Marginal Zone Lymphoma

Subtype Report

February 2017

LYMPHOMA COALITION
Worldwide Network of Lymphoma Patient Groups

Marginal Zone Lymphoma

Overview

The focus of this report is on marginal zone lymphoma (MZL). This report will provide a brief explanation of the biology and its sub categories. Furthermore, this report will consider the individual subtype needs, review therapy access as well as issues and challenges by country. It will outline the clinical trial availability and aspects of the patient experience as understood from the 2016 Lymphoma Coalition Global Patient Survey.

MZL, an indolent cancer, is thought to originate from B-cells present in the marginal zone of lymphoid follicles. These follicles are found in the spleen, lymph nodes and lymphoid tissues. The World Health Organization divides MZL into three sub-categories:

1) Extranodal marginal zone lymphoma (EMZL) or mucosa-associated lymphoid tissue (MALT) lymphoma
2) Nodal marginal zone lymphoma (NMZL)
3) Splenic marginal zone lymphoma (SMZL)

The only similarity between the subcategories is that they all originate in the marginal zone of the lymph node or the spleen. Consequently, diagnosing MZL can be difficult and requires the integration of specialised clinical and pathologic data. Having the diagnosis confirmed by a haematopathologist will guide in the choice of initial treatment.

The genetic relationship between the different subtypes of MZL remains unclear. However, one of the most promising targets for therapeutic agents is Bruton's tyrosine kinase (BTK), a protein essential to the development of B-cells. BTK inhibitors have demonstrated impressive clinical efficacy and safety in several indolent B-cell malignancies.

Since MZL is relatively uncommon, new treatments are not often studied because of the challenge in enrolling a sufficient number of patients in clinical trials. Consequently, treatment of advanced-stage MZL is guided by the practice for indolent follicular lymphoma. For patients who are asymptomatic a watch-and-wait approach with regular monitoring is often advised.

Based on information gathered from the Lymphoma Coalition (LC) database, there was a discrepancy between the number of therapies for MZL with regulatory approval and those funded/reimbursed. Mainstream therapies, e.g., CHOP-R and rituximab, were the most frequently funded while bendamustine ± rituximab was not as frequently funded. As a result, older therapies, e.g., fludarabine and CVP, which have higher comorbidities compared with newer treatment options are used. Ibrutinib, a BTK inhibitor, has recently been approved by the Food and Drug Administration (FDA) in the USA. It is the only MZL specific targeted therapy on the market.

Of the 122 clinical trials that included patients with MZL, only five focused solely on MZL. While the USA is involved in most of the trials, nine of the 44 LC member countries had no trials with MZL participation. Within the 103 phase II trials, 58 were in the relapsed setting with a focus on novel therapies. Only 12 trials were investigating a first-line therapy for MZL. None of the 19 phase III trials focused solely on MZL.

Key findings from the 2016 LC Global Patient Survey showed that only one in three respondents were told their subtype and 41% indicated they did not understand their subtype. Fatigue was reported as the highest physical effect affecting 67%. Fear of relapse was a major psychological burden for 61% of respondents with MZL. The major barrier to treatment was lack of personal support (33%).

EMZL, NMZL and SMZL are grouped under MZL although they have distinct clinical and molecular characteristics. A clearer understanding of the genomics of the MZL subgroups as well as improved data regarding biological markers can help improve patient diagnosis and outcomes.

To better analyse the efficacy of treatments, greater efforts are needed in increasing the number of trials for patients with MZL. Globally, patient access to care is often incomplete and sporadic. Using this information the lymphoma community and LC members can work together to find solutions to gain broader access for patients. The psychological burden of a long-term illness can be overwhelming for patients. Having healthcare providers work closer with patient groups to support the patient from the beginning for the long term can help improve the patient experience. We recommend that healthcare providers suggest that patients reach out to patient groups and support services within the clinic so patients and their families have someone to walk alongside them to answer questions and support their psychosocial concerns.

What is Marginal Zone Lymphoma?

MZL is an indolent 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. Lymphoma occurs when these cells grow and multiply uncontrollably. MZL is thought to originate from B-cells present in the marginal zone of lymphoid follicles. These can be found in the spleen, lymph nodes and lymphoid tissues.

The World Health Organization (WHO) has grouped MZL into three further sub categories based on specific diagnostic criteria, different behavior and therapeutic options;

1. Extranodal marginal zone lymphoma (EMZL) or mucosa-associated lymphoid tissue (MALT)
2. Nodal marginal zone lymphoma (NMZL)
3. Splenic marginal zone lymphoma (SMZL)

The only similarity between the sub categories of MZL is that they all originate in the marginal zone of the lymph node or the spleen, an organ which is part of the lymphatic system. The marginal zone is a B-cell-rich zone located between B-cell follicles and the T-cell area in the spleen.[13] It is believed that marginal zone B-cells may have originated from the germinal centre of lymph nodes (germinal centres are sites where B-cells proliferate and mutate during an immune response to an infection), but this claim is still debated in the research community.[20] Marginal zone lymphomas are frequently associated with chronic infections as described in each of the sections below.

Extranodal marginal zone lymphoma (EMZL) or mucosa-associated lymphoid tissue (MALT) lymphoma is the most common form of marginal zone lymphoma. It occurs outside the lymph nodes, in places that have a mucous lining such as the stomach, small intestine, salivary gland, thyroid, eyes, and lungs. MALT lymphoma is divided into two categories: gastric, which develops in the stomach, and non-gastric, which develops outside of the stomach. This form of lymphoma makes up about nine percent of all B-cell lymphomas.

In many cases of MALT lymphoma, there is a previous medical history of inflammation or autoimmune disorders. For example, Helicobacter pylori (H. pylori), a microbial pathogen linked to chronic gastritis, has been associated with a significant portion of patients with gastric MALT lymphoma. There is also evidence of a correlation between MALT lymphoma and bacterial infections such as Chlamydophila psittaci and Borrelia Burgdorferi. In addition to infections, chronic inflammation caused by autoimmune diseases, such as Sjögren syndrome or Hashimoto thyroiditis, can also carry a significant risk for the development of MALT lymphoma.

The following exams are recommended for a diagnosis: history and physical exam (including lymph node regions, eye and ear, nose and throat areas, liver and spleen evaluation; complete blood counts and basic biochemical studies), including evaluation of renal and liver function, lactate dehydrogenase (LDH) and β2-microglobulin, serum protein immunofixation, human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) serology; CT scan of the chest, abdomen, and pelvis; bone marrow aspirate and biopsy recommended.

For localised disease (disease confined to one area), there is increasing evidence indicating that antibiotics can be effectively employed as the sole initial treatment. For example, in the stomach, eradication of *H pylori* leads to complete regression of the lymphoma in nearly 80 percent of the cases.[6] However it is still unknown whether eradication of microbes will completely eradicate the lymphoma. Local treatment (either radiotherapy or surgery) will also achieve excellent disease control.[7, 8] Poor prognostic factors for EMZL include bulky tumor, high levels of lactate dehydrogenase, β2-microglobulin, and serum albumin.[9, 10]

Nodal marginal zone lymphoma (NMZL) usually affects adults over 60 and is slightly more common in women than in men. It occurs within the lymph nodes and accounts for about two percent of all B-cell lymphomas. NMZL generally only involves the lymph nodes, with the most common symptom usually being a painless swelling in the neck, armpit or groin caused by enlarged lymph nodes. More than one group of nodes may be affected, and NMZL can sometimes be found in the bone marrow. It is not uncommon for people with NMZL to have widespread disease at the time of diagnosis, where the cancer has spread to several areas of the body. There are no established positive markers for NZML and diagnosis is generally made through exclusion.[4] Similar to SMZL and EMZL there are reported cases NMZL patients with HIV, hepatitis C or H. pylori infections.
Not enough data and research is published regarding morphologic and clinical characteristics differentiating NMZL from other lymphomas. In all cases, but particularly for NMZL, a careful clinical history is important for a clear diagnosis. There has been no large scale clinical research on the efficacy of treatment options for NMZL and therefore it has been difficult to reach a consensus on any type of standard treatment recommendation for NMZL.

Splenic marginal zone lymphoma (SMZL) usually affects elderly or middle aged patients and occurs most often in the marginal zone of the spleen. It has been associated with Hepatitis C. This form of lymphoma makes up about one percent of all B-cell lymphomas. SMZL expresses B-cell antigens such as CD19, CD20, and CD22. Diagnosis is made usually by exemption. As an example: the lack of CD5 distinguishes SMZL from chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), while the lack of CD103 and CD25 distinguishes SMZL from hairy cell leukemia.[2]

Patients may be recommended to follow a watch and wait approach based on symptoms. The absence of treatment does not influence the course of the cancer and these patients often have stable disease for at least 10 years. When symptoms dictate, such as an occurrence of an enlarged spleen or cytopenia, splenectomy might be the recommended treatment. In some cases a splenectomy would not be recommended, for example in patients with advanced age and multiple comorbidities. In such cases chemotherapy may be suggested, based on alkylating agents (chlorambucil or cyclophosphamide) or purine analogues (fludarabine). In cases of hepatitis C-associated SMZL, antiviral treatment with interferon is shown to be an effective initial treatment as long as immediate tumour reduction is not required. [14]

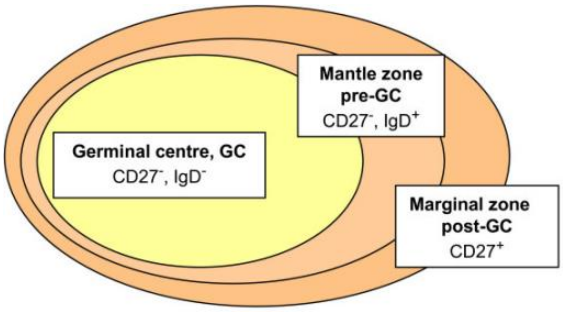
Detecting MZL and distinguishing between the different types can be difficult and requires the integration of specialised clinical and pathologic data.[2]

As an example, MZL has clinical and pathological features that may overlap with Waldenström's Macroglobulinemia (WM). However, the discovery of the MYD88 mutation in WM can act as a differentiating factor for WM from other B-cell lymphomas.

Given the heterogeneity of MZL it is vital to get an accurate diagnosis for optimising patient care. Therefore, having the diagnosis confirmed by an expert haematopathologist will help guide the choice of initial treatment and will also avoid over treatment of benign conditions.[1]

Understanding Biology of MZL

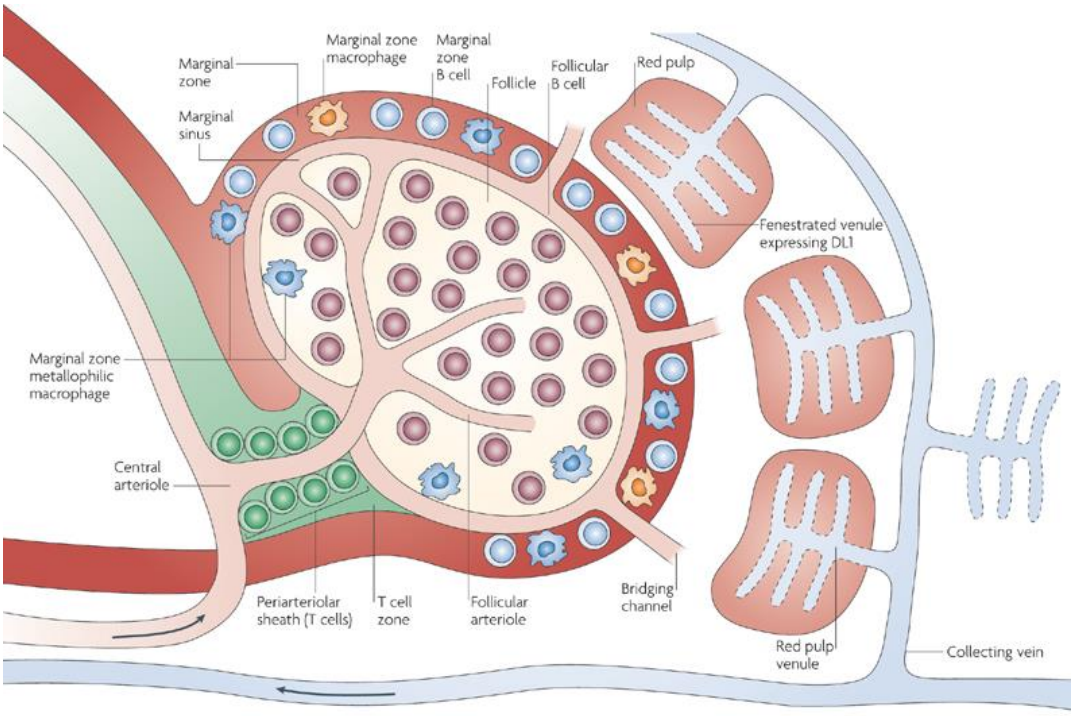
Figure 1. The Three Major B-cell Compartments in Peripheral Lymphoid Organs. Presence of the differentiation markers CD27 and IgD in each zone of a B-cell follicle is indicated.[16]



Source: Stranneheim, Henrik, et al. "A comparison between protein profiles of B cell subpopulations and mantle cell lymphoma cells." Proteome science 7.1 (2009)

The marginal zone surrounds the mantle zone of the germinal center of a cell and is usually not recognised morphologically in lymph nodes. However, the spleen and some mesenteric lymph nodes do show a marginal zone in normal situations, and, occasionally, other lymph nodes also have marginal zone development.[5] The germinal centre are sites located within lymph nodes where B-cells proliferate during an immune response.

Figure 2. Anatomy of the Spleen Showing the Marginal Zone [17]



Source: Pillai, Shiv, and Annaiah Cariappa. "The follicular versus marginal zone B lymphocyte cell fate decision." Nature Reviews Immunology 9.11 (2009): 767-777.

The genetic relationship between the different subtypes of MZL is still unclear. Translocation t (11; 18) (q21; q21) API2-MALT1 is found in around 30% of MALT lymphomas. Two other known genetic alterations include translocation t (14; 18) (q32; q21)/IGH-MALT1 found in roughly 10% of MALT lymphomas.[16] Most gastric lymphomas without such translocation can be cured by antibiotics. NMZL and SMZL share recurrent mutations affecting the Notch pathway and the transcription factor KLF2, but differ for the inactivation of 2 tumor-suppressor genes, detected exclusively (PTPRD) or much more commonly (KMT2D/MLL2) in the nodal type. [19]

Bruton's tyrosine kinase (BTK) is a protein that is essential in the development of B-cells. It is one of the most promising targets for therapeutic agents. BTK inhibitors, such an ibrutinib, have demonstrated impressive clinical efficacy and safety in several indolent B-cell malignancies both as a single agent and in combination therapy. In January 2017, ibrutinib was approved by the FDA for treatment of patients with MZL that have had at least one line of prior therapy. This represents a major step forward for patients with MZL, who, until now, have relied on therapy outlines from similar indolent lymphomas.

Despite this major breakthrough, there are no large scale studies that have been published specifically for MZL with data regarding clinical and biological prognostic markers.

This lack of data means it is often not possible to predict disease progression or which treatments will have the best outcomes, leaving patients unsure of their future.

Current Treatments

Since MZL is relatively uncommon, new treatments for this condition are not often studied rigorously because of the challenge of enrolling a sufficient number of patients in well-controlled clinical trials. For this reason, treatment of advanced stage MZL is guided by practice for indolent follicular lymphoma.

Presently, MZL is incurable, although in most cases the cancer is indolent and can be effectively managed with appropriate therapies.

For the purpose of this review and in order to determine what current treatments should be accessible to MZL patients, LC reviewed the information from both the European Society of Medical Oncology (ESMO) clinical practice guidelines and the National Comprehensive Cancer Network (NCCN) listing.

It is important to note that there are no stringent guidelines or a consensus on parameters to treat MZL. Therefore there is no algorithm for physicians to rely on.

The Ann Arbor staging system for prognostic markers is also unreliable in MZL due its pathogenesis. The listings in NCCN and ESMO mirror the treatment for indolent FL.

Table 1. NCCN Listing and ESMO Guidelines for MZL

NCCN (n=13)		ESMO (n=7)	
First Line	**Relapsed**	**First Line**	**Relapsed**
Bendamustine± rituximab	Bendamustine ±rituximab	Bendamustine ± rituximab	Bendamustine ±rituximab
	CHOP-R	CHOP-R	CHOP-R
CVP-R	CVP-R	CVP-R	CVP-R
Rituximab	Rituximab	Rituximab	Rituximab
Lenalidomide ±rituximab	Lenalidomide ±rituximab	-	-
Chlorambucil ±rituximab	Chlorambucil	Chlorambucil ±rituximab	Chlorambucil ± rituximab
Radioimmunotherapy	Radioimmunotherapy	-	-
Rituximab maintenance	Rituximab maintenance	Rituximab maintenance	Rituximab maintenance
	Idelalisib	-	-
	Fludarabine ± rituximab	-	-
	FNDR	-	-
	Stem cell transplant Autologous Allogenic		Stem cell transplant Autologous Allogenic

Patients need to be treated on an individual basis based on symptoms, site of lymphoma and clinical presentation. A watch and wait approach is often advised with regular monitoring for patients who are asymptomatic. There are numerous reasons why a watch and wait rationale is adopted, for instance - indolent lymphomas can remain stable for extended periods of time and are sometimes shown to regress without therapy, treatments have negative side effects, doctors can use this time to judge the progression of the lymphoma which can guide choice of treatment. Once symptoms are apparent, or if tumour bulk increases, then at that point relevant treatment options can be discussed.

The NCCN listing include newer therapies such as idelalisib and lenalidomide. Bendamustine with rituximab have shown promising outcomes in clinical trials and is recommended in both the first line and relapsed setting in ESMO and NCCN listings. Drugs under investigation in clinical trials are bortezomib, ibrutinib, vorinostat, alemtuzumab and mTOR inhibitors such as everolimus.

Therapy Access

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

As shown in Table 1, there are 13 therapies approved in the NCCN listing and 7 in the ESMO guidelines for MZL.

Table 2 shows the number of LC member countries that have regulatory approval for these therapies as well as those that are funded and reimbursed.

If we take a closer look at the therapies that are approved and/or funded, we note that there are few novel therapies listed.

On a global level there is quite a discrepancy in the number of therapies for MZL with regulatory approval compared to those same therapies being funded/reimbursed.

When looking at the mainstream therapies, those like CHOP-R and rituximab that have typically been used to treat other lymphoma subtypes, are the ones most heavily funded. Another common therapy, especially for non-gastric EMZL is bendamustine with rituximab (BR). As Table 2 shows BR is not as well funded/reimbursed especially in Eastern Europe, Asia Pacific and Latin America.

The BTK inhibitor, ibrutinib, which is the only targeted therapy for MZL on the market, was approved by the FDA in January 2017 and it is not yet listed by NCCN.

Lack of funding/reimbursement leaves patients in a vulnerable position. Fewer options mean treatment will often rely on older therapies with higher comorbidities.

These include fludarabine which can cause transformation or second malignancies, and oral alkylators which often lead to higher rates of neuropathy. CVP is another widely used therapy but the side effects of chlorambucil and vincristine can be a problem for many patients.

Countries that make up Western Europe have an even distribution of approved therapies. However, when it comes to funding, the Netherlands and Italy have fewer therapies reimbursed while Portugal has none. Outside the EU, the numbers of approved and funded therapies is much lower as we can see in Table 2 for countries such as Serbia, Russian Federation and Macedonia.

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. The number of therapies with regulatory approval in the USA is higher than in any other country globally.

With the approval of ibrutinib as a targeted drug for MZL the hope is that the funding landscape will change to eliminate the discrepancies of care. CHOP-R, B-R and CVP are the most widely used therapies. In most regions at least one of these is approved and reimbursed. The exceptions being Singapore, Macedonia, Bulgaria, Czech Republic, Portugal and Turkey which doesn't reimburse any of these therapies.

Table 2. MZL Therapies Approved and Funded/Reimbursed by Country

Region	Country	No. of approved therapies	No. of reimbursed therapies	Therapies	Region	Country	No. of approved therapies	No. of reimbursed therapies	Therapies
Africa/Middle East	Algeria	5	1	Ch, Ch-R, CHOP-R, CVP-R, SCT	Latin America	Brazil	6	1	B-R, Ch-R, CHOP-R, CVP-R, R, SCT
	Israel	6	6	Ch-R, CHOP-R, CVP-R, R, RM, SCT		Colombia	4	3	Ch-R, CHOP-R, CVP-R, SCT
Asia Pacific	Australia	5	4	BR, Ch-R, CVP-R, R, RM		Mexico	6	6	Ch, CHOP-R, CVP-R, F-R, FNDR, RM
	Japan	8	7	Ch, Ch-R, CHOP-R, CVP-R, F-R, R, RM, SCT		Venezuela	-	-	
	New Zealand	10	6	B-R, Ch, Ch-R, CHOP-R, CVP-R, F-R, RT, R, RM, SCT	North America	Canada	11	11	B-R, Ch, Ch-R, CHOP-R, CVP-R, F-R, FNDR, RT, R,
	Singapore	7	0	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, SCT		United States	13	13	B-R, Ch, Ch-R, CHOP-R, CVP-R, F-R, FNDR,
Eastern Europe	Bulgaria	8	0	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT	Western Europe	Belgium	8	6	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Croatia	9	4	B-R ,Ch, Ch-R, CHOP-R, CVP-R, RT, R, RM, SCT		Denmark	8	6	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Czech Republic	8	1	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT		France	8	6	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Hungary	8	2	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT		Germany	8	8	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Latvia	8	0	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT		Ireland	8	6	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Lithuania	8	3	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT		Italy	8	5	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Macedonia	1	0	SCT		Netherlands	8	5	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Poland	8	7	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT		Portugal	8	0	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Russian Federation	5	4	B-R, CHOP-R, CVP-R, FNDR, SCT		Spain	8	6	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Serbia	4	3	Ch-R, CHOP-R, CVP-R, RM		Sweden	8	8	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Slovakia	8	4	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT		Switzerland	8	8	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Slovenia	8	5	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT		United Kingdom	8	8	B-R, Ch, Ch-R, CHOP-R, CVP-R, R, RM, SCT
	Turkey	6	0	B-R, Ch-R, CHOP-R, CVP-R, R, SCT	Therapy reimbursed/funded	Therapy not reimbursed/funded			

Source: LC Global Database as of January 2017

Clinical Trials

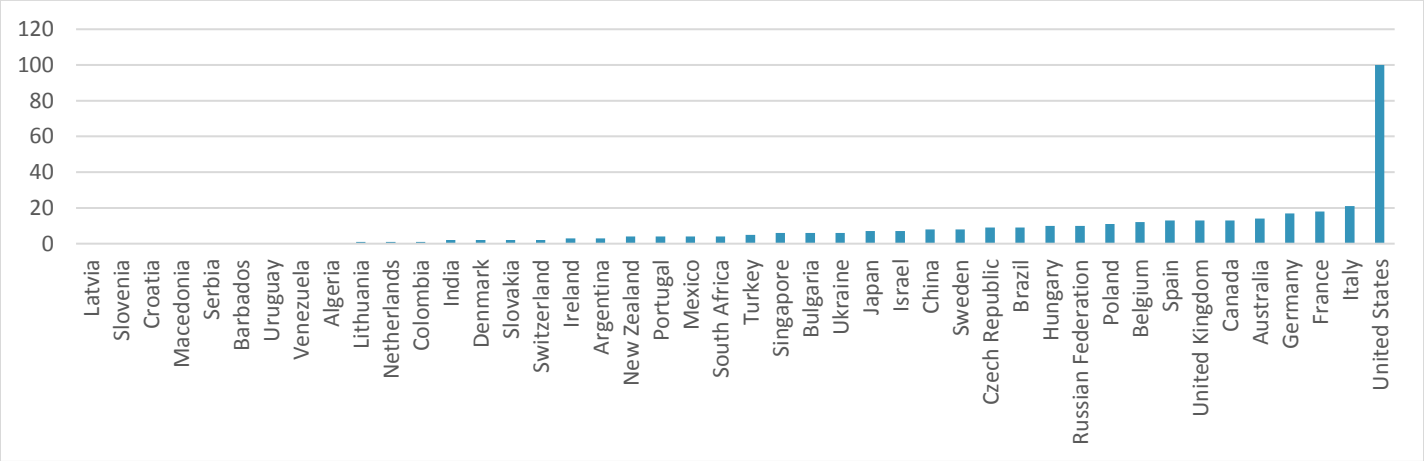
MZL is a rare type of cancer, accounting for approximately 10% of all B-cell lymphomas. There is still a need to understand the genomics of MZL.

A better insight of the evolution and progression of MZL and its distinguishing markers can improve the diagnosis and prognosis of MZL. Additionally, clinical trials help improve and advance medical care and this is critical for patients with MZL.

There are 122 trials underway that include MZL patients. Most of the 122 trials study MZL along with other heterogeneous lymphomas, while only 5 are solely for patients with MZL.

The USA is involved in most of the trials (100) as seen from Figure 3. Nine of the 44 LC member countries have no current trials with any MZL participation. There is no availability of trials in most countries of Eastern Europe, Africa, Asia Pacific and South America.

Figure 3. MZL Clinical Trial by Country



Source: LC Global Database as of January 2017

Looking at the Phase II trials, the majority are in the relapse setting with focus on novel therapies (58) followed by combination drugs (23). Of all the Phase II trials only 12 are investigating a first line therapy for MZL. Nine of those trials are using a novel therapy. The trials for MZL patients only are in Phase II. Two of these trials are using bendamustine and rituximab – one trial in the relapsed setting while another as a first line therapy. Another first line therapy being investigated is doxycycline, which is an antibiotic, particularly in treating MZL around the eye area. One of the novel therapies being studied is ibrutinib in the relapsed setting, which has been approved by the FDA for the treatment of MZL.

Currently there is only one therapy approved specifically for MZL, which points to a great unmet need.

Table 3. Phase II Trials for MZL

Phase II	Combination	Novel	Total
Both	2	8	10
First Line	3	9	12
Relapse	23	58	81
Total	**28**	**75**	**103**

Source: LC Global Database – as of January 2017

There are a total of 19 Phase III trials for MZL patients. These trials are multi subtype trials – i.e. none of these trials are exclusively for MZL patients. There are four trials in the first line setting of which one is a rituximab biosimilar.

A majority are in the relapsed setting using novel agents. [14]

Table 4. Phase III Trials for MZL

Phase III	Biosimilar	Combination	Novel	Total
First Line	1	1	2	4
Relapse		1	14	15
Total	**1**	**2**	**16**	**19**

Source: LC Global Database as of January 2017

It is encouraging to see the focus on novel therapies in the MZL trials, however there are no trials that are looking specifically at the subgroups of MZL.

There are three subgroups to MZL that share some common features but are still different in their biology and therefore they are likely to respond differently to treatment.

Randomised trials for MZL are scarce and the situation is unlikely to change in the near future with no trials (specific to MZL) openly recruiting as of January 2017.

Collaboration in defining stringent diagnostic criteria, will help in designing prospective clinical trials to define the optimal therapeutic guideline.

The Patient Experience

The LC 2016 Global Patient Survey (GPS) is the document LC references in this report to provide a sense of the patient experience.

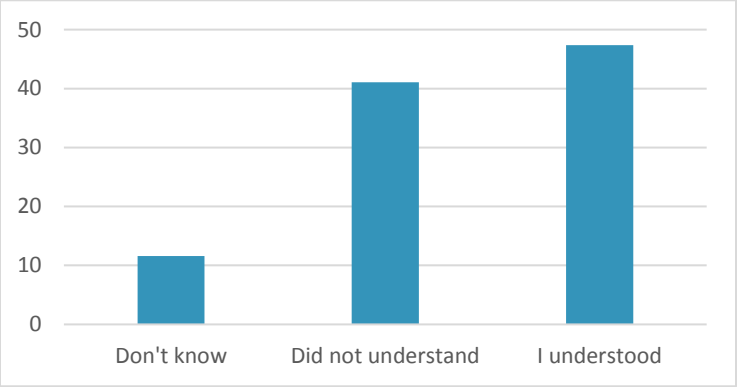
There were over 4,000 total respondents to the 2016 GPS, of which 101 were identified as MZL respondents.

When first diagnosed with MZL only one in three respondents were told which subtype of lymphoma they had and 41% reported that they did not understand their subtype. Without understanding their specific subtype, patients are unable to research the appropriate information and may be left unaware of the appropriate treatment and management options for their lymphoma.

There was a better level of understanding when it came to understanding treatment options. Seventy-three percent of respondents said they understood what their treatment options were. However, more than 20% of respondents did not understand the side effects of their treatment nor did they understand the management strategies for handling the side effects.

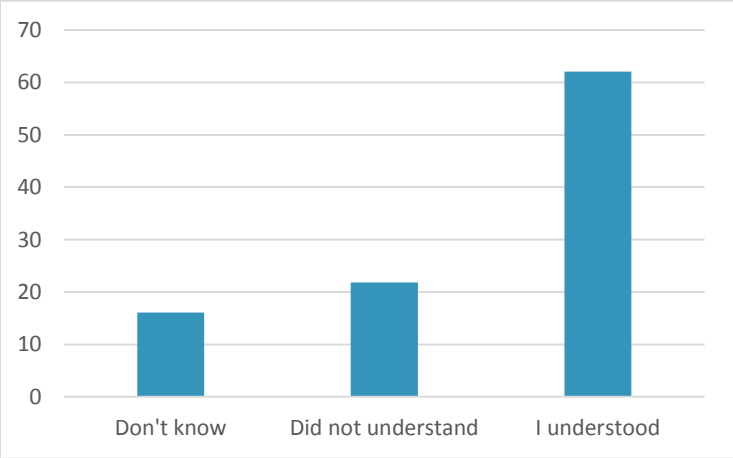
Treatments may often cause side effects and managing these side effects is an important part of patient care. In order to provide the best supportive care, patients need to know what to expect so they can communicate any concerns with their healthcare providers.

Figure 4. Understood Subtype Characteristics (%)



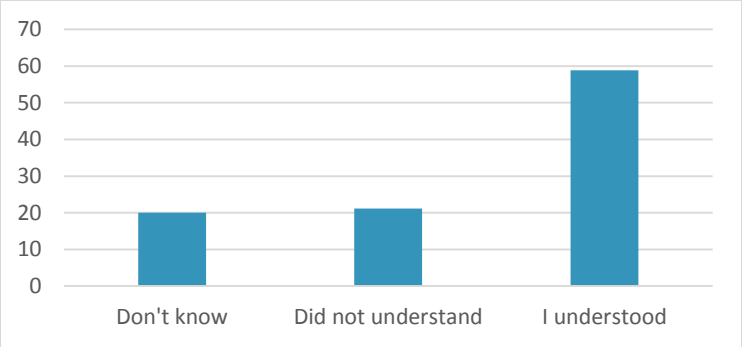
Source: LC 2016 Global Patient Survey

Figure 5. Understood Side Effects of Treatment (%)



Source: LC 2016 Global Patient Survey

Figure 6. Understood Side Effect Management (%)



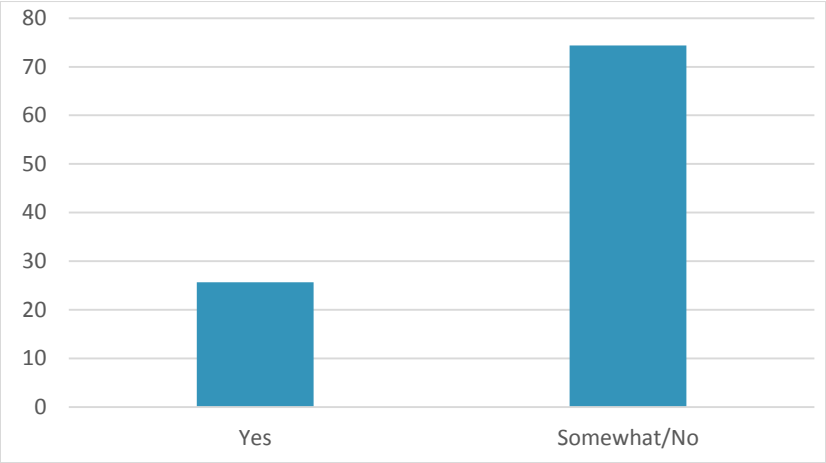
Source: LC 2016 Global Patient Survey

In order to determine if patients were raising their questions to their healthcare provider we asked if they had communicated their emotional and physical concerns to the doctor. Fifty-one percent said that they had while 47% said they had not. When asked if the doctor had been useful in addressing their concerns 74% said that the doctor had not successfully managed their concerns. On the other hand, 77% of respondents felt that the patient organisation had been useful to them (Figures 7, 8).

A communication strategy that allows patients to express their concerns to healthcare providers is a key element in treating any type of illness.

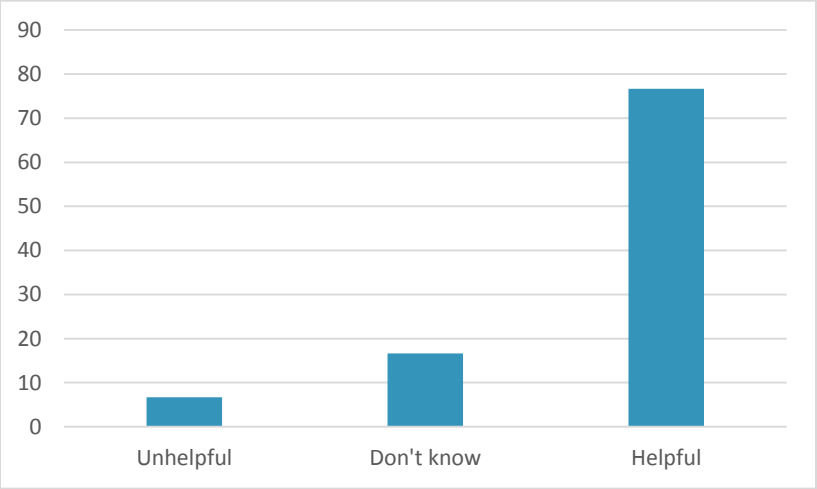
If healthcare professionals are pressed for time then we might suggest that a referral should be made to the social work department within the clinic or an appropriate patient organisation.

Figure 7. Was the Doctor Useful in Addressing Concerns? (%)



Source: LC 2016 Global Patient Survey

Figure 8. Usefulness of Patient Organisation (%)



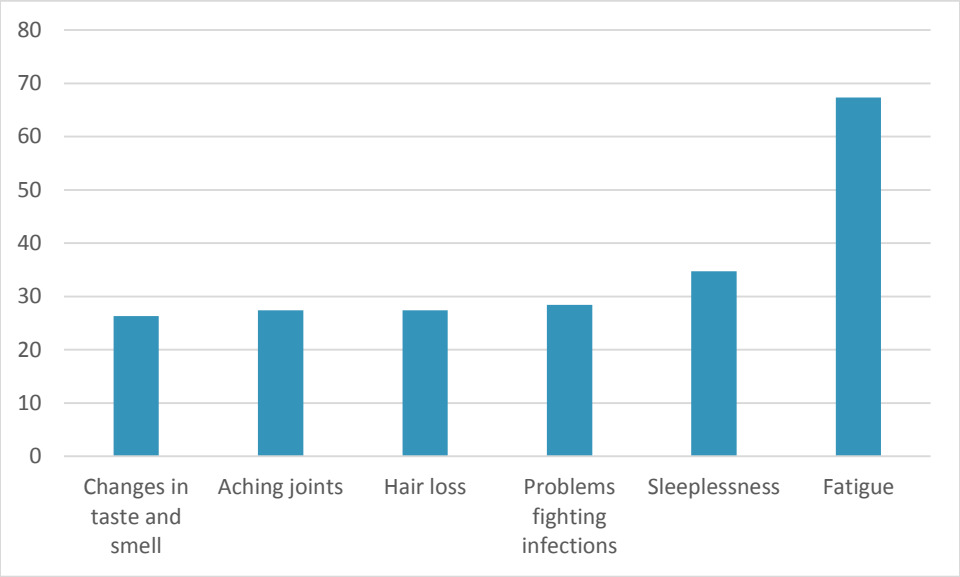
Source: LC 2016 Global Patient Survey

One of the most important aspects of patient care is to educate the patient on their illness and related treatment options and potential side effects.

An awareness of treatments and their side effects will allow patients to better manage their condition, remain compliant and reduce the fear.

As seen in Figure 9, fatigue is the biggest impact faced by MZL respondents. This is actually the case across all subtypes of lymphoma. Additionally, MZL respondents have indicated that sleeplessness, problems fighting infections, hair loss, aching joints and changes in taste and smell are the most prevalent problems.

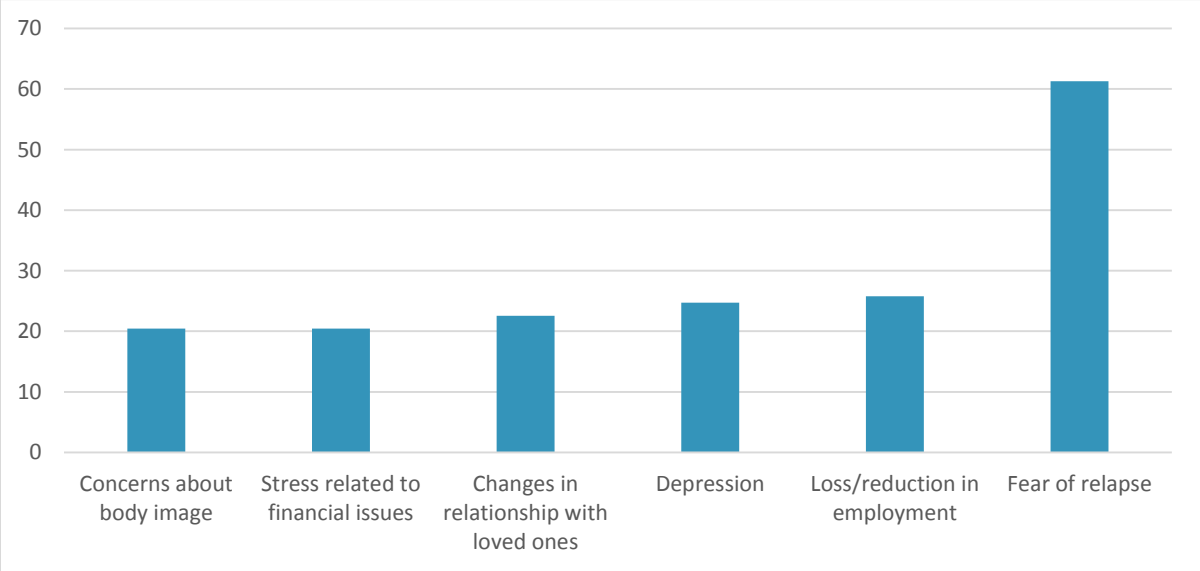
Figure 9. Physical Conditions Affecting MZL Patients (%)



Source: LC 2016 Global Patient Survey

The psychological burden of dealing with long term MZL often directly affects the patients' sense of well-being as indicated in Figure 10. The top most concern is fear of relapse at 61%. Another major concern is loss/reduction in employment with depression almost tied with it. The support structure for patients needs to be robust so it can be relied on in cases where the burden of such problems start affecting their daily living.

Figure 10. Psychosocial Concerns (%)

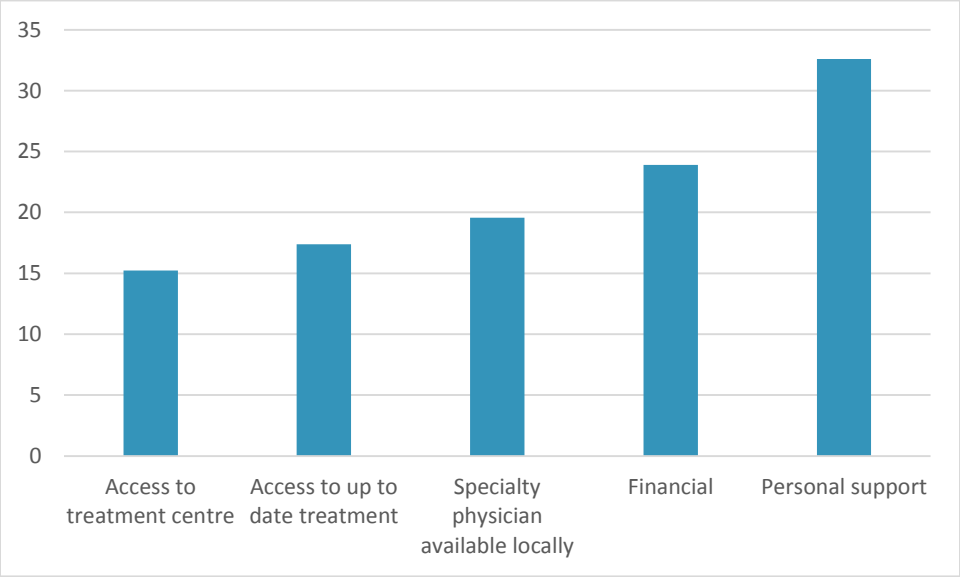


Source: LC 2016 Global Patient Survey

Barriers to Treatment

Fifty-two percent of respondents were not affected by any barriers to gaining treatment for MZL. Of the 48 percent that did encounter barriers the top concerns were personal support, financial and specialty physician not available locally.

Figure 11. Top Barriers to Treatment (%)



Source: LC 2016 Global Patient Survey

As is the case with other rare subtypes of lymphomas, the focus needs to be on establishing a best practice for the treatment of MZL. Only then will we be able to measure how successful the treatment is for patients both short and long term.

Currently, treatment recommendations should not only focus on the medical condition but also the psychological, emotional and social condition. A multi-faceted approach to treatment that provides information and care that corresponds to the patient needs will surely provide more sustainable outcomes. There are services outside of the doctor's office that can provide this support and it should be utilised and recommended to patients.

Conclusion

EMZL, NMZL and SMZL are all grouped together under the banner of MZL. This is despite the fact that their clinical and molecular characteristics are distinct from each other. A clearer understanding of the genomics of the subgroups of MZL as well as improved data regarding biological markers can help improve patient diagnosis and outcomes.

MZL has a distinct lack of large databases, clinical data and standard of care. There needs to be a more concentrated effort to increase clinical trials for MZL patients in order to analyse the efficacy of treatments. By working together and collaborating, national and international research groups have an opportunity to create a more tailored and relevant treatment protocol.

Globally, patient access to care is often incomplete and sporadic. There are 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. Having said that, the first step should be supporting research in developing a best practice for treatment of MZL.

As is the case with any long-term illness the psychological burden can be overwhelming for patients to deal with. Factors affecting patients' well-being, which include fear of relapse, loss/reduction in employment and depression, can increase the feeling of isolation and anxiety. A key element in treating patients and improving the patient experience is improving knowledge and awareness. Long term psychosocial burden such as fear of relapse can be alleviated if healthcare providers work together with patient groups to provide ongoing patient support.

Acronyms

BCL = B-cell lymphoma
BD = bortezomib, dexamethasone
BDR = bortezomib, dexamethasone, rituximab
B-R = bendamustine, rituximab
BTK = Bruton's tyrosine kinase
Ch = Chlorambucil
CHOP-R = cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab
CLL = chronic lymphocytic leukaemia
CPR = cyclophosphamide, prednisone with/without rituximab
CVP-R = Cyclophosphamide, vincristine, prednisone, rituximab
DLBCL = diffuse large B-cell lymphoma
ESMO = European Society of Medical Oncology
EU = European Union
FCR = fludarabine, cyclophosphamide, rituximab
FD = fludarabine, dexamethasone
FL = follicular lymphoma
FNDR = Fludarabine, mitoxantrone, dexamethasone, rituximab
F-R = 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
RM = rituximab maintenance
SCT = stem cell transplant
TOR = target of rapamycin
WHO = World Health Organization

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