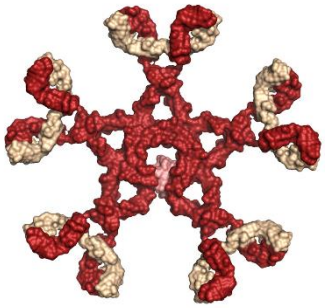
Cancer Association of South Africa (CANSA)

Fact Sheet
on
Waldenstrom Macroglobulinemia

Introduction

Blood cancers have the potential to affect the blood cells and bone marrow. Blood cancers, therefore, change the way blood cells behave and how well they work.



[Picture Credit: Walderstrom Picture]

There are three types of blood cells:

- White blood cells fight infection as part of the immune system
- Red blood cells carry oxygen to the body's tissues and organs and bring carbon dioxide to the lungs so one can breathe it out
- Platelets helps blood clot when one is injured

There are three major types of blood cancer:

- Leukaemia
- Lymphoma
- Myeloma

These cancers cause the bone marrow and lymphatic system to make blood cells that do not work as well as they should. They all affect different types of white blood cells, and they act in different ways.

Waldenstrom Macroglobulinemia (WM)

Waldenstrom macroglobulinemia (WM) is a rare type of blood cancer that begins in the white blood cells. If someone has Waldenstrom macroglobulinemia, the bone marrow produces too many abnormal white blood cells that crowd out healthy blood cells. The abnormal white blood cells produce a protein called macroglobulin that accumulates in the blood, impairs circulation and causes complications.

Waldenstrom macroglobulinemia is considered a type of non-Hodgkin's lymphoma. It is sometimes also referred to as lymphoplasmacytic lymphoma.

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The median age at diagnosis is 67. However, cases have been diagnosed in patients in their twenties. This disorder is considerably less common among people of African descent.

Lymphoid tissue is made up several types of immune system cells that work together to help the body resist infections. Lymphoid tissue is found in many places in the body:

- Lymph nodes, which are pea-sized collections of immune system cells throughout the body, including in the underarm area, in the groin, on the sides of the neck, and inside the chest and abdomen
- Bone marrow, the soft inner part of certain bones where new blood cells are made
- The thymus, a small organ behind the chest bone and in front of the heart
- The spleen, an organ on the left side of the abdomen next to the stomach
- The tonsils and adenoids in the throat
- Throughout body systems like the digestive system and respiratory system

Lymphocytes (lymph cells) are the main cells of lymphoid tissue. The 2 main types of lymphocytes are:

- B lymphocytes (B cells) respond to an infection by changing into a different type of cell called a plasma cell. Plasma cells make proteins called antibodies (also called immunoglobulins) that help the body attack and kill disease-causing germs like bacteria.
- T lymphocytes (T cells) help direct immune responses, but they also can kill invading germs directly.

Waldenstrom Macroglobulinemia (WM) is a cancer that starts in B cells. The cancer cells in people with WM are similar to those of 2 other types of cancer: multiple myeloma and non-Hodgkin Lymphoma. Multiple myeloma is considered a cancer of plasma cells, and non-Hodgkin lymphoma is a cancer of lymphocytes. WM cells have features of both plasma cells and lymphocytes and are called lymphoplasmacytoid.

WM cells make large amounts of a certain type of antibody (immunoglobulin M, or IgM), which is known as a macroglobulin. Each antibody (protein) made by the WM cells is the same, so it is called a monoclonal protein, or just an M protein. The buildup of this M protein in the body can lead to many of the symptoms of WM, including excess bleeding, problems with vision, and nervous system problems.

The WM cells grow mainly in the bone marrow, where they can crowd out the normal cells that make the different types of blood cells. This can lead to low levels of red blood cells (called anaemia), which can make people feel tired and weak. It can also cause low numbers of white blood cells, which makes it hard for the body to fight infection. The numbers of platelets in the blood can also drop, leading to increased bleeding and bruising.

Lymphoma cells can also grow in organs like the liver and spleen, causing these organs to swell and leading to abdominal pain.

Zanwar, S., Abeykoon, J.P., Durot, E., King, R., Perez Burbano, G.E., Kumar, S., Gertz, M.A., Quinquenel, A., Delmer, A., Gonsalves, W., Cornillet-Lefebvre, P., He, R., Warsame, R., Buadi, F.K., Novak, A.J., Greipp, P.T., Inwards, D., Habermann, T.M., Micallef, I., Go, R., Muchtar, E., Kourelis, T., Dispenzieri, A., Lacy, M.Q., Dingli, D., Nowakowski, G., Thompson, C.A., Johnston, P., Thanarajasingam, G., Bennani, N.N., Witzig, T.E., Villasboas, J., Leung, N., Lin, Y., Kyle, R.A., Rajkumar, S.V., Ansell, S.M., Le-Rademacher, J.G. & Kapoor, P. 2019.
"Histological transformation in Waldenström macroglobulinemia (WM) is an uncommon complication, with limited data, particularly regarding the impact of $MYD88^{L265P}$ mutation on transformation. We examined risk

factors and outcomes associated with transformation in WM, highlighting the role of $MYD88^{L265P}$ mutation. Patients with WM seen at Mayo Clinic, Rochester, USA and University Hospital of Reims, France, between 01/01/1996 and 12/31/2017 were included; 50 (4.3%) of 1147 patients transformed to a high-grade lymphoma, with median time-to-transformation of 4.5 (range 0-21) years in the transformed cohort. The $MYD88^{L265P}$ mutation status was known in 435/1147 (38%) patients (406 with non-transformed WM and 29 patients in transformed cohort). On multivariate analysis, $MYD88^{WT}$ status alone was an independent predictor of transformation [odds ratio, 7(95%CI: 2.1-23); p=0.003]. Additionally, the $MYD88^{WT}$ status was independently associated with shorter time-to-transformation [HR 7.9 (95%CI: 2.3-27; p=0.001)], with a 5-year transformation rate of 16% for $MYD88^{WT}$ versus 2.8% with $MYD88^{L265P}$ mutated patients. Patients with transformation demonstrated a significant increase in risk of death compared to patients who did not transform (HR 5.075; 95%CI: 3.8-6.8; p<0.0001). In conclusion, the $MYD88^{WT}$ status is an independent predictor of transformation and associated with a shorter time-to-transformation. Additionally, transformation conferred an inferior overall survival in patients with WM."

Incidence of Waldenstrom Macroglobulinemia in South Africa

The South African National Cancer Registry (2014) does not provide any information regarding the incidence of Waldenstrom Macroglobulinaemia.

Causes and Risk Factors of Waldenstrom Macroglobulinemia

Waldenstrom macroglobulinemia is thought to result from a combination of genetic changes. The most common known genetic change associated with this condition is a mutation in the MYD88 gene, which is found in more than 90 percent of affected individuals. Another gene commonly associated with Waldenstrom macroglobulinemia, CXCR4, is mutated in approximately 30 percent of affected individuals (most of whom also have the *MYD88* gene mutation).

Other genetic changes believed to be involved in WM have not yet been identified. Studies have found that certain regions of DNA are deleted or added in some people with the condition; however, researchers are unsure which genes in these regions are important for development of the condition. The mutations that cause WM are acquired during a person's lifetime and are present only in the abnormal blood cells.

Signs and Symptoms of Waldenstrom Macroglobulinemia (WM)

People with Waldenstrom's macroglobulinemia may experience the following symptoms or signs. Sometimes, people with Waldenstrom's macroglobulinemia do not have any of these changes. Or, the cause of a symptom may be a different medical condition that is not cancer.

- Fatigue
- Unexplained weight loss
- Enlarged lymph nodes or spleen
- Numbness, weakness or other nervous system problems, pain in the hands or feet, sometimes called peripheral neuropathy
- Abdominal swelling and diarrhoea
- Weakness and shortness of breath
- Infections

- Raised pink or flesh-coloured lesions on the skin

Certain symptoms, called B symptoms, may signal a more aggressive cancer. Doctors may refer to either “A” or “B” when describing the lymphoma.
A means that a person has not experienced B symptoms, listed below.
B means that a person has experienced the following symptoms:

- Unexplained weight loss
- Unexplained fever
- Heavy sweating, especially at night, which may drench one’s nightclothes or sheets on the bed.
- Severe and/or extensive skin itchiness

Complications of Waldenstrom Macroglobulinemia (WM)
Complications may include the following:
- Hyperviscosity syndrome
- Visual disturbances secondary to hyperviscosity syndrome
- Diarrhoea and malabsorption secondary to gastrointestinal (GI) involvement
- Renal disease (less common)
- Amyloidosis of the heart, kidney, liver, lungs, and joints
- Bleeding manifestations secondary to platelet dysfunction and coagulation factor and fibrinogen abnormalities due to interaction with plasma IgM
- Peripheral neuropathy
- Raynaud phenomenon secondary to cryoglobulinemia
- Increased predisposition to infection due to B-cell dysfunction (disease related) or T-cell dysfunction (therapy related, particularly after nucleoside analogues)
- Cardiac failure
- Increased incidence of lymphomas, myelodysplasia, and leukaemias

Rogers, A.P. & Estes, M. 2020.
“Hyperviscosity syndrome (HVS) is an oncologic emergency that classically presents with the triad of neurological deficits, visual changes, and mucosal bleeding. Elevated blood viscosity is the result of either red blood cell shape deformity or a pathological increase in serum proteins, red blood cells (RBC), white blood cells (WBC), or platelets. The most common cause of HVS is Waldenstrom macroglobulinemia (WM), and therefore, the term HVS is typically used to describe an increase in serum proteins. Management consists of supportive care with intravenous fluids, plasmapheresis, and treatment of the underlying hematological condition.”

Ueda, S., Ishii, K., Fujii, H., Mizutani, K., Komaki, K. & Nagao. 2019.
AIM: Waldenström macroglobulinemia is a type of non-Hodgkin lymphoma with poor prognosis observed in patients with hyperviscosity syndrome because of its tendency for fatal symptoms. This study investigated the risk of intraoral bleeding in patients with Waldenström macroglobulinemia based on hyperviscosity syndrome stage and oral health status, and described potential strategies for managing intraoral bleeding.
METHODS AND RESULTS: Between April 2012 and March 2017, seven patients with Waldenström macroglobulinemia underwent dental procedures or tooth extraction. Patient records were

retrospectively reviewed to obtain data of symptoms, clinical and radiographic findings, treatment details, pretreatment hematological findings, hyperviscosity syndrome status, perioperative method for local haemostasis, postoperative bleeding, and prognosis. The mean patient age was 71.2 years, and the male-to-female ratio was 6:1. Treatment modalities for oral management comprised tooth extraction, scaling, and oral cavity cleaning. Three patients were admitted for hyperviscosity syndrome; one of the patients exhibited postoperative bleeding because of poor oral hygiene, whereas the two other patients with good oral hygiene did not experience intraoral bleeding regardless of the presence of hyperviscosity syndrome.
CONCLUSION: We recommended that the risk of oral bleeding in patients with Waldenstrom's macroglobulinemia should be assessed for oral health in addition to the stage of hyperviscosity syndrome.

Diagnosis of Waldenstrom Macroglobulinemia
When patients show symptoms of an enlarged spleen and liver combined with bleeding of the retina, WMG is reasonably suspected. The results of a complete blood count (CBC) usually show low red blood cell counts as well as low platelet counts. In such circumstances, electrophoresis (subjecting blood plasma to an electric impulse) of serum samples will show a peak reading for IgM.

Smith, T., Wong, M., Goldson, T.M. & Forjuoh, S.N. 2019.
"Waldenström macroglobulinemia is a rare disorder affecting about 1400 people annually in the United States. This case report reviews from a primary care provider's perspective the initial presentation of a patient who complained of fatigue and dizziness that ultimately led to hospital admission with a diagnosis of Waldenström macroglobulinemia. The referral to hematology/oncology prompting the bone marrow biopsy that led to the diagnosis highlights the important role of the primary care provider in the initial workup, coordination among specialists, and overall management of patients with rare disorders."

Treatment of Waldenstrom Macroglobulinemia
Treatment may include one or more of the following:

Chemotherapy - this often is the most effective treatment, and a combination of drugs usually is used.
Radiation therapy
Immunotherapy - this may include:

- Monoclonal antibodies
- Biological therapies that develop antibodies that destroy tumour cells
- Proteasome inhibitors
- Immune modulators
- Targeted therapies

Stem cell transplantation
Plasma exchange – if a patient develops symptoms because their blood is too thick, plasma can be removed and replaced with normal plasma from a healthy donor. This quickly relieves the symptoms until chemotherapy or immunotherapy can destroy the Waldenstrom cells that are causing the buildup of abnormal protein.
Watchful waiting - careful monitoring of the disease and symptoms, suggesting treatment if needed.

Smolewski, P. & Rydygier, D. 2019.
"Ixazomib is a new, orally administered, reversible proteasome inhibitor which is under investigation for the treatment of refractory/relapsed multiple myeloma (MM), systemic light chain amyloidosis (AL) and Waldenström macroglobulinemia (WM). Areas covered: This article covers the mechanism of action, pharmacology and clinical trial results of ixazomib while under investigation for the treatment of various lymphoproliferative disorders. We examine the findings from several phase 3 clinical trials (i) the pivotal TOURMALINE-MM1 study investigating ixazomib versus placebo in combination with lenalidomide and dexamethasone; (ii) the TOURMALINE-MM3 study investigating ixazomib versus placebo as a maintenance therapy in newly diagnosed MM following induction therapy and autologous stem cell transplantation; (iii) the TOURMALINE-MM2 study investigating ixazomib versus placebo in combination with lenalidomide and dexamethasone in patients with newly diagnosed MM; and (iv) TOURMALINE-AL1 investigating ixazomib plus dexamethasone in patients with relapsed/refractory AL amyloidosis. Finally, we explore early phase clinical studies of this agent in Waldenström macroglobulinemia. Expert opinion: A key advantage of ixazomib is that it could allow an efficacious treatment approach to MM and other lymphoproliferative disorders through a convenient oral administration route. Ixazomib could soon be used in combination treatment regimens, but more work is necessary to define the place of this agent going forward."

Castillo, J.J. & Treon, S.P. 2019.
"Waldenstrom macroglobulinemia (WM) is a rare type of non-Hodgkin lymphoma. The diagnosis of WM is established by the presence of lymphoplasmacytic lymphoma in the bone marrow or other organs, a monoclonal IgM paraproteinemia and the recurrent MYD88 L265P somatic mutation. Some patients with WM can be asymptomatic, in which case treatment is not indicated. However, most patients with WM will become symptomatic during the course of the disease, due to anemia, hyperviscosity, neuropathy, or other processes, necessitating therapy. Current treatment options for symptomatic WM patients include alkylating agents, proteasome inhibitors and anti-CD20 monoclonal antibodies. The approval of the oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib alone and in combination with rituximab has expanded the treatment options for WM patients. The present Perspective would focus on exciting treatment strategies under development for WM patients, such as proteasome inhibitors (e.g., ixazomib), BTK inhibitors (e.g., acalabrutinib, zanubrutinib, vecabrutinib), BCL2 inhibitors (e.g., venetoclax), and anti-CXCR4 antibodies (e.g., ulocuplumab), among others. It is certainly an exciting time for WM therapy development with novel and promising treatment options in the horizon."

Dimopoulos, M.A. & Kastritis, E. 2019.
"Waldenström macroglobulinemia (WM) is an uncommon lymphoma characterized by the infiltration of the bone marrow by clonal lymphoplasmacytic cells that produce monoclonal immunoglobulin M (IgM). The disease may have an asymptomatic phase, or patients may present with symptoms and complications resulting from marrow or other tissue infiltration, or from physicochemical or immunological properties of the monoclonal IgM. Diagnosis of WM has been clearly defined, and genetic testing for somatic mutation of MYD88L265P is a useful tool for differential diagnosis from other conditions. Specific criteria that define symptomatic disease that needs treatment offer clinical guidance. The treatment of WM has evolved rapidly, with treatment options that include anti-CD20 monoclonal antibody-based combinations and BTK inhibitors. The choice of therapy is based on the need for rapid disease control, presence of specific disease complications, and patient's age. With the use of BTK inhibitors, the use of continuous therapy has been introduced as another option over fixed-duration chemoimmunotherapy. In this review, we focus on different clinical scenarios and discuss treatment options, based on the available data."

Abeykoon, J.P., Zanwar, S., Ansell, S.M., Gertz, M.A., Kumar, S., Manske, M., Novak, A.J., King, R., Greipp, P., Go, R., Inwards, D., Muchtar, E., Habermann, T., Witzig, T.E., Thompson, C.A., Dingli, D., Lacy, M.Q., Leung, N., Dispenzieri, A., Gonsalves, W., Warsame, R., Kyle, R.A., Rajkumar, V., Parikh, S.A. & Kapoor, P. 2019.

"Ibrutinib-related data in Waldenström macroglobulinaemia (WM) remain sparse, particularly outside of trials. We report on 80 patients [previously treated, n = 67 (84%), treatment-naïve, n = 13 (16%)] with WM, evaluated consecutively at Mayo Clinic, who received ibrutinib off-study after its approval in 2015 for WM. Overall response rate (ORR) was 91%; major-response rate (MRR) was 78%. The median time to first response and best response was 2·9 [95% confidence interval (CI): 2-4] and 5·7 (95% CI: 4-12) months, respectively. The median follow-up was 19 (95% CI: 14-21) months; 18-month progression-free survival (PFS) was 82%. The median time on therapy was 12·5 (95% CI: 9·3-16·7) months, and the median duration-of-response was 32 (range: 23-32) months. Twenty-five patients (31%) had discontinued therapy at last follow-up (68% due to treatment-related toxicities) and 18% of patients required dose reduction. Fatigue (12%) and atrial-fibrillation (11%) were common non-haematological toxicities. IgM rebound occurred in 36% of patients who abruptly discontinued ibrutinib. Following ibrutinib discontinuation, 84% of patients received subsequent treatment, achieving an ORR of 57% and MRR of 50%. The median PFS from commencement of subsequent salvage therapy was 18 months. Ibrutinib therapy, outside of clinical trials, is effective in WM, but is associated with toxicities and challenges, including IgM rebound and a high drug discontinuation rate for reasons other than disease progression."

Zheng, Y.H., Xu, L., Cao, C., Feng, J., Tang, H.L., Shu, M.M., Gao, G.X. & Chen, X.Q. 2019.

BACKGROUND: To evaluate the efficacy and safety of rituximab-based combination therapy for Waldenström macroglobulinemia (WM), we conducted this meta-analysis by pooling the rates of overall response, major response, complete response, and grade ≥3 hematological adverse events.

METHODS AND MATERIALS: We searched for relevant studies in the databases of PubMed, Web of Science, Embase, and the Cochrane Library. The qualitative assessment of all the included articles was conducted with reference to the Newcastle-Ottawa Scale. A random-effects model was selected to perform all pooled analyses.

RESULTS: We identified altogether 22 studies with a total of 806 symptomatic WM patients enrolled. The pooled analysis indicated that the rituximab-based combination therapy achieved an overall response rate (ORR) of 84% (95% CI: 81%-87%), a major response rate (MRR) of 71% (95% CI: 66%-75%), and a complete response rate (CRR) of 7% (95% CI: 5%-10%). Rituximab plus conventional alkylating agents-containing chemotherapy (subgroup A) yielded an ORR of 86% (95% CI: 81%-89%), an MRR of 74% (95% CI: 69%-79%), and a CRR of 8% (95% CI: 4%-14%). Rituximab plus purine analog (subgroup B) resulted in an ORR of 85% (95% CI: 79%-89%), an MRR of 74% (95% CI: 66%-81%), and a CRR of 9% (95% CI: 4%-15%). Rituximab plus proteasome inhibitor (subgroup C) resulted in an ORR of 86% (95% CI: 81%-90%), an MRR of 68% (95% CI: 58%-77%), and a CRR of 7% (95% CI: 3%-11%). Rituximab plus immunomodulatory drug (subgroup D) attained relatively lower response rates, with an ORR of 67% (95% CI: 51%-81%), an MRR of 56% (95% CI: 27%-83%), and a CRR of 5% (95% CI: 1%-12%). Common grade ≥3 hematological adverse events consisted of neutropenia (33%, 95% CI: 17%-52%), thrombocytopenia (7%, 95% CI: 3%-11%), and anemia (5%, 95% CI: 3%-9%).

CONCLUSION: Rituximab in combination with an alkylating agent, purine analog, or proteasome inhibitor is highly effective with tolerable hematological toxicities for WM.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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