LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

2017

GLOBAL

SUBTYPE REPORT

Hodgkin Lymphoma

The focus of this report is to review patient access to care in Hodgkin Lymphoma (HL); namely therapy access, clinical trials and aspects of the patient experience.

Summary

Hodgkin lymphoma (HL) accounts for 10% of the more than 60 subtypes of lymphoma. It occurs primarily in those aged 20 to 34 years. The causes of HL are still under investigation but may be linked to the Epstein-Barr virus and to a family history of HL.

The most common sites for HL are in the neck, chest and under the arms. Symptoms may include painless swelling of nodes, fatigue, fever and chills, night sweats, unexplained weight loss, pruritus and alcohol intolerance. However, not all patients may have symptoms and could be diagnosed incidentally. To help make a diagnosis, a number of diagnostic tests may be undertaken.

Malignant HRS cells are greatly outnumbered in the tumour microenvironment by other reactive cells. Many studies in HL have, therefore, focused on the cellular composition of the microenvironment, to not only better understand the cancer but also if the cells in the microenvironment in some way contribute to outcome prediction.

HL is primarily a curable cancer and with current treatments, 80% to 90% of patients can achieve permanent remission. The mainstay of treatment is multi-agent chemotherapy often in combination with radiation therapy.

Based on information gathered from the Lymphoma Coalition (LC) Global Database, traditional therapies for HL, e.g., ABVD and BEACOPP, were available and funded in most member countries. Newer therapies include nivolumab and brentuximab vedotin (BV). Only one member country out of 45 funded/reimbursed nivolumab while 31 member countries had regulatory approval for BV but only 17 funded/ reimbursed it.

Of the 852 clinical trials (phase II or III) focusing on lymphomas, 121 were studying either HL alone or with other forms of lymphoma. The USA being involved in most of these trials. The number of trials in regions such as Eastern Europe, South America, Asia/Pacific and Africa was low or nonexistent. Within the 121 HL trials, 72% were in the phase II setting while 9% were in phase III. A high number of trials (n = 83) were studying new therapies with 76% of them in the relapsed/refractory setting and only 21% in the first-line setting.

Key findings from the LC 2016 Global Patient Survey showed that fear of relapse had a profound effect on patients' sense of well-being. The physical effects that impacted patients the most were fatigue (78%) followed by hair loss and nausea and vomiting. Concern about body image affected 46% of respondents. Other major causes of concern were changes in relationships and depression.

Patients with HL felt financial issues were the greatest barrier to treatment followed by lack of personal support, wait time to treatment, access to a treatment centre and unavailability of a specialist physician. Financial issues also affected patients' sense of well-being.

Overview

HL is a cancer of the lymphatic system which originates in specialised white blood cells called B-cell lymphocytes. B-cells are responsible for creating antibodies or immunoglobulins which fight infections.

It is believed that there is generally an error in the programming of cancerous cells whereby instead of dying off they proliferate into clone cells which rapidly multiply.

In the case of HL, these abnormal cells are called Hodgkin cells and Reed-Sternberg (RS) cells, named after pathologist Thomas Hodgkin and two scientists, Dorothy Reed and Carl Sternberg.

Hodgkin and RS cells (or HRS) generally contribute to only one or two percent of the overall tumour mass. These other cells make up much of the tumour and are thought to help the cancer cells grow. They produce factors that attract many inflammatory cells which is what the overall tumour mass usually consists of.[2]

The WHO Classification recognizes two major subtypes of HL which differ in their morphology, immunophenotype, expression of B-cell genes, cellular background and clinical behavior.[3] These two subtypes are: classical HL (cHL), which is commonly a B-cell derived neoplasm and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) which is characterised by large 'popcorn' cells.

The focus of this report will be on cHL.

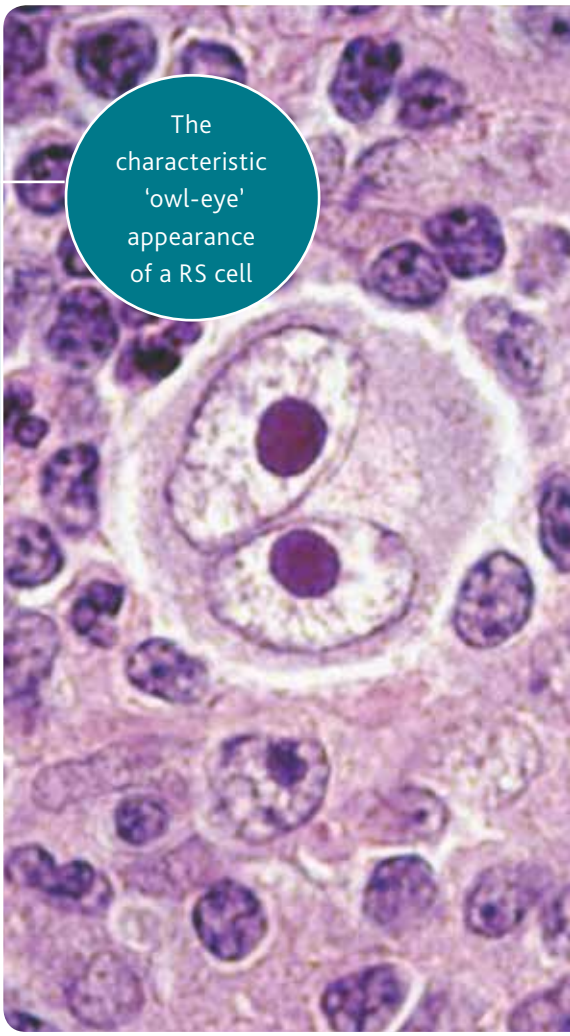
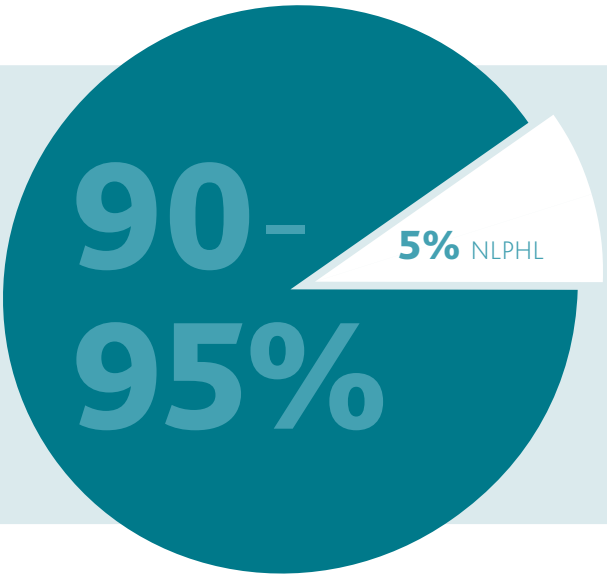


FIGURE 1: RS CELL UNDER MICROSCOPE



Classical HL accounts for 90-95% of all HL diagnoses.

It can be further be divided into 4 subtypes;

1. Nodular Sclerosis HL
2. Mixed Cellularity HL
3. Lymphocyte-Rich HL
4. Lymphocyte-Depleted HL

Classical HL subtypes:

1 Nodular Sclerosis

the most common subtype of HL, accounts for 60 to 80% of all HL cases.

It is most common in teens and young adults, but it can occur in people of any age. It tends to start in lymph nodes in the neck or chest. The involved lymph nodes contain RS cells mixed with normal white blood cells. The lymph nodes often contain a lot of scar tissue, which is where the name nodular sclerosis (scarring) originates. HL is more common in women than in men, and it usually affects adolescents and adults under the age of 50. The majority of patients are cured with current treatments.[16]

2 Mixed Cellularity

accounts for about 15 to 30% of all HL cases.

It is found more commonly in men than in women, and primarily affects older adults. It can start in any lymph node but most often occurs in the upper half of the body. With this type of HL, the lymph nodes contain many RS cells in addition to several other cell types. More advanced disease is usually present by the time this subtype is diagnosed.[16]

3 Lymphocyte-Rich

accounts for less than 5% of HL cases.

It usually occurs in the upper half of the body and is rarely found in more than a few lymph nodes. The cancer may be diffuse (spread out) or nodular in form and is characterized by the presence of numerous normal appearing lymphocytes and classic RS cells. This subtype of HL is usually diagnosed at an early stage in adults and has a low relapse rate.[16]

4 Lymphocyte-Depleted

is rarely diagnosed and makes up less than 1% of cases.

It is seen mainly in older people and is more likely to be found in lymph nodes in the abdomen as well as in the spleen, liver, and bone marrow. Abundant RS cells and few normal lymphocytes are present in the lymph nodes of patients with this subtype, which is aggressive and usually not diagnosed until it is widespread throughout the body.[16]

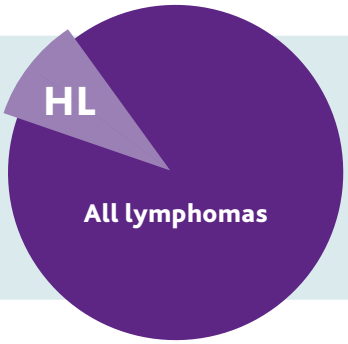
The presence of HRS cells is characteristic of classical HL and it is recommended that an excisional lymph node biopsy be undertaken or a sufficiently large surgical specimen.[4] HRS cells stain consistently positive for CD30 and CD15.[4, 5]

Other tests that might be prescribed to make a diagnosis are complete blood counts, erythrocyte sedimentation rate (ESR), metabolic panel to check liver and kidney function, testing for HIV and hepatitis B and C virus infections as well as positron emission tomography (PET) and computed tomography (CT) scans.

The most common site for HL are in the neck, under the arms and in the chest. HL will typically start in the lymph nodes and often spreads through the lymph vessels from one lymph node to the next. Very rarely does it spread through the blood stream to other organs.[2]

HL accounts for 10% of all lymphomas and less than 0.5% of all cancers diagnosed globally.

It is a cancer of young adults, primarily occurring in ages 20-34. A secondary peak of incidence occurs between the ages of 60 and 70.[7]



The causes of HL are still under investigation, however, the Epstein-Barr virus (EBV), which causes mononucleosis, may be linked to an increase in the risk of developing HL. Despite this finding, more than half of all HL patients have no evidence of a previous EBV infection, so a definitive relationship is still unclear. Siblings of HL patients have an above-average risk of developing this cancer but the significance of the family relationship as the primary cause is still not known.

The management of HL is determined by the stage and activity of the cancer. Patients with HL are staged according to the Ann Arbor staging system with Cotswold's modifications.[8, 9]

The stage of the cancer depends on the extent to which it has spread in the body. In stages I and II, the cancer is limited to one or two areas of the body (early stage). In stages III and IV, the cancer is more widespread (advanced stage). Patients with early stage HL are then further stratified into favourable and unfavourable subsets, which is based on the presence or absence of other clinical features as seen in Table 2.[10]

A further revision was proposed to the Ann Arbor staging system in 2014, the Lugano classification, which proposes to clarify the role of positron emission tomography (PET) and better define extra nodal involvement.[9, 11] It also indicates the bone marrow biopsy is no longer necessary for routine staging of HL and discourages routine surveillance scans.

TABLE 1. STAGING SYSTEM FOR HL [12]

Stage	Nodal extent*	Extranodal extent (and suffix 'E' if present)
I	One node or a group of adjacent nodes	Single extranodal lesion with no nodal involvement
II	Two or more lymph node regions on the same side of the diaphragm	Stage I or II by nodal extent with contiguous extranodal extension
II bulky	As for II; definition of 'bulky' depends upon histology**	Not applicable
III	Nodes on both side of the diaphragm or nodes above the diaphragm with splenic involvement	Not applicable
IV	Noncontiguous extranodal involvement	Not applicable

*Tonsils, Waldeyer's ring and spleen are considered nodal ** ≥ 10 cm for Hodgkin lymphoma, 6-10 cm suggested for diffuse large B cell lymphoma ≥ 6 cm suggested for follicular lymphoma

Included in the staging system for HL are the suffixes A and B. This denotes if additional symptoms are involved as shown in Table 3.

TABLE 2. SUFFIX TO ADD FOR HL PATIENTS[12]

Suffix	Meaning
A	Absence of constitutional symptoms
B	Constitutional symptoms: fever (>38°C), drenching sweats, weight loss (10% body weight over 6 months)

Patients with advanced HL can further be risk stratified using the International Prognostic Score (IPS), which includes further risk factors outlined as:

- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥ 45y
- Stage IV disease
- Haemoglobin level below 10.5 d/dL
- Leukocytosis: white cell count (WBC) > 15,000/µL
- Lymphopenia: lymphocyte count < 8% of WBC count and/or absolute lymphocyte count < 600 cells/µL

The presence of any of the above factors counts as one point. A good risk profile would be IPS 0-1, fair risk would have a score of IPS 2-3 and poor risk is IPS 4-7. [11]

Some patients will show no symptoms at all and will be diagnosed incidentally.

In other instances, the patient may go to the doctor with one of the following common signs and symptoms:

- Painless swelling of lymph nodes in your neck, armpits or groin
- Persistent fatigue
- Fever and chills
- Night sweats
- Unexplained weight loss — as much as 10% or more of your body weight
- Loss of appetite
- Pruritus
- Alcohol intolerance or pain in lymph nodes after drinking alcohol

The presence of these symptoms cannot be the only basis of a HL diagnosis.

Biology

Many studies in HL have focused on the cellular composition of the microenvironment to better understand the cancer and to determine if the cells in the microenvironment in some way contribute to outcome prediction.

As an example, the number of tumour-associated macrophages (white blood cells that ingest foreign particles or infectious microorganisms) has been identified as an adverse prognostic factor in many solid tumours.[13] Several molecules implicated in macrophage signaling might be promising targets for novel drug therapies.[14]

A major obstacle in identifying the origin of HRS cells was the rarity of their presence in affected tissues. Also, malignant HRS cells lose numerous B-cell markers making it difficult to identify its cell of origin.

Only recently has the B-cell nature of the Hodgkin and Reed–Sternberg (HRS) cells been revealed and the pathogenetic role for Epstein–Barr virus infection has also been substantiated. HRS cells in classical Hodgkin lymphoma have several characteristics that are unusual for lymphoid tumour cells, and understanding the biology is essential for the development of novel therapies.[17]

It is still not known what causes HL but in recent years, improved understanding of the biology of HL has uncovered some potential targets for treatment. Clarification of the complex interactions between the HRS cell and the HL microenvironment have provided new insights into the molecular structures and signaling pathways that are essential for HRS survival.[15]

Almost all HRS cells are positive for CD30, expressed on the cell membrane as well as within the Golgi apparatus.

CD30 can activate signaling pathways including PI3-kinase/ Akt/mTOR, ERK/MAPK and NF-kB.[15]

CD15 is also commonly expressed on HRS cells in a similar distribution to CD30.

These cells also express other B-cell markers including the B-cell-specific activator protein PAX5/BSAP and the plasma cell transcription factor IRF4/MUM.[15]

Current Therapy Recommendations and Guidelines

Despite the use of best available therapies, some patients may develop relapsed or refractory HL for which effective treatment options are limited.

To meet the needs of these patients, new therapies are being tested in patients with HL and results are encouraging.

These include agents that deliver cytotoxic chemotherapy to the interior of cancer cells using specific targets on the cell surface (antibody-drug conjugates [ADCs]) and agents that enable the patient's immune system to eliminate HL cells (checkpoint inhibitors).[6]

To determine what treatments should be accessible to HL patients in member countries, LC reviewed the information from both the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) and the treatment guidelines are shown in table 3 and 4.

Cure rates are higher than 80% in most cases but, it is the advanced stage HL (which are in stages III or IV or I and II with 'B') that may require more intensive therapy.

Diagnostic accuracy and the assessing stage migration using PET scans are essential to provide the right level and dosage of treatment to reduce future comorbidities and toxicities related to therapies, particularly, secondary cancers and cardiovascular disease.

HL is mostly a curable cancer and current treatments can eradicate

up to **80-90%** of cases.[4]

Multi-agent chemotherapy, often in combination with radiation therapy, is the mainstay of HL management and treatment intensity is tailored to the risk of relapse.

TABLE 3. ESMO TREATMENT GUIDELINES FOR HL[4]

Stage	Classic HL	NLPHL
Front-line Treatment		
Limited (no risk factors)	ABVD → RT	RT
Intermediate (≥1 risk factors)	**Possible options:** ABVD Or BEACOPPesc + ABVD → RT	ABVD Or BEACOPPesc + ABVD → RT
Advanced (large mediastinal mass; ≥50 y, elevated ESR, ≥4 nodal areas)	ABVD Or BEACOPPesc → RT	ABVD Or BEACOPPesc → RT
Relapsed Disease		
	DHAP Or IGEV Or ICE → high-dose chemotherapy → autoSCT **Low-risk patients:** BEACOPPesc	**Rituximab alone** **Advanced disease:** More aggressive salvage therapy + anti-CD20 antibody No data yet on efficacy of high-dose chemotherapy followed by autoSCT
	BV after autoSCT failure	

TABLE 4. NCCN TREATMENT GUIDELINE FOR HL[5]

	Classic HL	NLPHL
Front-line Treatment		
Stage I-II (bulky and non-bulky disease)	ABVD Or Stanford V Or BEACOPPesc + ABVD + RT	**Non-bulky disease:** Observation Or RT **Bulky disease:** ABVD + RT ± rituximab Or CHOP + RT ± rituximab Or CVP + RT ± rituximab
Stage III-IV	ABVD Or Stanford V Or BEACOPPesc	ABVD + RT ± rituximab Or CHOP + RT ± rituximab Or CVP + RT ± rituximab Or RT Or Rituximab
Relapsed Disease		
	HDT + autoSCT ± RT → BV Or Observation ± RT	Rituximab ± chemotherapy ± RT BV

Currently patients with limited stage HL are treated with ABVD followed by involved field radiation therapy (IFRT). Intermediate stage HL especially those who are under the age of 60 and have a higher tolerance for intensive treatment can be treated with BEACOPP in an escalated dose. Advanced stage HL are usually treated by ABVD or BEACOPP and radiation therapy (RT) is only used if residual lymphoma is present.

There is no mention in the ESMO guidelines of newer therapies.

The cure rate for HL is high, however, in the relapsed/refractory setting the survivorship is lower. For relapsed patients, high dose chemotherapy followed by autologous stem cell transplantation is the recommended choice of treatment.[4]

Targeted therapies such as BV is approved for treatment of patients failing ASCT and who have had multiple relapses.

The NCCN listing as seen in Table 5, has more approved therapies in both first line and the relapsed setting for HL. Most of the therapies in the relapsed setting are regimens such as DHAP, ICE or GVD; but newer therapies are also included. There is no mention in the ESMO guidelines of newer therapies such as nivolumab, everolimus or bendamustine.

Long term survivors of HL are most at risk of developing secondary cancers, cardiovascular disease, hypothyroidism and fertility issues. The incidence of these issues increase over time.

A tailored monitoring programme needs to be established for each patient based on age and severity of symptoms as well as response to treatment.

TABLE 5. APPROVED THERAPIES FOR HL IN NCCN LISTING AND ESMO GUIDELINES[4,5]

NCCN (n-22)		ESMO (n-8)	
First Line	**Relapsed**	**First Line**	**Relapsed**
ABVD ± R	Bendamustine	ABVD	Brentuximab Vedotin
BEACOPP	Brentuximab Vedotin	BEACOPP	DHAP
CHOP-R	DHAP	Radiation Therapy	ICE
CVP-R	ESHAP		IGEV
Radiation Therapy	Everolimus		Radiation Therapy
Rituximab	GCD		Stem Cell Transplant
Stanford V	GVD		
	ICE		
	IGEV		
	Lenalidomide		
	MINE		
	Mini-BEAM		
	Nivolumab		
	Pembrolizumab		
	Radiation Therapy		
	Rituximab		
	Stem Cell Transplant		

Source: LC Global Database – as of July 2016.

Therapy Access

For this report, we looked at access to treatment in LC member countries by subtype, a list can be found on the LC website.

Table 6 shows the specific HL therapies that have regulatory approval as well as those that are funded/reimbursed and listed by LC member countries. The number of therapies approved and funded/reimbursed by country, is shown in Table 7. There are 16 therapies approved for HL in the first line setting and 30 approved in the relapsed setting globally.

Hodgkin lymphoma is a curable form of cancer if treated at the right time with the right drug intervention.

Traditional therapies for HL include;
ABVD, BEACOPP which are available and funded in most countries with exceptions like Barbados where the therapies aren't approved or China and India where they are not funded or reimbursed.

When investigating if ABVD and BEACOPP were funded/reimbursed in all member countries, we only found partial funding in Lithuania and South Africa and no funding available in India for these therapies. In the other member countries either one or both regimens appear to be funded/reimbursed.

While DHAP, IGEV and ICE are among the recommended therapies noted in the ESMO guideline for the relapsed setting, only DHAP and ICE are listed among the regulatory-approved therapies in all member countries. Most member countries appear to fund/reimburse either DHAP or ICE or both regimens.

Novel therapies for HL include BV and novulimab. Of the 45 member countries reviewed only 31 countries have regulatory approval for BV, and of these, only 17 have the drug funded/reimbursed. The European Medicines Agency (EMA) has given full approval for nivolumab as a treatment for HL and it is now approved in all 21 EU member countries. The ESMO guidelines, however, have not been updated to include nivolumab as a therapy for relapsed HL yet. Nivolumab is funded/reimbursed only in the USA.

Lack of funding/reimbursement can have many negative repercussions on patients and their care providers. This would especially be the case if the therapies available to them are the older regimens. These have a history of higher comorbidities. This includes therapies such as MOPP – which have approval in Australia, Canada and Italy– and has shown to have poorer results than therapies such as ABVD.[24]

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

As shown in Table 7, Australia, UK, Denmark, Canada and the USA have the highest number of therapies approved and funded.

To create a list of available therapies by LC member country and compare it to the NCCN listing, go to the LC Global Database and view by country and by subtype.

TABLE 6. THERAPY ACCESS FOR HL IN LC MEMBER COUNTRIES

	HL Therapies with Regulatory Approval	HL Therapies with Funding/ Reimbursement Approval
Africa and the Middle East		
Algeria*	ABVD, BEACOPP, DHAP, ICE, MINE, RT	BEACOPP
South Africa	ABVD, ASHAP, BEACOPP, ChlVPP, cyclophosphamide, DHAP, ESHAP, GDP, GEM-P, ICE, IGEV, MINE, RT, SCT	Private health insurance for: ABVD, ASHAP, BEACOPP, cyclophosphamide, DHAP, ESHAP, GDP, GEM-P, ICE, IGEV, MINE, RT, SCT Government partially funds/ reimburses: ABVD, BEACOPP
Israel	ABVD, BEACOPP, BV, DHAP, ICE, MINE, RT, SCT	
Asia/Pacific		
Australia	ABVD, BEACOPP, BV, ChlVPP, COPP, cyclophosphamide, DHAP, GDP, ICE, MINE, MOPP, RT, Stanford V, SCT	ABVD, BEACOPP, BV, ChlVPP, COPP, cyclophosphamide, DHAP, GDP, ICE, MINE, RT, Stanford V
China*	ABVD, BEACOPP, DHAP, ICE, MINE, RT	DHAP
India	ABVD, BEACOPP, DHAP, ICE, MINE, RT, SCT	No government funding/ reimbursement provided
Japan*	ABVD, BEACOPP, BV, DHAP, ICE, IGEV, MINE, RT	ABVD, BEACOPP, BV, DHAP, ICE, IGEV, MINE, RT
New Zealand	ABVD, BEACOPP, ChlVPP, cyclophosphamide, DHAP, ICE, MINE, RT, SCT	ABVD, BEACOPP, ChlVPP, cyclophosphamide, DHAP, ICE, RT, SCT
Singapore	ABVD, ASHAP, BEACOPP, BV, DHAP, ICE, MINE, RT, SCT	ABVD, BEACOPP, DHAP
Eastern Europe		
Bulgaria	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT, SCT	ABVD, BEACOPP, DHAP, GDP, ICE, RT
Croatia	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, MINI-BEAM, RT, Stanford V, SCT	ABVD, BEACOPP, BV, DHAP, ICE, MINE, MINI-BEAM, RT, Stanford V, SCT
Czech Republic	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT	ABVD, BEACOPP, DHAP, ICE, RT
Hungary	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT, SCT	ABVD, BEACOPP, DHAP, ICE, RT
Latvia*	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT	ABVD, BEACOPP, DHAP, ICE, RT
Lithuania	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT, SCT	BEACOPP†, DHAP†, GDP†
Macedonia*	ABVD, BEACOPP, DHAP, ICE, MINE, RT, SCT	
Poland	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT, SCT	ABVD, BEACOPP, BV, DHAP, ICE, GDP, ICE, MINE, RT, SCT
Russian Federation*	ABVD, BEACOPP, DHAP, ICE, IGEV, MINE, RT	ABVD, BEACOPP, DHAP, ICE, RT
Serbia	ABVD, BEACOPP, BV, DHAP, ICE, MINE, RT, SCT	ABVD, BEACOPP, DHAP, ICE, RT
Slovakia	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT	ABVD, BEACOPP, ICE, RT
Slovenia	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT, SCT	ABVD, BEACOPP, BV, DHAP, ICE, RT, SCT
Turkey*	ABVD, BEACOPP, DHAP, ICE, MINE, RT, SCT	
Ukraine*	ABVD, BEACOPP, DHAP, ICE, MINE, RT	Information not available
Western Europe		
Belgium	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT	ABVD, BEACOPP, BV, DHAP, GDP, ICE, RT
Denmark	ABVD, ABVD-R, BEACOPP, BV, ChlVPP, CHOP, COPP, DHAP, GDP, GVD, ICE, IGEV, MINE, MINI-BEAM, RT	ABVD, ABVD-R, BEACOPP, BV, ChlVPP, CHOP, COPP, DHAP, GDP, GVD, ICE, IGEV, MINI-BEAM, RT
France	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, IGEV, MINE, RT, SCT	ABVD, BEACOPP, BV, DHAP, GDP, ICE, IGEV, RT, SCT
Germany	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT, SCT	ABVD, BEACOPP, BV, DHAP, GDP, ICE, MINE, RT, SCT
Ireland	ABVD, BEACOPP, BV, ChlVPP, COPP, DHAP, ESHAP, GDP, ICE, MINE, RT, SCT	ABVD, BEACOPP, BV, ChlVPP, DHAP, ESHAP, GDP, ICE, RT, SCT
Italy*	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, MOPP, RT, SCT	ABVD, BEACOPP, DHAP, ICE, MOPP, RT, SCT
Netherlands	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT, SCT	ABVD, BEACOPP, BV, DHAP, GDP ICE, RT, SCT
Portugal*	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT	
Spain	ABVD, BEACOPP, BV, COPP, DHAP, ESHAP, GDP, ICE, MINE, RT, SCT	ABVD, BEACOPP, DHAP, ESHAP, GDP, ICE, MINE, RT, SCT
Sweden	ABVD, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, MINI-BEAM, RT, SCT	ABVD, BEACOPP, BV, DHAP, GDP, ICE, MINI-BEAM, RT, SCT
Switzerland	ABVD, ASHAP, BEACOPP, BV, COPP, DHAP, GDP, ICE, MINE, RT, SCT	ABVD, BEACOPP, BV, DHAP, ICE, MINE, RT, SCT
UK	ABVD, ASHAP, BEACOPP, BV, ChlVPP, chlorambucil, COPP, cyclophosphamide, DHAP, GDP, ICE, MINE, RT, SCT	ABVD, ASHAP, BEACOPP, BV, chlorambucil, ChlVPP, cyclophosphamide, DHAP, GDP, ICE, MINE, RT, SCT
Latin America		
Argentina*	ABVD, BEACOPP, Bendamustine, BV, DHAP, ESHAP, GDP, GVD, ICE, IGEV, MINE, RT	
Barbados*	CVP, DHAP, ICE, MINE, RT	
Brazil*	ABVD, BEACOPP, BV, DHAP, ICE, MINE, RT, SCT	ABVD, DHAP, RT
Colombia	ABVD, BEACOPP, BV, DHAP, ICE, MINE, RT, SCT	ABVD, BEACOPP, DHAP, RT
Mexico*	ABVD, BEACOPP, DHAP, ICE, MINE, RT, SCT	ABVD, BEACOPP, DHAP, ICE, RT
Uruguay*	ABVD, BEACOPP, DHAP, ICE, MINE, RT	ABVD, BEACOPP, ICE
Venezuela*	ABVD, BEACOPP, DHAP, ICE, MINE, RT	
North America		
Canada	ABVD, BEACOPP, BV, CEP-R, CEPP, CEPP-R, ChlVPP, cyclophosphamide, DHAP, ESHAP, GDP, ICE, MINE, Mini-BEAM, MOPP, RT, SCT	ABVD, BEACOPP, BV, CEP-R, CEPP, CEPP-R, ChlVPP, cyclophosphamide, DHAP, ESHAP, GDP, ICE, MINE, MINI-BEAM, RT, SCT
USA	ABVD-R, BEACOPP, Bendamustine, BV, C-MOPP, CHOP-R, CVP-R, cyclophosphamide, DHAP, ESHAP, Everolimus, GCD, GVD, ICE, IGEV, Lenalidomide, MINE, MINI-BEAM, Nivolumab, RT, Stanford V, SCT, VIM-D	Medicare, Medicaid, private insurance

*LC assumes therapies have regulatory as well as funding/reimbursement approval. LC will continue efforts to confirm status of therapy availability in these member countries. †Partially funded/reimbursed.Source: LC Global Database – as of July 2016.

TABLE 7. NUMBER OF THERAPIES BY COUNTRY AND REGION

Country	Total Therapies Approved	Total Therapies Reimbursed
Algeria	7	1
Argentina	12	N/A
Australia	14	13
Barbados	5	N/A
Belgium	9	7
Brazil	8	3
Bulgaria	10	6
Canada	17	16
China	6	1
Colombia	8	4
Croatia	12	10
Czech Republic	9	5
Denmark	16	15
France	11	9
Germany	10	9
Hungary	10	5
India	7	N/A
Ireland	12	10
Israel	8	6
Italy	11	8
Japan	8	8
Latvia	9	5
Lithuania	10	7
Macedonia	7	N/A
Mexico	7	5
Netherlands	10	8
New Zealand	9	8
Poland	10	9
Portugal	9	N/A
Russian Federation	7	6
Serbia	8	5
Singapore	9	3
Slovakia	9	4
Slovenia	10	7
South Africa	14	13
Spain	11	9
Sweden	11	9
Switzerland	11	8
Turkey	7	N/A
Ukraine	6	N/A
United Kingdom	15	14
United States	23	23
Uruguay	6	3
Venezuela	6	N/A

Shaded areas show countries where less than 50% of the approved therapies are reimbursed/funded. Source: LC Global Database – as of July 2016.

Clinical Trial Activity

Some of the trials that are underway for patients with HL are looking at changing chemotherapy intensity depending on results of a positron emission topography and computed tomography (PET/CT) scan not only in the early phase but as treatment goes on.

This allows the healthcare provider to alter the dose of the chemotherapy based on patient response rates. This can ensure that not all patients undergo intensive therapy if it's not needed.

Other trials are looking at the genetic markers as well as biomarkers – high levels of substances released by cancer cells – to better understand the behavior of HL. This in turn, may lead to better targeted treatments.[18]

Another important area of research is studying the long-term and late effects of survivors. Research is being conducted on improving cure rates with standard therapy and creating less toxic side effects. The information can also be used to propose guidelines for long-term follow-up care for survivors.

BV is now being studied to see if it might be helpful earlier in the course of the disease and studies are also underway to see if rituximab can help treat cHL.

Drugs called histone deacetylase (HDAC) inhibitors, such as panobinostat and vorinostat, have also shown some early promise in clinical trials.

Other drugs being studied include lenalidomide and bortezomib. These drugs are more often used to treat multiple myeloma and some other forms of lymphomas, but they may prove to be useful in HL as well. Some newer targeted drugs, such as PLX3397, might affect the other cells in Hodgkin tumours, rather than the cancer cells themselves. These other cells make up much of the tumours and are thought to help the cancer cells grow. Research on these types of drugs is still in early stages.[19]

There are currently;

716

clinical trials focusing on lymphomas which are either in phase II or phase III status.

Of these trials;

16%

are studying either HL alone or with other forms of lymphoma.

A very high percentage of those trials;

54%

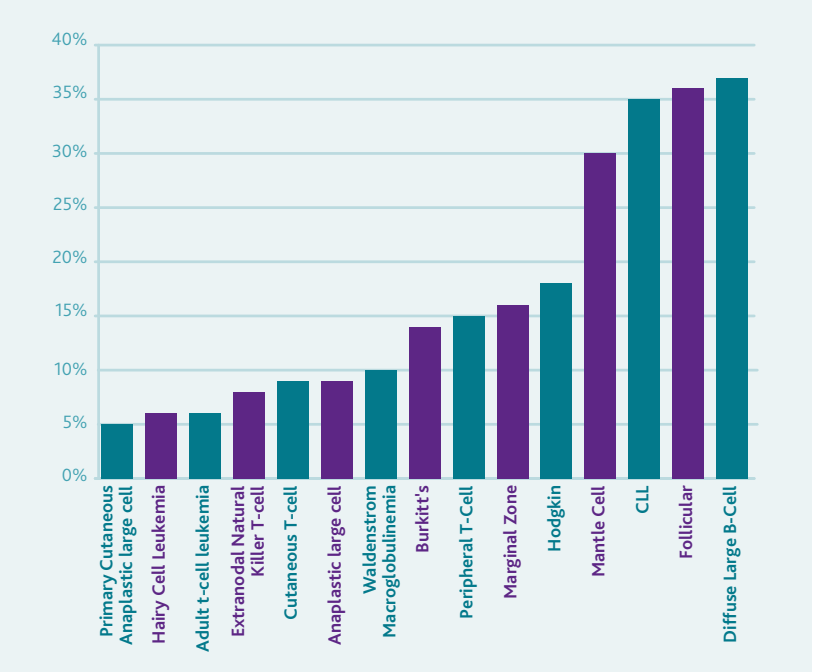
(out of 117) are solely for HL patients.

As seen in Figure 2, the USA is involved in most of the trials with 88 underway with the next highest in Germany with 16 trials. The number of trials in regions such as Eastern Europe, South America, Asia Pacific, Africa and Asia are incredibly low or none at all.

FIGURE 2. NUMBER OF CLINICAL TRIALS WITH HL PER COUNTRY

Source: LC Global Database – as of July 2016. Note that a clinical trial may be undertaken in more than one area of focus and in more than one location therefore the total number will not add up to the total number of trials.

FIGURE 3. PERCENTAGE OF TRIALS BY SUBTYPE



Source: LC Global Database – as of July 2016.

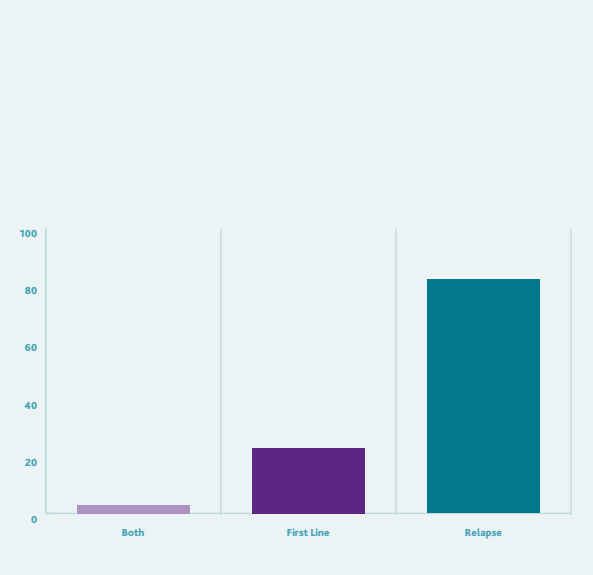
The number of trials with HL is still high compared to other rarer forms of lymphoma. However, trials with diffuse large B-cell (DLBCL) and Follicular (FL) lymphomas are almost double those of Hodgkin lymphoma. When we look at subtype specific trials HL has one the highest numbers after CLL and DLBCL.

There are a high number of trials studying novel therapies (78 out of 117). 73% of these trials are in the relapsed/ refractory setting while 26% are in the first line setting. (The remaining 1% of trials are listed for both relapsed and first line patients).

Most HL trials are focused on new therapies within the relapsed setting.

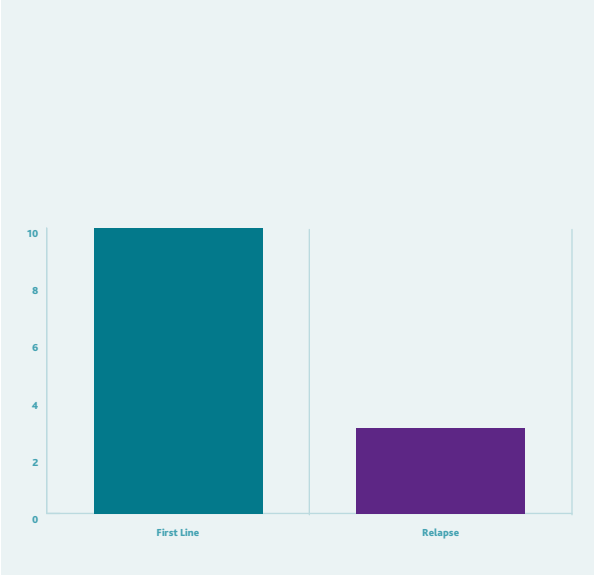
Of the 117 trials 91% are in a phase II setting; while 9% are in phase III.

FIGURE 4. PHASE II TRIALS FOR HL



Source: LC Global Database – as of July 2016. Note that a clinical trial may be undertaken in more than one area of focus and in more than one location therefore the total number will not add up to the total number of trials.

FIGURE 5. PHASE III TRIALS FOR HL



Source: LC Global Database – as of July 2016. Note that a clinical trial may be undertaken in more than one area of focus and in more than one location therefore the total number will not add up to the total number of trials.

Phase II Trials	Combination	Novel	Total
Both	2	1	3
First Line	5	18	23
Relapse	24	58	82
Total	31	77	108

Source: LC Global Database

Phase III Trials	Combination	Novel	Total
First Line	8	2	10
Relapse	0	3	3
Total	8	5	13

Source: LC Global Database

There are 13 trials in phase III all of which are specifically for HL patients only. Six of these trials are looking at BV in different settings.

As mentioned in the biology section, a characteristic of HL is the presence of HRS cells in the tumour environment. Newer therapies are being developed that either specifically target HRS cells, or target the inflammatory environment, or reverse the suppressed immune microenvironment.

Remission rates for patients with HL are favourably high, although there is a need to study front-line therapies that would improve quality of life and decrease long term negative effects.

In 2015 there were 14 LC member countries that had no clinical trials available for patients with HL. The number is now 18.

Patient Experience

Although 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.

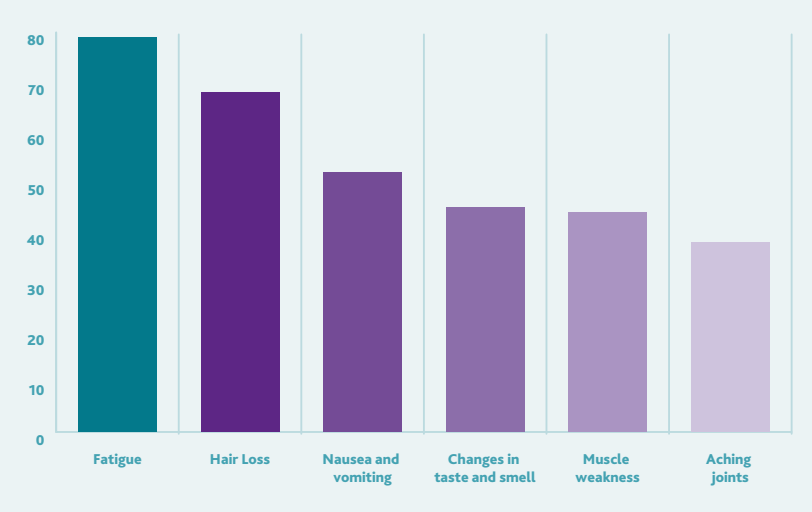
The LC 2016 GPS is the document LC references in this report to provide a sense of the patient experience.

There were over 4,000 respondents to the GPS, of which 23% were identified as patients with HL. The highest numbers of responses were between 30-45 years old (42%) followed by 18-25 years old (28%).

When first diagnosed with HL, respondents indicated that they had a better understanding of their subtype, treatment options and side effect management compared to other subtypes. However, the LC GPS results show that 25% of respondents still do not completely understand their HL subtype characteristics. Most respondents understand the side effects of their treatment (76%) but when it came to understanding side effect management the numbers fell to 64%.

As is the case with any treatment plan, the success of the patient experience can pivot on patient understanding and support. If patients have a clear view of their treatment options and the related risks and side effects they have the opportunity to manage their experience appropriately.

FIGURE 6. PHYSICAL CONDITIONS AFFECTING PATIENTS SENSE OF WELL-BEING, %



Source: LC 2016 Global Patient Survey

78%

of respondents are affected by;

fatigue, followed by hair loss, nausea and vomiting.

30%

of respondents are affected by;

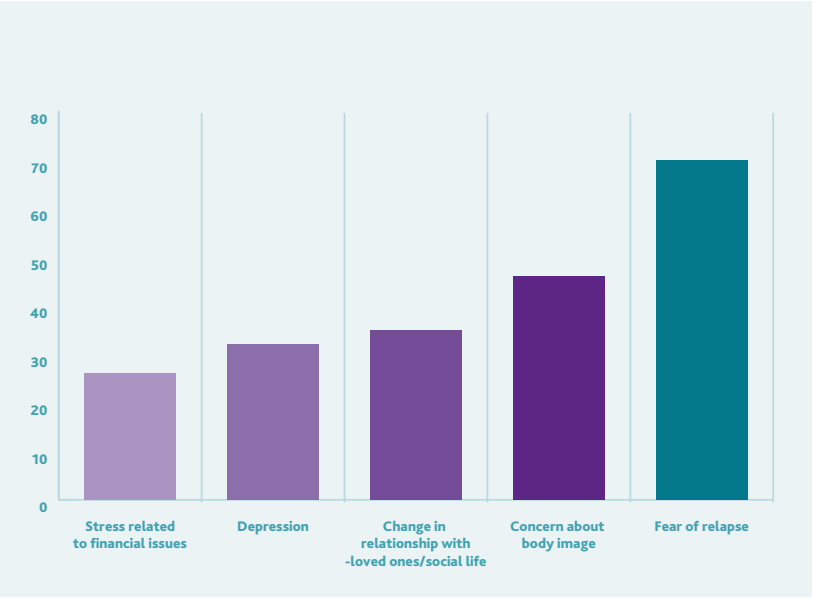
aching joints, muscle weakness and changes in taste and smell.

In comparison to other lymphomas, HL had some of the highest number of respondents affected by adverse physical conditions.

The survey also looked at other conditions that might have an impact on the patients' sense of well-being. One of the most common factors is the fear of relapse, which is the case for patients with all lymphomas, followed by concern about body image, which has impacted 46% of HL respondents.

Changes in relationships and depression are another major cause for concern, especially because at this point in the patients' journey these two factors can increase the sense of isolation.

FIGURE 7. PSYCHOSOCIAL FACTORS AFFECTING PATIENTS' WELL-BEING, %



Source: LC 2016 Global Patient Survey

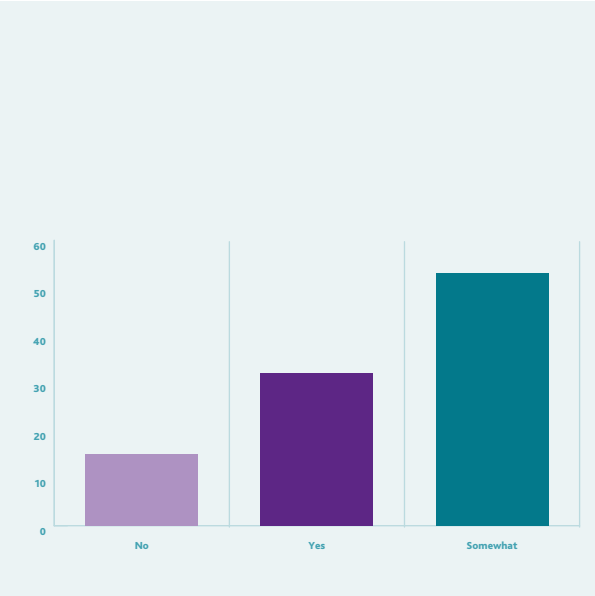
Healthcare professional and palliative care providers can play a major role in easing patients concerns, both physical and emotional.

When asked if their local patient organisation was helpful in addressing their concerns, 85% said that they were helpful. These findings indicate that healthcare providers and patient support organisations should work in tandem to create a more inclusive and comprehensive support structure for patients.

There is a marked gap between patients' needs and support.

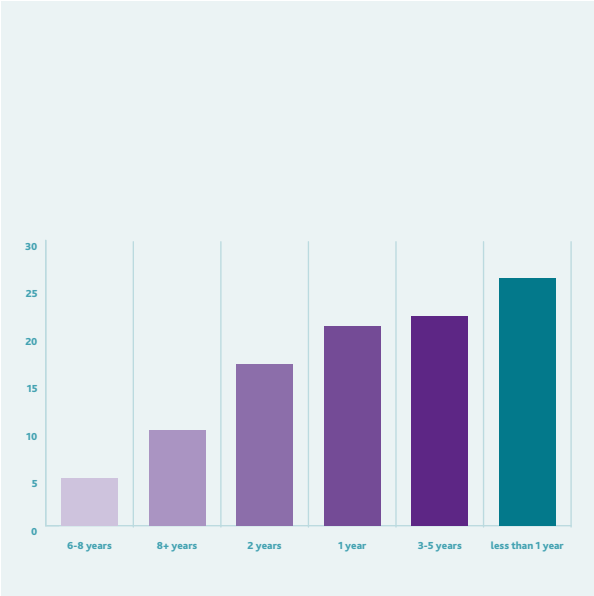
Of the 67% of HL respondents who said they went to the doctor with their emotional/ physical issues almost two-thirds came away with insufficient or no support at all.

FIGURE 8. WAS THE DOCTOR USEFUL IN SUPPORTING EMOTIONAL/PHYSICAL CONCERNS, %



Source: LC 2016 Global Patient Survey

FIGURE 9. TIME LENGTH OF ISSUES, %



Source: LC 2016 Global Patient Survey

When we look at the length of time that respondents reported issues after treatment, as seen in Figure 9, many people carry the burden of HL for many years.

HL patients are facing numerous problems affecting the quality of their life on an emotional, physical and economic level. These factors are all interrelated and allaying fears and providing the right support in one area may well ease the stress with other concerns.

As a result of the numerous quality of life problems faced by HL patients, LC has developed an app called Lyfe. It offers insightful articles and practical tips designed to help during all stages of the patient journey. It also has a community section, which allows patients and support-givers to share their stories and connect with others who are dealing with similar circumstances—locally, nationally and across the globe.

Barriers to Treatment

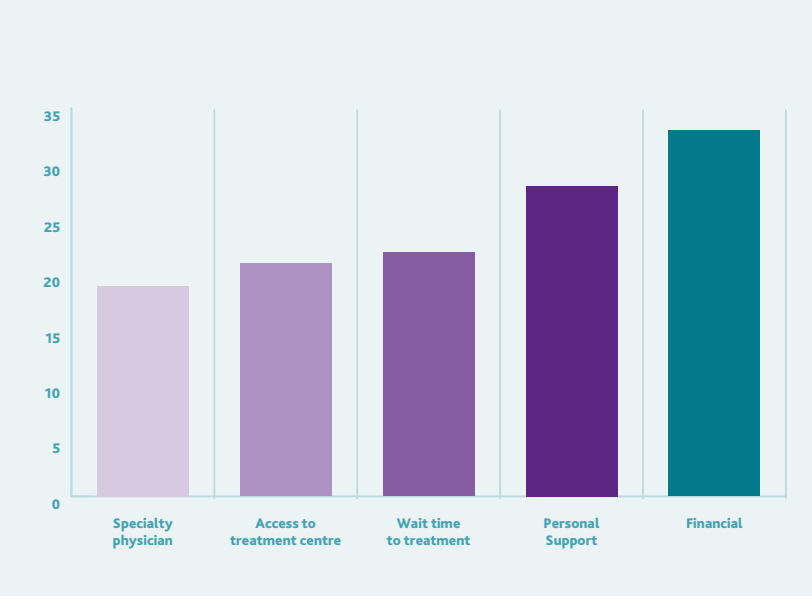
Patients with HL felt that financial issues were the greatest barrier to receiving treatment.

This was followed by lack of personal support, wait time to treatment, access to a treatment centre and unavailability of a specialist physician.

It is interesting to see both access to treatment and financial issues as major barriers to patients. If we take as an example the drug BV, one of the newer therapies for HL, it doesn't have regulatory approval in some member countries. Where it does have approval, it isn't always reimbursed/funded.

Wait time to treatment and lack of access to a specialty physician indicate the healthcare systems are failing patients and their expectations. In order to, at the very minimum, reduce anxiety for the patient at this very critical time, it is essential for doctors to provide as much information as early as possible. Empowering patients comes from knowledge and a semblance of control over their situation.

FIGURE 10. TOP 5 BARRIERS AFFECTING PATIENTS WITH HL, %



Source: LC 2016 Global Patient Survey

Finance is not only the greatest barrier to treatment, it was also mentioned as a factor affecting the patients' sense of well–being.

This ties in with the fact that barriers to treatment may well be influencing psychosocial and physical problems.

Conclusion

In the past decade there has been a greater understanding of the tumour microenvironment and the overall biology of HL. The discovery of the B-cell identity of HRS and its signaling pathways have the potential to be exploited therapeutically.

It is imperative that novel therapies are made available to all patients no matter where they live. There are huge discrepancies in access and outcome between countries and regions.

Additionally, trials should be available in a more diverse geographical scope to ensure novel therapies are widely researched.

The LC GPS indicated that financial constraints was the greatest barrier to treatment. This has the potential to lead to, or exacerbate already existing, psychosocial issues. LC members and the lymphoma community can work together to find solutions to gain broader access for patients.

In the current environment, healthcare providers should use evidence based guidelines and assessment tools to manage the treatment of HL with the aim of reducing the morbidity and mortality associated treatments especially for late stage patients.

Patients with HL can show a variable course of disease progression and early detection is the most important step in ensuring a favourable outcome for the patient.

LC Global Database

Click here to access the Global Database

Acronyms

ABVD±R	adriamycin, bleomycin, vinblastine, dacarbazine with/without rituximab
ASHAP	doxorubicin, methylprednisolone, cytosine arabinoside, cisplatinum
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
B±R	bendamustine with/without rituximab
Bortezomib+R	bortezomib, rituximab
BV	brentuximab vedotin
C-MOPP	cyclophosphamide, vincristine, procarbazine, prednisone
CEPP±R	cyclophosphamide, etoposide, procarbazine, prednisone with/without rituximab
ChlVPP	chlorambucil, vinblastine, procarbazine, prednisone
CHOP	cyclophosphamide, vincristine, doxorubicin, prednisone
CHOP±R	cyclophosphamide, vincristine, doxorubicin, prednisone with/without rituximab
COPP	cyclophosphamide, vincristine, procarbazine, prednisone
CT	clinical trial
CVP±R	cyclophosphamide, vincristine, prednisone with/without rituximab
DHAC	dexamethasone, doxorubicin, cytarabine, carboplatin
DHAP±R	dexamethasone, high-dose cytarabine, cisplatin, with/without rituximab
ESHAP±R	etoposide, methylprednisolone, cytarabine, cisplatin with/without rituximab
ESMO	European Society of Medical Oncology
EPOCH±R	etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin with/without rituximab
FC	fludarabine, cyclophosphamide
FCM	fludarabine, cyclophosphamide, mitoxantrone
FCMR	fludarabine, cyclophosphamide, mitoxantrone, rituximab
FCR	fludarabine, cyclophosphamide, rituximab
FMR	fludarabine, mitoxantrone, rituximab
GDP	gemcitabine, dexamethasone, cisplatin
GVD	gemcitabine, vinorelbine, doxorubicin
HDT	high-dose therapy
HL	Hodgkin lymphoma
HyperCVAD+R	cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine, rituximab
ICE±R	ifosfamide, carboplatin, etoposide with/without rituximab
IGEV	ifosfamide, gemcitabine, vinorelbine
LC	Lymphoma Coalition
MCP±R	melphalan, chlorambucil, prednisone with/without rituximab
MINE	mesna, ifosfamide, mitoxantrone, etoposide
Mini-BEAM	carmustine, etoposide, cytarabine, melphalan
MOPP	mechlorethamine, vincristine, procarbazine, prednisone
NCCN	National Comprehensive Cancer Network
NLPHL	nodular lymphocyte-predominant Hodgkin lymphoma
NORDIC	cyclophosphamide, vincristine, doxorubicin, prednisolone, rituximab, cytarabine
OPEC	vincristine, prednisolone, etoposide, chlorambucil
PCR	pentostatin, cyclophosphamide, rituximab
PEPC±R	prednisone, etoposide, procarbazine, cyclophosphamide with/without rituximab
PTCL	peripheral T-cell lymphoma
R	rituximab
RICE	rituximab, ifosfamide, carboplatin, etoposide
RT	radiation therapy
SCT	stem cell transplant
Stanford V	mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone
UK	UK United Kingdom
USA	USA United States of America
WHO	WHO World Health Organization

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