LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

2017

GLOBAL

SUBTYPE REPORT

Chronic Lymphocytic Leukaemia

The focus of this report is to review patient access to care in chronic lymphocytic leukaemia (CLL); namely therapy access, clinical trials and aspects of the patient experience.

Overview

Chronic lymphocytic leukaemia (CLL) is an incurable lymphoma found in the lymphocytes. The progression of CLL is extremely variable ranging from indolent disease not requiring treatment to one that progresses rapidly and is resistant to treatment. The average incidence of CLL varies between individuals in different geographic regions with incidence being lower in eastern Asia and slightly higher in Europe and the USA. Median age at diagnosis is 72 years.

Within CLL, there are two main subsets which are distinguished by whether the CLL cells express as unmutated or mutated immunoglobulin heavy-chain variable region gene (*IGHV*). Patients with CLL that expresses an unmutated *IGHV* usually have more aggressive disease than those that express a mutated *IGHV*.

Genetic factors play a role in the development of CLL with a six- to nine-fold increased risk for family members of patients with CLL. Approximately 80% of patients with CLL carry at least one or more common chromosomal alterations. The most common alterations are focal, i.e., limited to a specific area, deletions of chromosomes 13q14.3 (del(13q)), del(11q), del(17p) and trisomy 12.

Patients with CLL are often asymptomatic at the time of presentation and only become aware of the cancer following the detection of lymphocytosis during a routine blood count. CLL can, however, have a range of presentations with some patients feeling well and being fully active while others will have disease-related symptoms. Typical symptoms of CLL include fatigue, weight loss, night sweats, feeling of fullness while eating and increased frequency of infections. Patients may also have or develop enlarged lymph nodes, hepatomegaly or splenomegaly.

The management of CLL is determined by the stage and activity of the cancer. Two clinical staging systems are used to predict patient outcomes: the Binet staging system and the Rai staging system.

Significant advancements in the care of patients with CLL have occurred over the past decade. This is largely due to the ongoing investigation into the pathogenesis of CLL that has led to the development of novel treatments and therapeutic strategies. These efforts highlight a complex biology that includes inherited or acquired genetic changes, the role of the B-cell receptor (BCR) and BCR signalling, CLL cell make-up, and the interactions in the microenvironment between CLL cells and other immune cells.

Based on information gathered from the Lymphoma Coalition (LC) Global Database, there was a wide discrepancy among countries in terms of treatment protocols with regulatory approval compared with those that were funded/reimbursed, especially the newer therapies. For example, venetoclax while it had regulatory approval in 24 member countries, only six countries funded/reimbursed it.

Of the 211 clinical trials involving patients with CLL, 147 were specifically for patients with CLL. Among the 46 LC member countries, five had no current trials for CLL. The USA was involved in the majority of the clinical trials (n = 160). Most of the clinical trials (n = 170) underway in CLL were studying the use of novel agents. Within the phase II clinical trials, most (n = 78) were studying the use of novel therapies in the relapsed/refractory setting. Similarly in the phase III trials, most (n = 24) were examining the use of novel therapies in the relapsed/refractory setting.

Key findings from the 2016 Lymphoma Global Patient Survey showed that depression was of greatest concern among respondents in North America (33%) while the fear of relapse was of greatest concern among respondents in Western Europe (30%). Stress related to financial issues, changes in relationships with loved ones and isolation were other issues causing anxiety among all respondents. Fatigue was the physical effect of greatest concern for all respondents. Other physical effects of concern were trouble concentrating, muscle weakness, aching joints, sleeplessness and problems fighting infections.

Patients with CLL in North America and Asia Pacific indicated that access to a specialty physician was the biggest barrier to treatment (46% and 40%, respectively). In Eastern Europe, the biggest barrier to treatment was access to the treatment centre (37%). Other barriers of concern in all regions were financial issues, personal support and access to up-to-date treatment.

Acknowledgements

The Lymphoma Coalition would like to extend a special thanks to the advisors whose collaboration and support have made this report possible. We would like to say a special thanks to Dr. Aliki Xochelli, Institute of Applied Biosciences, Center for Research and Technology, Hellas Thessaloniki, Greece, Dr. John Seymour, Professor and Chair at the Department of Haematology & Medical Oncology at the Peter MacCullum Cancer Centre in East Melbourne, Australia, and Lorna Warwick, Vice Chair, CLL Advocates Network, who provided insight and expertise that greatly assisted our research for this report.

What is Chronic Lymphocytic Leukaemia?

Chronic lymphocytic leukaemia (CLL) is a lymphoproliferative disorder hence it is classified as a lymphoma. It is an incurable lymphoma found in the lymphocytes, a type of white blood cell involved in the body's immune system. CLL is classified by the accumulation and rapid reproduction of clonal B cells in the blood, marrow and lymph nodes. The progression of CLL is extremely variable ranging from indolent (slow growing) disease not requiring treatment to one that progresses rapidly and is resistant to treatment.[1]

The average incidence of CLL varies between individuals in different geographic regions with incidence being lower in eastern Asia and slightly higher in Europe and the USA.[2] Median age at diagnosis is 72 years. Most cases of CLL are diagnosed in patients over the age of 55 years with approximately only 10% of CLL cases being diagnosed in patients younger than 55 years.[3] The risk of CLL developing in men is twice as high as it is in women.[2]

Within CLL, there are two main subsets. These subsets are distinguished by whether the CLL cells express as unmutated, i.e., genetic material in the cell is unchanged, or mutated, i.e., genetic material in the cell has changed, immunoglobulin heavy-chain variable region gene (*IGHV*). Those CLL cells that express an unmutated *IGHV* originate from the B cell that has not undergone differentiation (a cell changes from one cell type to another) in the germinal centres. Germinal centres are sites where B cells proliferate, i.e., they grow rapidly through the production of new cells and mutate during an immune response to an infection. Patients with CLL that expresses an unmutated *IGHV* usually have more aggressive disease than those that express a mutated *IGHV*.[2] *IGHV* status is determined by flow cytometry.[4]

Most cases of CLL are diagnosed in patients **over the age of 55 years**.[3]

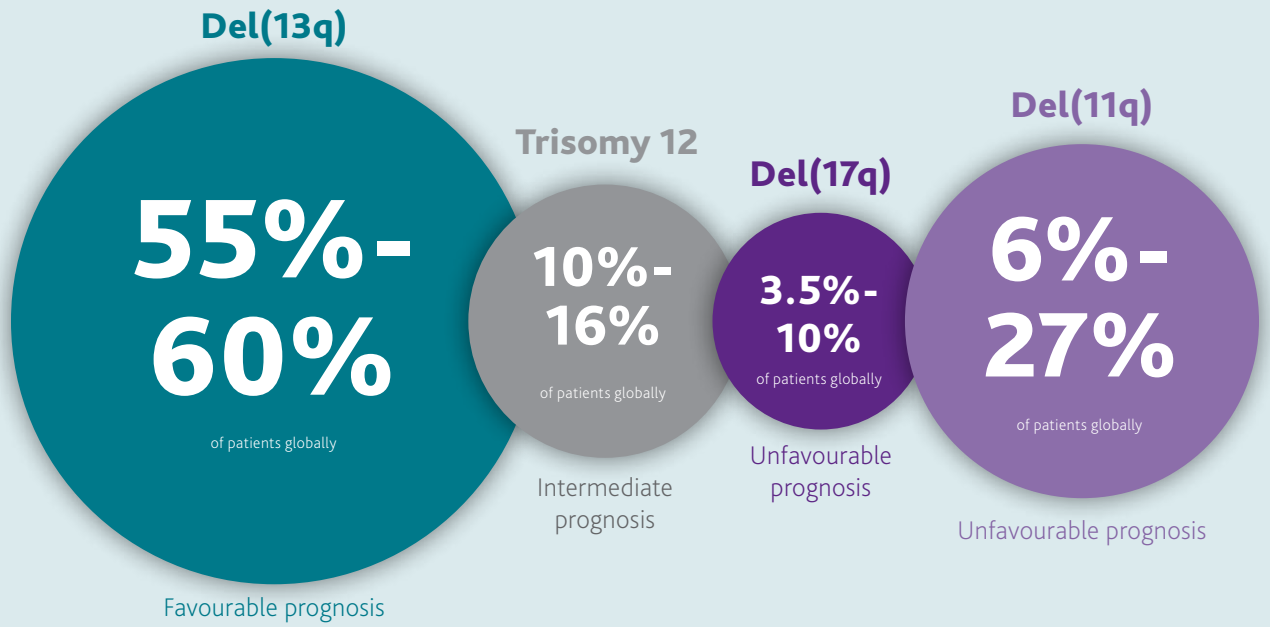
The risk of CLL developing in **men is twice as high** as it is in women.[2]

Genetic factors play a role in the development of CLL with a six- to nine-fold increased risk for family members of patients with CLL.[3] As well, among monozygotic (identical twins), if one has CLL the other is more likely to develop it compared with dizygotic (not identical) twins.[2]

Approximately 80% of patients with CLL carry at least one or more common chromosomal alterations. The most common alterations are focal, i.e., limited to a specific area, deletions of chromosomes 13q14.3 (del(13q)), del(11q), del(17p) and trisomy 12. Figure 1 shows the global prevalence of chromosomal alterations.

It is important to note that chromosomal abnormalities can change over time. These changes can be a result of therapy, in particular chemoimmunotherapy (a combination of chemotherapy and immunotherapy, CIT), where there may be a selection for cells that have del(17p).[5] Anecdotally, tests for mutations, markers and chromosomal abnormalities are not readily accessible in all countries. **This needs to change to ensure patients receive the best treatment otherwise they may not receive treatment that is appropriate for their type of CLL.**

FIGURE 1. PREVALENCE OF CHROMOSOMAL ALTERATIONS[1,2]



The understanding of the genetic diversity associated with CLL has greatly improved through the use of parallel as well as whole-exome sequencing. Recurrent mutations have been consistently observed in genes that play a role in DNA damage, e.g., *TP53* and *ATM*, mRNA processing, e.g., *SF3B1* and *XPO1*, chromatin modification, e.g., *HIST1H1E*, *CHD2* and *ZMYM3*, WNT signalling, Notch signalling, e.g., *NOTCH1*, and inflammatory pathways, e.g., MYD88. CLL is also associated with alterations in microRNA, specifically *mir-15a and mir-16-1*. They are deleted, altered or downregulated in approximately 60% of patients with CLL globally and dysfunctional in a few cases of familial CLL.[1,2]

Patients with CLL are often asymptomatic at the time of presentation and only become aware of the cancer following the detection of lymphocytosis (an increase in the number of lymphocytes in the bloodstream) during a routine blood count. CLL can, however, have a range of presentations with some patients feeling well and being fully active while others will have disease-related symptoms.

Typical symptoms of CLL include:

- Fatigue;
- Weight loss;
- Night sweats;
- Feeling of fullness while eating;
- Increased frequency of infections.

Patients may also have or develop enlarged lymph nodes, hepatomegaly (abnormal enlargement of the liver) or splenomegaly (abnormal enlargement of the spleen).[2]

A complete blood count (CBC) with differential is undertaken as part of the diagnostic process. This routine test helps determine a patient's general health status. The presence of at least 5,000 abnormal B cells per microlitre of blood (≥5,000 monoclonal B lymphocytes/µl) for at least three months is required to make the diagnosis.[3,6] However, in practice, if the lymphocyte count is slightly lower and there are other indications that the patient has CLL, clinicians will not wait another three months before retesting the patient.[7]

The World Health Organization (WHO) recently modified its classification of lymphoid neoplasms. In 2008, it was unknown if monoclonal B-cell lymphocytosis (MBL) was a precursor of CLL. It is now clear that it is and that it precedes nearly all cases of CLL. The updated WHO guideline requires that low-count MBL (peripheral blood CLL count of $<0.5 \times 10^9$/L) must be differentiated from high-count MBL. Patients with high-count MBL require yearly follow-up; those with low-count MBL rarely develop CLL.[8]

As part of the diagnostic work-up, peripheral blood flow cytometry may be used to identify specific proteins that may be on the cell surface, such as CD5, CD19, CD20 and CD23. This is called immunophenotyping.[3]

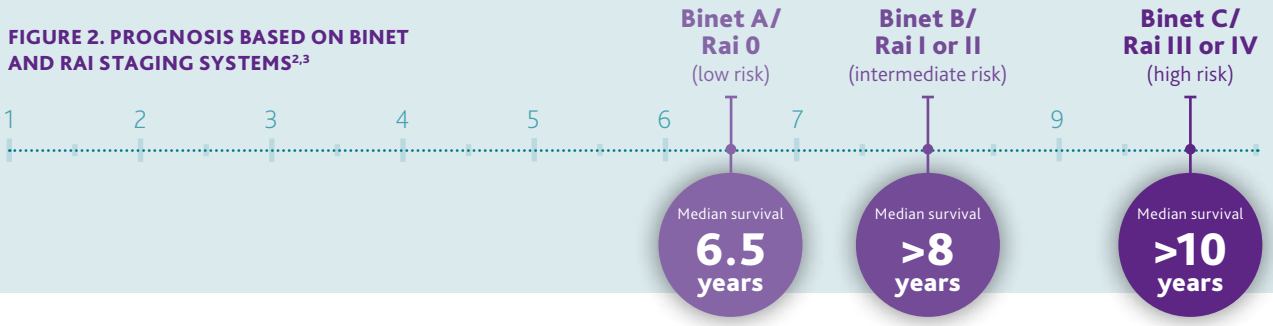
Other tests that may have prognostic value and provide an overall idea of the patient's status prior to the start of treatment include:

- Genetic and cell protein tests;
- A comprehensive metabolic panel;
- Hepatitis B testing;
- An echocardiogram;
- Immunoglobulin testing may be indicated for patients who develop repeated infections.

For further information on testing for CLL, click here.

The management of CLL is determined by the stage and activity of the cancer. Two clinical staging systems are used to predict patient outcomes. In Europe, the Binet staging system is more widely used, whereas in North America, the Rai staging system is more commonly applied. Both systems recognise the importance of bone marrow function and define late-stage or high-risk disease through the presence of pronounced anaemia or thrombocytopenia (low blood platelet count). In addition, both the Binet and Rai staging systems separate patients into three groups with different prognoses (see Figure 2). The Binet and Rai staging systems provide general guidelines as each patient is different and needs to be treated accordingly.

FIGURE 2. PROGNOSIS BASED ON BINET AND RAI STAGING SYSTEMS[2,3]



It is not recommended that patients who are asymptomatic with early-stage or intermediate stage cancer (Binet stage A or B; Rai stage 0-II) receive treatment. This is typically called watch and wait, watchful waiting or active surveillance. Treatment should only be given if patients have symptoms or there is evidence of disease progression. Studies have not shown that treating patients with early-stage CLL resulted in a survival advantage. However, these patients should have CBCs and a clinical examination every three to 12 months.[2,3]

Signs and symptoms of symptomatic disease or cancer progression may include:

- Enlarged lymph nodes, liver or spleen;
- Recurring infections;
- Loss of appetite or early satiety;
- Abnormal bruising (late-stage symptom);
- Fatigue;
- Night sweats.[2,6]

Once a patient has met the criteria for treatment, the choice of therapy is the next major decision. The key feature currently directing the choice of therapy is the presence of either del(17p) or mutated *TP53*. As well, in patients over the age of 65 years, the presence of comorbidities and the goal of treatment will play an important role in the choice of therapy.[2] Given the toxicities associated with therapies, it is helpful to predict which patients will need treatment as a way of ensuring the preservation of bone marrow function, reducing the exposure to treatment side effects, as well as reducing morbidity and mortality.

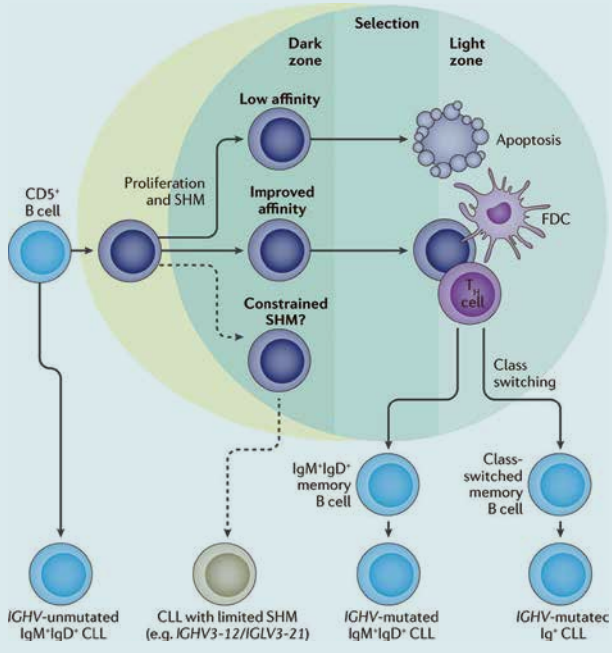
While the course of CLL is extremely variable, it is hoped that the improved understanding of the genetic diversity associated with CLL will lead to improved treatments as well as outcomes for patients.

Understanding the Biology of CLL

Significant advancements in the care of patients with CLL have occurred over the past decade. This is largely due to the ongoing investigation into the pathogenesis of CLL that has led to the development of novel treatments and therapeutic strategies.

Figure 3 provides an overview of the origins of CLL cells. These efforts highlight a complex biology that includes inherited or acquired genetic changes, the role of the B-cell receptor (BCR) and BCR signalling, CLL cell make-up, and the interactions in the microenvironment between CLL cells and other immune cells.

FIGURE 3: CELLULAR ORIGINS OF CLL CELLS



Reprinted by permission from Macmillan Publishers Ltd:
Nat Rev Dis Primers. 2017 Jan 19;3:16096. doi: 10.1038/nrdp.2016.96. 2017)

Normal naive B cells that have undergone successful V(D)J recombination and express functional B cell receptors that are capable of binding to antigen interact with CD4+ T cells and accessory cells, which aggregate to form follicles that become germinal centres. Germinal cells each have a dark zone, comprising rapidly dividing B cells, and a light zone, comprising B cells mixed with follicular dendritic cells (FDCs), macrophages and helper T cells (T_H cells). The B cells enter the dark zone of the germinal centre where they experience rapid proliferation and somatic hypermutation (SHM) in the genes encoding the immunoglobulin variable regions of the heavy chain (*IGHV*) and the light chain (*IGVL*). As they pass through to the light zone, the B cells that express the fittest B cell receptors for binding antigen are selected and may undergo immunoglobulin class-switch recombination. Chronic lymphocytic leukaemia (CLL) cells that use unmutated *IGHV* apparently originate from CD5+ B cells prior to experiencing SHM, whereas CLL cells that use mutated *IGHV* most likely originate from CD5+ B cells that have passed through and differentiated in the germinal centre. Some CLL cells might be derived from B cells that also have undergone immunoglobulin class-switch recombination and express immunoglobulin isotypes other than IgM and IgD, for example, IgG or IgA. Another subset is one with CLL cells that express immunoglobulin with only modest somatic mutations, such as CLL cells that use *IGHV3-21* with ~97% homology to the inherited *IGHV3-21* gene and an immunoglobulin light chain encoded by an unmutated *IGLV3-21*; these cells might derive from a B cell that has had constrained SHM, possibly owing to a limited need for immunoglobulin somatic diveresification and selection. Dashed arrows indicate speculated pathways.

As the biology of CLL is further established, both molecular and cellular markers have been identified that may predict the tendency for cancer progression in patients with CLL. For example, the mutational profile of genes, in this instance, mutated CLL or unmutated CLL, will determine two separate subtypes. Progress continues to raise questions that warrant further research. These research areas are:[7]

1. **Gaining a better understanding of the factors that contribute to the early pathogenesis of CLL to determine:**
   - Why people develop CLL;
   - Why CLL progresses;
   - The factors that regulate the rate of progression in patients who become symptomatic versus those remaining stable for many years.

2. **Determining optimal treatment:**
   - CIT versus the use of a targeted agent?
   - How to select the preferred targeted agent?
     - Are there subsets of patients where, because of their mutational profile, one targeted agent is better than another or are they equivalent?

3. **How to achieve the greatest efficacy from novel agents:**
   - Is combination treatment using ibrutinib plus venetoclax plus a CD20 antibody better than sequencing therapies?
   - What is the ideal combination regimen given the innumerable potential combinations?

4. **Continuous versus time-limited therapy:**
   - Do therapies need to be given continuously or, once remission is achieved, treatment stopped and only restarted at early evidence of progression?

5. **Mechanisms of resistance:**
   - How does CLL become resistant to the targeted agent?
   - Is it possible to identify the early development of resistance?
   - Can the emergence of resistance be used to pre-emptively switch treatments rather than waiting for profound resistance?

6. **Richter's transformation:**
   - What are the factors that lead to the development of Richter's transformation as it is the manifestation of CLL that is responsible for most deaths?

7. **Supportive care:**
   - How can infections be prevented as a result of treatment?
   - How can supportive care be optimised?
   - How can the development of secondary cancers be minimised?

LC looks forward to the results of this research and how these findings may relate to the clinical setting.

With increasing frequency, retrospective data show that patients with CLL have a threefold risk of developing a secondary malignancy and an eight- to 15-fold increased risk of developing skin cancers.

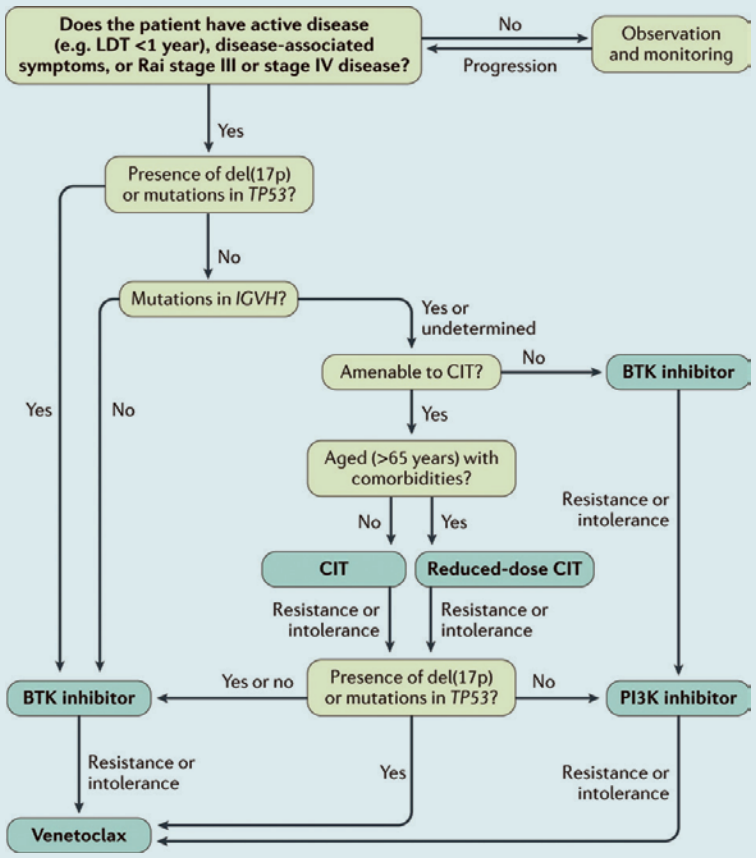
When skin cancers are excluded, the overall risk is twice that of age- and gender-matched control populations.[9,10] This risk is the same for men and women regardless of age or treatment history.[9] The risk of developing nonmelanoma skin cancer (NMSC) and prostate cancer is higher in men while women have a higher risk of developing breast, lung and gastrointestinal (GI) cancers.[9,11] This is a difficult outcome given that the average age of people diagnosed with CLL is 72 years. Among the commonly diagnosed secondary malignancies are NMSC, Kaposi sarcoma, malignant melanoma, lung cancer, GI malignancies, breast cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancers, and Richter's transformation to a very aggressive large B-cell lymphoma.[9,11-13]

Prolymphocytic transformation is rare occurring in less than 1% of patients. It is characterised by symptomatic splenomegaly and rapidly increasing number of leukaemia cells in the blood. Approximately 2% to 7% of patients will develop Richter's syndrome. This is the transformation of CLL to an aggressive lymphoma, usually diffuse large B-cell lymphoma. While it is possible for patients with CLL to develop acute leukaemia and myelodysplastic syndrome, it is uncommon.[2]

Current Treatment Protocols

The treatment of CLL may include chemotherapy, CIT or treatments that target the signalling pathways that promote the growth and/or survival of CLL cells. Figure 4 provides an overview of the management for patients with CLL.

FIGURE 4: MANAGEMENT ALGORITHM FOR PATIENTS WITH CLL



Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Dis Primers. 2017 Jan 19; 3:16096. doi: 10.1038/nrdp.2016.96. 2017)

BTK = Bruton tyrosine kinase; CIT = chemoimmunotherapy; CLL = chronic lymphocytic leukaemia; IGHV = immunoglobulin heavy-chain variable region; LDT = lymphocyte doubling time; PI3K = phosphoinositode 3-kinase

Within chemotherapy, different kinds of chemotherapy are used depending on the situation. There are purine analogues (fludarabine, pentostatin, cladribine) and alkylating agents such as chlorambucil, cyclophosphamide or bendamustine. CIT includes the use of anti-CD20 monoclonal antibodies such as rituximab, obinutuzumab or ofatumumab in combination with chemotherapy.[2,14] There are no head-to-head randomised studies comparing obinutuzumab and ofatumumab. In clinical trials that have compared ofatumumab plus chemotherapy versus rituximab plus chemotherapy, primarily chlorambucil, efficacy appears to be similar. However, comparisons of obinutuzumab plus chemotherapy versus rituximab plus chemotherapy showed the use of obinutuzumab to be superior. While this is an indirect comparison, it is highly likely that obinutuzumab is superior to ofatumumab.[7]

There are three main classes of drugs that can inhibit BCR signalling:

- Bruton tyrosine kinase (BTK) inhibitors (ibrutinib);
- Phosphatidylinositol 3-kinase (PI3K) inhibitors (idelalisib);
- Spleen tyrosine (SYK) inhibitors.

CLL cells with unmutated *IGHV* appear to be more sensitive to inhibitors of BCR signalling than CLL cells with mutated *IGHV*. What is unclear is whether inhibitors, such as ibrutinib, are more effective in patients with CLL who have unmutated *IGHV*. This needs to be validated in clinical trials. Idelalisib is the only PI3K inhibitor with regulatory approval globally in 24 member countries; additional ones are being evaluated in clinical trials.[2,14]

In the updated treatment guidelines issued by the European Society of Medical Oncology (ESMO) in 2016, in patients with the *TP53* deletion/mutation who are not suitable for treatment with a BTK inhibitor, idelalisib plus rituximab is recommended for use in first-line treatment. Ibrutinib can be considered as an alternative treatment option to chlorambucil-based CIT as a first-line treatment option but the lack of long-term experience with the use of ibrutinib in first line must be taken into consideration.[15] SYK inhibitors are still being evaluated in clinical trials. Venetoclax is a B-cell lymphoma (BCL)-2 inhibitor that kills CLL cells. It is effective in relapsed/refractory disease as well as in patients who have relapsed and have del(17p).[2,14]

When determining which regimen to use, patients with del(17p) will likely be resistant to standard regimens involving either alkylating agents or purine analogues.[6] For these patients the use of a BTK inhibitor or a P13K inhibitor plus rituximab is recommended.[15] For CLL without del(17p), it is recommended that that the ESMO clinical practice guideline be followed.[7,15]

For the purpose of this review and to determine what treatment protocols should be accessible to patients with CLL, LC reviewed the information from both the ESMO clinical practice guideline and the National Comprehensive Cancer Network (NCCN) listing. The ESMO clinical practice guideline for first-line treatment was updated in 2016; NCCN's guideline was updated in 2017.[3,4,15] Given the complexity of CLL, the treatment regimens listed in Table 1 are not categorised by any particular subtype or prognostic factor. For more specific information, please refer to either the ESMO guidelines or the NCCN listing.[3,4,15]

TABLE 1. NCCN LISTING AND ESMO GUIDELINE FOR CLL[3,4,15]

NCCN		ESMO	
First Line	**Relapsed**	**First Line**	**Relapsed**
Alemtuzumab ± rituximab	Alemtuzumab ± rituximab		
BR	BR	BR	BR
Ch			
Ch-R	Ch-R	Ch-R	Ch-R
	FCO		
FCR	FCR	FCR	FCR
FR			
HDMP±R	HDMP±R		
Ibr	Ibr	Ibr	Ibr
	Id-R	Id-R	Id-R
Lenalidomide maintenance	Lenalidomide maintenance		
	LR		
	Ob		
Ob-Ch		Ob-Ch	
	Of		
	OFAR		
	Ofatumumab maintenance		
Of-Ch		Of-Ch	Of-Ch
PCR	PCR		
	R-CHOP		
	Venetoclax ± rituximab		

BR = bendamustine±rituximab; Ch = chlorambucil; Ch-R = chlorambucil, rituximab; ESMO = European Society of Medical Oncology; FCR = fludarabine, cyclophosphamide, rituximab; FR = fludarabine, rituximab; HDMP±R = high-dose methylprednisolone + rituximab; Id-R = idelalisib, rituximab; Ibr = ibrutinib; LR = lenalidomide±rituximab; Ob-Ch = obinutuzumab, chlorambucil; NCCN = National Comprehensive Cancer Network; Of-Ch = ofatumumab, chlorambucil; OFAR = oxaliplatin, fludarabine, cytarabine, rituximab; PCR = pentostatin, cyclophosphamide, rituximab

Therapy Access

LC looked at access to treatment in LC member countries to determine what CLL therapies were available. A list of these treatment protocols is on the LC website. Table 2 shows which of the therapy protocols in the ESMO or NCCN listings had regulatory as well as funding/reimbursement approval in each member country. As the table shows, there was a wide discrepancy among countries in terms of the protocols with regulatory approval compared with those that were funded/reimbursed.

When LC reviewed therapy protocols by region, it was observed that in Africa none of the newer therapies were available with rituximab being the only anti-CD-20 monoclonal antibody with both regulatory and funding/reimbursement approval. In Asia/Pacific, China was the only country that did not have any of the newer therapies with either regulatory or funding/reimbursement approval.

With the exception of Macedonia, many of the newer therapies had regulatory approval in Eastern Europe although not all had reimbursement/funding approval. In Latvia, none of the newer therapies were funded or reimbursed, while in Macedonia none of the newer therapies had either regulatory or funding/reimbursement approval. Similarly in Western Europe, while most of the newer therapies had regulatory approval, not all were funded/reimbursed. This was particularly noticeable in Ireland. No reimbursement information was available for Portugal.

Patients with CLL living in Latin America likely struggle to receive current therapy. While Argentina had many of the newer therapies available, it was unclear how many, if any, were funded/reimbursed. Brazil was the only country that provided funding for ibrutinib and idelalisib ± rituximab.

In North America, the USA had the highest number of therapies with regulatory approval; however, access to them depends on the type of health insurance a patient has. In Canada, all the newer therapies, with the exception of venetoclax, which had not been reviewed at the time of this publication, were funded/reimbursed.

Venetoclax, indicated for del(17p), is one of the latest therapies to receive regulatory approval in 24 countries to date. However, only six countries provided funding/reimbursement. In the USA, coverage for venetoclax will depend on the patient's individual plan but co-payment from the patient will likely be required. A somewhat encouraging sign is that ibrutinib, another treatment indicated for relapsed/refractory CLL with del(17p), had regulatory approval in 30 LC member countries and funding/reimbursement approval in 23 countries. In the 2016 Lymphoma eInformation Project Report Card on Lymphomas, of the 12 countries examined, 10 had provided regulatory approval but only two countries funded/reimbursed ibrutinib. It is critical that patients gain access to these new therapies to ensure they are receiving optimal treatment.

TABLE 2. CLL: THERAPY ACCESS BY LC MEMBER COUNTRY

	Therapies with Regulatory Approval	Therapies with Funding/ Reimbursement Approval
Eastern Europe		
Bulgaria	B, B-Of, BR, Ch, CVP±R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	B, BR, Ch, CVP±R, F, FC, FCM±R, FCR, FR, Ibr, HDMP±R, Of, Of-Ch, R
Croatia	B, B-Of, BR, CFAR, Ch, Ch-R, CHOP-R, cladribine, CVP±R, EPOCH-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, hyperCVAD-R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, PCR, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax	B, BR, Ch, Ch-R, CHOP-R, cladribine, EPOCH-R, FC, FCM±R, FCR, FR, HDMP±R, hyperCVAD-R, Ibr, Id-R, Ob-Ch, PCR, R, SCT
Czech Republic	B, B-Of, BR, Ch, Ch-R, cladribine, cyclophosphamide, DHAP±R, DRC, ESHAP-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, ICE-R, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax	B, B-Of, BR, Ch, Ch-R, cladribine cyclophosphamide, DHAP±R, DRC, ESHAP-R, F, FC, FCM±R, FCR, FR, HDMP, Ibr, ICE-R, Id-R, Ob-Ch, Of-Ch, R, SCT
Hungary	B, B-Of, BR, Ch, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	B, BR, Ch, FC, FCM±R, FCR, FR, HDMP±R, Ibr, R
Latvia	B, B-Of, BR, Ch, F, FC, FCM, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	FC
Lithuania	B, B-Of, BR, Ch, Ch-R, CVP±R, FC, FCM±R, FCO, FCR, FNDR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	B, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCR, FNDR, FR, HDMP±R, Ibr, Id-R, Ob-Ch, Of-Ch, R
Macedonia	FC, FCR, FCM±R, F-prednisone, FR, HDMP±R	FC, FCR, FCM±R, F-prednisone, FR, HDMP±R
Poland	B, B-Of, BR, Ch, Ch-R, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	B, BR, Ch, Ch-R, FC, FCR, FR, HDMP±R, Ob-Ch
Russian Federation	BR, Ch, F, FC, FCMR, FCR, HDMP±R, Ibr, R	BR, Ch, F, FC, FCMR, FCR, HDMP±R, Ibr, R
Serbia	B, B-Of, BR, Ch, Ch-R, cyclophosphamide, F, FC, FCM±R, FCR, FR, Ibr, Ob-Ch, Of-Ch, R	B, BR, Ch, Ch-R, cyclophosphamide, F, FC, FCM±R, FCR, FR, R
Slovakia	B, B-Of, BR, Ch, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-R, Id-Of, Ob-Ch, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	B, BR, B-Of, Ch, Ch-R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-Of, Id-R, Ob-Ch, Of-Ch, R
Slovenia	B, B-Of, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	B, B-Of, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Ob-Ch, Of, Of-Ch, R
Turkey	B, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-R, Of, R	B, BR, Ch, Ch-R, CVP±R, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-R, Of, R
Ukraine	Ch, CHOP-R, FC, FCR	No information available

	Therapies with Regulatory Approval	Therapies with Funding/ Reimbursement Approval
Western Europe		
Belgium	B, B-Of, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	B, BR, Ch, Ch-R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-R, Ob-Ch, R
Denmark	Alemtuzumab, B, B-Of, BR, Ch, Ch-R, CHOP-R, cladribine, CVP±R, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	Alemtuzumab, BR, Ch, Ch-R, CHOP-R, cladribine, CVP±R, FC, FCM±R, FCR, FR, HDMP±R, Ibr, IBR, Id-R, Ob-Ch, Of, Of-Ch, R, venetoclax
France	Alemtuzumab, B, B-Of, BR, Ch, FC, FCO, FCM±R, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	Alemtuzumab, B, B-Of, BR, Ch, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, venetoclax
Germany	B, B-Of, BR, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax	B, B-Of, BR, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, SCT, venetoclax
Ireland	B, B-Of, BR, Ch, CVP±R, FC, FCM-R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax	B, BR, Ch, CVP±R, FC, FCR, FR, HDMP, Ob-Ch, R, SCT
Israel	B, B-Of, BR, Ch, cladribine, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Ob-Ch, Of, Of-Ch, R, venetoclax	B, B-Of, BR, Ch, cladribine, F, FC, FCM±R, FCR, HDMP±R, Ibr, Ob-Ch, Of, R, venetoclax
Italy	B, B-Of, BR, Ch, cladribine, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax	B, BR, B-Of, Ch, cladribine, F, FC, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Of, Of-Ch, R
Netherlands	Alemtuzumab, B-Of, BR, Ch, DHAP±R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax	Alemtuzumab, B-Of, BR, Ch, DHAP±R, F, FC, FCM±R, FCR, HDMP±R, Ibr, Id-R, Ob-Ch, Of, Of-Ch, R, SCT, venetoclax
Portugal	B, B-Of, BR, Ch, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	No information available
Spain	Alemtuzumab, B, B-Of, BR, Ch, Ch-R, F, FC, FCM-R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, PCR, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax	Alemtuzumab, B, BR, B-Of, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, PCR, R, SCT
Sweden	B, B-Of, BR, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax	B, B-Of, BR, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R
Switzerland	B, B-Of, BR, Ch, Ch-R, CHOP-R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id, Id-R, Ob-Ch, Of, Of-Ch, R, SCT	B, BR, Ch, Ch-R, CHOP-R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id, Id-R, Ob-Ch, R, SCT
UK	B, B-Of, BR, Ch, Ch-R, cladribine±R, CVP±R, cyclophosphamide, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, pentostatin, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax	B-Of, BR, Ch, Ch-R, cladribine±R, CVP±R, cyclophosphamide, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-R, Ob-Ch, Of, Of-Ch, pentostatin, R, SCT

Source: LC Global Database June 2017

TABLE CONTINUED ON PAGE 15

TABLE 2. CLL: THERAPY ACCESS BY LC MEMBER COUNTRY (CONTINUED)

	Therapies with Regulatory Approval	Therapies with Funding/ Reimbursement Approval
Africa		
Algeria	Ch, FC, FCR	Ch, FC, FCR
South Africa	Alemtuzumab, Ch, CHOP-R, CVP±R, cyclophosphamide, F, FC, FCR, R, SCT	Coverage provided through private insurance. Level of coverage depends on individual plans but usually requires co-payment from patient.
Asia/Pacific		
Australia	Alemtuzumab, B, BR, Ch, Ch-R, cladribine, cyclophosphamide, FC, FCM±R, FCR, FMD, FMR, FR, Ibr, Id-R, Ob-Ch, Of-Ch, R, venetoclax	BR, Ch, Ch-R, cladribine, cyclophosphamide, FC, FCM, FCR, FMD, FR, Ob-Ch, Of-Ch, R
China	Ch, FC, FCR	Ch, FC, FCR
India	B, BR, Ch, FC, FCR, R	No information available
Japan	Alemtuzumab, B, BR, Ch, Ch-R, FC, FCR, Ibr, Of, Of-Ch, R	Ch, Ch-R, FC, FCR, Ibr, Of, Of-Ch, R
New Zealand	B, BR, Ch, Ch-R, CHOP-R, cladribine, CVP±R, cyclophosphamide, F, FC, FCR, Ibr, Id-R, Ob-Ch, R	BR, Ch, cladribine, F, FC, FCR, Ob-Ch, R
Singapore	B, BR, Ch, Ch-R, CVP±R, FC, FCR, FR, Ibr, Of, Of-Ch, R	No information available
Latin America		
Argentina	Alemtuzumab, B, BR, Ch, Ch-R, CHOP-R, FC, FCR, FR, Ibr, Of, Of-Ch, R, SCT	No information available
Barbados	Ch, CVP	No information available
Brazil	B, BR, Ch, Ch-R, FC, FCR, Ibr, Id-R, Ob-Ch, R	FC, FCR, Ibr, Id-R, R
Colombia	Alemtuzumab, B, Ch, FC, FCR, FR, Ibr, R	Ch
Mexico	Ch, FC, FCR, Ibr, R	Ch, FCR, R
Uruguay	B, BR, CHOP-R, cyclophosphamide, FC, FCR, R	B, BR, CHOP-R, cyclophosphamide, FC, FCR, R
Venezuela	Information not available	Information not available
North America		
Canada	Alemtuzumab, alemtuzumab-F, alemtuzumab-R, B, BR, Ch, Ch-R, CHOP±R, CP-R, cyclophosphamide, F, FC, FCM±R, FCR, FP, FR, HDMP±R, Ibr, IBR, Id-R, Ob-Ch, Of, Of-Ch, R, R maintenance, RT, SCT, venetoclax	Alemtuzumab, alemtuzumab-F, alemtuzumab-R, B, BR, Ch, Ch-R, CHOP±R, CP-R, cyclophosphamide, F, FC, FCM±R, FCR, FP, FR, HDMP±R, Ibr, Id-R, Ob-Ch, Of, R, R maintenance, RT, SCT
USA	Alemtuzumab, alemtuzumab-F, alemtuzumab-R, B, BR, BRI, CFAR, Ch, Ch-R, ChIVPP, CHOP±R, cladribine, CP-R, cyclophosphamide, FC, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id, Id-R, lenalidomide, lenalidomide maintenance, LR, Ob, Ob-Ch, Of, Of maintenance, OFAR, Of-Ch, PCR, R, SCT, venetoclax, venetoclax-R	Therapies are covered by insurance plans. Level of coverage depends on individual plans. Usually requires co-payment from patient.

Source: LC Global Database June 2017

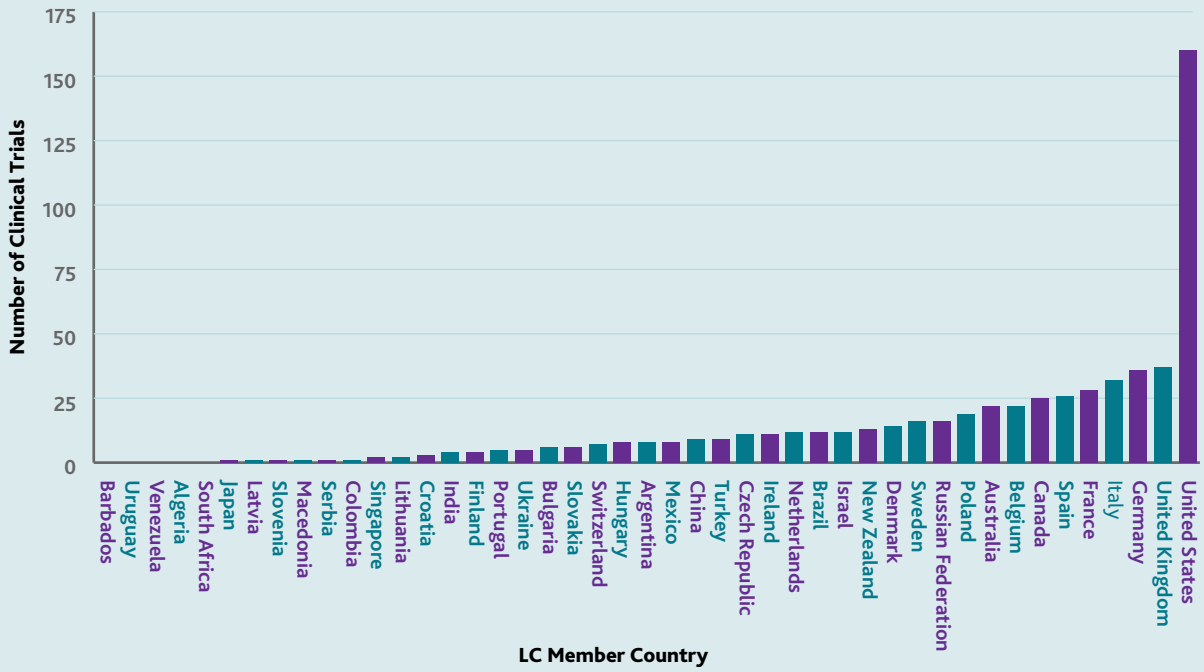
B = bendamustine; B-Of = bendamustine, ofatumumab; BR = bendamustine±rituximab; BRI = bendamustine, rituximab, idelalisib; CFAR = cyclophosphamide, fludarabine, alemtuzumab, rituximab; Ch = chlorambucil; Ch-R = chlorambucil+rituximab; ChIVPP = chlorambucil, vinblastine, procarbazine, prednisone; CHOP-R = cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab; CVP±R = cyclophosphamide, vincristine, prednisone±rituximab; DHAP±R = dexamethasone, cisplatin, cytarabine±rituximab; DRC = dexamethasone, rituximab, cyclophosphamide; EPOCH-R = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; ESHAP-R = etoposide, methylprednisolone, cytarabine, cisplatin, rituximab; F = fludarabine; FC = fludarabine, cyclophosphamide; FCM±R = fludarabine, cyclophosphamide, mitoxantrone ± rituximab; FCO = fludarabine, cyclophosphamide, ofatumumab; FCR = fludarabine, cyclophosphamide, rituximab; FMD = fludarabine, mitoxantrone, dexamethasone; FMR = fludarabine, mitoxantrone, rituximab; FNDR = fludarabine, mitoxantrone, dexamethasone,rituximab; FP = fludarabine, prednisone; FR = fludarabine, rituximab; HDMP±R = high-dose methylprednisolone±rituximab; hyperCVAD-R = cyclophosphamide, vincristine, doxorubicin, rituximab and dexamethasone alternating with high dose methotrexate and cytarabine; Ibr = ibrutinib; IBR = ibrutinib, bendamustine, rituximab; ICE-R = ifosfamide, carboplatin, etoposide, rituximab; Id = idelalisib; Id-Of = idelalisib, ofatumumab; Id-R = idelalisib+rituximab; Id-Of = idelalisib, ofatumumab; Id-R = idelalisib, rituximab; LR = lenalidomide±rituximab; Ob-Ch = obinutuzumab+chlorambucil; Of = ofatumumab; Of-Ch = ofatumumab+chlorambucil; OFAR = oxaliplatin, fludarabine, cytarabine, rituximab; PCR = pentostatin, cyclophosphamide, rituximab; R = rituximab; RT = radiation therapy; SCT = stem cell transplant

Overall, more research needs to look at combinations of therapies and sequencing of therapies to perfect the ideal treatment pathway, especially with the new treatments now available.

Clinical Trial Activity

As of March 2017, there were 211 clinical trials underway involving patients with CLL based on information from the six clinical trial registries LC follows.[a] Of these 211 clinical trials, 147 were specifically for patients with CLL. Among the 46 LC member countries, five had no current trials for CLL; namely Algeria, Barbados, South Africa, Uruguay and Venezuela (see Figure 5). The USA was involved in the majority of the clinical trials (n = 160).

FIGURE 5. CLL CLINICAL TRIALS BY COUNTRY



Source: LC Global Database March 2017

[a] The six clinical trial registries LC follows are Clinicaltrials.gov, Australian Cancer Trials, European Union Clinical Trials Register, World Health Organization, JAPIC Clinical Trials Information (Japan), Clinical Trials Registry, India

The majority of the clinical trials (n = 170) underway in CLL were studying the use of novel agents which is encouraging given the heterogeneity of the disease. Within the phase II clinical trials, most (n = 78) were studying the use of novel therapies in the relapsed/refractory setting. Similarly in the phase III trials, most (n = 24) were examining the use of novel therapies in the relapsed/refractory setting (see Figures 6 and 7).

While it is encouraging to see the extent of clinical trial activity for CLL, what is of concern is that few of the clinical trials specifically examine issues as they pertain to the elderly with CLL. Most clinical trials involve younger patients (under the age of 65 years), yet the median age of diagnosis is 72 years with the average time to first treatment being four to five years from the time of diagnosis.[14] Of the 211 CLL clinical trials in LC's global database, only seven were exclusively for patients aged 65 years and older. Anecdotally, this has also been identified as an issue by the CLL Advocates Network (CLLAN), an international collective representing CLL patient groups. Most patients in CLL clinical trials are younger than the typical patient with CLL, consequently, there is an unmet need in the understanding of the true impact of therapies on older patients who have comorbidities.[16]

FIGURE 6. PHASE II CLINICAL TRIALS FOR CLL

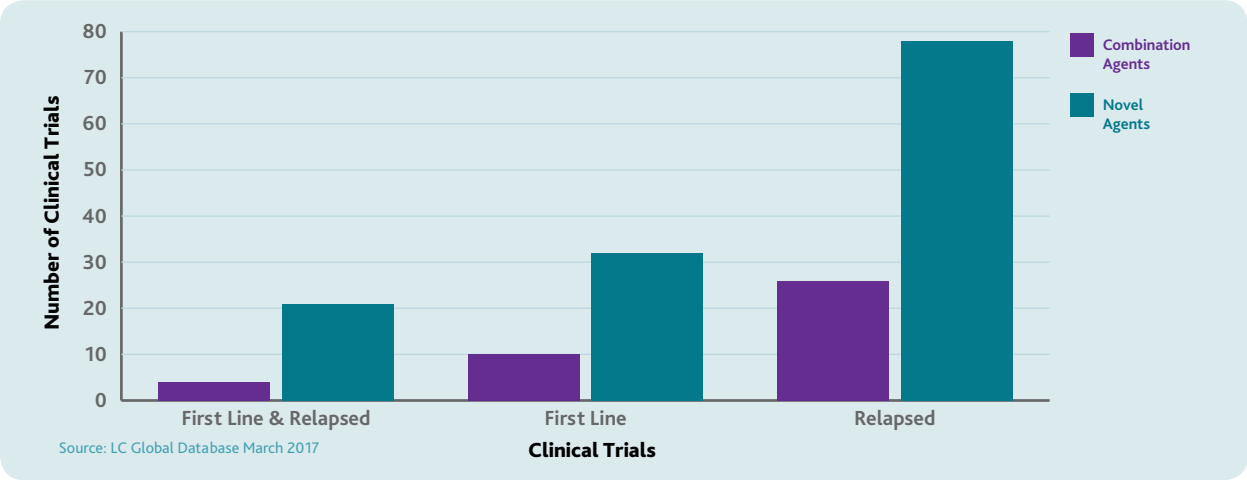
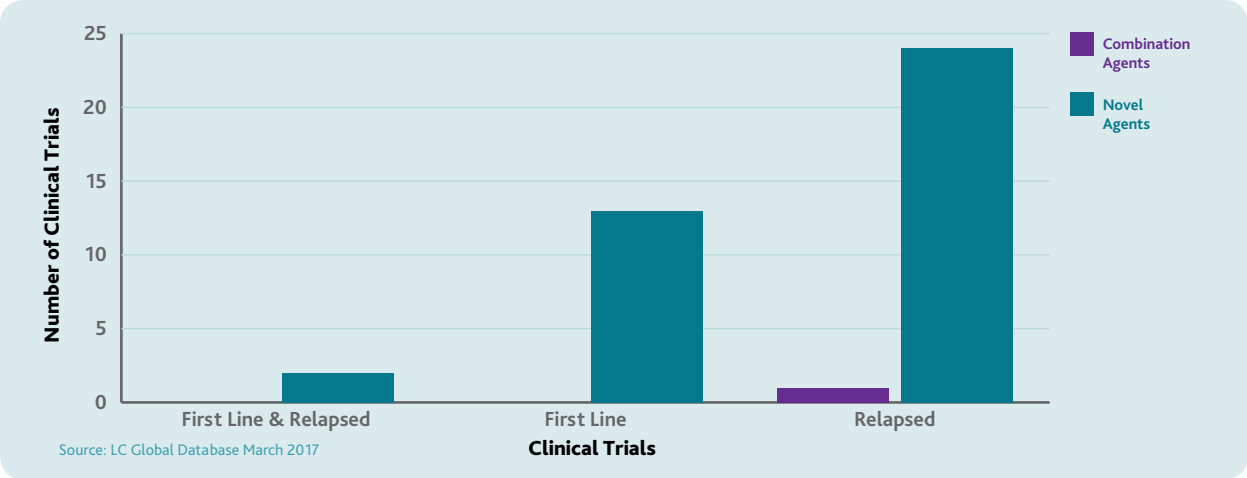


FIGURE 7. PHASE III CLINICAL TRIALS FOR CLL

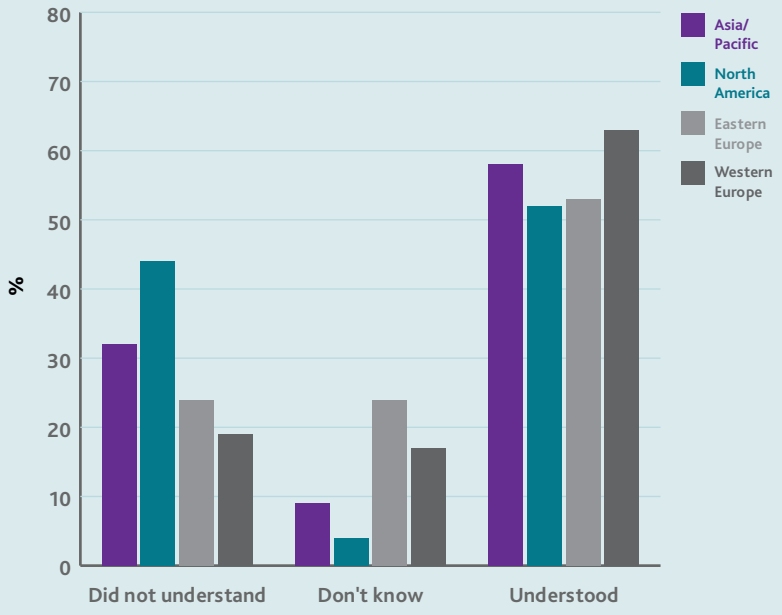


The Patient Experience

The 2016 Lymphoma Global Patient Survey (GPS) is the document LC references in this report to provide a sense of the patient experience. Of the more than 4,000 respondents in the GPS, 416 indicated they had CLL/SLL (small lymphocytic leukaemia) (the survey question was combined and not separated out). Findings in this section are reported for the CLL/SLL subtype by region. No findings can be reported for Latin America as no respondents from that region indicated they had CLL/SLL.

Respondents were asked if they were made aware of their subtype at their initial diagnosis. Most (81%) indicated they were told their subtype and 80% indicated that they had understood their diagnosis. However, when asked if they had understood their subtype's characteristics, only 56% said they had. From a regional perspective, respondents in Western Europe had the highest level of understanding (63%) while respondents in North America had the lowest level of understanding (52%). This is likely not surprising as 44% of respondents in North America indicated they did not understand their subtype's characteristics (see Figure 8).

FIGURE 8. LEVEL OF UNDERSTANDING OF SUBTYPE CHARACTERISTICS



2016 Lymphoma Global Patient Survey

81%
were told their subtype

80%
had understood their diagnosis

56%
understood their subtype's characteristics

Understanding the characteristics of CLL/SLL is key given its chronic nature as well as its heterogeneity. If patients do not have a good understanding about their subtype and the chromosomal alterations associated with CLL/SLL, they are unable to seek information that will help them be better informed.

Respondents were asked how well they had understood their treatment options. Findings showed that the level of understanding was highest among respondents in Western European (81%) and lowest among those in North America (53%) (see Figure 9). When looking at the percentage of participants who did not understand their treatment options, respondents in North America had the least understanding at 43%. This is of concern as patients with CLL/SLL need to understand their treatment options and in what order they will receive them as some patients, once treatment starts, will need to continue it for their lifetime. What determines whether a patient will achieve permanent remission are their prognostic factors and the therapy used. For example, among patients with *IGVH*-mutated CLL, no del(17p) or *TP53* mutation or *NOTCH1* and who receive fludarabine, cyclophosphamide and rituximab (FCR) as first-line therapy, between 40% and 60% will achieve ongoing remission lasting beyond eight to 15 years.[7,17-19] Those patients receiving CIT, regardless of type and whether in the first-line or the relapsed setting, will receive six cycles of FCR, six cycles of bendamustine plus rituximab and six cycles of obinutuzumab plus chlorambucil. The current standard approach for using a targeted agent – ibrutinib, idelalisib or venetoclax – is continuous treatment until progression.[7]

Respondents were also asked how well they understood the potential for side effects from treatment.

While 60% of respondents in Western Europe reported understanding the side effects associated with their treatment, 51% of respondents in North America did not (see Figure 10).

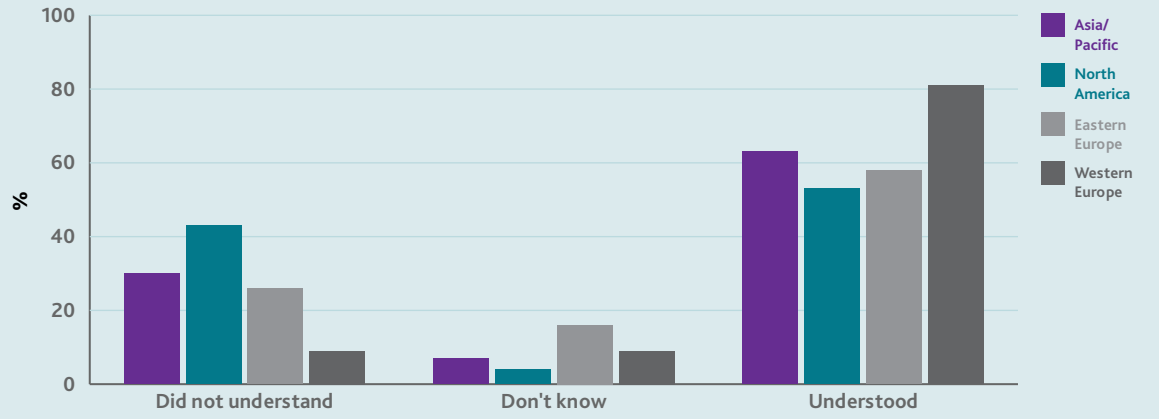
Again, this is of concern as patients need to understand what the likely side effects are with each treatment regimen they may be prescribed and how to balance this information against the effectiveness of a regimen.

Respondents were asked about how well they understood the side-effect management associated with their treatment. In all regions, the level of understanding was under 50% (see Figure 11).

Unfortunately, treatments often cause side effects; consequently, management is an important part of patient care. It is important for patients to know when to seek medical attention. Greater efforts are also needed to encourage patients to talk about side effects they may be experiencing. Anecdotally, LC has been told that many patients may not want to admit they are experiencing side effects for fear of having to stop treatment. Compounding this issue is that doctors do not ask patients about side effects such as nausea, diarrhea, neuropathy, fatigue and functional status.[20]

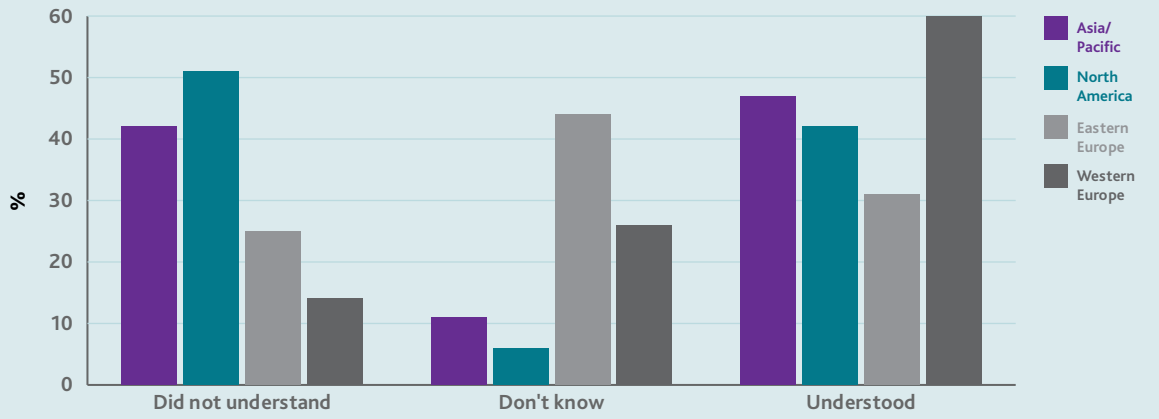
To determine if patients were raising their concerns with their healthcare provider (HCP), respondents were asked if they had told their doctor about their emotional and physical issues. While 60% of respondents in Western Europe and 59% of respondents in North America reported communicating their concerns, only 32% had done so in Eastern Europe (see Figure 12).

FIGURE 9. LEVEL OF UNDERSTANDING OF TREATMENT OPTIONS



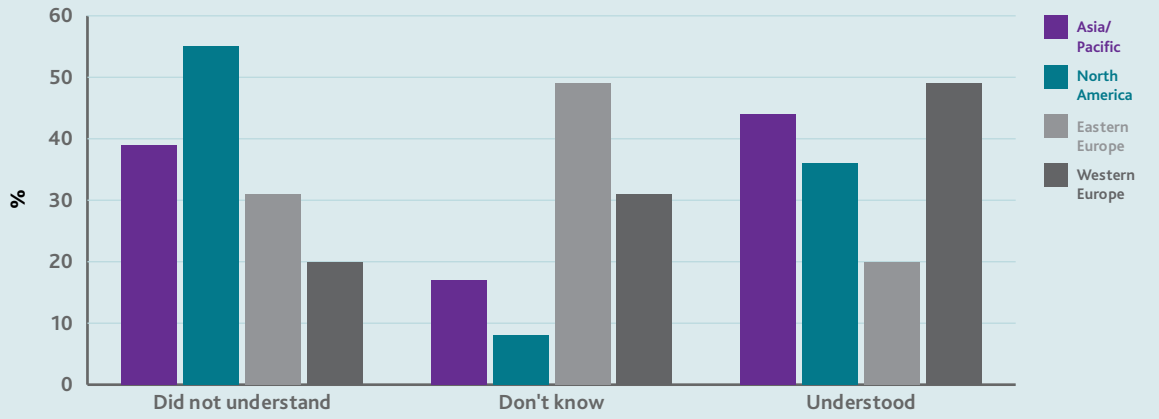
2016 Lymphoma Global Patient Survey

FIGURE 10. UNDERSTOOD SIDE EFFECTS OF TREATMENT



2016 Lymphoma Global Patient Survey

FIGURE 11. LEVEL OF UNDERSTANDING OF SIDE-EFFECT MANAGEMENT



2016 Lymphoma Global Patient Survey

When asked if the doctor was helpful in addressing their concerns, respondents in Eastern Europe, Western Europe and North America indicated overwhelmingly that doctors were only able to help them somewhat and **29% of all respondents indicated they did not get any support** (see Figure 13).

In Asia/Pacific, only 31% of respondents indicated that doctors were able to help them. A communication strategy that allows patients to express their concerns to HCPs is a key element in the treatment of any illness. If HCPs are pressed for time, it would be helpful if a referral was made for further support and dialogue to the nurse or social work department within the clinic, or to an appropriate local patient organisation.

LC asked respondents what kind of support they found helpful. Globally, **77% of respondents found patient organisations helpful.**

Figure 14 shows the degree of helpfulness by region.

One of the most important aspects of patient care is education about their illness and related treatment options, as well as potential side effects. This information allows patients to better manage their condition, remain compliant and reduce their fear. This is especially true in CLL/SLL.

To tell patients that their initial treatment is a watch-and-wait approach is counterintuitive and requires specific education and support.[16]

The impact on patients after being told they have a cancer that is incurable and for which they will not be receiving treatment may be beyond their comprehension.

FIGURE 12. RESPONDENTS COMMUNICATING WITH THEIR DOCTOR

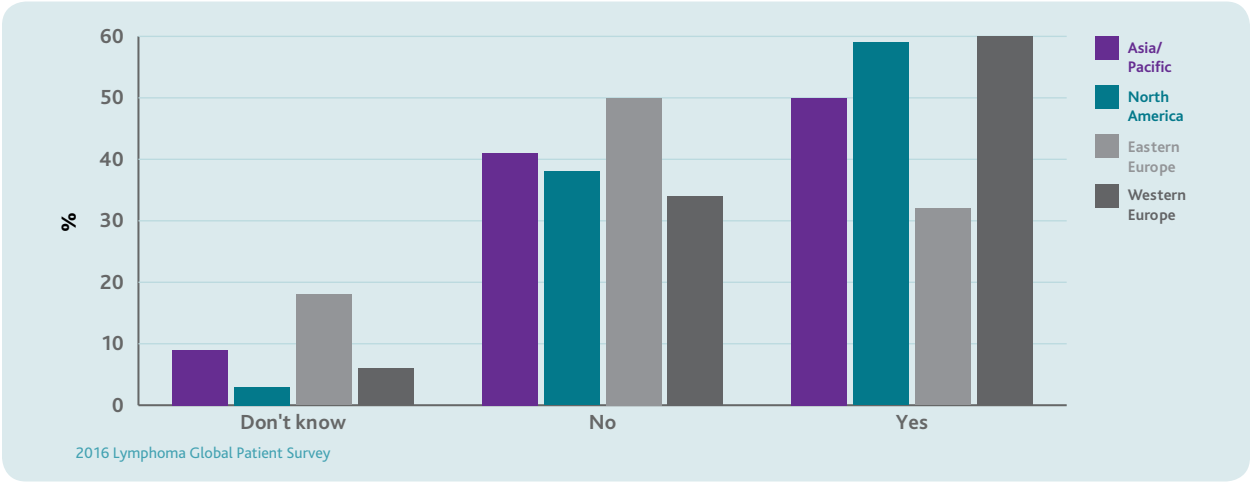


FIGURE 13. PATIENTS HELPED BY DOCTOR

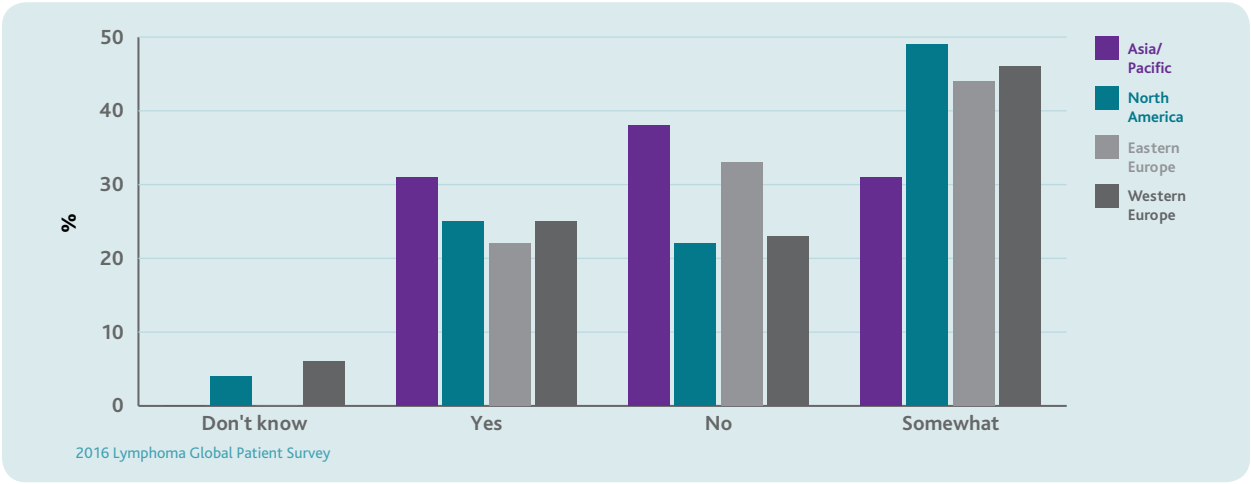
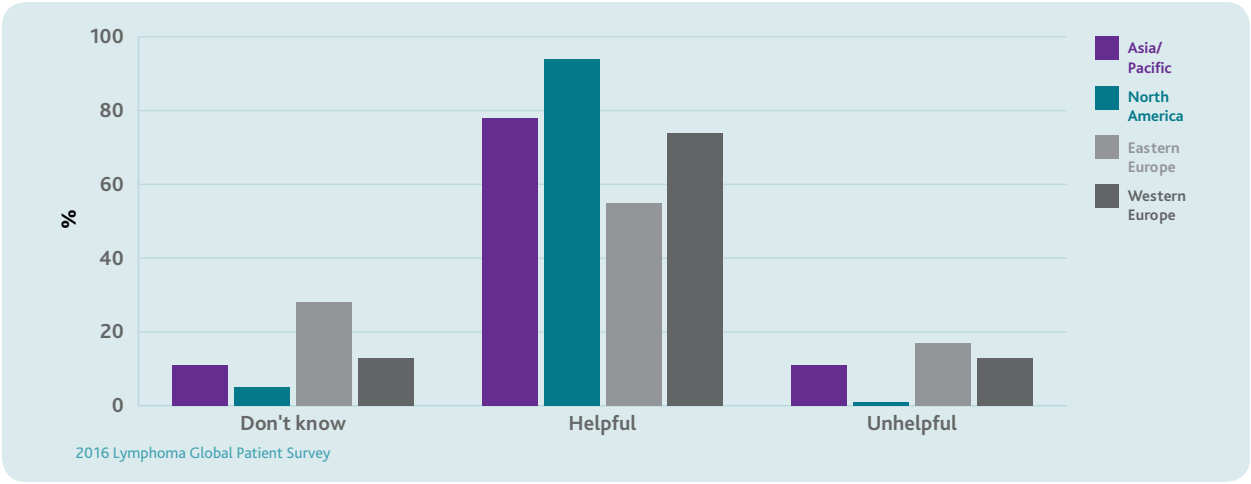


FIGURE 14. USEFULNESS OF PATIENT ORGANISATION



Physical Side Effects

Respondents were asked to indicate which physical effects had affected them the most. As in other subtypes of lymphoma, fatigue was the physical effect of greatest concern for all respondents (see Figure 15). Other physical effects that caused issues for respondents with CLL/SLL were trouble concentrating, muscle weakness, aching joints, sleeplessness and problems fighting infections. This leads to patients having to change their lifestyle as they adapt to resting more, avoiding crowds and, possibly, not being able to do the activities that they have built their self-worth around.[16]

The psychological burden of dealing with a long-term illness, like CLL/SLL, will often affect a patient's sense of well-being. Respondents were asked what psychological issues had been the most burdensome. Among respondents in North America, depression was of greatest concern (33%) while the fear of relapse was of greatest concern among respondents in Western Europe (30%) (see Figure 16). Many patients suffer from depression and anxiety as they adapt to living with an incurable cancer that is often not treated immediately upon diagnosis. Other issues of concern were stress related to financial issues, changes in relationships with loved ones and isolation.

Fatigue

was the physical effect of greatest concern.

Many patients suffer from

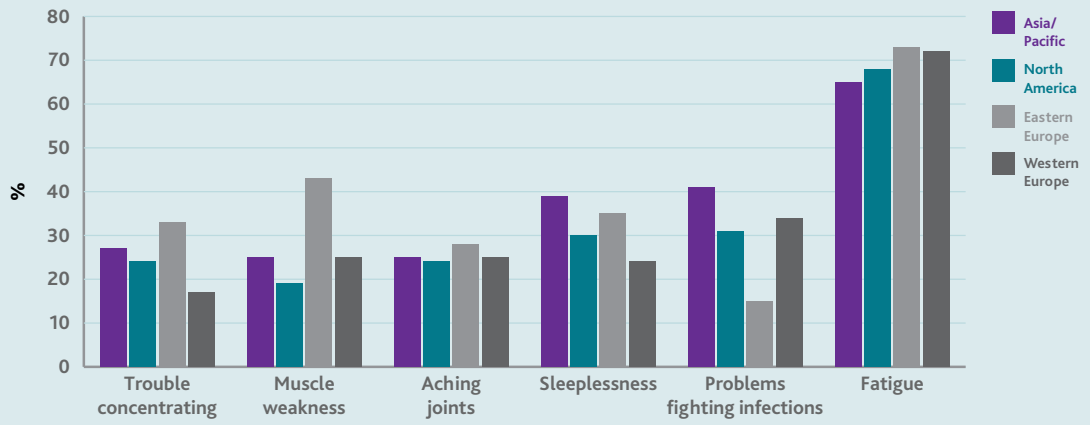
depression & anxiety

as they adapt to living with an incurable cancer.

Barriers to Treatment

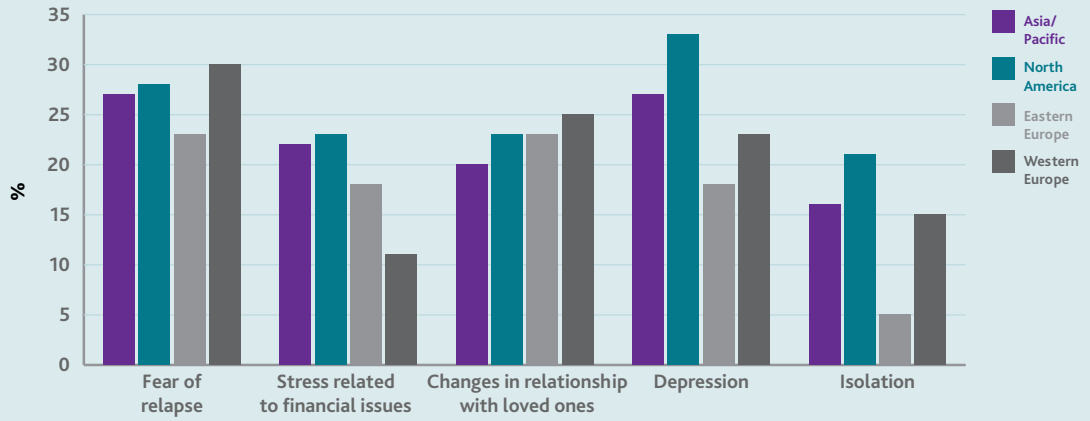
LC asked respondents what barriers, if any, they had experienced that prevented them from receiving adequate treatment. Among those who encountered barriers, access to a specialty physician was of greatest concern to respondents in North America (46%) as well as those in Asia/Pacific (40%). In Eastern Europe, the biggest barrier to treatment was access to the treatment centre (37%). Other barriers of concern in all regions were financial issues, personal support and access to up-to-date treatment (see Figure 17).

FIGURE 15. PHYSICAL SIDE EFFECTS



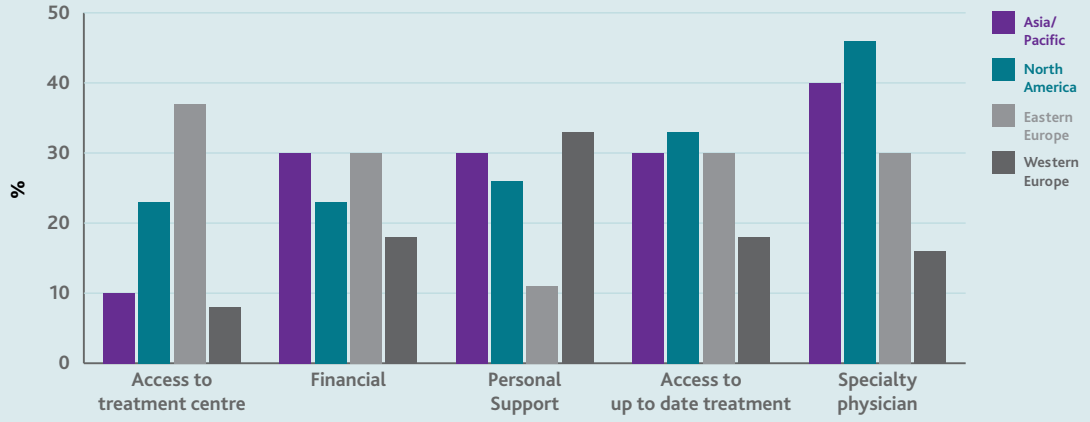
Source: LC Global Database March 2017

FIGURE 16. PSYCHOSOCIAL CONCERNS



2016 Lymphoma Global Patient Survey

FIGURE 17. BARRIERS TO TREATMENT BY REGION



2016 Lymphoma Global Patient Survey

Conclusion

To ensure patients with CLL receive the best possible care, it is key that the focus goes beyond the administration of therapy to include the psychological, emotional as well as physical effects associated with treatment. A multifaceted approach that provides information and care that corresponds to the patient's needs will likely result in patients being better able to cope with their lymphoma. There are services outside of the doctor's office that can provide such support and they should be used and recommended to patients. Given that CLL is a chronic as well as heterogeneous disease, this is of particular importance as each patient will present with their unique issues.

The lack of specialists and difficulty accessing a treatment centre also need to improve. Since general oncologists or general practitioners would have a difficult time staying current with all the treatment options now available for CLL along with their associated side effects, it is critical that patients can access specialists. Specialists play a critical role in the treatment process. Very often they will have run a clinical trial and will be very familiar with the issues pertaining to treatment regimens. This is knowledge that patients need. Solutions are also needed to help patients get to the treatment centre.

While it is encouraging that a great deal of research is occurring to better understand this subtype resulting in new treatments, more research is needed that examines the combination as well as sequencing of therapies to perfect the treatment pathway. There are also areas of concern with treatment as they relate to providing patients with optimal care. Access to the newer therapies needs to improve. There is now information to show which types of CLL will respond to which treatments. It is not acceptable for these newer therapies not to be easily available to patients who need them. The availability of CLL clinical trials in countries where there are none needs to improve. Improving access to clinical trials will result in better access to care.

Greater efforts are needed to ensure patients with CLL understand the nature of their subtype. Supporting patients while they are in the watch-and-wait phase of treatment is just as important as when they are undergoing treatment. Hence, the need for a holistic approach to treatment that encompasses both physical as well as psychological support.

A multifaceted approach that provides information and care that corresponds to the patient's needs will likely result in patients being better able to cope with their lymphoma.

There is now information to show which types of CLL will respond to which treatments.

It is not acceptable for these newer therapies not to be easily available to patients who need them.

Acronyms

B	bendamustine
BCL	B-cell lymphoma
BCR	B-cell receptor
B-Of	bendamustine, ofatumumab
BR	bendamustine±rituximab
BRI	bendamustine, rituximab, idelalisib
BTK	Bruton tyrosine kinase
CBC	complete blood count
CFAR	cyclophosphamide, fludarabine, alemtuzumab, rituximab
Ch	chlorambucil
CHOP-R	cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab
Ch-R	chlorambucil+rituximab
ChlVPP	chlorambucil, vinblastine, procarbazine, prednisone
CIT	chemotherapy plus immunotherapy
CLL	chronic lymphocytic leukaemia
CPR	cyclophosphamide, prednisone±rituximab
CVP±R	cyclophosphamide, vincristine, prednisone±rituximab
DHAP±R	dexamethasone, cisplatin, cytarabine±rituximab
DNA	deoxyribonucleic acid
DRC	dexamethasone, rituximab, cyclophosphamide
EPOCH-R	etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab
ESHAP-R	etoposide, methylprednisolone, cytarabine, cisplatin, rituximab
ESMO	European Society of Medical Oncology
F	fludarabine
FC	fludarabine, cyclophosphamide
FCM±R	fludarabine, cyclophosphamide, mitoxantrone±rituximab
FCO	fludarabine, cyclophosphamide, ofatumumab
FCR	fludarabine, cyclophosphamide, rituximab
FMD	fludarabine, mitoxantrone, dexamethasone
FMR	fludarabine, mitoxantrone, rituximab
FNDR	fludarabine, mitoxantrone, dexamethasone, rituximab
FP	fludarabine, prednisone
FR	fludarabine, rituximab
GI	gastrointestinal
GPS	Global Patient Survey
HCP	healthcare provider
HDMP±R	high-dose methylprednisolone±rituximab
hyperCVAD-R	cyclophosphamide, vincristine, doxorubicin, rituximab and dexamethasone alternating with high-dose methotrexate and cytarabine
Ibr	ibrutinib
IBR	ibrutinib, bendamustine, rituximab
ICE-R	ifosfamide, carboplatin, etoposide, rituximab
Id	idelalisib
Id-Of	idelalisib, ofatumumab
Id-R	idelalisib+rituximab
IGVH	immunoglobulin heavy-chain variable region
LC	Lymphoma Coalition
LR	lenalidomide±rituximab
MBL	monoclonal B-cell lymphocytosis
NCCN	National Comprehensive Cancer Network
NMSC	nonmelanoma skin cancer
Ob-Ch	obinutuzumab+chlorambucil
Of	ofatumumab
Of-Ch	ofatumumab+chlorambucil
OFAR	oxaliplatin, fludarabine, cytarabine, rituximab
PCR	pentostatin, cyclophosphamide, rituximab
PI3K	phosphatidylinositol 3-kinase
R	rituximab
RT	radiation therapy
SCT	stem cell transplant
SLL	small lymphocytic leukaemia
SYK	spleen tyrosine
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

References

1. Lazarian G et al. Clinical implications of novel genomic discoveries in chronic lymphocytic leukemia. J Clin Oncol 2017;35:984-93.
2. Kipps TJ et al. Chronic lymphocytic leukaemia. Nat Rev Dis Primers 2017;3:16096. doi:10.1038/nrdp.2016.96.
3. Eichhorst B, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines. Ann Oncol 2015;26(S5):v78-v84.
4. NCCN clinical practice guidelines in oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma. NCCN Evidence Blocks. Version 1.2017. December 8, 2016.
5. Detecting chromosomal abnormalities in CLL. http://www.onclive.com/peer-exchange-archive/chronic-lymphocytic-leukemia/chromosomal-abnormalities-and-treatment-decisions-in-chronic-lymphocytic-leukemia. Accessed June 20, 2017.
6. Hallek M et al., Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute—Working Group 1996 Guidelines. Blood 2008;111:5446-56.
7. Personal communication with Dr. John Seymour, July 19, 2017.
8. Swerdlow SH et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
9. Beiggi S et al. Increased risk of second malignancies in chronic lymphocytic leukaemia patients as compared with follicular lymphoma patients: a Canadian population-based study. Br J Cancer 2013;109:1287-90.
10. Tsimberidou Am et al. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol 2009;27:904-10.
11. Wiernik PH. Second neoplasms in patients with chronic lymphocytic leukemia. Curr Treat Options Oncol 2004;5:215-23.
12. Jain P et al. Richter's transformation in chronic lymphocytic leukemia. Oncology (Williston Park) 2012;26:1146-52.
13. Royle JA et al. Second cancer incidence and cancer mortality among chronic lymphocytic leukaemia patients: a population-based study. Br J Cancer 2011;105:1076-81.
14. Jain N. Initial treatment of CLL: integrating biology and functional status. Blood 2015;126:463-70.
15. Eichhorst B et al. eUpdate – chronic lymphocytic leukaemia treatment recommendations. European Society of Medical Oncology, September 2016. http://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Lymphocytic-Leukaemia/eUpdate-Treatment-Recommendations. Accessed March 31, 2017.
16. Email communication with Lorna Warwick, CLL Advocates Network, March 9, 2017.
17. Fischer K et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood 2016;127:208-15.
18. Thompson PA et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood 2016;127:303-9.
19. García-Marco JA et al. [National guidelines for the management of patients with chronic lymphocytic leukemia. Sociedad Espan˜ola de Hematologı´a y Hemoterapia and Grupo Espan˜ol de Leucemia Linfocı´tica Cro´ nica]. Med Clin (Barc) 2013;141:175.e1-8. doi: 10.1016/j.medcli.2013.04.041. Epub 2013 Jul 3.
20. Lowry F. Make patient-reported outcomes part of routine cancer care. Medscape Medical News. http://www.medscape.com/viewarticle/874289. Accessed March 31, 2017.

LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

know your subtype

Lyfe

www.lymphomacoalition.org

To ensure patients with CLL receive the best possible care, it is key that the focus goes beyond the administration of therapy to include the psychological, emotional as well as physical effects associated with treatment. A multifaceted approach that provides information and care that corresponds to the patient's needs will likely result in patients being better able to cope with their lymphoma.