

# Waldenstrom's Macroglobulinemia

A Guide to Treatment Options:

**Immunotherapy**



### Introduction

Waldenstrom's macroglobulinemia (WM) is a lymphoma, or cancer of the lymphatic system. WM develops in a type of white blood cell called a B lymphocyte or B cell. B lymphocytes typically develop into plasma cells whose job it is to manufacture immunoglobulins (antibodies) to help the body fight infection. In WM, there is a malignant change during the later stages of B cell maturation that results in the development of a clone of cells. This clone primarily resides in the bone marrow but is often also present in the lymph nodes and spleen. These clonal cells overproduce an antibody of a specific class called IgM.

Under the microscope, the malignant cells in WM have characteristics of both B lymphocytes and plasma cells and are called lymphoplasmacytic cells. For that reason, WM is classified as a type of non-Hodgkin's lymphoma called lymphoplasmacytic lymphoma (LPL). About 95% of LPL cases are WM. The remaining 5% do not secrete IgM and consequently are not classified as WM, but often have a similar disease course and are managed in much the same way as WM. WM is a very rare disease—only about 1,500 patients are diagnosed with WM each year in the US. WM is usually indolent (slow growing) and can be managed as a chronic disease for a number of years. Unfortunately, with our currently available therapies it is not yet curable.

As a result of proliferation in the bone marrow, the lymphoplasmacytic cells of WM may interfere with normal blood cell production as the WM cells “crowd out” the healthy blood cells. This may lead to a reduction in normal blood counts. WM may also cause enlargement or abnormal function of other organs, such as the liver, spleen, and lymph nodes.

The overproduction of IgM may also cause many of the symptoms associated with the disease. IgM is a large antibody that, unlike other types of antibodies, can bind with other IgM molecules to form a pentamer (a group of five IgM antibodies bound together). This pentamer, especially in the setting of high IgM levels, can make the blood thicker than normal, a condition called hyperviscosity. Additionally, sometimes the IgM may incorrectly recognize the body's tissues as “foreign” and attach to them, causing inflammation and injury. For example, in some patients, the IgM may bind to nerves and cause damage (peripheral neuropathy) or bind to red blood cells and cause red blood cell destruction in cold temperatures (cold agglutinins).

Although a cure for WM remains elusive, continuing research has resulted in multiple treatment options available to the WM patient, and careful evaluation of all options in formal consultation with one or more knowledgeable physicians is essential before any treatment is undertaken. Treatment recommendations need to be tailored to the individual patient, depending on the characteristics of his or her disease, as well as the patient's other medical issues.

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

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

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### Approach to Treatment

The goal of treatment for WM is to provide disease control and thereby improve quality and duration of life. This Guide and others in our Treatment Options series focus on drug therapies that are used for disease control, although there is the hope that drugs in clinical trials now or in the future may eventually provide a cure. There is no single standard of therapy to treat WM; instead, there are a number of treatment options currently recommended or in clinical trials for people with WM. They include the following:

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

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

Treatment is typically required when patients with WM become symptomatic and should not be initiated based on blood test results alone. This applies not only to consideration of first-line treatment but also to therapy for previously treated WM. Initiating treatment early in the course of the disease in most asymptomatic patients does not prolong survival and may result in a range of unpleasant or even serious side effects. Some patients may remain stable and continue to be asymptomatic for years without treatment.

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

- Hyperviscosity syndrome (symptoms related to excessive thickness of the blood from high IgM).
- Anemia (low red blood cell count and low hemoglobin) from infiltration of the bone marrow with WM cells or from destruction of red blood cells by IgM. Anemia is the most frequent condition that leads to treatment for WM. Generally speaking, a hemoglobin level less than 10 g/dL may be used as an indication to begin therapy.
- Thrombocytopenia (platelet count less than <100,000) from bone marrow infiltration.
- Constitutional symptoms – weakness, fatigue, night sweats, fever, and weight loss.
- Systemic light-chain (AL) amyloidosis, symptomatic cryoglobulinemia, symptomatic cold agglutinin disease, or moderate to severe peripheral neuropathy. (Explanations about these conditions can be found on the IWMMF website in the [Symptoms of WM](#) section.)
- Bing-Neel syndrome (infiltration of WM cells into the brain, the lining around the brain and/or spinal cord, or the fluid surrounding the brain and spinal cord).
- Progressive, symptomatic enlargement of the lymph nodes, liver, or spleen.
- Kidney disease (nephropathy) related to WM.

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

Given that WM is a disease affecting patients in many different ways, patients and clinicians must decide which treatment to use based on the individual patient's situation and disease characteristics. These may include the presence of one or more cytopenias (decreased production of blood cells); the need for rapid control of aggressive disease; age; co-morbidities (other chronic health conditions); the need for deep responses in certain situations, such as peripheral neuropathy or amyloidosis; and overall health status.

When immediate IgM reduction is required (such as for hyperviscosity syndrome, symptomatic cryoglobulinemia, severe anemia from cold agglutinin disease, etc.), the most rapidly acting therapy is plasmapheresis, which is a procedure to withdraw plasma containing excess IgM from the blood. After plasmapheresis, IgM levels can be reduced significantly, but the effect is only temporary, and drug therapy is required for disease control. More information about plasmapheresis can be found in a Fact Sheet on the IWMMF website at [IWMMF & Global Partner Publications](#).

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

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

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

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

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

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

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

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

The following is a review of **immunotherapy treatments used or being considered for WM**. The other drug treatment options listed above are discussed in a short series of Treatment Options Guides available on the IWMF website at [IWMF & Global Partner Publications](#).

## Immunotherapy

Immunotherapy is a type of cancer treatment that uses one's own immune system to help fight cancer. The immune system is the body's primary defense against infection and cancer, and it is made up of a complex network of molecules, cells, tissues, and organs working together. To do this, the immune system must distinguish between cells that naturally belong in the body (self) and foreign cells like bacteria, viruses, etc. (non-self). It does this by identifying antigens, or surface molecules, found on all cells. Once the immune system determines that a cell is foreign by identifying its surface antigens as non-self, it begins a series of reactions to identify, target, and eliminate the foreign cell. White blood cells, including B cells, T cells, and natural killer cells play an important role in this immune system response. Once the immune system discovers a foreign antigen on a cell, it produces B cells that secrete antibodies to attack the foreign cell and/or activates T cells and natural killer cells to destroy it.

Many cancers are likely prevented by the immune system's ability to recognize and destroy abnormal cells before they become cancer. Immunosurveillance is a term used to describe how the immune system patrols the body for pre-cancerous conditions, such as cancer-causing proteins on the surface of cells. Immunosurveillance removes these cells before they can build up to a critical mass and develop into cancer. However, even a healthy immune

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system cannot always prevent cancers from forming. Some cancer cells can develop and grow even in the presence of a healthy immune system.

Immunotherapy seeks to boost or change how the immune system works to find and destroy cancer cells that have escaped immunosurveillance. Several types of immunotherapies are approved by the US Food and Drug Administration (FDA) and other regulatory agencies or are in clinical trials to determine their effectiveness in treating various blood cancers, including WM. These include, but are not limited to, traditional monoclonal antibodies, antibody-drug conjugates, bispecific T cell engager antibodies, CAR-T cell therapies, and immune checkpoint inhibitors. Several of these immunotherapies below, such as the monoclonal antibodies, are in clinical use now for WM, while others are still experimental and in clinical trials.

### Monoclonal Antibodies

Traditional monoclonal antibody therapy is one of the oldest immunotherapies and is based on laboratory-produced biologic molecules that are carefully engineered to attach to a specific antigen on the surface of cells, for instance, cancer cells. Monoclonal antibodies mimic the antibodies your body naturally produces as part of your immune system's response to infection from bacteria, viruses, and parasites and to vaccination.

When a monoclonal antibody attaches to a cell, it can make the cell more “visible” to the body's own immune system and thus assists the immune system to kill the cell. The first monoclonal antibodies were developed from mice, but these were short-lived and not very compatible with human immune systems. Monoclonal antibodies in use today are chimeric (a combination of mouse and human antibodies that is approximately 65% human), humanized (a combination that is 95% human), or fully human. All monoclonal antibody therapies are of the IgG type.

While quite a number of traditional monoclonal antibodies have been devised to treat cancer, the two currently used for WM include rituximab and obinutuzumab, with rituximab more common by far. Both are discussed below.

#### Rituximab (Rituxan or Mabthera)

Rituximab was the first monoclonal antibody to receive FDA approval, which was for the treatment of relapsed non-Hodgkin's lymphoma in 1998. It is prescribed off-label for WM and is now used as a single agent, in combination therapies with other agents, and as maintenance therapy for both first-line and previously treated WM patients. Rituximab targets the CD20 surface antigen on B cells, including WM B cells.

Two schedules for single agent rituximab have been studied in WM: the standard one, in which one weekly intravenous infusion of 375 mg/m<sup>2</sup> is administered for four weeks; and the extended one, in which responding patients receive four more weekly intravenous infusions during weeks 12-16. Reported overall response rates vary between 25-45%. In the NCCN<sup>®</sup> Guidelines for WM, single agent rituximab is one of the “Other Recommended Regimens” for primary therapy and “Useful in Certain Circumstances” for previously treated patients and can be helpful in treating peripheral neuropathy caused by IgM anti-MAG (myelin-associated glycoprotein) antibodies.

Infusion reactions are possible with rituximab. Typically, the most common reactions take place when it is administered for the first time, with subsequent infusions usually better tolerated. Infusion reaction symptoms may include headache, fever, chills, flushing, nausea, and dizziness. More severe allergic symptoms include hives, chest tightness, trouble breathing, and swelling of the face, lips, tongue, or throat. In order to minimize reactions, pre-medication with acetaminophen, antihistamine, and sometimes a corticosteroid, is standard. If a

reaction is noted during the infusion, the rate of administration can be adjusted and more of the pre-medication drugs can be given to relieve symptoms.

Subcutaneous (under the skin) administration of rituximab has been approved by the FDA and other regulatory agencies for several blood cancers and may be prescribed off-label for WM patients. The subcutaneous formulation is called rituximab hyaluronidase (Rituxan Hycela) and is given by injection in 5-7 minutes rather than the typical several hours needed for intravenous infusion. The approval stipulates that the subcutaneous option can be used only after patients have received at least one full dose of rituximab intravenously. In clinical trials, the effectiveness of the subcutaneous formulation was equivalent to that of intravenous rituximab, and the side effects of subcutaneous administration, in addition to those seen with intravenous administration, include skin issues such as rash, blistering, and peeling.

About 50% of WM patients treated with rituximab experience a temporary increase (greater than 25%) in serum IgM levels—referred to as the IgM “flare” phenomenon. This flare may lead to symptomatic hyperviscosity, as well as worsening of other IgM-related conditions. Flare occurs mostly during the first 2-4 months of treatment; it is not associated with a higher risk of treatment failure, and one should be cautious not to interpret flare as a lack of response or even disease progression. To avoid complications from IgM flare, patients with symptomatic hyperviscosity or with serum IgM concentrations greater than 4,000 mg/dL should avoid single agent rituximab when possible. If a serious IgM flare during single agent or combination treatment is considered a possibility, plasmapheresis before therapy should be considered to reduce the IgM level, or rituximab should be avoided during the first one or two cycles of combination therapy until the IgM declines to a safer level.

Rarely, patients may be intolerant to rituximab, meaning that they have worsening infusion reactions that result in the therapy becoming unsafe. For such patients, very slow infusion rates should be tried, or other drugs considered for treatment.

Late-onset neutropenia (low neutrophil count) has been observed with rituximab, mostly when combined with chemotherapy. The underlying mechanism is not well understood. Reactivation of the hepatitis B virus has also been observed, and screening for prior hepatitis B exposure is recommended. Hepatitis B carriers should be closely monitored for clinical and laboratory signs and symptoms of active infection during therapy and for several months afterward, and treatment with an anti-viral therapy may be recommended during and after rituximab use.

Rituximab has been combined with alkylating agents, nucleoside analogs, proteasome inhibitors, and targeted therapies to B cell signaling pathways. It is a part of almost every combination regimen for both first-line and previously treated WM.

Biosimilars for rituximab have been approved in Europe and the US. A biosimilar is a biological product that is highly similar to and has no clinically meaningful difference from an existing approved reference product. As patent protections for rituximab and similar drugs are expiring, biosimilars are being developed to provide more treatment options, increase access to medications, and potentially lower healthcare costs through competition. Although rituximab biosimilars are considered equivalent to the original product and may be prescribed off-label for WM, they have not been specifically studied in WM patients.

While rituximab maintenance therapy has been studied extensively in other blood cancers, there has been controversy about its role in WM. Maintenance therapy is prolonged treatment given after the initial treatment course (typically combination therapy including rituximab) has resulted in a response. The rationale for its use has been to prolong the amount of time before disease progression occurs. There is no standardized rituximab

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maintenance dosing schedule for WM; in clinical practice, it has varied from one weekly infusion every two or three months to four weekly infusions every six months. The duration of maintenance is typically two years.

An unpublished randomized Phase 3 trial of maintenance rituximab in 218 WM patients used bendamustine and rituximab as front-line therapy. Participants who achieved at least a partial response to treatment were randomly assigned to either two years of maintenance rituximab given every two months or to observation (no maintenance). The median progression-free survival in the maintenance arm of the study was 101 months, and in the observation arm was 83 months; however, this difference was not statistically significant. The median overall survival had not yet been reached in either arm. The current IWMMF consensus panel opinion is that maintenance rituximab should not be recommended for WM patients who have achieved a partial response or better after chemoimmunotherapy. This is based on the risk vs. benefit of long-term rituximab use, which can lead to an increased risk of infection because of continuous B cell depletion from maintenance therapy.

### **Obinutuzumab (Gazyva)**

Obinutuzumab is a humanized anti-CD20 monoclonal antibody approved for the treatment of chronic lymphocytic leukemia and follicular lymphoma. It has not been extensively studied in WM patients, but results from a Phase 2 study suggest that it has clinical activity in WM. A total of 23 patients achieved an overall response rate of 52.2%, with 21.7% achieving a very good partial response (VGPR) or better. Progression-free survival and overall survival rates at 18 months were 68% and 90%, respectively. However, side effects occurred in 95.7% of patients, with the most common being infections, neutropenia, and thrombocytopenia. In WM patients who are unable to tolerate rituximab, NCCN<sup>®</sup> Guidelines suggest that obinutuzumab may be considered as an option.

### **Antibody-Drug Conjugates (ADCs)**

Antibody-drug conjugates are a type of cancer therapy combining a monoclonal antibody that binds to a surface protein on a cancer cell with a cytotoxic drug that kills the cell. Once the antibody binds to the cancer cell, the entire drug complex is taken into the cell, where a chemical linker releases the cytotoxic drug. ADCs are designed to deliver the cytotoxic drug specifically to cancer cells, reducing the amount of drug that needs to be used and minimizing damage to healthy tissue, potentially leading to fewer side effects. Antibody-drug conjugates are given intravenously.

The antibody-drug conjugate called loncastuximab tesirine (Zynlonta) is currently in a Phase 2 clinical trial for previously treated WM. The drug is approved by the FDA and the European Medicines Agency for the treatment of diffuse large B cell lymphoma. It utilizes a monoclonal antibody targeting the CD19 surface antigen on B cells linked to an anti-cancer drug called pyrrolobenzodiazepine, which irreversibly binds to the cell's DNA, inhibiting its synthesis and causing cell death. Patients enrolled in the trial are receiving the drug on the first day of each 28-day cycle for up to six cycles.

The most common side effects of loncastuximab tesirine in clinical trials of diffuse large B cell lymphoma patients were increased levels of the liver enzyme GGT (which can indicate liver damage), neutropenia, fatigue, anemia, thrombocytopenia, nausea, peripheral edema (swelling of ankles and feet), and rash.

### **Bispecific T Cell Engager (BiTE) Antibodies**

Bispecific antibodies are composed of two different monoclonal antibodies and thus can attach to two different targets at the same time. When used as cancer immunotherapy, a specialized kind of bispecific

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antibody called a bispecific T cell engager (BiTE) antibody binds to both a surface antigen on a cancer cell and a surface antigen on one of the body's T cells; in this manner, the BiTE antibody brings the cancer cell and the T cell together, thereby activating the T cell to attack and destroy the cancer cell.

There are over 100 BiTE antibodies in clinical development. Since 2014, the FDA, Health Canada, and the European Medicines Agency have approved several such drugs to treat different cancers, including blood cancers such as leukemia, multiple myeloma, diffuse large B cell lymphoma, and follicular lymphoma. In lymphoma, typically either the surface antigen CD19 or CD20 on a B cell serves as the binding site for the cancer cell, and the surface antigen CD3 is the binding site for the T cell. In multiple myeloma, a surface antigen called BCMA (B cell maturation antigen) serves as the binding site for the cancer cell.

This type of therapy is given as an injection under the skin (usually in the abdomen or thigh) or intravenously. For the first two or three doses, a smaller amount of the drug, called a "step-up" dose, is given to help prevent common side effects. If there are no complications, a full dose can then be used. Step-up dosing may be done in the hospital for older or more frail patients or as outpatient therapy, and careful monitoring is necessary during the step-up period to deal with side effects. Currently, BiTE antibodies are relatively short-lived in the body. They must be given periodically until they no longer work or they cause intolerable side effects, but researchers are trying to develop longer-lasting antibodies.

One potential side effect with immunotherapies involving T cells, including BiTE antibodies, is cytokine release syndrome (CRS). It is a system-wide over-reaction of the immune system as T cells attack the cancer cells, causing a release of cytokines (immune system proteins) and can range from mild-flu-like symptoms (fever, fatigue, headache, rash, muscle and joint pain) to severe or life-threatening symptoms, characterized by low blood pressure and high fever and potentially progressing to shock and multi-organ failure. Laboratory test abnormalities that are common in patients with CRS include low blood counts, elevated creatinine and liver enzymes, abnormal blood clotting studies, and a high C-reactive protein (CRP) level.

Another side effect particularly associated with T cell therapies is immune effector cell-associated neurotoxicity syndrome or ICANS. Experts do not fully understand why ICANS occurs, but it may be because the cytokines released from the T cell attack on cancer cells cause inflammation that leads to a breakdown in the blood-brain barrier, which is the protective layer of cells that control what can pass from blood vessels into the brain. The possible symptoms of ICANS include headache, difficulty concentrating, lethargy, agitation, hallucinations, tremors, problems with language, confusion, memory loss, and personality changes. Most patients who experience ICANS have mild symptoms that can be managed with corticosteroids like dexamethasone, fully recover, and do not experience long-term problems.

A BiTE antibody called epcoritamab (Epkinly) is currently being studied in a Phase 2 clinical trial enrolling previously treated WM patients. It uses the CD20 surface antigen on B cells as the cancer cell target and has received FDA approval for both diffuse large B cell lymphoma and follicular lymphoma.

### Chimeric Antigen Receptor (CAR)-T Cell Therapies

CAR-T cell therapy involves genetically engineering one's T cells to recognize the surface antigens on cancer cells. The process of CAR-T cell therapy is highly individualized for each patient and significantly more complex than treatment with BiTE antibodies. Using a procedure called apheresis, blood is temporarily removed from a patient's veins, the white blood cell component with T cells is removed, and the remaining blood is returned to the patient. The T cells are sent to a specialized laboratory that genetically modifies the cells to produce artificial

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receptors on their surfaces that recognize surface antigens on cancer cells. These genetically modified T cell receptors are called “chimeric antigen receptor” T cells or CAR-T cells. The earliest and most commonly used cancer surface antigen in this type of therapy has been CD19, but CD20, CD22, and BCMA have also been used or are being developed.

In the next step, the number of genetically modified T cells is increased by growing them in a laboratory culture. When there are a large number, the CAR-T cells are frozen and sent to the hospital or treatment center where the patient is receiving care. Many patients are given a brief treatment with one or more chemotherapy agents to reduce the number of normal T cells in the body. This is called “lymphodepletion” and is done because it “makes space” for the CAR-T cells in the patient. The genetically modified CAR-T cells are then thawed and intravenously infused into the patient’s bloodstream. The infusion process usually takes less than 30 minutes, while the entire process from collection to infusion usually takes from 2-4 weeks. Careful monitoring is necessary, typically for a month after infusion, and patients are advised to remain in close proximity to their treatment centers in case side effects occur. In contrast to BiTE antibodies that must be given periodically, CAR-T cells are a “one and done” treatment.

In the body, the CAR-T cells seek out cancer cells that express the antigen they have been genetically modified to target and destroy them. These T cells also begin making copies of themselves and increase in number throughout the body. The CAR-T cells can not only eradicate cancer cells in the body but also remain for months after infusion, helping to guard against cancer recurrence. This therapy has resulted in long-term remissions for some patients with certain types of blood cancer. However, CAR-T cell therapy comes with potentially serious side effects, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). For an explanation of both, see the discussion above in the section on **Bispecific T Cell Engager (BiTE) Antibodies**.

As more blood cancer patients have been treated with CAR-T cells, and as longer follow-up data are becoming available, it has been recognized that approximately 30-50% of patients who achieve remission will have disease relapse, the majority within one year of treatment. Furthermore, approximately 10-20% of patients fail to enter remission after receiving CAR-T cell therapy. There are several reasons for this. It is possible for CAR-T cells to either not expand sufficiently after infusion or not persist for very long afterward. Also, the cancer cells can downregulate or “lose” their expression of CD19, CD20, or other surface antigens and are, therefore, no longer targeted by the CAR-T cells.

Since 2017, several CAR-T cell therapies have been approved by the FDA, Health Canada, and the European Medicines Agency for the treatment of blood cancers, including relapsed or refractory diffuse large B cell lymphoma, follicular lymphoma, mantle cell lymphoma, and multiple myeloma, but no CAR-T cell therapy is approved for WM.

Several clinical trials of CAR-T cell therapies are offering enrollment to previously treated WM patients. A Phase 1/2 clinical trial of the CD20-targeted CAR-T cell therapy called MB-106 achieved promising preliminary results in WM patients. Among 20 evaluable patients with relapsed or refractory WM, 95% attained a response, with 80% of patients achieving a complete response. Low-grade CRS was noted in 30% of patients, and no patient exhibited ICANS-related symptoms, suggesting a favorable side effect profile. At the time of the data cut-off, WM remained under control in ten patients (50%). Fatal events (one COVID-19-related and one second cancer-related death) occurred in two patients, who had ongoing complete responses at the time of their deaths.

### Immune Checkpoint Inhibitors

Immune checkpoints are molecules found on T cells that act as “brakes” on the T cells. If a cell is foreign or cancerous, the T cell normally attacks it; however, cancer cells can sometimes send misleading signals to these immune checkpoints, telling the T cells that the cancer cells are not harmful and should not be attacked. Immune checkpoint inhibitors are specialized monoclonal antibodies that work by “taking the brakes” off and restoring normal function to the T cells.

The immune checkpoint inhibitors most commonly studied are monoclonal antibodies that target the immune checkpoint molecules PD-1, PD-L1, and CTLA-4. These are primarily given as intravenous infusions (although one or two can also be given subcutaneously), and the side effects include typical infusion-related reactions, as well as diarrhea, fatigue, cough, nausea, skin rash, poor appetite, constipation, and muscle and joint pain. These drugs are also associated with cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). For an explanation of both, see the discussion above in the section on **Bispecific T Cell Engager (BiTE) Antibodies**. Another potentially serious side effect from this drug class occurs if the immune system goes into overdrive, attacking other parts of the body such as the lungs, intestines, liver, kidneys, and other organs.

While many immune checkpoint inhibitors have been FDA-approved for the treatment of solid cancers like melanoma, lung cancer, breast cancer, and more, some have also been used for B cell lymphomas. These include pembrolizumab (Keytruda) and nivolumab (Opdivo). There is no immune checkpoint inhibitor approved for WM, although WM patients have been and are being included in clinical trials of pembrolizumab combined with either rituximab or ibrutinib.

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### About IWMF

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

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

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