Follicular Lymphoma

Subtype Report

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LYMPHOMA COALITION
Worldwide Network of Lymphoma Patient Groups

Follicular Lymphoma

Introduction

The focus for this report is to review patient access to care in Follicular Lymphoma (FL); namely therapy access, clinical trials, incidence and mortality and some aspects of the patient experience.

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 ones subtype since it is a critical piece of information in determining the best treatment required. The LC created the Global Database to house subtype information for this purpose. It provides LC with the opportunity to analyse the individual subtype needs and review any issues or challenges by country.

Follicular Lymphoma Overview

Lymphoma is cancer of the lymph system (or lymphatic system), which is part of our immunity. It is characterised by the formation of solid tumours in the immune system. The cancer affects immune cells called lymphocytes, which are white blood cells.[1]

Follicular lymphoma (FL) is a subtype of lymphoma.

FL, a B-cell lymphoma, is a low-grade (indolent) form of lymphoma. Common signs of FL include enlargement of the lymph nodes in the neck, underarm, stomach, or groin, as well as fatigue, shortness of breath, night sweats, and weight loss.[2] Often people with FL may have no obvious symptoms of the tumour at diagnosis. Many patients respond well to treatment and live with the condition as a chronic disease.

FL is divided into 3 grades, where the grade refers to the number of large cells that appear under the microscope. Large cells tend to behave a bit more aggressively than small cells. Although more large cells appear in Grade 2, it is for all intents and purposes considered the same as Grade 1, from a prognosis and treatment point of view. However Grade 3 is somewhat cloudy because it can appear to be either the indolent or aggressive form.[3] Over time few patients with FL may eventually develop a transformed lymphoma, which is often more aggressive and usually requires different types of treatment.

Of course, a cure is always the ultimate goal in treating any life threatening cancer. FL is said to be an incurable lymphoma based on the current treatments available and the multiple relapses of the disease. With this in mind, the goals of currently available treatments for FL patients, include:

- Bringing about and prolonging remissions (Progression Free Survival)
- Minimising the number of lymph nodes and /or organs affected
- Preventing the development of symptoms and treating existing ones[4]

Current Patient Needs

FL is considered an indolent but incurable cancer marked by multiple relapses. It is currently considered to be chronic which may be successfully managed over a long period of time (10 to 20 years or more), and may never become life threatening in some patients. Many patients initially may not have symptoms or problems related to their condition, where 'watchful waiting' is an acceptable treatment.

Reasons to treat FL include large or rapidly growing tumours, causing uncomfortable symptoms, injuring the body's organs or decreasing healthy blood cells.

Over the lifetime of a patient with FL, the cancer may need to be treated intermittently with the various treatments available, including immunotherapy, chemotherapies, stem cell transplants and radiation. Hence patients are required to manage the many physical conditions and medical issues resulting from the various treatments and cumulative side effects which will be discussed further in the patient experience.

Understanding Biology

It would seem despite many recent insights regarding the understanding of the biology of FL, it may be years before it may be translated to the clinics.

Many novel therapies have been developed over the past few decades to treat FL however progress hasn't been shown in providing a cure and the cause is still unknown. Despite this there is a great deal of intriguing research being conducted in order to make larger strides towards understanding the biology of FL.

In recent telephone discussions with both Professor John Seymour, MD, the Director of Cancer Medicine at Peter MacCallum Cancer Center, Australia, and Professor Gilles Salles, MD, PhD, Professor of Medicine, University of Lyon, France, they shared some of these exciting and promising research topics.

Here are a few key highlights that were discussed. More information is available in the members section of the LC resource library.

Shorter term research may lead to advances in interventions and targeted therapies, such as;

Host Immune Response:

- Why does a person's own immune system fail to recognise cancer cells as being foreign or different?
- What prevents the host immune system from killing these cancer cells and identifying them as lymphoma?

Genetic Mutation Profiling:

- Identifies potential actions in mutations in lymphoma.
- What leads to the transformation of FL to a more aggressive lymphoma?
- Assist in the selection of therapy and identify patients who may develop a more aggressive lymphoma.

Longer term research is aimed at improvements in screening and prevention, such as;

Precursor Lesions:

- Identification of these profiles in patient's blood which may open up the prospect of screening and prevention, especially in secondary cancers.

Early Changes in Gene Methylation:

- Retrospectively, looking for recognisable differences in methylation profiles in blood samples and comparing these findings to patient outcomes found in the many cancer registries.

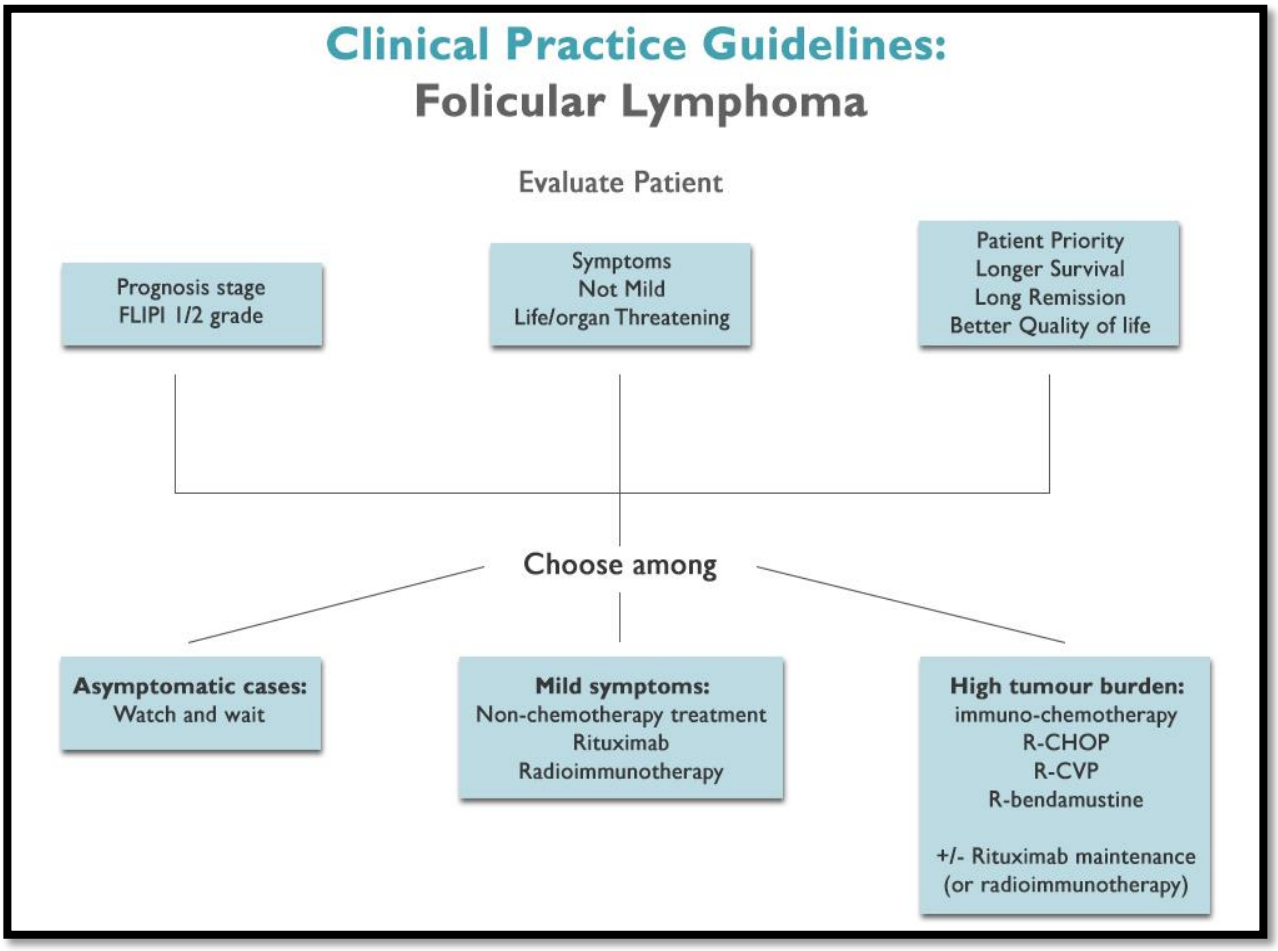
This research being conducted may further define a subset of patients, leading to either prognostic implications or perhaps longer term, therapeutic interventions.

Current Recommendations and Guidelines

LC will use the information from the European Society of Medical Oncology (ESMO) consensus driven recommendations[5] and the treatment guidelines from the National Comprehensive Cancer Network (NCCN) [6] to determine what treatments should be accessible to FL patients. The British Committee in Standards for Haematology guidelines (BCSH) was reviewed but LC found it to be similar to ESMO's and therefore will not be included.

As various therapeutic approaches may achieve durable responses in the vast majority of patients, the selection of optimal treatment is mainly based on clinical risk factors, symptoms and patient perspective. This is shown in Figure 1. The therapeutic algorithm in treating newly diagnosed and relapsed follicular lymphoma taken from the ESMO clinical practice guidelines for diagnosis, treatment and follow-up.[5]

Figure 1. ESMO Clinical Practice Guidelines - Algorithm of Treatment for FL [5]



In comparing the therapies recommended in ESMO recommendations in Table 1 to those of the NCCN listing shown in Table 2, the therapies listed by NCCN include more treatments. These regimens include the newer agents and combinations of rituximab with lenalidomide, and idelalisib monotherapy.

Table 1. ESMO Recommendations

ESMO Consensus Driven Recommendations Outside Clinical Studies

Low Tumour Burden		High Tumour Burden	
Stage I/II	**Stage III/IV**	**Stage III/IV** (<65 years*)	**Stage III/IV** (<65 years*)
Front Line			
Radiotherapy (involved field) In selected cases, watch and wait	**Watch and Wait** In symptomatic cases, consider rituximab monotherapy	**Chemoimmunotherapy** (e.g. R-CHOP, R-CVP, BR) In selected cases, rituximab monotherapy **CR/PR** Rituximab maintenance (every 2 months, up to 2 years)	**Chemoimmunotherapy** (e.g. R-CHOP, R-CVP, BR) or brief chemoimmunotherapy In selected cases, rituximab-chlorambucil rituximab monotherapy **CR/PR** Rituximab maintenance (every 2 months, up to 2 years)
Relapse/progress			
Watch and Wait Rituximab monotherapy in selected cases, palliative radiation	**Chemoimmunotherapy** (e.g. BR, R-CHOP, R-CVP) In selected cases, rituximab monotherapy	**Dependant on first-line regimen and remission duration** • Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) • Discuss high-dose consolidation with ASCT • Rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy • In selected cases, discuss alogeneic transplantation	**Dependant on first-line regimen and remission duration** • Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) • Rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, cyclophosphamide, vincristine and prednisolone; BR, bendamustine-rituximab; CR, complete response; PR, partial response; ASCT, autologous stem-cell transplantation.

*According to biological age

Table 2. Suggested Treatment Regimens from the NCCN Listing [6]

First Line	Relapsed/Refractory
BR	BR
RCHOP	RCHOP
RCVP	RCVP
Rituximab	Rituximab
R^2	R^2
RC	Chlorambucil
Radioimmunotherapy	Radioimmunotherapy
Rituximab maintenance	Rituximab maintenance
	Idelalisib
	RF
	RFND
	Autologous stem cell transplant
	Allogeneic stem cell transplant

Source: NCCN Guidelines BR, bendamustine, rituximab; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCVP, rituximab, cyclophosphamide, vincristine, prednisone; R^2, lenalidomide, rituximab; RC, rituximab, chlorambucil; RF, rituximab, fludarabine; RFND, rituximab, fludarabine, mitoxantrone, dexamethasone.

Therapy Access in FL

As stated above in both the ESMO guidelines and NCCN listings, there are a number of therapies and regimens recommended for FL patients, 9 and 14 respectively. Table 3 shows the number of LC member countries (44 in total) that have regulatory approval for these therapies, as well as those which are funded/reimbursed. To create a list of available therapies by country go to the LC Global Database www.lymphomacoalition.org.

According to the LC Global Database, there are 49 therapies and regimens with regulatory approval worldwide for the treatment of FL. However, in reviewing these more closely, 14 of them are considered 'rarely used' and are not recommended in either guideline. In fact, apart from the 9 to 14 therapies recommended by ESMO and NCCN, many of these additional therapies in the LC countries are considered outdated; an example is CVP (chlorambucil, vincristine, prednisone). This observation leads to questioning why these therapies are still listed and are they being used to treat FL patients.

Clearly, many FL patients globally do not have access to funded/reimbursed therapies that are recommended which is highlighted in the Table 3. Once again, specific therapies by country are listed in the LC Global Database. www.lymphomacoalition.org.

Table 3. Therapies Recommended by NCCN or ESMO Guidelines

Therapies Recommended by NCCN or ESMO Guidelines	No. of LC Member Countries with Regulatory Approval	No. of LC Member Countries with Funding/Reimbursement
Bendamustine-Rituximab	25	10
Chlorambucil	36	13
Chlorambucil-Rituximab	33	11
CHOP-R	40	31
CHVP-R	20	0
CVP-R	40	32
FNDR	3	3
Fludarabine-Rituximab	26	5
Idelalisib	23	4
Lenalidomide-Rituximab	1	1
Radiation Therapy	4	3
Rituximab	33	27
Rituximab Maintenance	29	15
Stem Cell Transplant	44	28

Source: Global Database December 2015

As is anticipated with FL, many patients will relapse requiring multiple lines of treatment as shown above by both ESMO and NCCN. These establish that the majority of FL patients should be treated with rituximab alone or in combination with another therapy at least once during their course of treatment. Despite this it would appear that not all patients in all LC member countries have access to rituximab, regardless of the regimen; such as in Argentina, China, Latvia, and Portugal, where no evidence of funding/reimbursement information is available.

Additionally many countries have limited funding/reimbursement for currently recommended therapies.

Regionally there are differences in patient access to FL treatments as well as discrepancies within the regions. Within North America, two completely different health care systems exist, both in their approval of therapies and their reimbursement/funding processes, making it very difficult to compare.

Europe has regulatory approval for the majority of the ESMO guidelines however the funding/reimbursement of these therapies within Europe varies greatly as shown in Table 4. Western European countries have greater access to FL therapies with the majority funded/reimbursed whereas Eastern European countries have limited number of therapies; namely R-CHOP, RCVP and rituximab. Of these treatments there are still some countries within Eastern Europe that do not have any funding/reimbursement. In many cases, older, salvage therapies are used instead which have repercussions on both their effectiveness, side effects and the patient experience.

Table 4. Therapies: Approved & Reimbursed/Funded

North America	Regulatory Approved Therapies	Therapies Reimbursed/Funded
Canada	23	21
United States	33	Funding provide by public payers, private payers and individual states

Western Europe	Regulatory Approved Therapies	Reimbursed/ Funded Therapies	Eastern Europe	Regulatory Approved Therapies	Reimbursed/ Funded Therapies
Belgium	20	7	Bulgaria	19	7
Denmark	20	6	Croatia	20	6
France	21	13	Czech Republic	22	8
Germany	19	11	Hungary	21	6
Ireland	22	10	Israel	14	12
Italy	20	8	Latvia	20	2
Netherlands	20	13	Lithuania	23	13
Portugal	20	N/A	Macedonia	3	N/A
Spain	20	7	Poland	20	6
Sweden	21	12	Russian Federation	7	5
Switzerland	22	13	Serbia	10	8
United Kingdom	24	14	Slovakia	20	6
			Slovenia	20	7
			Turkey	7	N/A
			Ukraine	4	N/A

Africa/Middle East	Regulatory Approved Therapies	Reimbursed/Funded Therapies
Algeria	7	2
South Africa	20	20
Asia/Pacific		
Australia	25	16
China	5	N/A
India	6	N/A
Japan	10	5
New Zealand	9	7
Singapore	14	N/A

Latin America	Regulatory Approved Therapies	Reimbursed/Funded Therapies
Argentina	11	N/A
Barbados	3	N/A
Brazil	5	N/A
Colombia	14	6
Uruguay	11	11
Venezuela	3	N/A
Mexico	7	7

Source: Global Database December 2015

Africa/Middle East, Asia/ Pacific and Latin America have dismal patient access, where, not only are there few recommended therapies with regulatory approval, the majority are not funded/reimbursed. With so many therapies available worldwide for a chronically treated cancer, it is unacceptable for FL patients to not have funded/reimbursed treatments available to them. To access this information by country please visit the LC Global Database at www.lymphomacoalition.org.

Clinical Trial Activity

When reviewing the clinical trial activity in LC's Global Database, the 3 subtypes (from the subtypes LC is tracking) with the most activity are CLL, FL and DLBCL. The number of clinical trial activity increased in 2015 from 2014 with the largest increase being in the USA.

Of the 652 phase II/III clinical trials taking place globally in 2015, 32% were in FL which also showed an increase from 2014.

Of the 208 global trials in FL, the USA is involved in the majority at 154 of the 208 and Italy and France with the next highest at 35 and 32 respectively as is shown in Table 5. While the overall number of FL trials is drastically lower in both Italy and France compared to the USA, as a subtype they all represent approximately 32% of each countries total clinical trial activity. This seems to be the trend in many of the 44 LC member countries.

Some countries to note have a larger portion of activity in FL, over 45% in Bulgaria, India, Japan, Singapore and South Africa. Denmark, Ireland and the Netherlands all had under 20% of the clinical trials in FL. There are 7 of the 44 LC member countries that currently have no FL clinical trials in their country, 3 of those are in Europe, 3 in Latin America and 1 in Africa/Middle East.

Table 5. Phase II & III Clinical Trials; Lymphoma Compared to FL

North America	Lymphoma	FL
Canada	83	24
United States	451	154

Western Europe	Lymphoma	FL	Eastern Europe	Lymphoma	FL
Belgium	73	22	Bulgaria	14	7
Denmark	29	5	Croatia	7	3
France	101	32	Czech Republic	48	11
Germany	107	30	Hungary	33	12
Ireland	18	2	Israel	41	12
Italy	113	35	Latvia	1	0
Netherlands	33	6	Lithuania	2	0
Portugal	20	7	Macedonia	2	1
Spain	90	24	Poland	63	16
Sweden	39	12	Russian Federation	48	18
Switzerland	17	6	Serbia	4	1
United Kingdom	94	28	Slovakia	13	4
			Slovenia	2	0
			Turkey	25	8
			Ukraine	20	8

Africa/Middle East	Lymphoma	FL
Algeria	0	0
South Africa	13	8

Asia/Pacific	Lymphoma	FL
Australia	70	23
China	36	10
India	16	6
Japan	24	13
New Zealand	19	6
Singapore	18	8

Latin America	Lymphoma	FL
Argentina	19	6
Barbados	0	0
Brazil	31	13
Colombia	14	6
Mexico	17	4
Uruguay	0	0
Venezuela	2	0

Source Global Database December 2015

Focus of Clinical Trial Activity

In reviewing LC's Global Database, there are 208 clinical trials in FL, the majority are taking place in the treatment of relapsed or refractory (RR) setting. There is a substantial number, 113 of the 208 trials, involving novel agents and or regimens that provide patients with the promise of new opportunities. These consist of both single and combination regimens in both front line and RR patients. See further details in Table 6 or for country specifics, search the LC Global Database www.lymphomacoaltion.org.

Table 6. Focus of Clinical Trials in FL

Focus of Clinical Trials in FL	No. of FL trials in LC Member Countries
Total Number of FL Clinical Trials	208 (32% of all phase II & III trials)
First Line Treatment Trials	51 (25%)
Relapsed/Refractory Trials	144 (69%)
Both First Line and Relapsed Trials	13 (6%)
Existing Therapy Combination Trials	95 (46%)
Trials Involving Novel Agents	113 (54%)
First Line Combination Trials	29 (14%)
Relapsed/Refractory Combination Trials	58 (28%)
First Line Novel Agent Trials	22 (11%)
Relapsed/Refractory Novel Agent Trials	86 (41%)

Source Global Database December 2015. Note that a clinical trial may be undertaken in more than one area of focus, therefore, the total number will not add up to the total number of trials.

In reviewing the distribution of the FL trials in LC's Global Database, the ratio of phase II to phase III trials is 4:1 which also suggests a continuum in the development of FL therapies. Median survival 25 years ago was 5-10 years and with the extensive number of novel agents that have been made available to patients it is now approaching 20 years.[7]

Of the 113 FL clinical trials that contain a novel therapy, there are 21 in phase III and 92 in phase II. These phase III clinical trials, for the most part, include existing FL therapies (regulatory approved) investigating the feasibility of new combinations to add to the ever growing choices in FL. Primary and secondary outcome measurements include safety, response rates (RR), overall survival (OS) and progressions free survival (PFS). The majority of these phase III trials are taking place in the USA, 14 involve a European country and 9 involve at least one country outside of the USA and EU. This worldwide distribution of clinical trials is critical in providing universal patient access to trials. For country specific details please visit the LC Global Database at www.lymphomacoalition.org.

Of the 91 trials in phase II the majority involve novel use of existing FL therapies. Thirteen of these trials take place in first line, 75 in relapsed/refractory patients while 3 involve both. Many of the phase II clinical trials do include 'experimental' therapies and are being studied in all hematological malignancies. Pending results will determine their development in FL. Some of these include immuno-oncology (IO). More research is needed to substantiate these early results and address the long-term implications of altering the body's immune system and what impact this will have on other organs in the body. Before anticipating where and how these 'experimental' therapies will be used in treating patients, caution must be used as clinical trials are early phase I/II and safety has not yet been determined.

Incidence and Mortality

The change in incidence and mortality between 2010 and 2011 for each country are shown in Table 7[12-21]. More recent data is unavailable from any of our sources. The information was gathered from the 362 national and regional registries that are part of the IACR, eight statistical agencies and LC member organisations. However, it is a work in progress and should be interpreted with caution. For those countries where there is incidence and mortality data, not having current data makes it difficult to compare with the current clinical trial and therapy information that LC has available.

Based on this information, the average incidence per 100,000 people with FL in 2011 was 2.76 cases. The average mortality rate per 100,000 for FL in 2011 was 0.277 which was unchanged from 2010. Incidence and mortality data could only be obtained for 18 of the 44 LC member countries. No data was available from countries in Africa/Middle East or Latin America. Only 1 of 6 countries had data in the Asia/Pacific region. Six countries in both the Eastern and Western European countries had data. Clearly, the lack of incidence and mortality data by subtype is a universal problem. As a community we need to endeavour to find solutions so we can, one day report meaningful information by subtype.

TABLE 9. INCIDENCE AND MORTALITY DATA, BY REGION, 2010 vs. 2011: FL [8-15]

		2010			2011		
		Population	Incidence rate (per 100,000)	Mortality rate (per 100,000)	Population	Incidence rate (per 100,000)	Mortality rate (per 100,000)
Africa/ Middle East	Algeria	37,062,820	Information not available		37,762,962	Information not available	
	South Africa	50,791,808	Information not available		51,553,479	Information not available	
Asia/Pacific	Australia	22,031,800	4.5	0.2	22,340,000	4.3	0.2
	China	1,337,705,000	Information not available		1,344,130,000	Information not available	
	India	1,205,624,648	Information not available		1,221,156,319	Information not available	
	Japan	128,070,000	Information not available		127,817,277	Information not available	
	New Zealand	4,350,700	Information not available		4,384,000	3	0.5
	Singapore	5,076,700	1.2	Information not available	5,183,700	0.8	Information not available
Eastern Europe	Bulgaria	7,395,599	0.6	0.8	7,348,328	0.5	0.4
	Croatia	4,417,781	1.3	0.2	4,280,622	1.5	0.2
	Czech Republic	10,474,410	2.2	0.6	10,496,088	Information not available	
	Hungary	10,000,023	2.5		9,971,727	Information not available	
	Israel	7,623	2.9	0.2	7,765,800	2.7	0.2
	Latvia	2,097,555	1.1	0.3	2,059,709	1.3	0.5
	Lithuania	3,097,282	0.5	0.2	3,028,115	0.8	0.2
	Macedonia	2,102,216	Information not available		2,103,890	Information not available	
	Poland	38,042,794	Information not available		38,063,255	Information not available	
	Russian Federation	142,849,449	Information not available		142,960,868	Information not available	
	Serbia	7,291,436	Information not available		7,234,099	Information not available	
	Slovakia	5,391,428	Information not available		5,398,384	Information not available	
	Slovenia	2,048,583	Information not available		2,052,843	Information not available	
	Turkey	72,137,546	Information not available		73,058,638	Information not available	
	Ukraine	45,870,700	0.2	0.1	45,706,100	0.2	0.1
Western Europe	Belgium	10,920,272	Information not available		11,047,744	Information not available	
	Denmark	5,547,683	Information not available		5,570,572	Information not available	
	France	65,023,142	3.6	Information not available	65,338,149	Information not available	
	Germany	81,776,930	3.4	0.2	81,797,673	3.4	0.2
	Ireland	4,560,155	3.1	0.2	4,576,794	3.2	0.2
	Italy	59,277,417	Information not available		59,379,449	Information not available	
	Netherlands	16,615,394	3.2	0	16,693,074	3.2	0
	Portugal	10,573,100	Information not available		10,557,560	Information not available	
	Spain	46,576,897	Information not available		46,742,697	Information not available	
	Sweden	9,378,126	3.2	0.4	9,449,213	3.5	0.5
	Switzerland	7,824,909	4.9	0.3	7,912,398	5.6	0.4
	UK						
	-England	52,642,452	3.9	0.3	53,107,169	3.8	0.3
	-Scotland	5,262,200	4.0	0.5	5,299,900	4.4	0.4
	-Wales	3,050,000	4	0.3	3,060,000	3.7	0.4
Latin America	Argentina	40,374,224	Information not available		40,728,738	Information not available	
	Barbados	280,396	Information not available		281,804	Information not available	
	Brazil	195,210,154	Information not available	0.1	196,935,134	Information not available	0.1
	Colombia	46,444,798	Information not available		47,078,792	Information not available	
	Mexico	117,886,404	Information not available		119,361,233	Information not available	
	Uruguay	3,371,982	Information not available		3,383,486	Information not available	
	Venezuela	29,043,283	Information not available		29,500,625	Information not available	
North America	Canada	34,005,274	4.1	0.2	34,342,780	Information not available	0.3
	USA	309,326,295	3.9	0.1	311,582,564	3.8	0.1

Patient Experience

The patient experience is often captured through many anecdotal discussions between LC member organisations from around the world. The LC 2016 Global Patient Survey (GPS) is reviewed below to provide a sense of the concerns patients have which supports the discussions we hear from members.

When reviewing the 2016 GPS, and isolating survey responses for FL patients, the physical conditions that had the greatest impact on patients are highlighted in Table 7. Of the 778 FL responders, more than half have been affected by the top 6 physical conditions listed below, with fatigue having the greatest impact. Fatigue is a common side effect for almost all subtypes of lymphoma including FL. It might be possible that aggressive treatment regimens are responsible for the high rates of respondents with physical conditions that pertain to hair loss, sleeplessness and muscle weakness.

Table 7. Physical Conditions

How has FL impacted patient's physical condition?	Responses
Fatigue	77%
Hair Loss	45%
Sleeplessness	38%
Muscle weakness	35%
Aching joints	34%
Trouble concentrating	33%

Source: LC 2016 Global Patient Survey

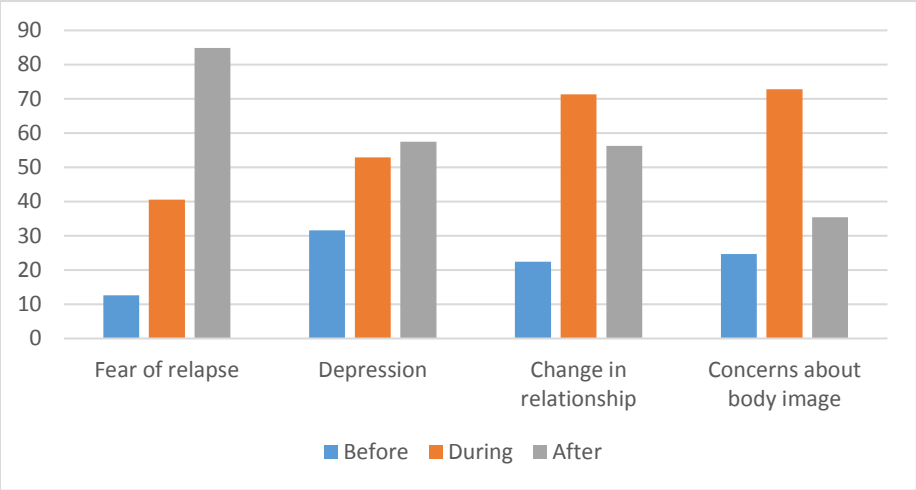
Of the 80% of respondents with FL who have experienced an impact on their sense of well-being, the top most negative effects are the ones shown in Table 8.

Table 8. Patient's Sense of Well-Being

How has FL impacted patient's sense of well-being?	Responses
Fear of relapse	70%
Depression	31%
Changes in relationship with loved ones, friends or co-workers/social life	31%
Concerns about body image/physical appearance changes	25%

Source: LC 2016 Global Patient Survey

Chart 1. Affected By Issues Before, During or After Treatment



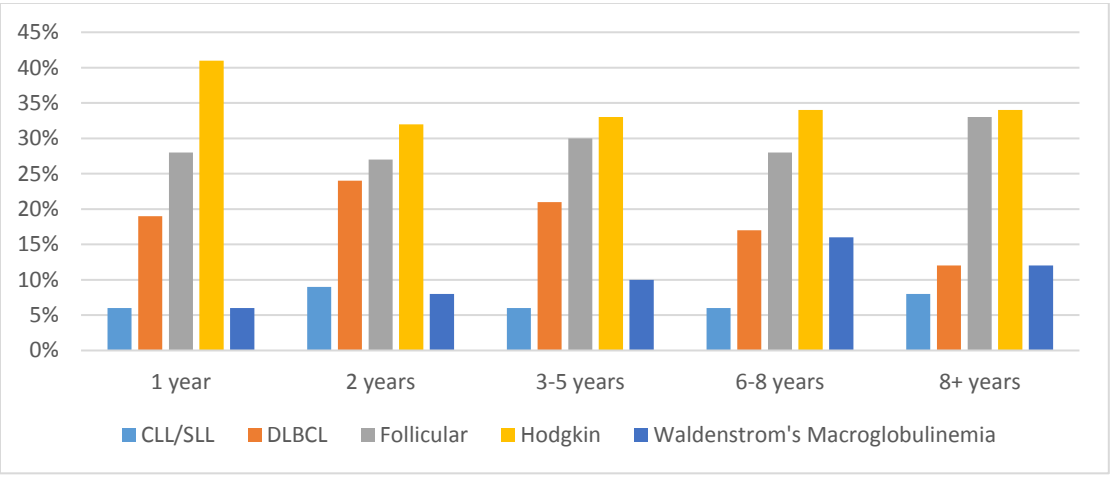
Source: LC 2016 Global Patient Survey

The perspective that many of us overlook when considering the concerns with body image and physical appearance changes is the outward manifestation of their cancer which may impact their relationships, their sense of self and their work place experience until these changes they could keep their cancer diagnosis to themselves.

If we look at Chart 1 we see that concerns about body image goes down after treatment but is considerably high during treatment. On the other hand fear of relapse and depression go up after treatment which raises concerns about the level of care and emotional support these patients are, or rather are not, receiving.

As mentioned in the Overview section, FL is an incurable cancer which is characterised by multiple relapses. This would explain why fear of relapse is at the top of the list. Patients with FL show that the impact on their wellbeing last longer than in other major lymphoma subtypes. Living in fear of relapse coupled with other factors that affect their well-being, such as financial stress, can aggravate psychosocial issues such as depression and exacerbate sleeplessness and fatigue.

Chart 2. After Treatment – Length of Time Patients Faced Concerns



Source: LC 2016 Global Patient Survey

It is a concern that patients are struggling with not only the physical but psychosocial implications of treatment as well. We wanted to know if they were reaching out for support so we asked if they talked to their doctor about it. According to the GPS of all the FL patients that discussed their physical and/or emotional needs with their doctor, 70% felt the doctor only helped somewhat or didn't help at all.

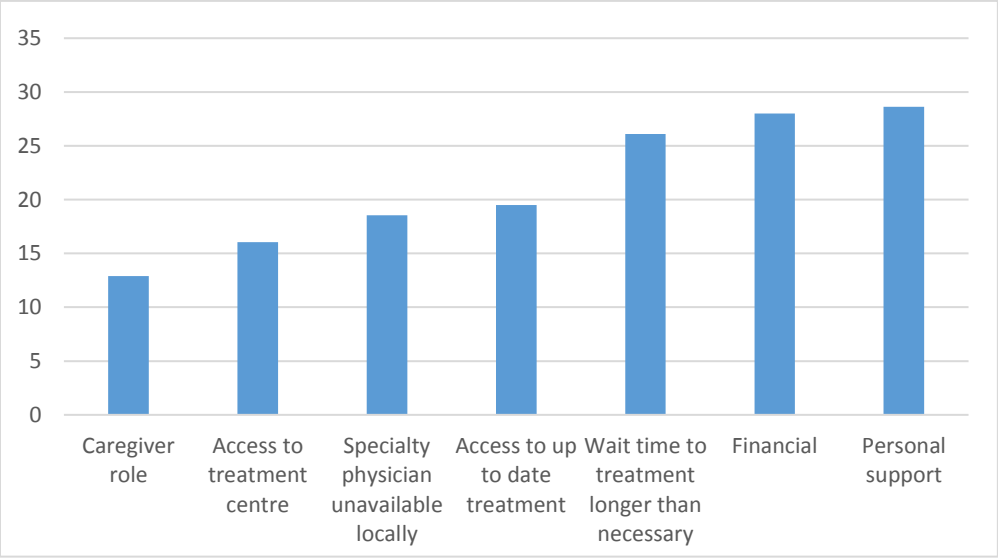
Health care providers working along with patient organisations have an opportunity to improve communication with patients and provide a well-rounded approach to care. This will allow patients both emotional and physical support not only during treatment but also post-treatment as well.

Barriers to Receiving Adequate Treatment

Responders were asked to indicate what barriers they had experienced when trying to get adequate FL treatments. Almost half had experienced at least one barrier to receiving therapy, see Chart 3. The most common barriers were personal support, financial, wait times to treatment and access to the most up to date treatment. Looking back at therapy access in Table 4, it is no wonder that one of the significant barriers is financial. As was noted, there are few therapies funded/reimbursed especially if we look at the Asia/Pacific countries. Financial stress is a big concern for most countries while personal support seems to be a problem particularly in the UK, Italy and France.

Once again as mentioned in the therapy access section, the funding/reimbursement of drugs approved for FL is pretty low especially in Africa/Middle East, Asia/Pacific and Latin America. With sometimes multiple lines of treatment necessary for FL patients, the most urgent need is to have readily accessible and funded/reimbursed novel therapies.

Chart 3. Barriers to Adequate FL Treatment



Source: LC 2016 Global Patient Survey

Conclusion

Follicular lymphoma continues to be treated as an incurable cancer, with a substantial and growing subset of patients achieving long-term disease-free survival from aggressive multiple treatment approaches. With the expectation of inevitable relapses, patients no doubt live in fear of when and how their FL will return. Patients are also expected to manage both the physical and medical issues that arise from the intermittent treatments and the negative impact that comes with cumulative side effects and comorbidities.

Their support is of concern as those that are reaching out to their doctors are not getting what they need and are not being referred to places that might be of support to them.

There is a considerable large body of active clinical trials in FL suggesting there may be continued improvements in treatment outcomes. Whether these potential newer therapies and combinations will provide a cure for FL is to be determined. Many of them are in their infancy, with unanswered questions around safety. We will continue to monitor and report on these trials as evidence comes forward.

Even more exciting is the research that is being conducted in the biology of FL, with the intent to positively impact both the clinical setting and the screening and prevention of this cancer.

FL, one of many lymphoma subtypes, requires independent reporting to ensure proper trending analysis and outcome reporting. The challenge in gathering accurate data, especially incidence and mortality by subtype, is a global issue that needs to be addressed. In order to effectively understand the unmet concerns and needs of FL patients, specific subtype information remains at the forefront to providing analysis that is reflective of those patients. In the age of 'personalised' medicine and care, shouldn't we also give that same importance to the ability to report by subtype?

Patient access to care is limited, varies regionally and access to novel and recommended therapies is not universal. Currently, patients are living with treatments that do not offer a cure and many with long term side effects and medical ramifications. We look forward to the research presently underway to provide a less toxic more durable treatment for FL patients.

References

1. Lymphoma Hub Website www.lymphomahub.com
2. https://www.macmillan.org.uk/information-and-support
3. Cyberfamily Website. http://www.nhlcyberfamily.org/types/indolent.htm
4. https://www.lymphoma.ca/lymphoma/patient-journey/treatment/goals-therapy
5. Dreyling, M. et al. "Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 25 (Supplement3): iii76-iii82, 2014
6. http://www.nccn.org/ Version 2.2015.
7. Lui, Qi et al. Improvement of Overall and Failure-Free Survival in Stage IV Follicular Lymphoma: 25 Years of Treatment Experience at The University of Texas M.D. Anderson Cancer Center. JCO, ASCO 2006
8. International Association of Cancer Registries. www.iacr.com.fr/index.php?option=com_comprofiler&task=usersList&Itemid=476&limitstart=0&search=&cbsecuritym3=cbm_0b06fb35_14c934c4_8324d130550cecb02f034090483d282e&listid=2&name=. Accessed February 2, 2015.
9. Brazil Mortality Information System. Information provided by email on April 1, 2015.
10. Statistics Belgium. Information provided by email on May 9, 2015.
11. Statistics Canada. Information provided by email on May 21, 2015.
12. Institute of Health Information and Statistics, Czech Republic. www.uzis.cz/en/catalogue/cancer-incidence. Accessed February 2, 2015.
13. Federal Statistical Office, Germany. Information provided by email on April 13, 2015.
14. Central Bureau of Statistics, Israel. Information provided by email on May 27, 2015.
15. Statistical Netherlands Infoservice. Information provided by email on June 18, 2015.
16. Statistics South Africa. Information provided by email on April 29, 2015.
17. World Bank. data.worldbank.org/indicator/SP.POP.TOTL. Accessed July 31, 2015.