolonged immunosuppression, stem cell toxicity, disease transformation, and future secondary malignancies have limited their use in younger patients who may be potential stem cell harvest candidates. Similarly, chlorambucil is very effective as a single agent and well tolerated, particularly in older patients, but is also associated with risk of stem cell damage and disease transformation when used long-term.

The bendamustine-rituximab combination has proven to be very effective. Nonetheless, long-term safety data is limited, and clinicians are uncertain at this point in time regarding the safety profile of bendamustine with respect to stem cells, as well as the incidence of secondary myelodysplasia and acute leukemia, disease transformation, etc.

Treatment options for salvage therapy of WM are comparable to the primary treatment options, apart from the addition of a few newer novel agents as well as the option of stem cell transplant. Similar considerations exist for salvage therapy as for primary therapy: stem cell toxicity, neuropathy concerns, risk of disease transformation, etc. The newer targeted therapies are slowly emerging and are slowly being added to the list of recommended treatment options – everolimus is the first of these new agents to be offered as salvage therapy. The monoclonal antibody alemtuzumab (Campath) remains an option; the newer CD-20 antibody ofatumumab can be used in rituximab-intolerant individuals, but the IgM flare phenomenon must still be considered in patients with hyperviscosity syndrome.
Finally, the autologous stem cell transplant option in salvage therapy remains an important option for the selected patient. High response rates and durable remissions have been observed and can compare quite favorably to other salvage treatment options. The use of myeloablative and non-myeloablative allogeneic transplants remains less appealing given the treatment toxicity profiles. Allogeneic stem cell transplants should be considered preferentially in the setting of a clinical trial.
APPENDICES

APPENDIX 1

Response Criteria from the Sixth International Workshop on Waldenstrom’s Macroglobulinemia (IWWM6); and NCCN Guidelines® Version 2.2013 Response Criteria for WM/LPL:

- **Complete Response (CR):** IgM in normal range and disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement and resolution of any adenopathy/organomegaly (if present at baseline), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required by repeat immunofixation studies.

- **Very Good Partial Response (VGPR):** A ≥90% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.

- **Partial Response (PR):** A ≥50% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.

- **Minor Response (MR):** A ≥25% but <50% reduction of serum IgM. No new symptoms or signs of active disease.

- **Stable Disease (SD):** A <25% reduction or <25% increase of serum IgM without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms or signs due to disease.
• **Progressive disease (PD):** A ≥25% increase in serum IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings due to disease (i.e., anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis) attributable to WM.

**APPENDIX 2**

**General Recommendations NCCN Guidelines® Version 2.2013 for the Management of Newly Diagnosed Symptomatic WM Patients:**

• Plasmapheresis for symptomatic hyperviscosity (including before/during treatment with rituximab-containing regimen in patients with IgM ≥ 5000 mg/dL)

• Primary therapy:
  - Combination therapy
  - Single agent (such as rituximab)
  - Clinical trial

• Complete Response:
  - Observe until progressive disease
  - Consider rituximab for maintenance therapy

• Partial Response:
  - Asymptomatic: Observe until progressive disease
  - Consider rituximab for maintenance therapy

• No Response/Progressive Disease:
  - Choose alternative therapy (see Salvage Therapy Appendix 5)
APPENDIX 3

General Recommendations NCCN Guidelines® Version 2.2013 for the Management of Relapsed Patients Following Primary Treatment for WM/LPL:

- Relapse < 12 months:
  - Choose alternative therapy
- Relapse ≥ 12 months:
  - May use previous treatment or consider alternative therapy
- No response from initial primary therapy:
  - Choose alternative treatment
- Disease Transformation:
  - Follow NCCN Guidelines for non-Hodgkin’s lymphoma

APPENDIX 4

NCCN Guidelines® Version 2.2013 Suggested Treatment Regimens for Primary Therapy of WM/LPL – updated from the initial recommendations from the Fourth International Workshop on WM:

- Non-stem cell toxic:
  - Bortezomib ± rituximab (BR)
  - Bortezomib/dexamethasone (BD)
  - Bortezomib/dexamethasone/rituximab (BDR)
  - Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab (CHOP-R; R-CHOP)
  - Rituximab (R)
  - Rituximab/cyclophosphamide/prednisone (RCP, CPR)
• Rituximab/cyclophosphamide/dexamethasone (RCD)
• Thalidomide ± rituximab (TR)

• Possible stem cell toxicity and/or risk of transformation (or unknown)
  • Bendamustine ± rituximab (R-Benda)
  • Cladribine ± rituximab (2CdA-R)
  • Chlorambucil
  • Fludarabine ± rituximab (FR)
  • Fludarabine/cyclophosphamide/rituximab (FCR)

APPENDIX 5

NCCN Guidelines® Version 2.2013 Suggested Treatment Regimens for the Salvage Therapy of WM/LPL – updated from the initial recommendations from the Fourth International Workshop on WM:

• Non-stem cell toxic:
  • Alemtuzumab (Campath)
  • Bortezomib ± rituximab (BR)
  • Bortezomib/dexamethasone (BD)
  • Bortezomib/dexamethasone/rituximab (BDR)
  • Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab (CHOP-R; R-CHOP)
  • Everolimus (RAD001)
  • Ofatumumab (for rituximab-intolerant individuals)
  • Rituximab (R)
  • Rituximab/cyclophosphamide/prednisone (RCP, CPR)
  • Rituximab/cyclophosphamide/dexamethasone (RCD)
  • Thalidomide ± rituximab (TR)
- Possible stem cell toxicity and/or risk of transformation (or unknown)
  - Bendamustine ± rituximab (R-Benda)
  - Cladribine ± rituximab (2CdA-R)
  - Chlorambucil
  - Fludarabine ± rituximab (FR)
  - Fludarabine/cyclophosphamide/rituximab (FCR)

- Stem cell transplant:
  - In selected cases stem cell transplantation may be appropriate with either:
    - Autologous stem cell transplant (ASCT) - High dose therapy with stem cell rescue
    - Allogeneic stem cell transplant (ablative or non- ablative) – ideally in the context of a clinical trial

APPENDIX 6

Commonly used abbreviations for single agents:

2CdA – cladribine (Leustatin)
B – bortezomib (Velcade)
Benda – bendamustine (Treanda or Levact)
C – cyclophosphamide (Cytoxan)
D – dexamethasone
F – fludarabine (Fludara)
H – hydroxydaunorubicin or doxorubicin
O – oncovin (vincristine)
P – prednisone
RAD001 – everolimus (Afinitor)
R – rituximab (Rituxan or Mabthera)
T – thalidomide (Thalomid)
V – Velcade (bortezomib)
SUGGESTED READINGS

The IWMF provides numerous services for people with Waldenstrom’s macroglobulinemia, including support groups, dissemination of information, and promotion of research. The IWMF distributes information to members through newsletters, booklets, annual conferences, and the IWMF website.

IWMF booklets available on-line at www.iwmf.com:


- *Blood Tests* compiled and edited by Barb Hauser.

Articles by IWMF members available on-line at www.iwmf.com:

- Immunoglobulin Explanation.

- Serum Beta-2 Microglobulin Explanation.

- Summary of lectures and scientific posters from the Fifth, Sixth, and Seventh International Workshops on Waldenström’s Macroglobulinemia (Stockholm 2008, Venice 2010, Newport 2012).
Recommended journal articles:


REFERENCES


41. Preliminary report on the phase II clinical trial of carfilzomib, rituximab and dexamethasone in Waldenstrom’s macroglobulinemia (CaRD). 7th International Workshop on Waldenstrom’s Macroglobulinemia (IWWM7) Newport 2012.


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GLOSSARY

**Albumin:** The most abundant protein found in the blood circulation, albumin is needed to maintain the osmotic pressure within blood vessels, without which fluids would leak out of the circulation; also found in egg white, milk, and other substances.

**Alkylating agent:** A type of chemotherapy drug that interferes with the cell’s DNA and inhibits cancer cell growth (e.g. chlorambucil or cyclophosphamide).

**Allogeneic:** Having a genetic dissimilarity within the same species (e.g. taken from different individuals of the same species); also known as allogenic.

**Amyloidosis:** A group of conditions of diverse etiologies characterized by the accumulation of insoluble fibrillar proteins (amyloid) in various organs and tissues of the body such that vital function is compromised. The associated disease states may be inflammatory, hereditary, or neoplastic, and the deposition can be local or generalized or systemic. Amyloidosis in WM is usually caused by fragments of light chains and affects predominantly the kidneys and heart.

**Anemia:** A condition in which the number of red cells and the amount of hemoglobin in the blood is abnormally low.

**Angiogenesis:** The formation of blood vessels in tissue; process by which tumors grow.

**Antibodies:** Proteins produced by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind only to one specific antigen. Its purpose is to destroy the antigen; also known as immunoglobulins.
**Antigen:** Any foreign substance that activates the immune system.

**Antimetabolite:** A substance that replaces or inhibits the utilization of a metabolite. A metabolite is a substance that takes part in chemical reactions in the body such as DNA replication and repair (among others).

**Antipyretic:** A drug that reduces body temperature; usually refers to fever reduction.

**Apheresis:** A procedure in which blood is removed, a portion separated (stem cells, platelets), and the remainder returned, often with replacement fluid. See Plasmapheresis.

**Apoptosis:** A normal cellular process involving a genetically programmed series of events leading to the death of a cell.

**Asymptomatic:** Without symptoms.

**Autologous:** Derived from the same individual, “self”; as in autologous transplantation when the patient’s own stem cells are used.

**β2-microglobulin (beta2-microglobulin):** A protein found on all cells with a nucleus; it is frequently elevated in people with multiple myeloma and lymphoma.

**B-cells:** Lymphocytes that develop in the bone marrow. In response to antigens, B-cells produce antibodies; also known as B-lymphocytes.

**Bone marrow:** Bone marrow is the soft tissue found in the middle of certain bones (hip and pelvis, sternum, spinal vertebrae, among others) and is the site where red blood cells, white blood cells, and platelets are produced.
**Bone marrow biopsy (BMB):** A bone marrow biopsy can be performed to establish a diagnosis; to assess the status of a known hematological disease; to determine if treatment is required; to determine if a treatment for a known disorder requires further modification; or simply to assess the result of a particular treatment (e.g. after chemotherapy). A large-bore needle (trocar) is inserted into the bone marrow, a fluid specimen is aspirated, and a solid core of marrow cells accompanied by bone is removed.

**Bone marrow microenvironment:** The bone marrow microenvironment is the immediate neighborhood of the cells in the bone marrow and comprises cells that facilitate the survival, differentiation, and proliferation of hematopoietic cells. This environment serves as a safe haven not only for normal but also for malignant hematopoietic cells, in some cases offering protection from chemotherapeutic agents.

**Bulky adenopathy:** Markedly enlarged lymph nodes that are easily palpable or seen by an imaging test such as a CT scan.

**CD-4+ T cells:** T-cells are specialized white blood cells that play an important role in the body's immune system. These cells have molecules called CD-4 on their surfaces. These “helper” cells initiate the body's response to invading microorganisms such as viruses.

**Catheter:** A thin, flexible tube through which fluids enter or leave the body. A central line is a catheter that is passed through a vein to end up in the thoracic (chest) portion of the vena cava (the large vein returning blood to the heart). Central lines have a number of different uses; some have two lumens permitting concomitant removal and infusion of fluid. A central line allows concentrated solutions to be infused with less risk of complications. The central line may be inserted for a short term or a long term.
**Chronic lymphocytic leukemia (CLL):** An indolent (slow-growing) cancer in which too many immature lymphocytes (a type of white blood cells) are found mostly in the blood and bone marrow. Sometimes, in later stages of the disease, cancer cells are found in the lymph nodes, and the disease is called small lymphocytic lymphoma.

**Cold agglutinin disease:** An autoimmune hemolytic anemia caused by auto-antibodies that bind to red blood cells at lower temperatures found in the capillaries of the skin and subcutaneous tissues, causing red blood cell destruction. The IgM antibodies are monoclonal in origin, having either kappa or lambda light chains but not both, and are seen in certain patients with WM.

**Colony stimulating factors (CSFs):** Proteins that stimulate the development of cells in the bone marrow; also called growth factors.

**Complement:** A group of serum proteins involved in the control of inflammation and the destruction of pathogens; it is activated by interaction with antibodies of the immune system.

**Cryoglobulinemia:** Clinical disease characterized by cryoglobulins in the serum; often associated with immune complex antigen-antibody (cryoprecipitable immunocomplex) deposits in the kidneys and other tissues. Three types of cryoglobulinemia have been described: Type I (monoclonal cryoglobulinemia); Type II (mixed cryoglobulinemia) was first noted in WM and can be seen as well is seen in autoimmune disorders; Type III (mixed polyclonal-polyclonal cryoglobulinemia) can be seen with autoimmune diseases, infections, and other diseases.

**Cryoglobulins:** Abnormal proteins detected in the laboratory by chilling serum to below 32 degrees Celsius where they become insoluble. At a normal body temperature of 37 degrees Celsius,
cryoglobulins are soluble. Serum specimens from patients with cryoglobulins must be kept warm until testing.

**CT or CAT (Computerized Axial Tomography) scan:** A radiologic procedure that uses narrow X-ray beams to examine a body section from many different angles and produces a precise image of that area. The CT scan is noninvasive and can be performed with or without contrast medium (X-ray dye). IV contrast material helps outline blood vessels and kidney function, whereas oral contrast helps better define the hollow organs such as the stomach and intestines.

**Cytokines (lymphokines):** A generic term for non-antibody proteins released by one cell population which act as intercellular mediators, as in the generation of an immune response.

**Cytomegalovirus (CMV):** A virus that may be carried in an inactive state for life by healthy individuals. It is a cause of severe pneumonia and other serious complications in people with a suppressed immune system, such as those undergoing bone marrow transplantation or those with leukemia or lymphoma.

**Cytopenia:** A condition in which there is a lower-than-normal number of blood cells.

**Disease transformation:** A biological event where the WM cells in a small percentage of patients transform into a new kind of aggressive blood cancer called diffuse large B-cell lymphoma (DLBCL), either spontaneously or as a result of treatment, particularly with alkylating agents and nucleoside analogs.

**Dosimetric:** Measuring the dose of radiation emitted by a radioactive source.
Erythropoietin: A hormone produced mainly by the kidneys that is required for the normal production of red blood cells (RBCs). Epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp) are laboratory-made forms of the human hormone that can be used to treat anemia.

Flow cytometry: A process in which an instrument uses a laser beam to scatter light from cells as they pass through a liquid in the instrument’s chamber; the laser beam light bounces off each cell, is picked up by detectors, and provides information about the cell’s characteristics, such as size and inner structure. Flow cytometers can also use antibodies tagged with fluorescent stains that bind to specific antigens on the cell surfaces – in the case of leukemias and lymphomas, these fluorescent-tagged antibodies bind with and identify protein surface markers on the immune cells.

Funduscopic (exam): The examination of the back of the eye (fundus) with an ophthalmoscope, which is part of the routine eye examination of a patient; allows a magnified evaluation of the blood vessels, nerves, and retina. Retinal hemorrhages, retinal detachments, swollen blood vessels (often in patients with elevated serum viscosity), and other abnormalities can be easily viewed using this technique.

Graft vs. host disease (GVHD): A serious condition that results when the immune cells of a transplant (the graft – usually of bone marrow) react against the tissues of the person receiving the transplant (the host). Symptoms may range from a minor skin rash to more serious problems resulting in a life-threatening condition.

Graft vs. tumor effect: In allogeneic transplantation, the donor’s immune cells (the graft) may recognize residual tumor cells as being different and destroy them.
Granulocytes: A white blood cell type of the immune system filled with granules of toxic chemicals that enable them to digest microorganisms. See Neutrophils.

Growth factors: A complex family of hormones or biological factors that are produced by the body to control growth, division, and maturation of blood cells by the bone marrow.

Hematopoietic stem cells (HSCs): Residing in the bone marrow, the HSCs are the single common ancestor to all the functional cells found in the blood and immune system. The stem cells represent less than 0.01% of bone marrow cells in adults and give rise to a larger, intermediately differentiated population of progenitor cells. These progenitor cells in turn divide and differentiate further through several stages into mature cells responsible for specific tasks. The stem cells are also able to re-create themselves through self-renewal: this potential for unlimited life span and future proliferation is their most important defining property.

Hemoglobin (Hb): A protein in red blood cells that carries oxygen from the lungs to all cells of the body.

Hemolytic anemia: a condition in which there is premature destruction of red blood cells, and the bone marrow is unable to increase production to make up for the loss of red blood cells. There are various types of hemolytic anemias; in WM-related “immune hemolytic anemia” the red blood cells are destroyed by the immune system (usually due to IgM attaching to the red blood cells). Similarly, “idiopathic autoimmune hemolytic anemia” is an acquired disease that occurs when antibodies form against a person’s own red blood cells. As opposed to WM-related immune hemolytic anemia, the cause of idiopathic autoimmune hemolytic anemia is unknown (hence the term “idiopathic”). Idiopathic autoimmune hemolytic anemia accounts for one-half of all immune hemolytic anemias.
**Hyperviscosity**: Excessive blood thickness. When there is an excess of certain proteins or cells, blood can become thicker, more viscous, than it should normally be. In WM, hyperviscosity is caused by excessive IgM in the circulation. The thicker the blood, the more difficult it is to move through the vessels.

**Hyperviscosity syndrome**: A group of symptoms triggered by increase in the viscosity of the blood. Symptoms of high blood viscosity include spontaneous bleeding from mucous membranes, visual disturbances due to retinopathy, and neurologic symptoms ranging from headache, dizziness, and vertigo to seizures and coma.

**Idiotype**: The unique set of antigenic determinants of the variable portion of an antibody or cell surface molecule that can be used to help identify a particular cell.

**Immunoglobulin (Ig)**: Any of the structurally related molecules formed by B-cells that form as antibodies; divided into five basic classes or isotypes (IgM, IgG, IgA, IgE, IgD) on the basis of structure and biologic activity. An excess of IgM characterizes WM. See Antibody.

**Immunohistochemistry**: Refers to the use of special stains to identify antigens (proteins) in the cells of a tissue section for purposes of identification, using the principle that labeled antibodies bind specifically to antigens; immunohistochemical staining is widely used in the diagnosis of abnormal cells such as those found in cancerous tumors.

**Immunosuppressive**: Lowering the body’s normal immune response to invasion by foreign substances.

**Indolent**: Slow growing.
**Leukemia:** A cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.

**Leukopenia:** A condition in which there is a lower-than-normal number of leukocytes (white blood cells) in the blood.

**Lymph nodes:** Small bean-shaped organs, part of the immune and lymphatic system; found in the underarms, groin, neck, and abdomen; act as filters for the lymph fluid as it passes through them. The lymph nodes are major sites of antigen trapping by lymphocytes, which in turn can activate an immune response. Lymph nodes are populated by B-, T-, and other types of immune cells.

**Lymphocytes:** Any one of a group of white blood cells of crucial importance to the adaptive part of the body’s immune system. Lymphocytes occur in two forms: B-lymphocytes, which produce antibodies, and T-lymphocytes, which participate in the cell-mediated immune response.

**Lymphoma:** Cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin’s lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell. The other category is non-Hodgkin’s lymphoma, which includes a large, diverse group of cancers of immune system cells. Non-Hodgkin’s lymphomas can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course.

**Lymphoplasmacytic lymphoma (LPL):** An indolent (slow-growing) type of non-Hodgkin’s lymphoma marked by the presence of lymphoplasmacytic cells in the bone marrow and sometimes an enlarged liver, spleen, or lymph nodes; WM is a type of LPL that produces monoclonal IgM.
Marginal zone lymphoma (MZL): A type of indolent B-cell lymphoma, it can be difficult to differentiate from WM. There are three types of MZL: splenic (found in the spleen); nodal (found in the lymph nodes), and extranodal (found in the gastrointestinal tract, thyroid gland, or skin.

Mast cells: Non-mobile cells distributed near blood vessels in most tissues, including the bone marrow; these cells are full of granules containing inflammatory mediators and are often associated with allergic reactions. Bone marrow mast cells are increased in WM patients and are believed to offer support to the malignant WM cells.

Median survival: A term used to denote how long patients survive with a disease in general or after a certain treatment. It is the time (expressed in months or years) when half the patients are expected to be alive, and it means that, statistically, the chance of surviving beyond that time is 50%. It gives an approximate indication of the survival as well as the prognosis of a group of patients.

Mini-allo transplants: See Non-myeloablative stem cell transplantation.

Monoclonal: Pertaining to identical cells or cellular products that are derived from a single cell. In the case of WM, the excessive IgM protein that is produced is monoclonal.

Monoclonal antibodies: Laboratory-produced identical antibodies from a culture of identical cells grown from a single clone that can target a specific antigen; a monoclonal antibody is an immunoglobulin directed against a specific antigen (e.g. CD-20 on B-cells).
MRI (magnetic resonance imaging) scans: Also known as nuclear magnetic resonance imaging or magnetic resonance tomography, MRI is a medical imaging technique used in radiology to visualize detailed internal structures. Images are produced by passing the patient through a tubular structure that generates a powerful electromagnetic field. The hydrogen ions in the body respond by emitting a radio frequency signal that is then processed by computer to produce an image.

Multiple myeloma (MM): A cancer of the plasma cells in bone marrow.

Myeloablation: The severe or complete depletion of bone marrow cells.

Myelodysplasia: Any of various conditions characterized by the faulty or inadequate production of bone marrow or blood cells and by risk of transformation to acute myelogenous leukemia (AML). Myelodysplasia is a diagnosis that includes several subcategories with very different findings and different prognoses.

Myelosuppression: A bone marrow condition that results in decreased platelets and red and white blood cells.

Neutropenia: A condition in which there is a lower-than-normal number of neutrophils (a type of white blood cell).

Neutrophils: A type of white blood cell that is one of the first cell types to travel to the site of an infection. Neutrophils help fight infection by ingesting microorganisms and releasing enzymes that kill the microorganisms.

Non-Hodgkin’s lymphoma (NHL): Any of a large group of cancers of white blood cells (lymphocytes). Non-Hodgkin’s lymphomas can occur at any age and are often marked by lymph nodes
that are larger than normal, fever, and weight loss. There are many different types of non-Hodgkin’s lymphoma. These types can be divided into aggressive (fast-growing) and indolent (slow-growing) types, and they can be formed from either B-cells or T-cells. B-cell non-Hodgkin’s lymphomas include chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma, diffuse large b-cell lymphoma, follicular lymphoma, mantle cell lymphoma, WM, and others. T-cell non-Hodgkin’s lymphomas are much rarer.

Non-myeloablative stem cell transplantation: Non-myeloablative allogeneic stem cell transplants (mini-allo transplants, reduced-intensity transplants) are allogeneic transplants where lower doses of chemotherapy or radiotherapy are used to prepare the patient for the transplant. The non-myeloablative transplant aims just to suppress the patient’s immune system sufficiently to allow engraftment of the donor cells rather than to destroy the entire bone marrow.

Nucleoside analogs (purine analogs): Part of a larger class of anti-cancer drugs termed antimetabolites, which, unlike alkylating agents, act specifically on proliferating cells. Fludarabine (Fludara) and cladribine (2CdA or Leustatin) are two nucleoside or purine analogs commonly used in treating WM.

Organomegaly: An abnormal enlargement of an organ, particularly an organ of the abdominal cavity. In WM it most often refers to an enlarged spleen (splenomegaly), enlarged liver (hepatomegaly), or both (hepatosplenomegaly).

Palliative: Medical care that specializes in the relief of the pain, symptoms, and stress of a serious illness.
**Paraprotein:** An abnormal plasma protein, such as a macroglobulin (IgM), cryoglobulins, or myeloma protein.

**Peripheral blood stem cells:** Hematopoietic stem cells that circulate in the blood. See Hematopoietic stem cells and Stem cells.

**Peripheral neuropathy (PN):** Numbness, tingling, or pain in peripheral nerves, usually in hands or feet.

**PET (positron emission tomography) scans:** Positron emission tomography is an imaging test used to diagnose and monitor cancer and other conditions. This radiology test helps physicians to detect biochemical changes that may suggest the presence of cancer or other illnesses. The changes on a PET scan may appear before a patient exhibits visible symptoms. PET scans can identify how aggressive a cancer is and the extent of its metastasis (spread) to other parts of the body.

**Plasma:** The colorless watery fluid of the blood in which the blood cells are suspended.

**Plasma cells:** White blood cells of the B-cell lineage that produce antibodies to fight infection. In multiple myeloma, the plasma cell becomes malignant and in most cases produces large amounts of IgG antibodies. In WM, the malignant plasma cell produces large amounts of IgM antibodies.

**Plasmapheresis (PP):** The process of removing a patient's plasma to extract a specific component (IgM in the case of Waldenstrom's macroglobulinemia) and returning the remaining parts to the patient usually with saline solution and albumin. Using continuous circulation of blood from the patient through an apparatus and back to the patient, this process makes it possible to remove specific elements from large volumes of plasma. Apheresis is a similar procedure whereby platelets, red cells, white cells, stem cells or plasma constituents can be removed, separately.
Platelets (thrombocytes): Cells formed in the bone marrow from hematopoietic stem cells that circulate in the blood and are needed to help the blood clot and to control bleeding.

Polymorphism: A generic term that means “many shapes” and refers to a form of genetic variation within plant and animal species in which distinct forms exist together in the same population, even the rarest of them being too common to be maintained solely by mutation. The human blood groups (ABO) are examples of polymorphism.

Prognosis: A prediction of the course of a disease and its outcome.

Progression-free survival: The length of time during and after treatment for a disease that a patient lives with the disease but it does not get worse.

Prophylaxis: A measure taken to prevent a health problem.

Protocol: A detailed plan of a scientific or medical experiment or treatment or procedure.

Radioisotpe: A form of an element that produces radiation.

Serum viscosity (SV): The physical property of serum as it relates to its “thickness.” The term “viscosity” describes the degree of fluidity of liquids. Blood is thicker and more viscous than water. The serum viscosity is affected by the concentration of constituents in the serum; the greater the number of soluble molecules in the serum, the higher the viscosity. Normal blood viscosity is 1.8 cp. In WM the large IgM molecules are the cause of increased viscosity.

Signs: Objective evidence of disease, usually observed by the physician; compare with Symptoms.
**Smoldering:** In the context of WM, this is asymptomatic disease that does not require treatment.

**Spleen:** The largest structure in the lymphoid system, the spleen is a gland-like organ situated in the left upper abdomen. It serves as a reservoir of blood, produces lymphocytes and plasma cells, and functions as a “filter” for the blood by removing damaged red blood cells from the circulation.

**Stem cells:** Non-specialized cells that have the capacity to self-renew and to differentiate into more mature cells. See *Hematopoietic stem cells*.

**Subcutaneous injection:** Under the skin – as opposed to intra-venous (IV) or intra-muscular (IM).

**Symptoms:** Subjective evidence of a disease, usually observed by the patient; compare with *Signs*.

**T-cells:** Also known as T-lymphocytes, T-cells are a type of white blood cell involved in rejecting foreign tissue, regulating immunity, and controlling the production of antibodies to fight infection.

**Thrombocytopenia:** An abnormally low number of platelets in the blood.