

# Waldenström's Macroglobulinemia

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Subtype Review

August 2016

**LYMPHOMA  
COALITION**

Worldwide Network of  
Lymphoma Patient Groups



## Introduction

The Lymphoma Coalition (LC) continues to examine access to care for patients with lymphoma by subtype through the patient experience lens. LC believes it is necessary to report by subtype and not combine the information under one heading such as non-Hodgkin lymphoma (NHL). NHL is not a disease in itself but a series of subtypes that require independent tracking to ensure proper trending analysis and outcomes reporting. **It is important to know your subtype since it is a critical piece of information in determining the best treatment required.** LC created the [Global Database](#) to house subtype information for this purpose. It provides LC and its members with the opportunity to analyse the individual subtype needs, review any issues or challenges by country, and review what subtype information is missing to determine what approach is required to provide patient support.

Lymphoma is the most common blood cancer with over 60 different subtypes classified by the World Health Organisation (WHO). Waldenström's macroglobulinemia (WM) is a subtype of lymphoma. There have been numerous advances in the understanding of the biology of WM over the past few years and consequently a rise in clinical trials with novel therapies.

The focus for this report is to review WM to give an overview and biology as well as determine therapy access, clinical trial availability, incidence and mortality, and some aspects of the patient experience.

## Overview

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

WM is characterized by the occurrence of a monoclonal IgM paraprotein in blood serum and the infiltration of the bone marrow with malignant lymphoplasmacytic cells, which have characteristics of both B-lymphocytes and plasma cells. For that reason, WM is classified as a type of lymphoma called lymphoplasmacytic lymphoma (LPL). About 95% of LPL cases are WM, but it is a very rare disease – comprising approximately 1%-2% of haematological malignancies<sup>1</sup>. It is also considered a disease of the elderly with an average age of  $\geq 63$  with a male predominance. It has a reported incidence rate of 3.4 per million among the male population and 1.7 per million among the female population in the United States, and 7.3 and 4.2 per million, respectively, in the European standard population<sup>2,3</sup>. WM is usually indolent (slow growing) and can be managed as a chronic cancer for a number of years. However, it is not yet curable.

As a result of proliferation in the bone marrow and other sites, the lymphoplasmacytic cells of WM may interfere with normal functioning. In the bone marrow where blood cells are produced, the WM cells “crowd out” the normal blood cells and may lead to a reduction in normal blood counts; in the lymph nodes and other organs, the WM cells may lead to enlargement of these structures and other complications.<sup>4</sup>

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

There is a strong familial predisposition in WM; therefore, a good family history is important. Approximately 25% of patients with WM have family members with a history of lymphoproliferative disorders, and first-degree

relatives have a 20-fold higher risk of developing WM than those in the general population<sup>5,6</sup>. Although the identification of such familiarity does not at this time influence treatment decisions, it may spawn a discussion in families with multiple cases of WM or related B-cell disorders to participate in familial studies aimed at identifying genetic predispositions to WM.<sup>5</sup>

One of the risk factors for WM is a condition known as monoclonal gammopathy of uncertain significance (MGUS) of the IgM type. IgM-MGUS is an age-related condition that is characterised by the presence of an IgM paraprotein in the blood. There are very few LPL cells in the body at this point and a detectable amount of abnormal IgM. This may be picked up on a blood sample done for an unconnected reason, and at this stage people are typically feeling normal and have no symptoms. Over time (usually years), the LPL cells may gradually build up and accumulate. If they accumulate enough to affect the functioning of the body, symptoms such as fatigue, weight loss, sweats, fevers, or infections may develop. MGUS can transform into chronic lymphocytic leukemia (CLL), IgM multiple myeloma, primary amyloidosis, or WM. It is not yet known what causes MGUS.

WM often develops over a long period of time and many people have no symptoms at all. This means that the condition is sometimes found by chance while having investigations for another condition or on a routine blood test. About a quarter of people with WM are diagnosed like this by chance. Most people with WM, however, gradually develop symptoms due to the cancer. Symptoms develop for two main reasons. The first is that abnormal B-cells fill up the bone marrow or collect in the lymph nodes or the spleen (and, rarely, in other places in the body). The second reason for developing symptoms in WM is the presence of large amounts of IgM paraprotein circulating in the blood.

Because patients with WM have wide variability in survival, it is important to determine prognostic factors in the assessment of patients. The International Prognostic Scoring System for Waldenström's macroglobulinemia (IPSSWM) was developed by Dr. Pierre Morel of France and presented at the Fourth International Workshop on WM in 2007. It is now internationally accepted as a predictive model to characterise long-term outcome for symptomatic patients requiring therapy.<sup>7</sup>

The clinical manifestations of WM include:

- Cytopenias
- Hyperviscosity
- Peripheral neuropathy
- Organomegaly
- Splenomegaly
- Night sweats
- Hemolytic anemia
- Hepatomegaly
- Weight loss
- Recurrent fevers
- Fatigue
- Cryoglobulinaemia
- Cold agglutinin disease
- Amyloidosis
- Masses of WM cells outside the bone marrow – treatment is based on the location, size, and rate of growth of the masses

## Understanding Biology of WM

The causes of WM are unknown. Like other cancers, it is not infectious and cannot be passed on to other people. WM is thought to arise from B-cells that are arrested after somatic hypermutation in the germinal center and before they turn into plasma cells<sup>8,9</sup>. Analysis indicates that WM may originate from an IgM+ and/or IgM+IgD+ memory B-cell with a deficiency in the initiation of the class switching process.<sup>10</sup>

WM usually arises sporadically, but about 20-25% of cases are familial with at least one first degree relative with WM or other B-cell disorders<sup>10</sup>. Population based studies have also shown an increased risk of WM and other lymphomas associated with auto-immune and other inflammatory conditions. Currently the only known risk of developing WM is the presence of MGUS.<sup>12</sup>

What causes MGUS to transform into WM is unknown. The rate of progression from MGUS to WM may span a number of years. The rate of progression by 5 years is 10%; by 10 years, 18%; and by 15 years, nearly a quarter of patients with MGUS progress to WM.

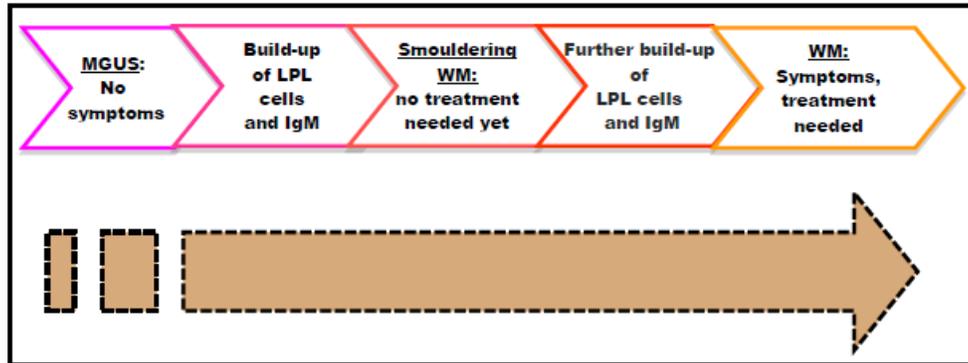


Figure 1: Course of WM progression from MGUS Source: [www.wmuk.org.uk](http://www.wmuk.org.uk)

Knowledge about the genetics of WM made a major leap forward in 2011 with the discovery of a single mutation in a gene called MYD88, with a prevalence in over 90% of WM patients. This was the first time that an entire set of DNA, also known as the genome, of patients with WM was sequenced. The aim of the study was to establish which genes were present in the cancer cells as opposed to the normal cells of these patients. The same study also reported that the MYD88 mutation, designated MYD88 L265P, was not nearly as prevalent in most other types of lymphoma or in multiple myeloma.<sup>9</sup>

Mutations in CXCR4 also play a crucial role in modulating the biology of WM. Research has found that cells from patients with the most aggressive disease were the most likely to have CXCR4 mutations. It is hypothesised that the CXCR4 mutations drive the disease, in other words that they spur WM cells to grow, divide, and spread. When researchers treated WM carrying mice with an antibody that targets CXCR4, progression of the disease halted, providing hope of a novel therapy to target these mutations in the future.

Dr. Steven Treon, Attending Physician for the Department of Medical Oncology at the Dana-Farber Cancer Institute and Brigham and Women’s Hospital, Associate Professor of Medicine at Harvard Medical School in Boston, and Director of the Bing Centre for Waldenström’s Macroglobulinemia, Boston, USA, is working with his research team at the Bing Centre, studying the role that these mutations play in the progression of WM and the mechanism and effects of their downstream pathways. Researchers now have a fairly good idea of the complex pathways affected by these mutations and how they might in turn promote the growth and proliferation of WM cells.<sup>9</sup>

As a result of this work and its subsequent confirmation by other researchers, the USA National Comprehensive Cancer Network (NCCN) recently (Feb 2016) updated its guidelines for WM to include AS-PCR testing for the presence of MYD88 L265P in the bone marrow cells of suspected patients and has characterized the test as essential for the diagnosis of WM.

Another significant area of study is the microenvironment of WM – in particular the bone marrow. In WM, there is continuous trafficking of cells in and out of the bone marrow leading to cell dissemination. The bone marrow microenvironment plays a crucial role in tumor cell proliferation, survival, and drug resistance, a clearer understanding of which can be used to inhibit dissemination of WM cells.<sup>11</sup>

Recently identified genetic abnormalities found in patients with WM are being further explored to examine their significance for prognosis and treatment.

## Current Treatment Recommendations

Presently, WM cannot be cured, although in most cases the disease is indolent (slow growing) and can be effectively managed with appropriate therapies.

As is the case with other lymphomas such as chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBCL), rapid changes are occurring in the understanding of WM biology and treatment options.

For the purpose of this review and in order to determine what current treatments should be accessible to WM patients, LC reviewed the information from both the European Society of Medical Oncology (ESMO)<sup>14</sup> clinical practice guidelines and the NCCN listing.<sup>13</sup>

It is important to note that the NCCN guidelines for the treatment of WM were updated in 2016, while those of ESMO are from 2013. ESMO guidelines do not reflect the NCCN updates which include:

- Testing of MYD88 L265P of bone marrow essential
- Using plasmapheresis to lower an IgM  $\geq 4,000$  mg/dL to avoid serum viscosity on the basis of rituximab-related IgM flare.
- Ibrutinib, carfilzomib/rituximab/dexamethasone, alemtuzumab, everolimus, ofatumumab and thalidomide/rituximab in either first line or relapsed treatment

There is no current and updated treatment algorithm in Europe for physicians to refer to. For this reason, this report relies on the NCCN listings of therapies and treatment guidelines.

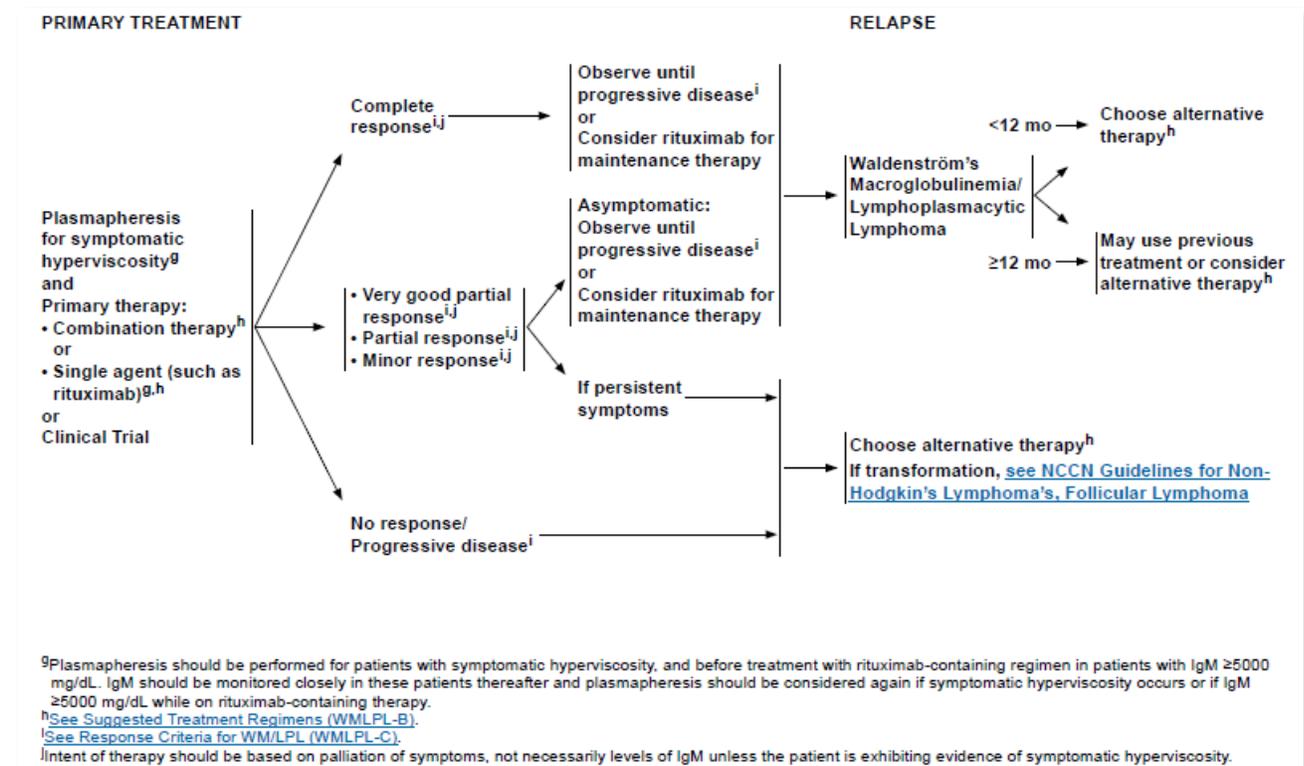


Figure 2: NCCN Treatment Algorithm for Waldenström's Macroglobulinemia

An International Prognostic Scoring System for Waldenström’s Macroglobulinemia (ISSWM) was developed in 2007 to ensure that a more informed decision could be made regarding treatment according to the prognosis. The ISSWM as shown in the table below clearly defines the criteria for diagnosis and initiation of treatment.

The ISSWM five adverse covariates are identified:

- advanced age (>65 years)
- hemoglobin less than or equal to 11.5 g/dL
- platelet count less than or equal to  $100 \times 10^9/L$
- beta 2-microglobulin more than 3 mg/L
- and serum monoclonal protein concentration more than 7.0 g/dL

If the patient has  $\leq 1$  adverse variable, the risk category is Low. If the patient has 2 adverse variables or is over 65 years of age, then the risk category is Intermediate, and if the patient has more than 2 adverse characteristics, then the risk is High.

Risk Group	Low	Intermediate	High
Score	0–1 (except age)	Age or 2	$\geq 3$
5-year OS <sup>a</sup> (%)	87	68	36
Risk Factors	Score		
Age $\geq 65$ years	1		
Other risk factors <sup>b</sup>			
Hb <sup>c</sup> $\leq 11.5$ g/dl	1		
Thrombo <sup>d</sup> $\leq 100.000 \times 10^9/l$	1		
Beta-2 M <sup>e</sup> $>3$ mg/l	1		
IgM <sup>f</sup> $>70$ g/l	1		

<sup>a</sup>OS, overall survival.  
<sup>b</sup>Each of the risk factors is counted as one.  
<sup>c</sup>Hb, haemoglobin.  
<sup>d</sup>Thrombo, thrombocytes.  
<sup>e</sup>beta-2 M, beta-2 microglobulin.  
<sup>f</sup>IgM, monoclonal protein concentration.

Figure 3: International Prognostic Scoring System for Waldenström’s Macroglobulinemia (ISSWM)<sup>8</sup>

In order to be diagnosed with WM it is essential to have detected levels of monoclonal IgM in the bloodstream and LPL cells in the bone marrow. As mentioned earlier over 90% patients with WM have shown a MYD88 mutation that can be useful in differentiating Waldenström’s macroglobulinemia and non-IgM LPL from B-cell disorders that have some of the same features.

Not all patients with a diagnosis of WM need immediate therapy but close observation is recommended.<sup>5</sup> Patients who are asymptomatic will be advised to adopt a ‘watch and wait’ approach with regular monitoring.

Treatment plans will often be discussed if the patient has:

- Increased symptoms attributable to WM
- High levels of IgM causing hyperviscosity, cold agglutinin, cryoglobulinaemia, amyloidosis, neuropathy
- Changes in blood count of haemoglobin or platelets.

Patients should be treated when they have symptoms and not on the basis of blood test results alone. Furthermore, treatment decisions have to take into account the individual characteristics of symptomatic patients. Half of the WM patients are over 70 years, often suffer from non-lymphoma-related comorbidities, and may only tolerate low-intensity treatments. On the other hand, younger fit patients with an aggressive clinical course might be candidates for high-dose treatments<sup>8</sup>. There are also differences in how quickly a patient needs disease control. Taking this into account, treatment of WM patients has to be individualized and cannot strictly follow treatment

algorithm schedules. Treatments should also be aimed at improving quality of life and keeping patients well, with the least possible side effects

When initial or front-line treatment is being considered, patients are advised, if possible, to consult a WM expert as many hematologist-oncologist consultants may have little or no experience with a rare disease like WM.

Table I shows a list of the recommended treatment protocol for WM by the NCCN in both first line and refractory disease. The treatments highlighted are newer treatments for WM. Some of these treatment options use drugs already known to be effective in other lymphomas but are used here for WM combining them in new ways and/or using different doses.

Ibrutinib is the first drug specifically designated for the treatment of WM. The US Food and Drug Administration (FDA) approved the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib for the treatment of WM, and the European Commission approved ibrutinib for patients who have received at least one prior therapy, or as first line treatment for patients unsuitable for chemo-immunotherapy. It is understood that The MYD88 L265P mutation is upstream of BTK and increases the activity of BTK signaling.

Prior to this most of the treatments in use had already been approved for the related cancers of follicular lymphoma, chronic lymphocytic leukemia, and multiple myeloma. While ibrutinib is a very important step forward in the treatment of WM, it is not a cure for and not everyone responds to it well.

Other treatment options for WM include alkylating agents (e.g. chlorambucil, cyclophosphamide), nucleoside analogues (fludarabine and cladribine), the monoclonal antibody rituximab, and the proteasome inhibitor bortezomib<sup>15-17</sup>.

**Table I: NCCN Treatment Protocol Listing\***

<b>First Line</b>	<b>Relapsed</b>
Bortezomib ± rituximab	Bortezomib ± rituximab
-	Alemtuzumab
-	Allogeneic stem cell transplant
Bendamustine ± rituximab	Bendamustine ± rituximab
Bortezomib/dexamethasone/rituximab	Bortezomib/dexamethasone/rituximab
Bortezomib/dexamethasone	-
Carfilzomib/rituximab/dexamethasone	Carfilzomib/rituximab/dexamethasone
Chlorambucil	Chlorambucil
Cladribine ± rituximab	Cladribine ± rituximab
CP-R	CP-R
-	Everolimus
FCR	FCR
Fludarabine ± rituximab	Fludarabine ± rituximab
Ibrutinib	Ibrutinib
-	Ofatumumab
R-CHOP	R-CHOP
Rituximab	Rituximab
Rituximab/cyclophosphamide/dexamethasone	Rituximab/cyclophosphamide/dexamethasone
Thalidomide ± rituximab	Thalidomide ± rituximab
Bortezomib ± rituximab	Bortezomib ± rituximab

\*Treatments are listed in alphabetical order.

In a discussion with Dr. Steven Treon, he mentioned that one of the greatest achievements in WM to date is the whole genome mapping of 30 WM patients which led to the discovery of the MYD88 gene mutation prevalence in WM patients.

In his paper “How I treat Waldenström’s Macroglobulinemia”<sup>5</sup>, Dr. Treon provides a guide for the primary therapy of WM as well as a guide for previously treated patients as seen in Figure 4 and 5.

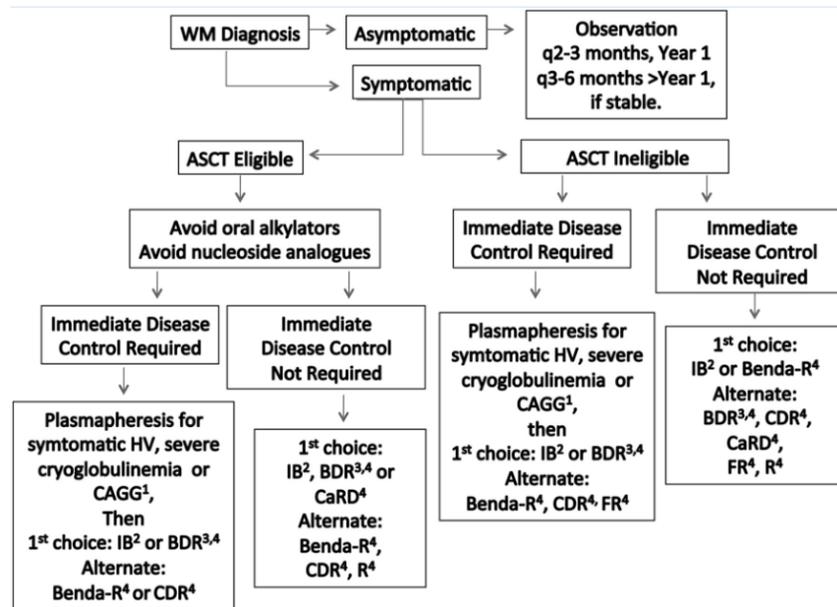


Figure 4: Guide to the primary therapy of WM<sup>5</sup>

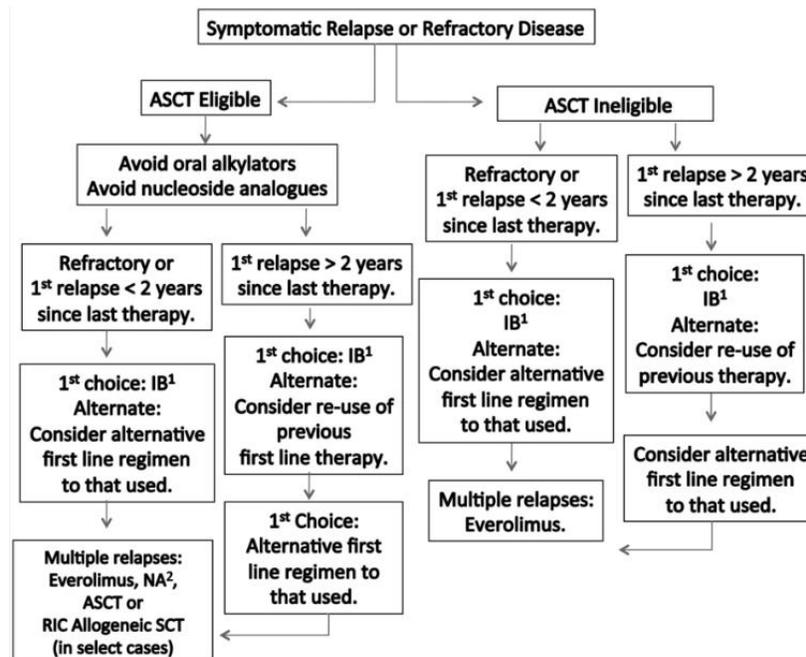


Figure 5: Guide to therapy of previously treated WM<sup>5</sup>

The future continues to look exciting with the new advances in our understanding of the pathogenesis of WM. Many novel therapeutic agents are showing activity against WM cells such as PI3K/mTOR inhibitors, new generation proteasome inhibitors, BTK inhibitors, HDAC inhibitors, IMiDs, and also inhibitors for MYD88, CXCR4, and BCL2 pathways. Some of these are in clinical trial while some have shown preclinical efficacy and clinical trials are still to follow.

## Therapy Access

There are huge advances in the understanding of biology and therapy of WM, but these can only be advantageous to patients by more effective dissemination of information and also better access to treatment options.

For this report we looked at access to treatment in member LC countries, a list of which can be found on the website <http://www.lymphomacoalition.org/>.

On a global level there is quite a discrepancy in the number of therapies for WM with regulatory approval compared to those same therapies being funded/reimbursed. When looking at the mainstream therapies, those like CHOP-R, FCR, FR, and rituximab that have typically been used to treat other lymphoma patients are the ones most heavily funded.

Novel therapies such as alemtuzumab are funded in only 2 countries, ofatumumab in only 11, while ibrutinib, which is the only targeted therapy for WM on the market, is funded in only 6 countries.

Lack of funding/reimbursement leaves patients in a vulnerable position. Fewer options mean treatment will often rely on older therapies with higher comorbidities for WM patients. These include rituximab which leads to an IgM flare, fludarabine which can cause transformation or second malignancies, and oral alkylators which often lead to higher rates of neuropathy.

There are several LC member countries where funding/reimbursement information is unavailable, which makes it difficult to determine patients' accessibility to these treatments in those countries.

When we look at regulatory approvals and funding/reimbursed therapies on a regional level for first line treatments, there is a vast difference in patient access to WM treatments as seen in Table 2.

The European Union is the only region that has an even distribution of therapies with 22 unique approved drugs. However, when it comes to funding, Belgium, Denmark, and Sweden have the most number of therapies reimbursed/funded while Latvia and Portugal have none. Outside the EU, Ukraine has only 7 therapies available while its neighbouring EU countries, Poland, Slovakia, and Hungary, have 14.

Within North America, two completely different health care systems exist, both in their approval of therapies and their reimbursement/funding processes, making it very difficult to compare. However, the number of therapies with regulatory approval in the USA is higher than in any other country, while those of Canada are more in line with countries that make up the EU.

To create a list of available therapies by LC member country and compare it to the NCCN listing, go to the LC Global Database [www.lymphomacoalition.org/](http://www.lymphomacoalition.org/) and view by country and subtype.

Certain therapies as shown in the treatment algorithm in Figure 4 are poorly reimbursed/funded globally. Ibrutinib is only reimbursed/funded in Sweden and the USA; while BDR is only in Sweden, the USA, and the Netherlands. Another new combination for WM is CaRD (carfilzomib, rituximab, dexamethasone), which isn't approved or funded/reimbursed in any LC country. Carfilzomib on its own is approved only in the USA.

It would seem that there is a paucity of funding and support for newer treatment options for WM in most countries. Combinations such as BDR, BR, and CRD are only available and funded in a select few European

countries and the USA. There are more drugs available in the second line setting which include alemtuzumab, ofatumumab, and everolimus but the funding obstacle still exists.

**Table 2: WM First Line Drugs Available by LC Member Country**

Region	Country	Approved	Reimbursed/ Funded
<b>Africa</b>			
	South Africa	9	9
<b>Asia</b>			
	Japan	14	11
	Singapore	12	0
<b>Eastern Europe</b>			
	Russian Federation	9	9
	Switzerland	13	7
	Turkey	11	0
	Ukraine	7	0
<b>EU</b>			
	Belgium	18	14
	Bulgaria	14	4
	Croatia	14	2
	Czech Republic	14	4
	Denmark	18	13
	France	14	8
	Germany	14	11
	Hungary	14	5
	Ireland	14	5
	Italy	14	8
	Latvia	14	0
	Lithuania	14	5
	Netherlands	16	7
	Poland	15	7
	Portugal	14	0
	Slovakia	14	5
	Slovenia	14	5
	Spain	15	6
	Sweden	15	14
	United Kingdom	15	10
<b>Middle East</b>			
	Israel	8	6
<b>North America</b>			
	Canada	15	13
	Mexico	6	0
	United States	20	20
<b>Pacific</b>			
	Australia	6	2
	New Zealand	7	5
<b>South America</b>			
	Argentina	12	0
	Brazil	8	0
	Colombia	5	0
	Uruguay	5	0

**Table 3: WM Second Line & Subsequent Drugs Available by LC Member Country**

Region	Country	Approved	Reimbursed/Funded
<b>Africa</b>			
	South Africa	10	10
<b>Asia</b>			
	Japan	15	13
	Singapore	12	0
<b>Eastern Europe</b>			
	Russian Federation	9	9
	Switzerland	14	9
	Turkey	12	0
	Ukraine	7	0
<b>EU</b>			
	Belgium	18	14
	Bulgaria	15	4
	Croatia	15	3
	Czech Republic	15	5
	Denmark	18	14
	France	15	9
	Germany	15	12
	Hungary	15	6
	Ireland	15	6
	Italy	15	9
	Latvia	15	0
	Lithuania	15	6
	Netherlands	17	11
	Poland	16	8
	Portugal	15	0
	Slovakia	15	6
	Slovenia	15	7
	Spain	16	8
	Sweden	16	15
	United Kingdom	16	12
<b>Middle East</b>			
	Israel	10	8
<b>North America</b>			
	Canada	13	11
	Mexico	7	0
	United States	23	23
<b>Pacific</b>			
	Australia	8	4
	New Zealand	9	7
<b>South America</b>			
	Argentina	12	0
	Colombia	6	0

## Clinical Trial Activity

WM is a very rare cancer and, as referred to above in the biology of WM, only recently has there been a better understanding of the genomics of this subtype. This is reflected in the number of WM clinical trials currently being held globally. When reviewing the clinical trials in the LC Global Database, there are 706 clinical trials focusing on lymphomas which are either in Phase II or Phase III status. Of these trials 66 are studying WM along with other, often indolent, lymphomas. Only 4 of these 66 trials are solely for WM patients.

The USA is involved in a good majority of the WM trials with Italy coming in at a distant second. Eighteen of the 44 LC members have no current trials with any WM participation. The number of trials falls in line with other rare lymphomas such as cutaneous T-cell (55 trials), extra-nodal NKT cell (52 trials), or anaplastic (59 trials) lymphoma among others. Similarly, a majority of the trials have USA participation with numbers staggeringly low in the Eastern Europe, Africa, Asia Pacific, and South America.

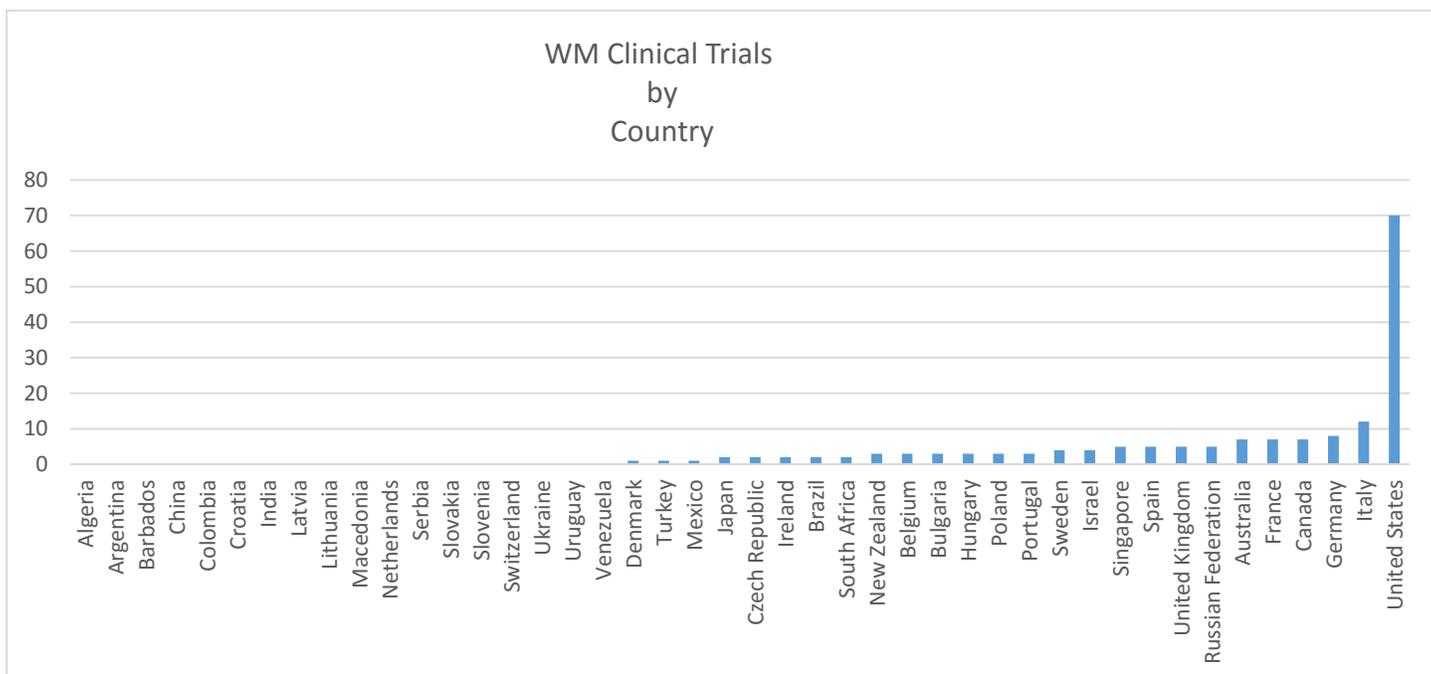
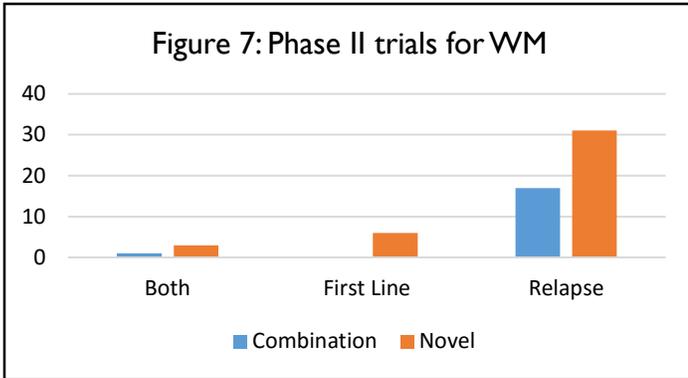


Figure 6: WM Trials by Country

Generally, when looking at the number of clinical trials in Phase II compared with Phase III, it is anticipated that the number of Phase II trials will be greater due to the sequencing of clinical drug testing. In reviewing the distribution of the WM trials in the LC's Global Database, the trend holds for all LC member countries, as the ratio of Phase II to Phase III trials is approximately 5:1, with 40 Phase II trials and 8 Phase III trials studying the use of novel therapies and only 18 Phase II trials studying combination therapy.

Looking at only Phase II trials, as mentioned 18 are combination therapies while the rest are novel drugs (40 trials). A large percentage of these trials (80%) are in relapsed/refractory patients with novel therapies, while 12.5% are for first line patients. Only 7.5% of the Phase II trials are looking at both first line and relapsed patients. As seen in Table 4 there are currently 58 Phase II trials, and the USA is involved in 56 of these.

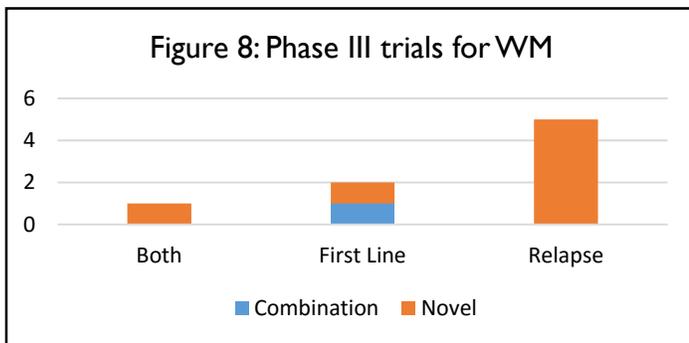


Source: LC Global Database

Phase II trials	Combination	Novel	Total
Both	1	3	4
First Line		6	6
Relapse	17	31	48
Total	18	40	58

Table 4: Phase II Trials for WM

There are only 8 Phase III trials and of these, 2 are for WM patients exclusively. These are “Ibrutinib/Rituximab in Adults with WM” and “Efficacy of First Line DRC +/- Bortezomib for Patients with WM”.



Source: LC Global Database June 2016

Phase III trials	Combination	Novel	Total
Both		1	1
First Line	1	1	2
Relapse		5	5
Total	1	7	8

Table 5: Phase II trials in WM

Note that a clinical trial may be undertaken in more than one area of focus, therefore, the total number will not add up to the total number of trials.

Most of the Phase II and III trials have a focus on novel therapies. WM patients are involved in a number of combined studies partly due to a better understanding of the signalling pathways. The expectation is that this will eventually lead to more targeted therapies. Also, patients with WM are found to be at a greater risk of neuropathy with more conventional drugs such as CHOP-R, CPR, BDR, and CDR among a few, which suggests a need for therapies with fewer comorbidities.

Many new novel therapeutic agents are currently in trials, some of which include proteasome inhibitors such as ixazomib, immunomodulatory drugs such as lenalidomide, and copanlisib (a PI3K inhibitor) to name a few. However, trials grouping heterogeneous lymphoma patients have a relatively small number of WM patients. In order to establish benchmarks for novel and/or combination drugs and a suitable treatment regimen, it is essential to conduct large scale WM trials. At present there are two Phase III trials for WM exclusively. Without large randomised trials it would be exceedingly difficult to provide a standard of care and survival rates with fewer side effects for patients.

## Patient Experience

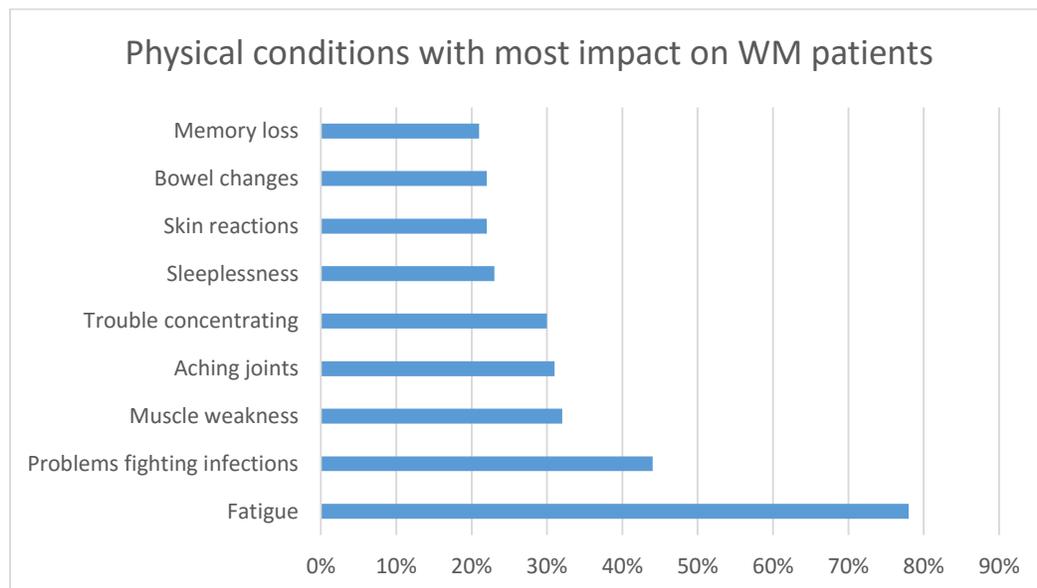
The patient experience is always at the forefront when reviewing subtypes in lymphomas. The LC 2016 Global Patient Survey (GPS) is the document LC references in this report to provide a sense of the patient experience.

There were over 4,000 total respondents to the GPS, of which 8.5% were identified as WM patients; this is up from 4.5% from the 2014 survey. This is a high number of respondents especially when considering how rare the disease is, which in turn gives us a better perspective of the global patient experience.

When first diagnosed with WM, one in five patients did not understand their diagnosis and almost one third of patients did not understand their subtype. When it came to treatment options, 25% did not understand what options they had and 21% did not understand the side effects. A communication strategy between the health care professional and the patient is a key element in treating this cancer.

According to Dr. Steven Treon, one of the most important patient needs is to understand treatment options and their related side effects. Many drugs are leveraged due to a lack of awareness of latest therapies or availability. If patients better understand the potential side effects, they have the opportunity to be aware of and manage them appropriately. Rituximab as an example is known to induce an IgM flare in a majority of patients. Nucleoside analogues such as fludarabine and oral alkylators such as chlorambucil have long term side effects such as secondary cancers, stem cell toxicity, and myelodysplasia.

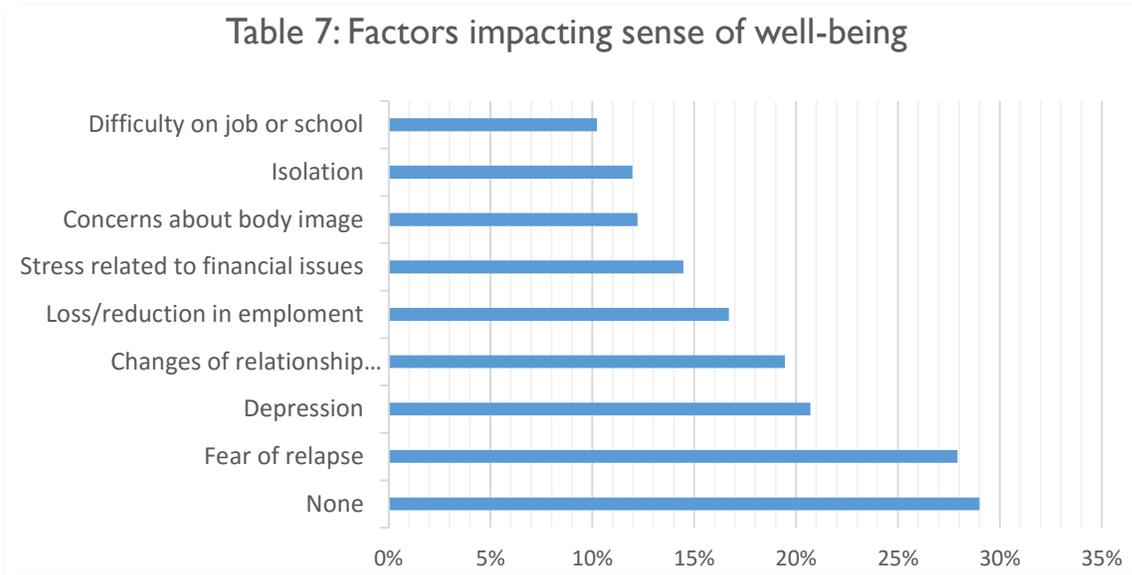
As seen in Table 6 one of biggest physical impacts faced by WM patients is fatigue followed by problems fighting infections. Additionally, numbness, muscle weakness, and aching joints were among the most prevalent physical conditions affecting over a quarter of the participants.



Source: LC Global Patient Survey 2016

The psychological burden of dealing with long term disease often directly affects the patient's sense of well-being. One of the most common factors affecting that sense of well-being is the fear of relapse which was a cause of concern for 28% of the WM respondents to the survey. This number is relatively low as compared to other lymphomas, possibly due to the fact the WM is incurable which means treatments will usually need to continue to keep the disease in control.

Another major issue is depression which is where the patient's support structure can and should be relied on. However, health care providers and palliative care might be failing patients here. Almost 38% of the respondents went to their doctor with physical and emotional issues, of which only 8% felt that it helped. Sixty eight percent found the support from patient organisation groups helpful while only 6% found the services of a social worker useful to them. The advances we see in the biomedical arena for WM are not congruent with the care being provided on a psychological level.



Source: LC Global Patient Survey 2016

Treating any form of cancer is a complex, multi-tiered task that involves physiological, psychological, emotional, and social interventions. It is an integral part of quality care to address all these aspects. Health care providers, doctors, and patient care centres need to provide information and care that is matched and appropriate for each patient. Establishing a best practise for the treatment of WM is the first step to this.

## Conclusion

Patients with WM show a variable course of disease progression and it is therefore critical to identify the need for treatment. There are multiple options for treatment; however, the regimen requires thoughtful selection keeping in mind the patient's age, comorbidities, IgM levels, and genetic mutations.

Within the course of a few years our understanding of WM has been substantially increased. One of the greatest discoveries was the prevalence of MYD88 somatic mutations in patients with WM. Further studies have shown that this mutation in 80% of patients with IgM MGUS significantly increases their chances of early diagnosis. It has also helped with the difficulties faced by haematologists in differentiating between marginal zone lymphoma, multiple myeloma, and chronic lymphocytic leukemia due to overlapping characteristics.

These breakthroughs can be exploited therapeutically. Downstream targets of MYD88 such as IRAK1, IRAK4, BTK, and TAK1 can all prove to be important markers for future drug targets. BTK is targeted by ibrutinib which translates into the efficacy of the drug with patients shown to have MYD88 L265P.

New therapies provide an opportunity to drastically affect patient outcomes positively and improve overall survival, rather than relying on inherited treatments from other lymphomas which often lead to comorbidities such as secondary cancers and complications from IgM flare.

There is no cure for WM which means current therapies manage the WM rather than treat it. With the expectation of inevitable progression, patients no doubt live in fear of when and how their WM manifests itself. Patients are also expected to manage both the physical and medical issues that arise from treatments and the negative impact that comes with cumulative side effects and comorbidities.

Many new agents have emerged in the last couple of years that improve responses and reduce long term toxicities. However, better understanding of the biology can further improve outcomes. Whole genome sequencing studies are helping to identify specific mutations in subgroups of patients with WM. Understanding the role of epigenetic modifications and how to target these changes are being examined. In addition, the role of the bone marrow environment, which plays a crucial role in tumor cell proliferation, survival, and drug resistance, is being studied. These advances in the understanding of the underlying pathogenesis of WM will lead to the development of novel therapeutic agents and targeted therapies for patients with this disease <sup>18</sup>

The only country to show a large range of access to care is the USA. Countries in Eastern Europe, for example, have little or no access to novel therapies. Patients are left with no option but to deal with treatments that leave them with long term side effects and other medical ramifications. Clinical trials currently underway are researching novel treatments, often in combination, which suggests there may be more continued improvements in treatment outcomes.

Globally, patient access to care is often incomplete and sporadic, especially as it relates to other subtypes. There are still regional differences where access to novel and recommended therapies is not universal. With this information the lymphoma community and LC members can work together to find solutions to gain broader access for patients. Although WM is a rare lymphoma subtype, it still requires independent reporting to ensure proper trending analysis and outcome reporting. The challenge in gathering accurate data, especially incidence and mortality by subtype, is a global issue that needs to be addressed. In order to effectively understand the unmet issues and needs of WM patients, subtype information remains at the forefront of providing information that is reflective of those patients.

## Acronyms

BCL = B-cell lymphoma  
BD = bortezomib, dexamethasone  
BDR = bortezomib, dexamethasone, rituximab  
BR = bendamustine plus rituximab  
BTK = Bruton's tyrosine kinase  
CaRD = carfilzomib, rituximab, dexamethasone  
CHOP-R = cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab  
CLL = chronic lymphocytic leukaemia  
CPR = cyclophosphamide, prednisone with/without rituximab  
CRD/CDR= cyclophosphamide, dexamethasone, rituximab  
CXCR4 = chemokine receptor type 4  
DLBCL = diffuse large B-cell lymphoma  
ESMO = European Society of Medical Oncology  
EU = European Union  
FCR = fludarabine, cyclophosphamide, rituximab  
FD = fludarabine, dexamethasone  
FR = fludarabine, rituximab  
GPS = Global Patient Survey  
HDAC = histone deacetylase  
HL = Hodgkin lymphoma  
IMiD =immunomodulatory drug  
LC = Lymphoma Coalition  
MCL = mantle cell lymphoma  
MYD88=myeloid differentiation primary response gene 88  
NCCN = National Comprehensive Cancer Network  
NHL = non-Hodgkin lymphoma  
PCR = pentostatin, cyclophosphamide, rituximab  
PI3K = phosphatidylinositol 3-kinase  
R = rituximab  
TOR = target of rapamycin  
WHO = World Health Organization

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