Mantle Cell Lymphoma

Subtype Report

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LYMPHOMA COALITION
Worldwide Network of Lymphoma Patient Groups

Mantle Cell Lymphoma

Introduction

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). Mantle cell lymphoma (MCL) is a subtype of lymphoma. There have been numerous advances in the understanding of the biology of MCL over the years and consequently a rise in clinical trials with targeted therapies.

The focus for this report is to review MCL 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

MCL is a rare cancer of the lymphatic system which originates in specialised white blood cells called B-cell lymphocytes. B-cells are responsible for creating antibodies or immunoglobulins which fight infections. When the abnormal B-cells are part of the mantle zone – which is the outer zone of a lymph node follicle, it is deemed as MCL.

MCL is linked to a translocation in chromosomes 11 and 14. A small part of each chromosome breaks off and switches places expressed as: t (11; 14) (q13; q32), which leads to an overexpression in the production of a protein called cyclin D1, which is detected in over 90% of patients. This protein causes abnormal B-cells or the MCL cells to grow rapidly without check[1]. There are two main types of variants to MCL typical or blastoid which proliferate in either a nodular or diffuse pattern. The blastoid variant has intermediate to large-sized cells and is more aggressive in nature. 'Typical' cases show smaller to medium sized cells with irregular nuclei.[1]

The evolution of MCL cells within the body is relatively aggressive with a history of low response rates to conventional treatment regimens, frequent relapses and a median overall survival of 3–5 years.[2] This behavior has led to the recommendation for early treatment, usually with intensive regimens.[2] However, recent clinical and pathological observations have recognised subsets of patients whose lymphoma has an indolent nature and may not need an aggressive treatment regimen and may benefit from a 'watch and wait' approach.[3-6]

MCL is diagnosed in 3%-6% of patients with lymphoma[1, 7]. The median age at diagnosis is 68 with a male dominance of 3:1.[8] Classically, many newly diagnosed patients are already in the advanced stages of MCL with digestive tract and bone marrow involvement.

Some of the symptoms that patients with MCL may have include:

- Loss of appetite
- Weight Loss
- Fever
- Upset stomach
- Stomach pain
- Splenomegaly
- Adenopathy
- Fatigue
- Night sweats
- Enlarged lymph nodes

In order to get a diagnosis, a biopsy, preferably a lymph node biopsy, is needed. Due to its heterogeneous nature, it can often be hard to detect MCL and a review by an expert haematopathologist is advised [9]. Other tests that may be necessary include an immunohistochemistry for the detection of cyclin DI overexpression or SOX-11, positron emission tomography (PET) or computed tomography (CT) scan which may determine which parts of the body are affected, gastrointestinal endoscopy, and or colonoscopy among others.[9]

MCL is often distinguished from other lymphomas such as chronic lymphocytic leukemia/small cell lymphoma (CLL), follicular lymphoma (FL), and marginal zone lymphoma (MZL) based on immunohistochemical staining (IHC) for CD5, CD23, and CD10.[10] CLL generally lacks CD23 while FL lacks both CD5 and CD23, while MZL is typically negative for all 3 antigens. In rare instances CLL maybe show CD23 and MZL with CD5+. Cyclin D1 overexpression is unique to MCL – but patients have been found to lack CCND1 expression[10]. The presence of SOX-11 is specifically expressed in the nucleus of MCL compared with other lymphomas and benign lymphoid tissue and can also be a useful tool for diagnosis in those instances where overexpression of cyclin D1 doesn't exist.[10]

The most sensitive detection is through fluorescence in situ hybridization (FISH) targeting the specific gene translocation but this method is not used widely.

Initial staging of MCL uses the Ann Arbour classification and for further prognostic purposes a MCL International Prognostic Index (MIPI) is used.[11]

Biology

MCL originates in mature B-cells and its most distinct characteristic is the overexpression of cyclin D1 resulting in cell proliferation. Several pathways contribute to the development of MCL, including the PI3K/AKT/mTOR pathway, which promotes tumour proliferation and survival as well as the WNT, Hedgehog, and NF-κB pathways which may be an important marker for future treatments.[2]

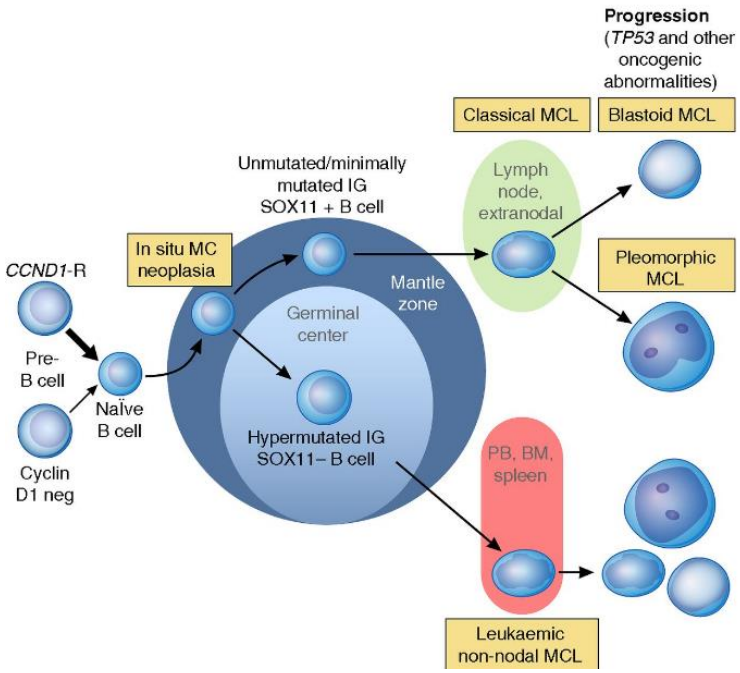
It is well-recognized that MCL has a wide spectrum of growth patterns. Most cases have a vaguely nodular and/or diffuse growth pattern, very rare cases have a follicular growth pattern, while others have a mantle zone growth pattern in which the lymphoma grows as an expanded ring around reactive lymph nodes.

Cyclin D1 positive B-cells can be found in the mantle zone of follicles, referred to as In situ mantle cell lymphoma, which are usually an incidental finding and have an indolent behavior. These cases may often not require immediate

treatment and should be differentiated from the mantle cell lymphoma with a mantle zone pattern and overt mantle cell lymphoma.

MCL is believed to develop along a couple of different pathways as shown in Figure 1.

Figure 1. Proposed Model of Molecular Pathogenesis in the Development and Progression of Major Subtypes of MCL[1, 12]



Professional illustration by Patrick Lane, ScEYEnce Studios

Immature B-cells mature into abnormal naïve B-cells which may initially settle in the inner portion of the mantle zones – this may transform into in situ MCL. At this stage the B cells already possess certain genetic abnormalities such as inactivating ATM mutations. As seen in Figure 1, classic MCL may progress, without going through the germinal centre, while acquiring additional abnormalities related to cell cycle dysregulation, the DNA damage response pathway, cell survival, and other pathways. Ultimately, this leads to either blastoid or pleomorphic MCL, these are generally SOX-11 positive.[1] A smaller proportion of neoplastic mantle cells may undergo somatic hyper mutation, presumably in germinal centers, leading to SOX-11 negative MCL that is more stable for long periods of time and involves peripheral blood, bone marrow and sometimes the spleen.[1]

MCL may undergo additional abnormalities, particularly TP53 abnormalities, leading to disease progression. Other mutations that may be present in <15% of MCL cases, including some such as *NOTCH1* and *NOTCH2* can be of prognostic and therapeutic importance.[13,14] It has also been learned that about half of MCL that lack cyclin D1 expression have *CCND2* translocations, which can also be used as a target for future novel therapies.[15]

Current Treatment & Recommendations

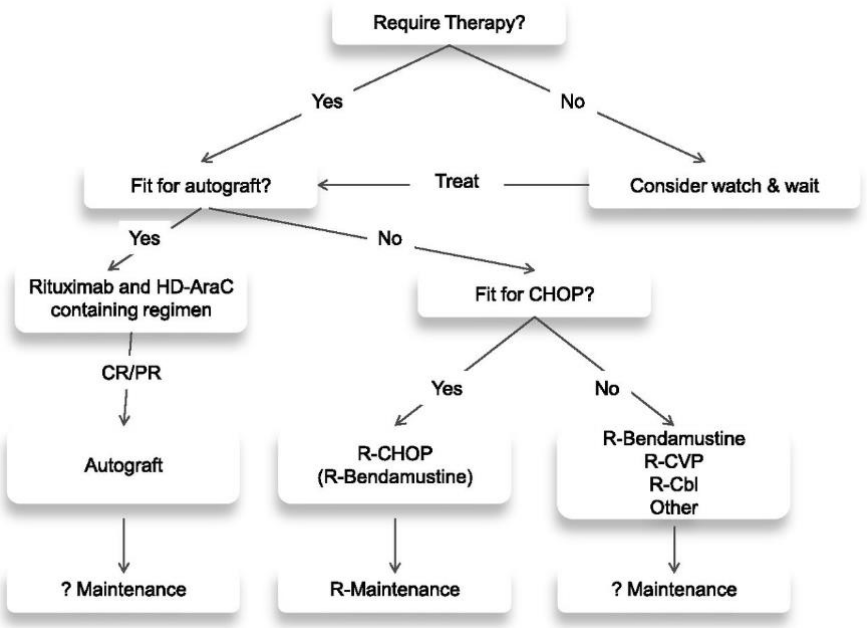
MCL is one of the most difficult B-cell lymphomas to treat. Although conventional chemotherapy induces high-remission rates in previously untreated patients, relapse within a few years is common, contributing to a rather short median survival of 5-7 years.[16,17] Intensification of first-line treatment has improved progression-free survival, but no curative regimen has been defined so far.[18,19]

LC has examined two treatment guidelines to determine the treatment of MCL in both the first line and relapsed/refractory setting. The guidelines were taken from ESMO and NCCN and compared for patient access to therapies.

It is essential to stratify patients according to their stage and prognosis. This can be done either using the Ann Arbor classification as well as the MIPI index. Treatment will vary according to the stage, performance status, lactic dehydrogenase, leukocyte count as well as the age of the patient.[9]

Comparison studies show that no active regimens have a better survival rate over the other. The therapy is often individualised according to the overall goal. For example, if the goal is for a stem cell transplant then an intensive therapy such as CHOP-R may be chosen.[19]

Figure 2. Current First-line Therapy Pathway for MCL[20]



Proteasome inhibitors (bortezomib), mTOR inhibitors (temsirolimus), and immunomodulatory drugs (lenalidomide) are the newer regimens that have been licensed for use in MCL. Targeted agents and immunotherapy have shown activity in relapsed patients and these compounds are now in clinical trials.

It is common for patients with MCL to acquire resistance to ibrutinib. The outcome and management of patients who experience Ibrutinib failure is still unclear.[21]

While MCL is incurable for most patients there is still no established standard of care. There is still debate on whether to use high vs low intensity induction therapy, or stem cell transplant and also the effectiveness of maintenance therapy.

Therapy Access

The LC Global Database shows therapies and regimens with regulatory approval worldwide. These are compiled based on information gathered from member country regulatory approval and reimbursement agencies, as well as information provided by member contacts. For the purposes of this review, LC has used information from ESMO and NCCN to examine which of the therapies noted in respective listings have regulatory as well as funding/reimbursement approval.

There are a number of therapies approved for patients with MCL. Table 1 lists all the approved drugs from both NCCN and ESMO. Table 2 shows the therapies with regulatory approval and those with funding/reimbursement approval by country while Table 3 shows the number of therapies that have access by country and region.

Table 1. Therapies listed by ESMO and NCCN [9, 24]

NCCN		ESMO	
First Line	**Relapsed**	**First Line**	**Relapsed**
HyperCVAD +/- Rituximab	Bendamustine ± rituximab	HyperCVAD +/- Rituximab	Bendamustine + rituximab
CALGB regimen	Bortezomib ± rituximab	CHOP-R	DHAP-R
NORDIC	Cladribine - rituximab	Rituximab maintenance	FC ± rituximab
CHOP-R	FC ± rituximab	Stem Cell Transplant	Ibrutinib
DHAP-R	FCMR	Bendamustine + rituximab	Rituximab maintenance
ICE-R	FMR	Rituximab maintenance	Stem Cell Transplant
Bendamustine + rituximab	Ibrutinib		
CAP-VcR	Lenalidomide ± rituximab		
Cladribine + Rituximab	PCR		
Rituximab maintenance	PEPC ± rituximab		
Stem Cell Transplant	Stem Cell Transplant		

Table 2. Therapy Access for MCL

	MCL Therapies with Regulatory Approval	**MCL Therapies with Funding/Reimbursement Approval**
Africa and the Middle East		
Algeria*	HyperCVAD	Information not available
South Africa	CHOP±R, CNOP, CNOP±R, cyclophosphamide, DHAP±R, FCM, fludarabine, GDP, hyperCVAD±R, RT, rituximab, SCT	Private health insurance available for: CHOP±R, CNOP, CNOP±R, cyclophosphamide, DHAP±R, FCM, fludarabine, GDP, hyperCVAD±R, RT, rituximab, SCT

		Government funds/reimburses: hyperCVAD±R
Israel	CAP VcR, CHOP, DHAP, FCR, hyperCVAD, ibrutinib, lenalidomide, rituximab, rituximab maintenance, SCT, temsirolimus	CAP VcR, CHOP, DHAP, FCR, hyperCVAD, ibrutinib, lenalidomide, rituximab, SCT, rituximab maintenance, temsirolimus
Asia/Pacific		
Australia	B±R, CHOP±R, CHOEP, COPP, cyclophosphamide, DHAP±R, ESHAP±R, GDP, GemOX-R, hyperCVAD±R, ibrutinib, ICE±R, RT, rituximab, rituximab maintenance, SCT, temsirolimus	B±R, CHOP±R, CHOEP, COPP, cyclophosphamide, DHAP±R, ESHAP±R, GDP, GemOX-R, hyperCVAD±R, ICE±R, rituximab, rituximab maintenance, SCT, temsirolimus
China*	HyperCVAD	HyperCVAD
India	Bortezomib, hyperCVAD	No funding/reimbursement
Japan*	Bendamustine, bortezomib, cladribine, DHAP, fludarabine, hyperCVAD, rituximab, SCT	DHAP, hyperCVAD, rituximab, SCT
New Zealand	Bendamustine, CHOP±R, CHOEP, cyclophosphamide, GDP, hyperCVAD, Ibrutinib, ICE, NORDIC, rituximab, SCT	CHOP±R, CHOEP, cyclophosphamide, GDP, hyperCVAD, ICE, rituximab, SCT
Singapore*	Bendamustine, CHOP±R, FCR, hyperCVAD, rituximab	Information not available
Eastern Europe		
Bulgaria	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, SCT, temsirolimus	Information not available
Croatia	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, temsirolimus	CHOP-R, CVP-R, DHAP-R, HyperCVAD±R
Czech Republic	Bendamustine, CAP-VcR ,CHOP±R, COPP, CVP±R, DHAP±R, FMR,	CAP-VcR, DHAP, HyperCVAD, temsirolimus

	hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, temsirolimus	
Hungary*	Bendamustine±R, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FCR, FMR, hyperCVAD±R , ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, SCT, temsirolimus	CHOP±R
Latvia*	Bendamustine, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, temsirolimus	HyperCVAD
Lithuania	Bendamustine±R, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, SCT, temsirolimus	Bendamustine±R , CHOP±R, CVP±R, DHAP±R, HyperCVAD, rituximab, SCT
Macedonia*	CHOP, DHAP, HyperCVAD, SCT	Information not available
Poland	Bendamustine±R, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FCR, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, SCT, temsirolimus	Bendamustine, CHOP±R, CVP±R, DHAP±R, FCR, HyperCVAD±R
Russian Federation*	Bendamustine±R, CEPPR, CHOP-R, DHAP-R, EPOCH-R, HyperCVAD±R, rituximab, rituximab maintenance, SCT	CEPP-R, CHOP-R, DHAP-R, EPOCH-R, HyperCVAD±R, rituximab, rituximab maintenance, SCT
Serbia	CHOP-R, FCR, HyperCVAD, ibrutinib, rituximab, temsirolimus	CHOP-R, FCR, HyperCVAD, rituximab
Slovakia*	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FCR, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, temsirolimus	FCR
Slovenia	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FCR, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R,	Bendamustine, CHOP-R, DHAP±R, FCR, HyperCVAD, IVAC (ara-C)±R, rituximab, SCT, temsirolimus

	MCP±R, NORDIC, rituximab, SCT, temsirolimus	
Turkey*	Bendamistine-R, Bortezomib, CHOP-R, DHAP±R, hyperCVAD±R, SCT	Information not available
Ukraine*	CHOP±R, hyperCVAD	Information not available
Western Europe		
Belgium	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, temsirolimus	CHOP±R, DHAP±R, HyperCVAD, ibrutinib, IVAC (ara-C)±R, rituximab, temsirolimus
Denmark*	Bendamustine±R, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FCMR, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, SCT, temsirolimus	Bendamustine-R, CHOP-R, CVP-R, DHAP-R, FCMR, hyperCVAD±R, ibrutinib, SCT, temsirolimus
France	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FCR, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, SCT, temsirolimus	CAP-VcR, CHOP±R, DHAP±R hyperCVAD±R, Ibrutinib, SCT, temsirolimus
Germany	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP-R, NORDIC, rituximab, SCT, temsirolimus	Bendamustine, CAP-VcR, CHOP±R, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, NORDIC, rituximab, SCT, temsirolimus
Ireland	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, cyclophosphamide, DHAP±R, ESHAP, FCM, FCMR, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, rituximab maintenance, SCT, temsirolimus	CHOP±R, DHAP±R, ESHAP, FCM, FCMR, hyperCVAD±R, rituximab, rituximab maintenance, SCT
Italy*	Bendamustine±R, bortezomib±R, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, lenalidomide, MCP±R, NORDIC, rituximab, SCT, temsirolimus	Bendamustine±R, bortezomib±R, CHOP±R, hyperCVAD±R, lenalidomide, rituximab, SCT

Netherlands	Bendamustine, Bortezomib-R, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FCR, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, lenalidomide, MCP±R, NORDIC, rituximab, SCT, temsirolimus	Bortezomib-R, CHOP±R, CVP±R, DHAP±R, FCR, hyperCVAD±R, ibrutinib, IVAC (ara-C), lenalidomide, SCT
Portugal*	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, temsirolimus	Information not available
Spain	Bendamustine, CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, temsirolimus	CHOP±R, DHAP±R, HyperCVAD±R, rituximab
Sweden	Bendamustine±R, CAP-VcR, CHOP±R, COPP, CVP±R, cyclophosphamide, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, NORDIC, rituximab, temsirolimus	Bendamustine±R, CAP-VcR, CHOP±R, CVP-R, DHAP±R, hyperCVAD±R, IVAC (ara-C)±R, rituximab, temsirolimus
Switzerland	CAP-VcR, CHOP±R, COPP, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, lenalidomide, MCP±R, mini-BEAM, NORDIC, SCT	CHOP±R, CVP±R, DHAP±R, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, SCT
UK	Bendamustine±R, bortezomib±R, CAP-VcR, CEPP±R, CHOP±R, COPP, CVP±R, cyclophosphamide, DHAP±R, FCM, FCMR, fludarabine, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, mini-BEAM, NORDIC, rituximab, rituximab maintenance, SCT, temsirolimus	Bendamustine±R, CAP-VcR, CEPP±R, CHOP±R, COPP, CVP±R, cyclophosphamide, DHAP±R, FCM, FCMR, fludarabine, FMR, hyperCVAD±R, ibrutinib, IVAC (ara-C)±R, MCP±R, mini-BEAM, NORDIC, rituximab, rituximab maintenance, SCT

Latin America		
Argentina*	Bendamustine±R, BDR, bortezomib, CHOP±R, DHAP±R, FCR, FMR, hyperCVAD, IVAC (ara-C), rituximab, rituximab maintenance, SCT	Information not available
Barbados*	CVP, hyperCVAD	Information not available
Brazil*	Bendamustine-R, CHOP-R, DHAP-R, FCR, HyperCVAD, ibrutinib, SCT	Ibrutinib
Colombia*	Bortezomib, CHOP-R, DHAP-R, FCR, hyperCVAD, SCT	CHOP-R, DHAP-R, FCR, hyperCVAD
Mexico	CHOP-R, FCM, FCMR, HyperCVAD, SCT	CHOP-R, FCM, FCMR, HyperCVAD, SCT
Uruguay*	CHOP±R, cyclophosphamide, FCM, FCMR, fludarabine, FCM, FCMR, fludarabine, FMR, hyperCVAD±R, rituximab	CHOP±R, cyclophosphamide, FCM, FCMR, fludarabine, FCM, FCMR, fludarabine, FMR, hyperCVAD±R, rituximab
Venezuela*	HyperCVAD	Information not available
North America		
Canada	Bendamustine±R, bortezomib, CHOP±R, COPP, cyclophosphamide, DHAP±R, ESHAP±R, gemcitabine, hyperCVAD, ibrutinib, IVAC (ara-C)±R, mini-BEAM, RT, rituximab, SCT	Bendamustine±R, bortezomib, CHOP±R, cyclophosphamide, DHAP±R, ESHAP±R, gemcitabine, hyperCVAD, IVAC (ara-C)±R, mini-BEAM, RT, rituximab, SCT
USA	Bendamustine±R, bortezomib±R, CAP-VcR, CHOP±R, cladribine±R, cyclophosphamide, DHAP±R, EPOCH±R, FCM, FCMR, fludarabine-cyclophosphamide, FMR, hyperCVAD±R, ibrutinib, lenalidomide±R, NORDIC, PCR, RT, rituximab, rituximab maintenance, SCT	Medicare, Medicaid, private insurance

Source: Global Database July 2016

*LC assumes therapies have regulatory as well as funding/reimbursement approval. LC will continue efforts to confirm status of therapy availability in these member countries.

Table 3. NCCN and ESMO Listed MCL Therapies by Country and Region

Region	Country	Total Therapies Approved	Total Therapies Reimbursed	Region	Country	Total Therapies Approved	Total Therapies Reimbursed
Africa/ Middle East	Algeria	1	N/A	Latin America	Argentina	15	N/A
	Israel	11	11		Barbados	2	N/A
	South Africa	15	15		Brazil	7	1
Asia/ Pacific	Australia	23	20		Colombia	6	4
	China	1	1		Mexico	5	5
	India	2	N/A		Uruguay	10	10
	Japan	10	6		Venezuela	1	N/A
	New Zealand	14	10	North America	Canada	20	18
	Singapore	8	N/A		United States	31	31
Eastern Europe	Bulgaria	22	N/A	Western Europe	Belgium	21	10
	Croatia	19	5		Denmark	24	10
	Czech Republic	21	4		France	22	11
	Hungary	24	2		Germany	21	17
	Latvia	21	1		Ireland	25	11
	Lithuania	22	10		Italy	25	11
	Macedonia	4	N/A		Netherlands	24	14
	Poland	23	10		Portugal	21	N/A
	Russian Federation	9	8		Spain	21	7
	Serbia	6	4		Sweden	22	14
	Slovakia	21	1		Switzerland	20	13
	Slovenia	23	12		United Kingdom	38	31
	Turkey	8	N/A				
	Ukraine	3	N/A				

Source: Global Database July 2016

In Africa and the Middle East, South Africa has many of the therapies recommended in the guidelines with regulatory approval, but none of the newer therapies such as lenalidomide or temsirolimus are included. Government funding/reimbursement is provided for some but not all components of recommended therapy regimens. For example, with R-CHOP, funding is not provided for cyclophosphamide and prednisone. Private health insurance is available for some of the recommended regimens. Israel has funding available for most of its regulatory approved therapies including ibrutinib, temsirolimus and lenalidomide. There is little information available for Algeria which has only one therapy approved for the treatment of MCL.
Uruguay has the highest regulatory approval and funding /reimbursement in Latin America. Brazil has funding/reimbursement for only ibrutinib.

Australia is the only country in the Asia/Pacific region that has a number of the recommended MCL therapies with both regulatory as well as funding/reimbursement approval. China only has one approved and funded/reimbursed therapy which is hyperCVAD.

In Eastern Europe, the number of therapies that are funded/reimbursed is fairly low. Slovakia and Latvia have only one drug that is funded/reimbursed. Countries that are members of the EU have a higher number of approved therapies, but funding/reimbursement is still poor in countries such as the Czech Republic and Hungary. While in Western Europe there are a high number of approved therapies. UK has the highest number of approved and funded/reimbursed therapies globally. In comparison, places like Spain, Belgium and Denmark have lower rates of funding/reimbursement.

When looking at access to the targeted therapies recommended by ESMO; namely lenalidomide and temsirolimus, not many countries have funding/reimbursement. Only five countries have regulatory approval for lenalidomide. Ibrutinib is approved in 27 countries but is only funded/reimbursed in ten countries. Approval for bortezomib is seen in ten countries, but is funded/reimbursed in only three. Temsirolimus has regulatory approval in 23 countries but is only funded in eight. Canada and the USA do not have regulatory approval or funding/reimbursement for temsirolimus.

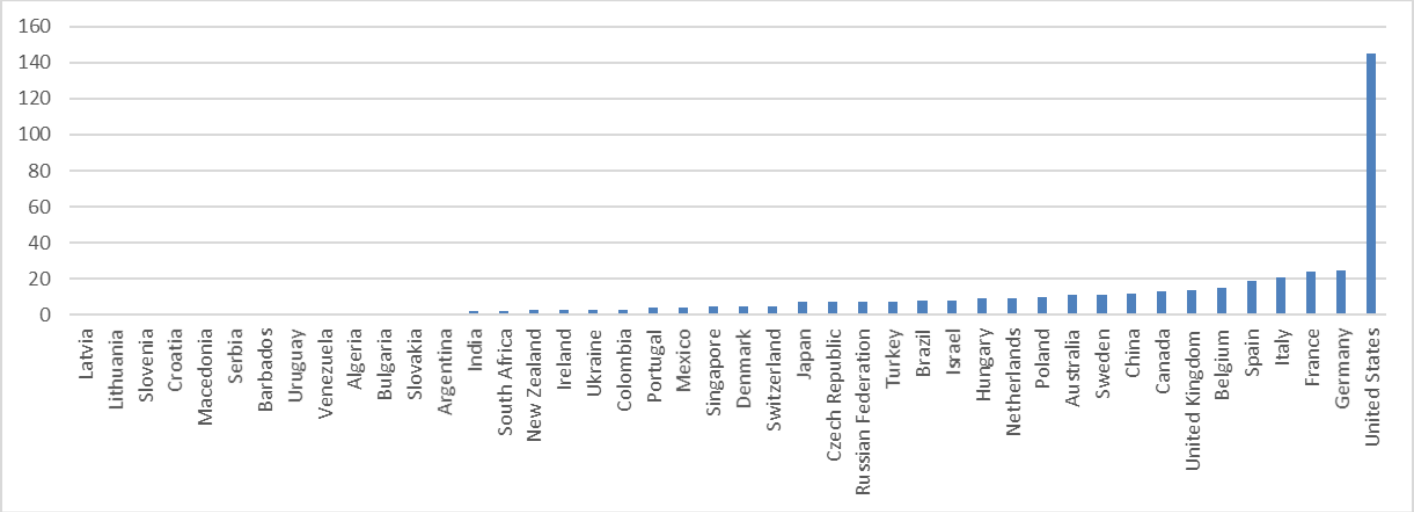
Very few countries appear to provide full funding/reimbursement for therapies outlined by ESMO and NCCN guidelines making it challenging for most patients. It would seem that there is a paucity of funding and support for newer treatments in many countries as well. The number of approved drugs is high, but the obstacle of funding still exists which would make it very difficult and often impossible to consider those drugs as a treatment option.

Clinical Trial Activity

When reviewing clinical trials in LC's Global Database, focusing on Phase II and Phase III trials, MCL is showing an increasing trend with 154 trials in 2014, 188 in 2015 and 198 in 2016.

Of the 198 trials, 52 are solely for MCL patients. Many of those trials include lenalidomide and ibrutinib; lenalidomide can have severe adverse effects while ibrutinib resistance is not completely understood in patients with MCL. Combination therapy may improve the depth and duration of response to ibrutinib, but this is still a big unknown and further research is required.

Figure 3. MCL Trials by LC Member Country



Source: LC Global Database October 2016

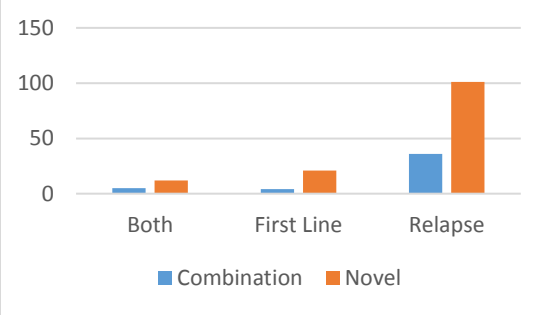
The USA is involved in all the Phase II and Phase III trials for MCL, with Germany and France following with 25 and 24 trials respectively.

There are no trials available for patients in Eastern Europe as well as places like Barbados and Argentina. The numbers of trials in India, South Africa, New Zealand and Denmark are also staggeringly low as seen in Figure 3.

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 MCL trials in LC's Global Database the trend holds for all LC member countries with 179 Phase II and 19 Phase III trials.

Looking at Phase II trials, 45 are combination therapies while 134 are novel drugs. A large percentage of these trials are for relapsed/refractory patients (77%). Of the 179 trials in the Phase II setting only 21 are studying novel therapies in the first line setting. There needs to be a stronger push to identify effective drugs with enduring remissions that can be used in the front line setting.

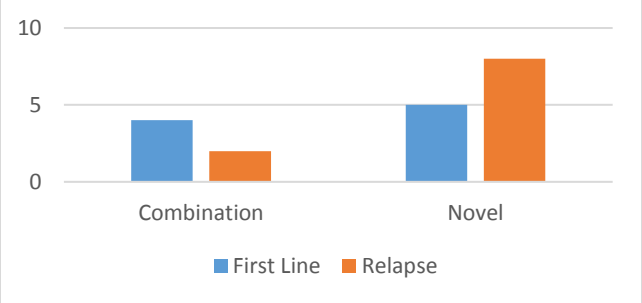
Figure 4. Phase II Trials for MCL



Phase II	Combination	Novel	Total
Both	5	12	17
First Line	4	21	25
Relapse	36	101	137
Total	45	134	179

Source: LC Global Database October 2016

Figure 5. Phase III trials for MCL



Phase III	Combination	Novel	Total
First Line	4	5	9
Relapse	2	8	10
Total	6	13	19

Source: LC Global Database October 2016

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

In the Phase II setting there are a total of 19 trials currently underway of which 10 are in the relapsed and 9 in the first line setting. Of the 5 trials studying novel therapies in the first line setting, 4 are exclusively for patients with MCL. The agents being studied include; Bendamustine, rituximab and Ibrutinib, CHOP-R, CAP-VcR and lenalidomide in various combinations.

Currently, targeting the BCR and PI3K-AKT-mTOR signaling pathways would appear to be the most promising areas of research; while targeting mTOR does not appear to have promising results as observed with temsirolimus and more recently with everolimus.[20, 22] There are around 20 Phase II and Phase III trials underway with ibrutinib – which has been known to show poor clinical outcomes for patients with MCL with primary or secondary ibrutinib resistance. Future trials should focus on understanding the mechanisms of ibrutinib resistance and on treatment after ibrutinib.[21]

There are a number of trials grouping heterogeneous lymphoma patients as well as those serving just those with MCL. Due to the rarity of the cancer and the disparate nature of its course it may be difficult to conduct a large scale MCL trial. Without large scale randomized trials it would be exceedingly difficult to provide a standard of care and survival rates with fewer side effects. A starting point would be to make trials more widely available across different regions and informing patients about clinical trial options at diagnosis.

Patient Experience

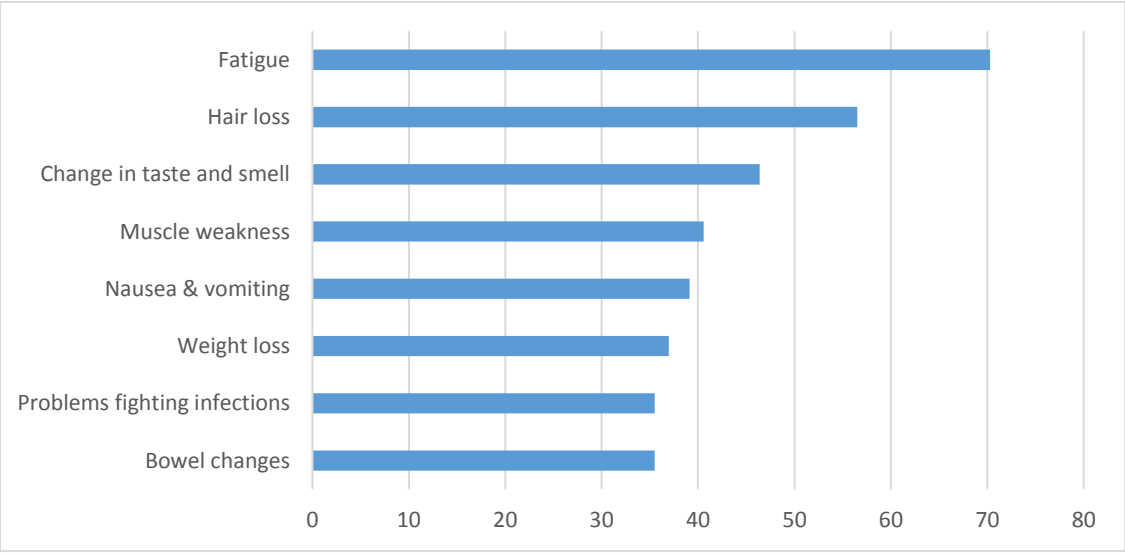
The patient experience is always at the forefront when reviewing subtypes in lymphomas. The LC 2016 Global Patient Survey (GPS) is the document LC references in this report to provide a sense of the patient experience.

There were over 4,000 total respondents to the GPS, of which 138 were identified as MCL patients. This is a high number of responses considering MCL is a rare lymphoma.

When first diagnosed with MCL, 30% of respondents did not understand the characteristics of their subtype. When it came to understanding side effects 21% did not understand and the number was even higher (27%) of those who didn't understand how to manage those side effects. A better dialogue needs to be established between doctors and patients in order to alleviate any anxiety during such a stressful time. Both health care providers and patients need to be aware that active communication is a key element during the treatment process.

As seen in Figure 6 one of the biggest physical impacts faced by patients with MCL is fatigue, followed by hair loss, changed in taste and smell and muscle weakness. Additionally, over a quarter of respondents faced problems with nausea & vomiting, weight loss, problems fighting infections and bowel changes.

Figure 6. Physical Conditions with Most Impact on MCL Patients (%)

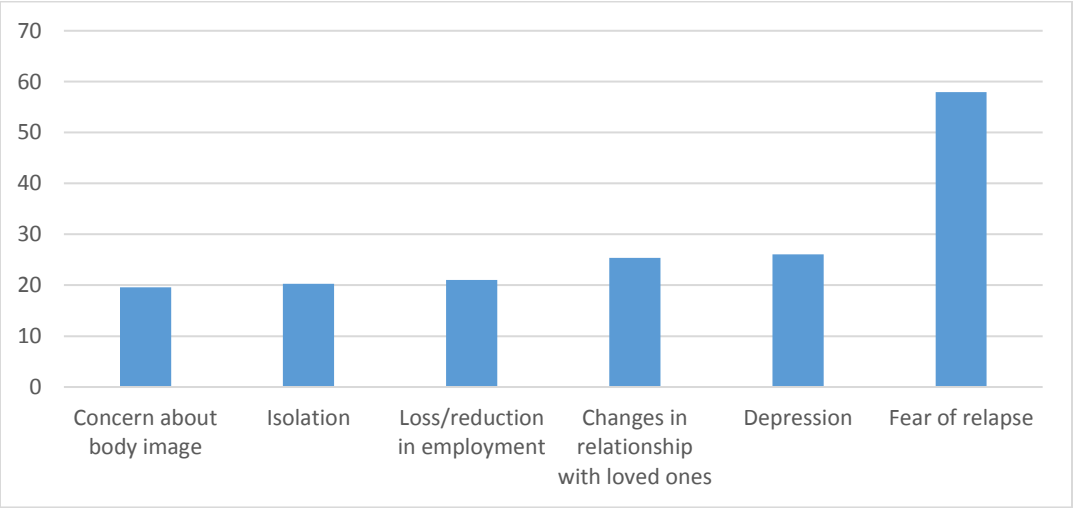


Source: 2016 LC Global Patient Survey

The burden of dealing with a long-term cancer can manifest in both physical and emotional conditions. Psychosocial concerns can affect patients' sense of well-being and can be challenging to leading a normal life. The factors that MCL respondents felt affected them most was the fear of relapse followed by depression and changes in relationship from loved ones.

If we take into consideration the nature of MCL progression and the relapse rates it is understandable why fear of relapse is so high. Health care providers and palliative care have a greater responsibility to provide not only clinical support but also aid patients with managing the emotional as well as physical effects of these concerns. Partnering with patient support organisations makes sense for additional long term support.

Figure 7. Psychosocial Factors Impacting Sense of Well-Being (%)



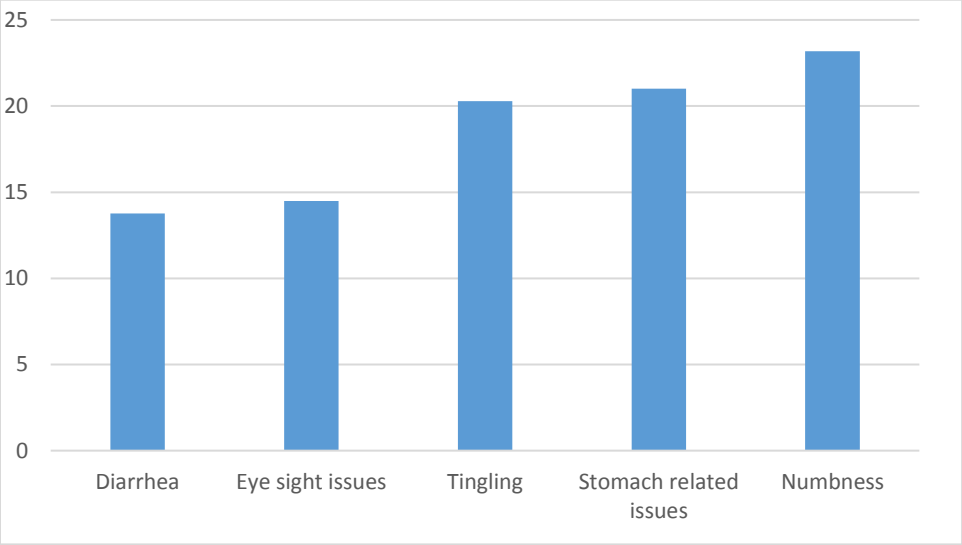
Source: 2016 LC Global Patient Survey

In comparison to other lymphomas, such as DLBCL, respondents with MCL faced fewer additional medical concerns in addition to their lymphoma. Of all the MCL responses 23% suffered from numbness and the second largest concern was stomach related issues.

GI tract involvement is fairly common in MCL and probably accounts for stomach related issues and diarrhea being major concerns.

Newer therapies, regardless of how effective they are, need to have fewer adverse effects so patients do not have to deal with them in addition to all the other factors they have reported.

Figure 8. Medical Adverse Effects (%)

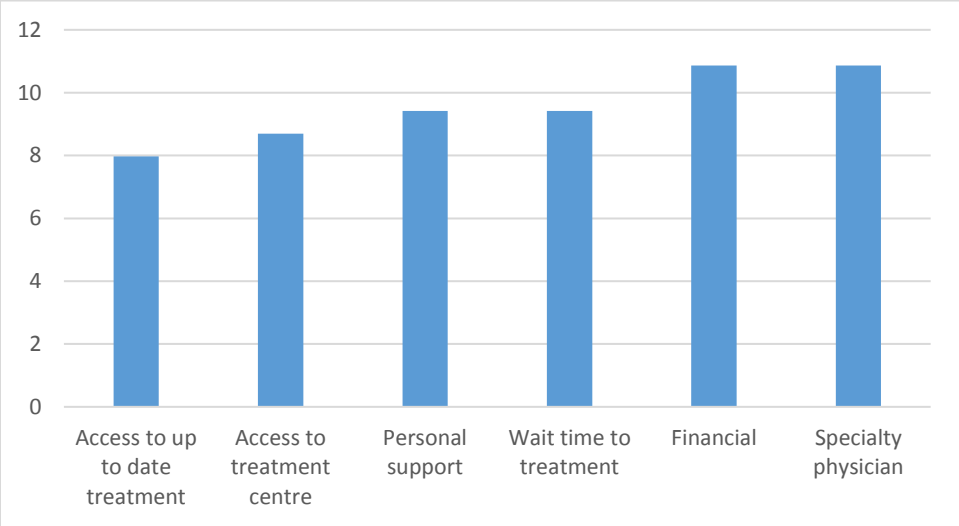


Source: 2016 LC Global Patient Survey

In the 2016 GPS, we asked respondents if they had talked to the doctor about their physical and emotional issues and how useful they felt the doctor was. According to the survey 56% came away from the doctor without their concerns being answered. 71% of respondents who went to patient support groups found them helpful.

It is essential to improve communication between the healthcare provider and patient. Better understanding of the specific subtype, treatment options and their related side effects can lead to a robust healthcare strategy for the patient.

Figure 9. Barriers to Treatment (%)



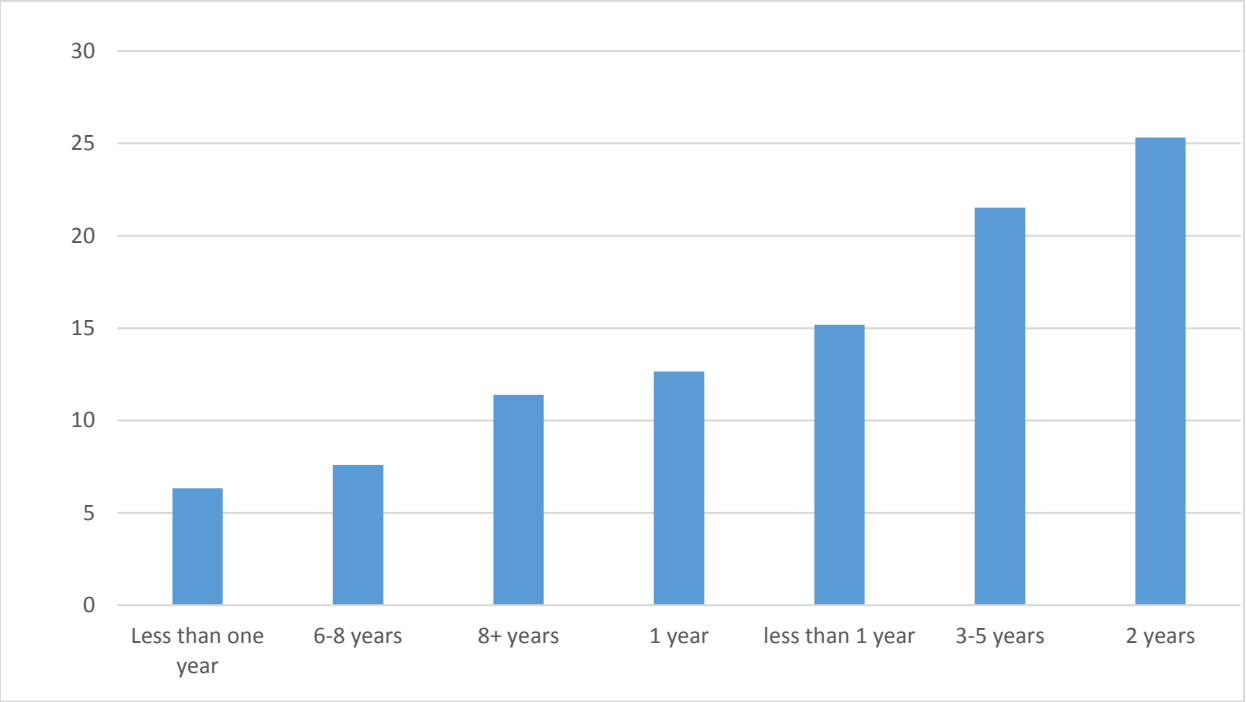
Source: 2016 LC Global Patient Survey

When looking at barriers to treatment, LC found that access to a specialty physician and financial barriers were an issue for responders.

Other barriers to note were wait time to treatment, personal support and access to treatment centre. All these barriers have a negative impact on the patient's sense of well-being. Also, over 70% of respondents faced issues longer than 2 years.

Treating any form of cancer, particularly one with an aggressive pathogenesis needs to incorporate the patients' physical as well mental health with a framework in place for interventions when needed. Health care providers and patient care organisations have an opportunity to work together to provide appropriate care as per individual patient needs.

Table 10. Length of Time Issues Faced by MCL Patients (%)



Source: 2016 LC Global Patient Survey

Conclusion

Patients with MCL show a variable course of disease progression and early detection can often prove to be difficult. There is no standard of care or recommended treatment regimen for MCL with many questions around intensity of therapy and efficacy of maintenance therapy. As is the case with many other rare cancers the need for a specialist is increasing. Patients are usually incidentally diagnosed and that too at a later stage of disease progression. This makes it critical to identify the correct treatment, with thoughtful selection keeping in mind the patients age and physical condition.

There have been many advances in understanding the biology of MCL. In particular, understanding the disease progression along two very different pathways. One course is indolent in nature and may not even require immediate treatment. The discovery of *NOTCH1* and *NOTCH2* mutations and the CCND2 translocation can prove to be important markers for therapy and diagnosis.

It is encouraging to see the number of MCL trials particularly those that are for MCL patients only. Clinical trials targeting the BCR and PI3K-AKT-mTOR signaling pathways would appear to be the most promising areas of research and can further broaden the available therapeutic options for patients with MCL. The challenge will be to incorporate these therapies in to the front line setting to achieve immediate response rates with minimum toxicity.

There is still no cure for MCL and current therapies manage the cancer rather than treat it. With the expectation of inevitable progression many patients live the fear of relapse. Patients have to deal with not only the physical comorbidities, but side effects of treatment and the negative psychosocial impacts. Health care providers and patient organisations can work together to find solutions in helping patients navigating and overcoming the barriers that they may face.

While targeted therapies are approved for MCL the reimbursement in many countries is still lacking. With financial concerns being one of the top barriers to treatment these patients may be confined to conventional therapies.

MCL is one of the most aggressive lymphomas and can lead to poor patient outcomes. With this in mind it is imperative to provide independent reporting to ensure proper trending analysis and outcome reporting. Subtype reporting can be effective in providing specific unmet needs of patients with MCL.

Acronyms

B±R = bendamustine with/without rituximab
BR = bendamustine, rituximab
BTK = Bruton's tyrosine kinase
Bortezomib+R = bortezomib, rituximab
CHOP = cyclophosphamide, vincristine, doxorubicin, prednisone
CHOP±R = cyclophosphamide, vincristine, doxorubicin, prednisone with/without rituximab
CLL = chronic lymphocytic leukaemia
COPP = cyclophosphamide, vincristine, procarbazine, prednisone
CT = clinical trial
CVM = methotrexate, vinblastine
CVP±R = cyclophosphamide, vincristine, prednisone with/without rituximab
DHAP±R = dexamethasone, high-dose cytarabine, cisplatin, with/without rituximab
DLBCL = diffuse large B-cell lymphoma
ESMO = European Society of Medical Oncology
EPOCH±R = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin with/without rituximab
EU = European Union
FC = fludarabine, cyclophosphamide
FCM = fludarabine, cyclophosphamide, mitoxantrone
FCMR = fludarabine, cyclophosphamide, mitoxantrone, rituximab
FCR = fludarabine, cyclophosphamide, rituximab
FL = follicular lymphoma
FMR = fludarabine, mitoxantrone, rituximab
HyperCVAD+R = cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine, rituximab
IVAC (ara-C) ±R = etoposide, ifosfamide, mesna, cytarabine, methotrexate with/without rituximab
LC = Lymphoma Coalition
LR = lenalidomide, rituximab
MCL = mantle cell lymphoma
MCP±R = melphalan, chlorambucil, prednisone with/without rituximab
Mini-BEAM = carmustine, etoposide, cytarabine, melphalan
NCCN = National Comprehensive Cancer Network
NHL = non-Hodgkin lymphoma
NORDIC = cyclophosphamide, vincristine, doxorubicin, prednisolone, rituximab, cytarabine
NOTCH 1 = Notch homolog 1, translocation-associated
NOTCH 2 = Neurogenic locus notch homolog protein 2
PCR = pentostatin, cyclophosphamide, rituximab
PEPC±R = prednisone, etoposide, procarbazine, cyclophosphamide with/without rituximab
PTCL = peripheral T-cell lymphoma
R = rituximab
RT = radiation therapy
SCT = stem cell transplant
TOR = target of rapamycin
UK = United Kingdom
USA = United States of America
VR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone
WHO = World Health Organization

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