



GLOBAL
SUBTYPE REPORT

Burkitt
Lymphoma

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

Overview

Burkitt lymphoma (BL) is a rare but highly aggressive B-cell lymphoma. It has one of the fastest tumour growth rates of any known cancer. The tumour can double in size in 18 hours.³ This cancer may affect the jaw, central nervous system, bowel, kidneys, ovaries, or other organs.

BL is usually associated with a mutation involving chromosome 8, affecting a transcription factor known as c-MYC which controls many aspects of cell growth. This mutation usually arises by way of a swapping of genes (translocation) between a part of chromosome 8 and a part of one of either chromosome 14, 2 or 22.

Dr. Denis Burkitt and colleagues discovered BL in 1957, where cases were clustered in regions where malaria was endemic—the so-called lymphoma belt in Africa. The search to find the link between malaria and BL led to the discovery of the Epstein-Barr virus (EBV), the virus that causes infectious mononucleosis. It is believed that malaria is a risk factor for BL because it leads EBV-infected cells through the germinal centre (GC) consequently leading to DNA damage and potentially lymphoma.

BL is most common in male adults and male children—more than two-thirds of adults with BL are men. It makes up over a third of all the lymphomas seen in children. It is seen in adolescents and young adults too.

Three forms of BL are currently recognised: endemic, sporadic, and immunodeficiency-related. All look the same under a microscope and have similar clinical behaviour, but are different from the perspective of epidemiology, clinical presentation, and genetic features. For example, EBV plays a role in both the endemic form and, to a lesser extent, the immunodeficiency

form. Regrettably, none of the current therapies available take advantage of this fact.

BL is curable in > 80% of patients if detected early and treated immediately. Due to the aggressive nature of BL, patients are generally always treated with high intensity chemotherapy. In patients with refractory/relapsed BL some patients may achieve long-term remissions, however, in general the outcome of patients with chemotherapy-resistant disease is poor.²⁰

Cure rates for BL in western countries approach 90% in children, whereas only 30% to 50% of children in Africa are cured due to an inability to provide timely, effective treatment. Thus, there is an important need for not only less toxic drugs but also cheaper, widely accessible therapies.

LC reviewed the treatment listing by the National Comprehensive Cancer Network (NCCN) to determine available treatment options for BL. It should be noted that European Society for Medical Oncology (ESMO) has no published guidelines for the treatment of BL.

There are few countries in which all the protocols outlined in the NCCN listings are approved making it a challenge for most patients to access medication. Although there are some countries where treatment protocols have been approved the obstacle of funding still exists making it difficult for those with financial constraints to consider these as a treatment option.

BL respondents to the Global Patient Survey (GPS) felt that personal support was the greatest barrier to receiving treatment. This was followed by access to a treatment centre, financial concerns and access to up to date treatments. All these barriers have a negative impact on the patient's sense of well-being.

When reviewing the clinical trials in LC's Global Database, there were 73 active trials as of October 2017. Of the 73 trials there were only four trials specific to BL and only one in Phase III. Among the 47 LC member countries, there are 33 countries that have trials for BL, with the USA conducting the most trials (n=59).

To assess whether patients were taking their concerns to their doctors the LC asked respondents in the GPS if they had told their doctors about their physical and/

or emotional issues. While 53% responded saying they had communicated their concerns with their doctor, 27% of respondents had not raised any concerns at all.

When asked if the doctor was helpful in addressing their concerns, 44% of respondents felt the doctor helped somewhat while 30% came away with no support at all. In essence a staggering 74% of patients received insufficient support from their healthcare professionals.

Tingling, numbness, issues with other organs and heart-related issues were of the greatest concern for patients with BL. As is the case for most lymphomas, fatigue was the top most physical concern for patients with BL at 71%. This is followed by hair loss, muscle weakness, mucositis and changes in taste and smell.

Acknowledgements

The Lymphoma Coalition would like to extend a special thanks to the advisors of this report whose collaboration and support have made this report possible. We would like to personally recognize retired Professor Peter Hesselling, Paediatric Oncologist, Cape Town, South Africa as well as Lauren Pretorius, CEO of Campaigning for Cancer, whose expertise greatly assisted our research.

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What is Burkitt Lymphoma?

Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumour.

The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B-cells) and T lymphocytes (T-cells). Approximately 90% of people diagnosed with lymphoma have B-cell lymphoma and 10% have T-cell lymphoma, with less than 1% having Natural Killer lymphoma (NK).²

Burkitt lymphoma (BL) is a rare but highly aggressive B-cell lymphoma. It has one of the fastest tumour growth rates of any known cancer. The tumour can double in size in 18 hours.³ This cancer may affect the jaw, central nervous system, bowel, kidneys, ovaries, or other organs.

The disease was named after Dr. Denis Burkitt, an Irish missionary and surgeon who worked in Africa. Burkitt and his colleagues discovered BL in 1957, where cases were clustered in regions where malaria was endemic—the so-called lymphoma belt in Africa. However, malaria is a parasite that infects the red blood cells, not the white blood cells of lymphoma, and so the exact link has been a mystery. The search to find the link between malaria and BL led to the discovery of the Epstein-Barr virus (EBV), the virus that causes infectious mononucleosis. It is believed that malaria is a risk factor for BL because it leads EBV-infected cells through the germinal centre (GC) consequently leading to DNA damage and potentially lymphoma (Figure 1).

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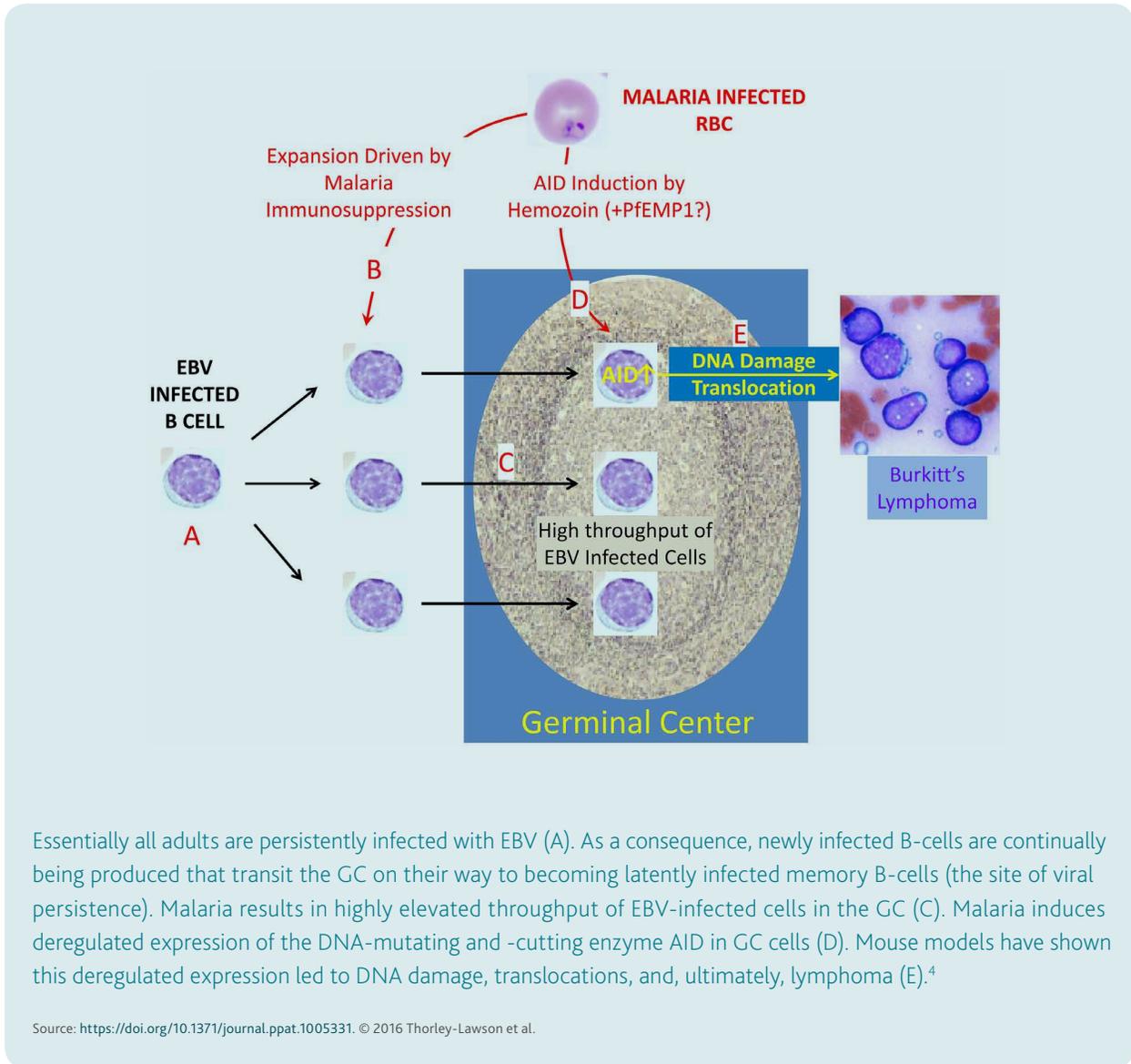
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FIGURE 1. THE LINK BETWEEN MALARIA AND BL⁴



BL is a rare disease particularly outside of Africa: only 1 in every 30–50 people with a B-cell lymphoma will have this type of lymphoma.⁵ In Uganda, the estimated prevalence of Burkitt lymphoma is between 5 and 20 cases per 100,000 inhabitants, whereas in the United States, for 2001–2009, prevalence was 0.4 cases per 100,000 inhabitants.⁵

Burkitt tumours occur predominantly in children (between 4 to 7 years) in the tropical zones of Africa, New Guinea and South America. In parts of Africa, it accounts for 30% to over 60% of all paediatric cancers. It is the most common childhood malignancy in Ethiopia and much of the rest of Africa. In Latin America it accounts for 2-5% of childhood lymphomas. Cases have also been recorded in North America, Europe (particularly Spain), North Africa, the Middle East, as well as Israel.⁶

BL is most common in male adults and male children— more than two-thirds of adults with BL are men. It makes up over a third of all the lymphomas seen in children. It is seen in adolescents and young adults too.

Three forms of BL are currently recognised: endemic, sporadic, and immunodeficiency-related. All look the same under a microscope and have similar clinical behaviour, but are different from the perspective of epidemiology, clinical presentation and genetic features. For example, EBV plays a role in both the endemic form and to a lesser extent, the immunodeficiency form. Regrettably, none of the current therapies available take advantage of this fact.

- Endemic BL is the most common of the three forms, originating in Africa, where it is still the most common paediatric cancer; and is rare outside of Africa. There is a strong correlation between EBV and BL in the endemic form. In children with the endemic type the lymphoma often affects the jaw and face, and about half of the children also have abdominal tumours. There is a strong ecological link to malaria, however epidemiological evidence is weak and the exact mechanism is still being investigated.⁷
- Sporadic BL occurs throughout the world. The sporadic form seen in the United States (USA) and Western Europe accounts for less than one percent of B-cell lymphomas in adults; however, it accounts for 30% of all childhood lymphomas. It usually presents as tumours involving abdominal organs or bone marrow.⁸
- Immunodeficiency-related variety is most common in people with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). It can also occur in patients who have inherited immune deficiencies or those who take immunosuppressive medications to prevent rejection after organ transplant.⁹ The most common site of occurrence is in the abdomen. Immunodeficiency-associated BL accounts for about 30% of lymphomas in HIV patients.¹⁰ The link between immunodeficiency and BL has not yet been fully understood.

The symptoms of BL come on rapidly as the cancer divides very quickly. During the time of diagnosis patients may be found to have this lymphoma in several places.

Symptoms may include:

- swelling of lymph nodes
- abdominal pain – BL commonly affects the bowel
- swollen abdomen (due to fluid being collected)
- paralysis of the legs and incontinence
- lymphoma in extranodal site(s)
- night sweats
- low blood counts in the bone marrow
- anaemia
- low platelets
- lymphoma cells in brain and spinal cord

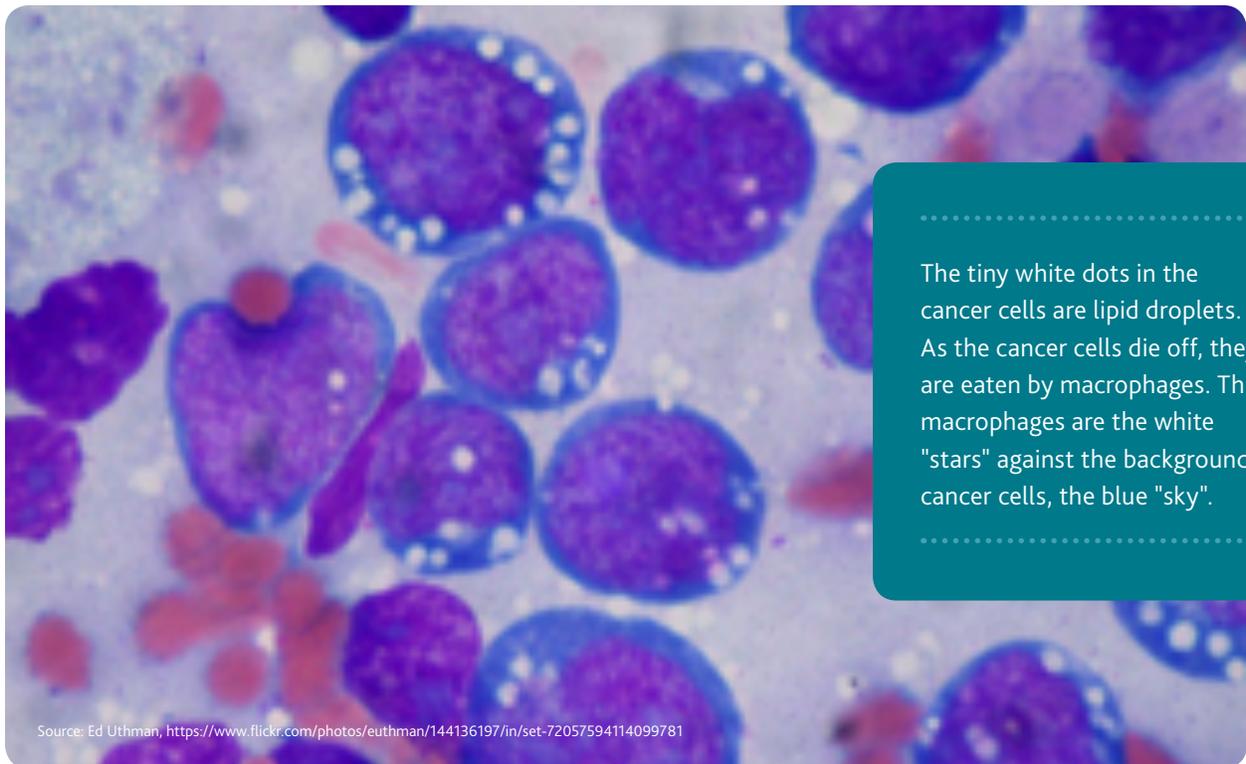
Please note the presence of these symptoms cannot be the basis of a BL diagnosis.

BL is usually diagnosed by a biopsy of a swollen lymph node or another affected tissue. In a few people, BL will be found first in the bone marrow or in tissues removed for other reasons – in these cases, lymphoma may not have been suspected before. Other tests may include, but are not limited to: abdominal ultrasound; CT scan; PET scan; kidney and liver function tests; HIV tests; spinal tap.

BL may also spread to the central nervous system (CNS; i.e., brain and spinal cord). At diagnosis, a sample of cerebrospinal fluid should be taken to determine if the disease has spread to the CNS.

It is important to identify BL correctly because it is treated differently from other lymphomas.

FIGURE 2. CHARACTERISTIC STARRY EYE APPEARANCE UNDER THE MICROSCOPE¹¹



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The tiny white dots in the cancer cells are lipid droplets. As the cancer cells die off, they are eaten by macrophages. The macrophages are the white "stars" against the background cancer cells, the blue "sky".
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Source: Ed Uthman, <https://www.flickr.com/photos/euthman/144136197/in/set-72057594114099781>

Biology

BL is usually associated with a mutation involving chromosome 8, affecting a transcription factor known as c-MYC which controls many aspects of cell growth. As shown in Figure 3, this mutation usually arises by way of a swapping of genes (translocation) between a part of chromosome 8 and a part of either chromosome 14, 2 or 22.¹² Expression of c-MYC leads to the proliferation of the B-cells that bear the translocation, increasing their risk for developing genetic errors, which ultimately increases the risk of BL.¹³

While the translocation of the MYC gene is a hallmark of BL, making this an important finding for diagnosis of the cancer; abnormalities in this gene can also be found in other aggressive mature B-cell lymphomas. In fact, in adults, BL is often indistinguishable from DLBCL. Accurately diagnosing BL is critical because BL and DLBCL should be treated differently.

There is also a strong link between areas where malaria is endemic and BL. As seen in Figure 4, the black horizontal stripes on the image show regions where the temperature and rainfall support malaria. The grey area represents

the areas in which Dr. Burkitt's surveys found BL to be endemic.¹⁴ Repeated malaria infection also helps EBV to cause lymphomas. Working with mice, researchers at Rockefeller University led by Michel Nussenzweig found that the same enzyme that helps make antibodies to fight malaria also causes DNA damage that can lead to BL.¹⁵

BL has also been shown to have a strong correlation with EBV. The restricted geography of BL in Africa indicated a possible viral link and further investigation led to the discovery of EBV. In particular, having an early EBV infection is linked with the development of BL. EBV is found in nearly all cases of BL and has been shown to be a potent transforming virus for human B-cells. The presence of EBV is thought to break the apoptosis cycle and allow cancerous B-cells to survive.

EBV is pervasive worldwide and doesn't explain the geographic distribution, particularly in Africa. The interactions between the parasite that causes malaria, EBV and BL needs further investigation. Furthermore a look into other environmental and lifestyle choices may uncover further risk factors for BL.

FIGURE 3. CHROMOSOMAL TRANSLOCATION IN BL¹²

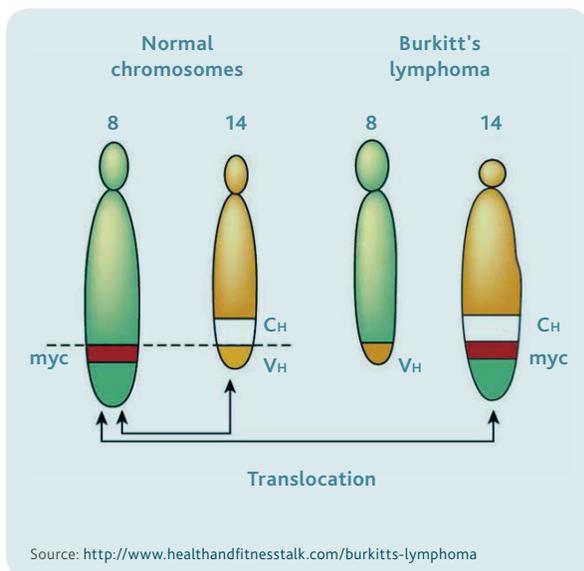
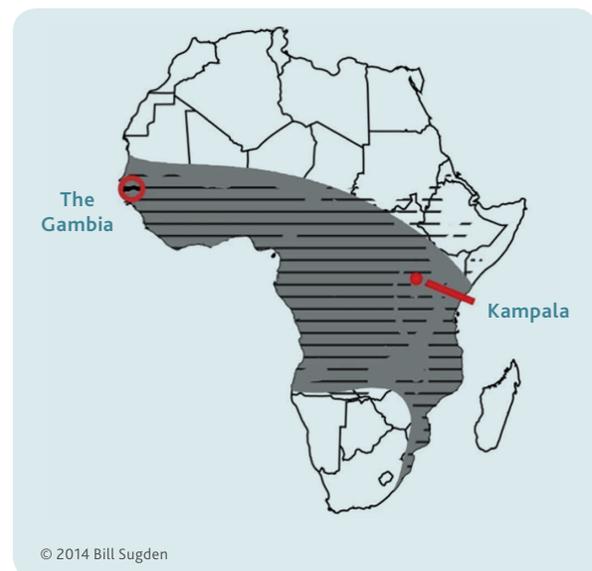


FIGURE 4. BL LINK WITH MALARIA¹⁴



Staging & Treatment

BL is staged using one of the following staging systems:

- the Ann Arbor system – the system used for most other lymphomas, particularly in adults, or
- the St Jude/Murphy staging system – a system more often used for lymphomas in children.

TABLE 1. ANN ARBOR STAGING SYSTEM

Stage	Area of involvement
I	One lymph node region
IE	One extralymphatic organ or site
II	Two or more lymph node regions on the same side of the diaphragm
IIIE	One extralymphatic organ or site (localised) in addition to criteria for stage II
III	Lymph node regions on both sides of the diaphragm
IIIE	One extralymphatic organ or site (localised) in addition to criteria for stage III
IIIS	Spleen in addition to criteria for stage III
IIISE	Spleen an one extralymphatic organ or site in addition to criteria for stage III
IV	One or more extralymphatic organs with or without associated lymph node involvement (diffuse or disseminated); involved organs should be designated by subscript letters (P, lung; H, liver; M, bone marrow)

Class A patients experience no symptoms; class B patients experience unexplained fever of ≥ 101.5 °F; unexplained, drenching night sweats; or loss of > 10% body weight within the previous 6 months.

TABLE 2. ST JUDE/MURPHY STAGING SYSTEM FOR BL

Stage	Description
I	A single tumour (extranodal) or a single anatomic area (nodal) with the exclusion of the mediastinum or abdomen
II	<ul style="list-style-type: none"> • A single extranodal tumour with regional node involvement • Two single extranodal tumours on the same side of the diaphragm with or without regional node involvement • Primary gastrointestinal tumour with or without involvement of associated mesenteric nodes only • Two or more nodal areas on the same side of the diaphragm
IIR	Completely resected intra-abdominal disease
III	<ul style="list-style-type: none"> • Two single extranodal tumours on opposite sides of the diaphragm • All primary intrathoracic tumours (mediastinal, pleural, thymic) • All paraspinal or epidural tumours, regardless of other tumour sites • All extensive primary intra-abdominal disease • Two or more nodal areas on opposite sides of the diaphragm
IIIA	Localised but not nonresectable intra-abdominal disease
IIIB	Widespread multi-organ abdominal disease
IV	Any of the above with initial CNS and/or bone marrow involvement (less than 25% involvement; greater than 25% involvement is defined as L3 ALL)

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Tests should be carried out to look for signs of tumour lysis syndrome (TLS), a condition where tumour cells rapidly release their contents into the bloodstream.

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Burkitt lymphoma has an aggressive clinical course; therefore, management should be directed towards an expedited diagnosis, followed by therapy within 24 hours.

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BL is curable in approximately 80% of patients if detected early and treated immediately. Due to the aggressive nature of BL, patients are generally treated with high intensity chemotherapy. Survival rates and treatment are dependent on availability of drugs and access to medical care.

Tests should be carried out to look for signs of tumour lysis syndrome (TLS), a condition where tumour cells rapidly release their contents into the bloodstream. This needs to be monitored closely. Symptoms of TLS may include nausea and vomiting, shortness of breath, irregular heartbeat, clouding of the urine, lethargy, or joint discomfort. This condition can occur spontaneously or after patients have received chemotherapy and it can be very serious. TLS can cause kidney damage, irregular heartbeat, seizures, loss of muscle control and in some cases death. However, this condition can be managed with increased fluids and supportive medications.

Treatment may also be needed that targets the brain and spinal cord (also called CNS-directed therapy or CNS prophylaxis), which often includes methotrexate and cytarabine.

Aggressive management of this potentially life-threatening complication should be clearly addressed.

Burkitt lymphoma has an aggressive clinical course; therefore, management should be directed towards an expedited diagnosis, followed by therapy within 24 hours.

Intensive systemic chemotherapy is the treatment of choice for this aggressive disease in all its stages. All clinical variants of BL are treated generally the same. The overall survival rate associated with BL depends upon the stage of the disease at initial diagnosis. Patients with localised disease respond well to chemotherapy and have an excellent survival rate. Patients with disseminated disease don't respond as well to chemotherapy and have less favourable outcomes. Increasing age has also been associated with inferior outcome in most clinical trials.¹⁶

LC reviewed the treatment listing by the NCCN to determine available treatment options for BL. It should be noted that ESMO has no published guidelines for the treatment of BL.

The NCCN listing suggests combination therapies for both low and high risk patients which include CALGB 10002, CODOX-M, dose adjusted EPOCH, and HyperCVAD. There are no definitive second line therapies according to the NCCN guidelines, but there is limited data for regimens such as ICE-R, dose-adjusted EPOCH, IVAC-R, GDPR, and high dose cytarabine+rituximab.¹⁷

The NCCN guidelines have stated that CHOP is not an adequate therapy for the management of BL. Intensive rotational multi-agent chemotherapy is needed.¹⁷

For patients who can tolerate it, aggressive multi-agent therapies are believed to offer the best chance for durable disease control.

In sub-Saharan countries where BL is more frequent, limited resources for drugs mean patients are given less-optimal treatment. In this setting a disease-free survival rate of 60% is possible with short cyclophosphamide – based treatment regimens.²⁸ The International Society of Pediatric Oncology (SIOP) has published guidelines for the treatment of children with endemic BL in a resource limited setting.²⁹

Given that BL is CD-20 positive, the addition of rituximab, which is an anti CD-20 monoclonal antibody has shown slightly better results in some case studies.^{16,18} However, there are no randomised comparisons with respect to complete response rates with and without rituximab.¹⁶ **The impact of rituximab on the management of BL needs further evaluation.**¹⁹

Most adult Burkitt lymphoma regimens were initially adopted from the paediatric study protocols that used several known active agents, including cyclophosphamide, vincristine, methotrexate, doxorubicin, and cytarabine. **The French (LMB 81, 84, 86, and 89) and the German (BFM, B-NHL 83, B-NHL 86) protocols as well as the CODOX-M/IVAC regimen (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate / ifosfamide, etoposide, high-dose cytarabine), were modified and used in adult patients with acceptable outcomes (2-y overall survival: 40-74%).**

A study by Todeschini et al found that intensive paediatric-based chemotherapy regimen increased remission and survival rates in both children and adults with Burkitt lymphoma.¹⁹

The standard therapies used for BL are associated with a significant toxicity profile. **No toxic deaths were reported in an initial study done by Magrath (CODOX-M/IVAC), but the rate of grade 3/4 neutropenia was 100%; thrombocytopenia, 96%; mucositis, 61%; and sepsis, 22%. Similar toxicities were seen on the CALGB 9251 protocol.**^{19,22}

Despite the fact that no direct comparison has been done among these different approaches, the short-duration, more intense regimens are often preferred, because they are faster to administer and less complicated than stem cell transplant.

In patients with refractory/relapsed BL, some patients may achieve long-term remissions, however, in general the outcome of patients with chemotherapy-resistant disease is poor.²⁰ Current results indicate that new treatment options are imperative for this group of patients.

Newer approaches in the treatment of BL are greatly needed. These approaches may make current therapies more efficacious or provide options in the case of relapsed or refractory disease. Recent work suggests that targeting the PI3-kinase pathway or cyclin-dependent kinase-6 may be of benefit. Another potential approach involves suppressing MYC transcription. Preclinical data of MYC-driven lymphoma suggests this is a very promising approach.²¹

Barriers to Care

The patient journey is a long and arduous one. There are many phases a patient goes through, from the time they are diagnosed, to when they receive care and treatment.

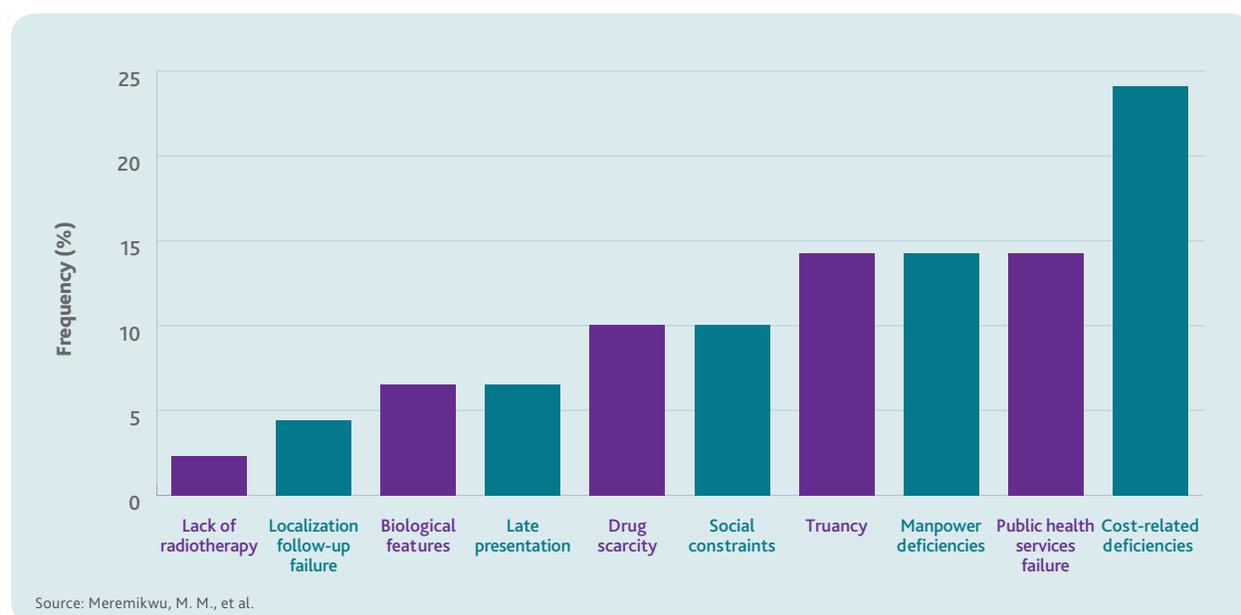
Along this journey patients may face a multitude of barriers, such as access to healthcare, access to treatment, access to clinical trials or socioeconomic inequality.

A study in Nigeria has shown that delayed referral to a treatment centre, low socioeconomic status of patients and the strain on the healthcare system have impeded access to drugs, such as rituximab and other expensive chemotherapy regimens (Figure 5).³¹

The social, cultural and economic challenges outlined in the study are not exclusive to Nigeria. These problems are relevant to many individuals across the globe, especially in areas where the public healthcare system is not well structured.

In some African countries such as Cameroon, traditional healers are often consulted first, causing missed diagnoses, delays in treatment and poor outcomes.³⁰ There is also a stigma attached to certain conditions such as HIV and cancer which play a huge influence in patients seeking and continuing treatment.

FIGURE 5. FACTORS ATTRIBUTED TO FAILURE OF BL THERAPY IN NIGERIAN STUDIES (1984-2014)³¹

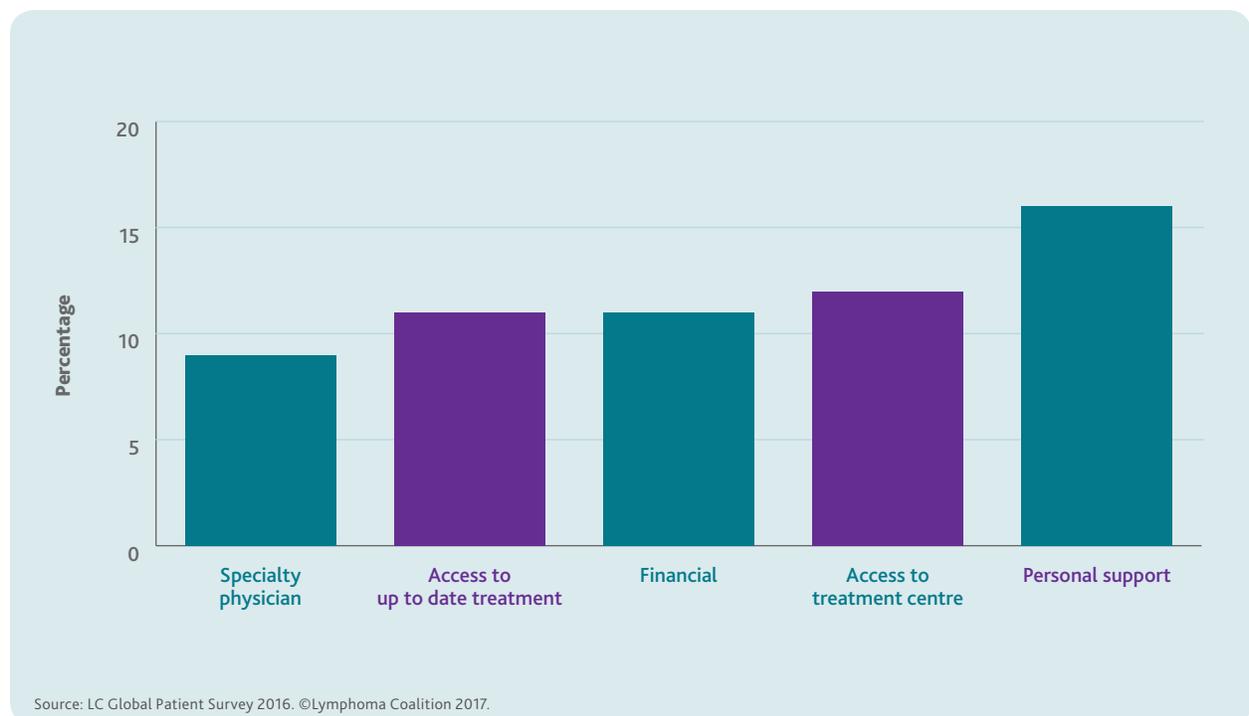


To further examine these barriers the LC gathered data from its 2016 Global Patient Survey (GPS) and treatment protocol information from its Global Database, both of which can be found on the [LC website](#). The LC 2016 GPS has over 4,000 respondents of which 59 were identified as patients with BL. Most of the respondents were from Europe and there were no responses from any of the member countries in Africa.

BL respondents to the GPS felt that personal support was the greatest barrier to receiving treatment. This was followed by access to a treatment centre, financial concerns and access to up-to-date treatments (see Figure 6). All these barriers have a negative impact on the patient's sense of well-being.

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

FIGURE 6. BARRIERS TO TREATMENT FOR BL



Therapy Access

Therapy access in each of the LC member countries was examined to determine availability of treatment. For the purposes of this review, LC has used information from the NCCN to examine which of the therapies noted in respective listings have regulatory as well as funding/reimbursement approval, which is shown in Table 3 (ESMO has no clinical guidelines for BL).

Therapies for BL outlined by NCCN are available and funded in most countries, with exceptions such as Barbados, Turkey, Ukraine, Uruguay and Serbia.

In the Asia/Pacific region Australia, Japan and New Zealand have regulatory approval and funding available for standard therapies. In Singapore none of the therapies are reimbursed/funded.

In Eastern Europe, while there are a few therapies approved for BL patients, countries such as Bulgaria, Hungary, Latvia, Lithuania, Slovakia and Ukraine have poor funding/reimbursement. Patients in Serbia are likely to struggle the most to receive therapy. The only approved therapies for BL is cyclophosphamide. Patients in Latin American countries are likely to face the same challenges with a scarcity of approved drugs.

In Western Europe a greater number of therapies are approved as well as funded/reimbursed. A noticeable absence is seen for dose adjusted EPOCH-R. No reimbursement information was available for Portugal.

The highest number of approved and funded drugs are available in the USA, although availability is dependent on the type of health insurance a patient has.

There are few countries in which all the protocols outlined in the NCCN listings are approved making it a challenge for most patients to access medication. Although there are some countries where treatment protocols have been approved, the obstacle of funding still exists making it difficult for those with financial constraints to consider these as a treatment option.

It is apparent when reviewing treatment outcomes for BL that there is the need for newer treatment approaches.

TABLE 3. BL THERAPIES APPROVED AND FUNDED/REIMBURSED BY COUNTRY

Country	Approved therapies	Country	Approved therapies
Asia/ Pacific		Caribbean	
Australia	CODOX-M, IVAC±R, EPOCH-R, ESHAP±R, GDP, GemOX-R, HyperCVAD, ICE±R, SCT, CODOX-MR, C, SCT	Barbados	CVP
Japan	CODOX-M±R, EPOCH±R, GDPR, HyperCVAD±R, ICE-R, IT, IVAC-R, CALGB 10002	Latin America	
New Zealand	CODOX-MR, CODOX-MR/IVAC, C, DHAP-R, EPOCH-R, ESHAP±R, GDP, GemOX-R, HyperCVAD, ICE±R, IVAC±R, SCT	Mexico	CODOX-M±R, IVAC±R
Singapore	CODOX-M±R, EPOCH±R, HyperCVAD±R, ICE±R, IVAC±R	Uruguay	C
Eastern Europe		North America	
Bulgaria	CODOX-M, GDP, HyperCVAD, IVAC(ara-c), CODOX-MR, HyperCVAD-R, ICE-R, IVAC-R	Canada	CODOX-M±R, CODOX-MR/IVAC, C, GDP±R, IVAC±R, MINI-BEAM, RT, SCT
Croatia	CODOX-M±R, CODOX-MR/IVAC, ICE-R, IVAC±R, SCT, GDP, HyperCVAD±R	United States	CALGB 10002, CODOX-M±R, CODOX-MR/IVAC, CHOEP±R, C, EPOCH±R, GDP±R, HyperCVAD±R, ICE±R, IT, IVAC±R, RT, SCT
Czech Republic	CODOX-MR, C, DHAP-R, EPOCH-R, ESHAP-R, HyperCVAD-R, ICE-R, IVAC-R, CODOX-M, GDP, HyperCVAD, IVAC	Western Europe	
Hungary	CODOX-M±R, GDP, HyperCVAD±R, ICE-R, IVAC±R	Belgium	CODOX-M, CODOX-MR, EPOCH±R, HyperCVAD±R, IT, IVAC-R, SCT, GDP, ICE-R, IVAC
Latvia	CODOX-M±R, GDP, HyperCVAD±R, ICE-R, IVAC±R	Denmark	CODOX-M±R, CODOX-MR/IVAC, DHAP-R, GDP±R, HyperCVAD±R, ICE-R, IVAC±R, SCT
Lithuania	CODOX-M, GDP, HyperCVAD, IVAC(ara-c), CODOX-MR, HyperCVAD-R, ICE-R, IVAC-R	France	CODOX-M±R, GDP±R, HyperCVAD±R, ICE-R, IVAC±R
Macedonia	CODOX-M±R, GDP±R, HyperCVAD±R, ICE-R, IVAC±R	Germany	CODOX-M±R, GDP, HyperCVAD±R, ICE-R, IVAC±R
Poland	CODOX±R, EPOCH-R, GDP±R, HyperCAD±R, ICE-R, IT, IVAC±R, SCT	Ireland	CODOX-M, CODOX-MR/IVAC, GDP, HyperCVAD, IVAC(ara-c), CODOX-MR, HyperCVAD-R, ICE-R, IVAC-R
Russian Federation	CODOX-MR, CODOX-MR/IVAC, EPOCH-R, HyperCVAD-R, ICE-R, IVAC-R	Italy	CODOX-M±R, CODOX-MR/IVAC, HyperCVAD±R, ICE-R, IVAC±R, SCT, GDP
Serbia	C	Netherlands	CODOX-M±R, CODOX-MR/IVAC, GDP±R, HyperCVAD±R, ICE-R, IVAC±R
Slovakia	CODOX-M±R, GDP±R, ICE-R, HyperCVAD±R, IVAC±R	Portugal	CODOX-M±R, GDP, HyperCVAD±R, ICE-R, IVAC±R
Slovenia	CODOX-M±R, HyperCVAD±R, ICE-R, IVAC±R, GDP±R	Spain	CODOX-M±R, GDP±R, HyperCVAD±R, ICE-R, IVAC±R
Turkey	CODOX-M±R, EPOCH-R, GDPR, HyperCVAD±R, ICE-R, IVAC-R	Sweden	CODOX-M±R, EPOCH±R, GDP±R, HyperCVAD±R, ICE-R, IVAC±R
Ukraine	CODOX-M±R, CHOP±R, EPOCH±R, HyperCVAD±R, IVAC±R	Switzerland	CODOX-M±R, EPOCH-R, GDP±R, HyperCVAD±R, ICE-R, IVAC±R
Africa/ Middle East		United Kingdom	CODOX-M±R, GDP±R, HyperCVAD±R, ICE-R, IVAC±R, SCT
South Africa	CODOX-M, CODOX-MR/IVAC, C, DHAP±R, EPOCH, HyperCVAD±R, ICE, RT, SCT	<div style="display: flex; align-items: center;"> <div style="width: 15px; height: 15px; background-color: #0070C0; margin-right: 5px;"></div> Therapy reimbursed/funded </div> <div style="display: flex; align-items: center;"> <div style="width: 15px; height: 15px; background-color: #800080; margin-right: 5px;"></div> Therapy not reimbursed/funded </div>	

Source: Global Database Sept 2017. ©Lymphoma Coalition 2017.

In Africa, clinical trials/treatments is supported by World Child Cancer in Cameroon, Malawi and Ghana, and in Francophone countries by the French Africa Pediatric Oncology Group (FAPOG). West African countries like Tanzania, Uganda and Kenya also have international academic links and sponsors.

Clinical Trials

Several successful therapies have been developed for BL but have never been compared in a randomised trial because of the rarity of the tumour.

Among experimental drugs, evidence is accumulating in favour of histone deacetylase inhibitors (HDAC) and mTOR inhibitors (temsirolimus). These drugs may inhibit BL cell growth.^{23,24}

Other highly effective inhibitors of cell proliferation already tested with success are proteasome inhibitors (bortezomib) and the BCL2 inhibitor venetoclax.^{25,26,27}

When reviewing the clinical trials in LC's Global Database, there were 72 active trials as of October 2017. Of those, there are four trials that are specific to BL and only one of the four is in Phase III. The challenges faced by researchers when conducting a clinical trial for rare diseases are complex. The most obvious of which is recruiting patients with such a rare disease due to the small sample population. Multi-centred trials may be one solution, but the logistical challenges faced with running these trials can be costly and produce unsatisfactory data. Regardless of the challenges, there are opportunities that can be availed by conducting trials across diverse geographies particularly carrying out trials where the incidence rates are higher than in other populations. In the case of Burkitt lymphoma that would be in regions of Africa. Currently there is only one clinical trial available for patients with BL in Africa.

FIGURE 7. NUMBER OF CLINICAL TRIALS BY COUNTRY



Source: Global Database Sept 2017. ©Lymphoma Coalition 2017.

Among the 47 LC member countries, there are trials that include BL in 33 countries. The USA has the most trials, (n=59), followed by Germany (n=9), and then Canada, Italy and the UK with 7 trials each.

As seen from Table 4, most trials are investigating protocols for patients in a relapsed setting. It is encouraging to see that quite a few are investigating novel therapies (n=40).

As mentioned earlier in the report, BL is one of the most prevalent lymphomas seen in children. When we looked at the eligibility criteria of the active trials, LC found that 28 of them were open to children under the age of 14. Of these 14 trials, only one was specific to patients with BL.

Cure rates for BL in western countries approach 90% in children, whereas only 30% to 50% of children in Africa are cured due to an inability to provide timely, effective treatment. Thus, there is an important need for not only less toxic drugs but also cheaper, widely accessible therapies. Future progress in the treatment of BL will only result from the continued evaluation of new treatments in clinical trials.

TABLE 4. PHASE II AND III BL TRIALS

	Phase II			Phase III		
	Combination	Novel	Total	Combination	Novel	Total
First Line	5	1	6	4	0	4
Relapse	20	33	53	1	1	2
Both	2	5	7			

Source: Global Database Sept 2017. ©Lymphoma Coalition 2017.

Patient Experience

As part of the 2016 GPS respondents were asked if they understood their diagnosis, to which 75% responded that they had understood, while only 61% felt they understood the characteristics of their subtype. Respondents were also asked if they understood their treatment options and 73% felt that they understood, while 81% understood what their initial treatment would be.

However, when asked about understanding treatment side effects and side effect management the numbers were much lower. Only 56% understood what the side effects of treatment would be and 51% understood how to manage their treatment side effects.

Patient understanding of not only their subtype, but also their treatment plan and side effects is an integral part of patient care. An overall more comprehensive understanding of the journey gives patients and their caregivers an opportunity to manage their experience in a more informed manner while allowing them to participate in informed decision making that best suits their circumstances. This is especially important in countries where BL is prevalent and health literacy is very low.

The aggressive nature of BL often requires intense chemotherapy which can be debilitating for many patients. It is imperative that healthcare professionals communicate well with their patients and caregivers to ensure that their concerns are being discussed and understood. To assess whether patients were taking their concerns to their doctors the LC asked respondents in the GPS if they had told their doctors about their physical and/or emotional issues. While 53% responded saying they had communicated their concerns with their doctor, 27% of respondents had not raised any concerns at all.

FIGURE 8. UNDERSTANDING SUBTYPE CHARACTERISTICS

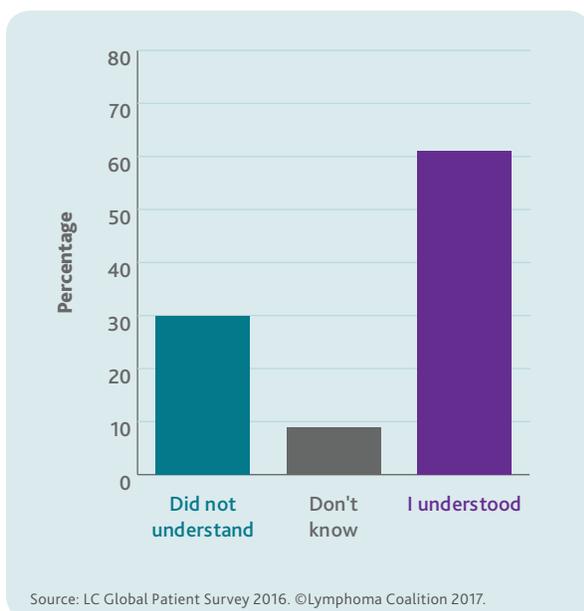


FIGURE 9. UNDERSTANDING SIDE EFFECT MANAGEMENT

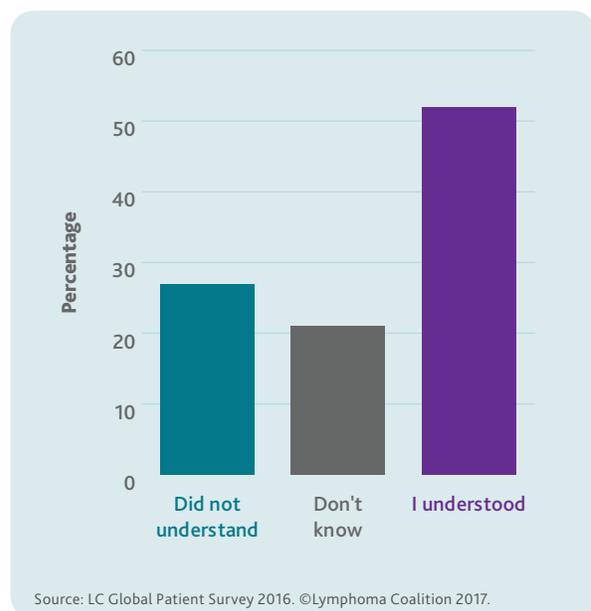
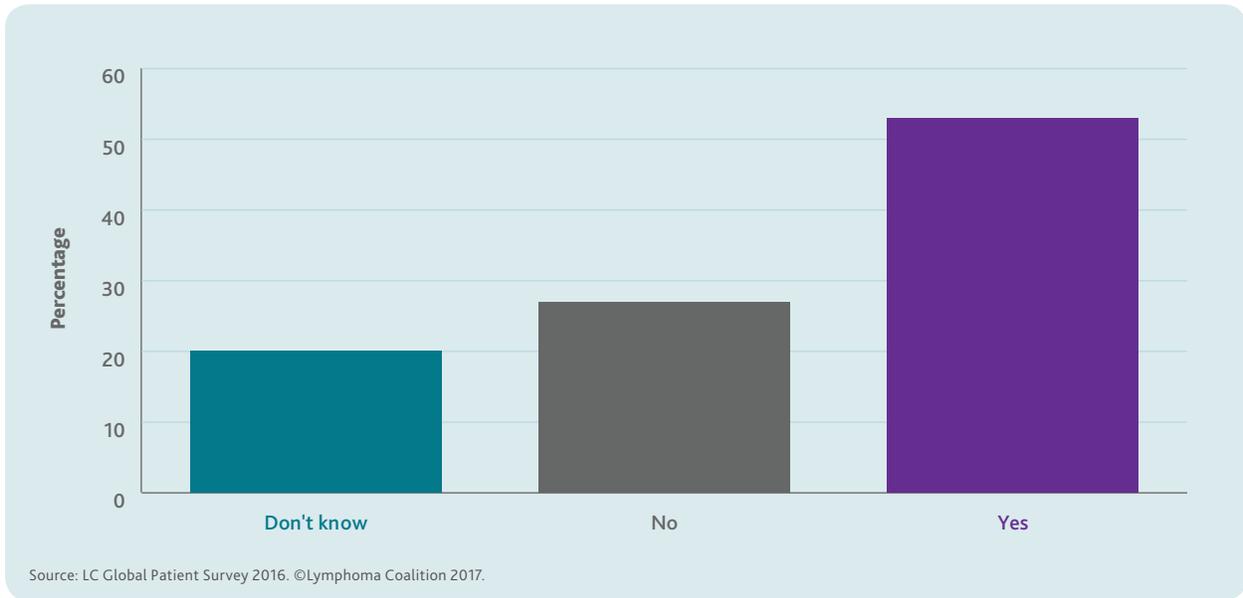


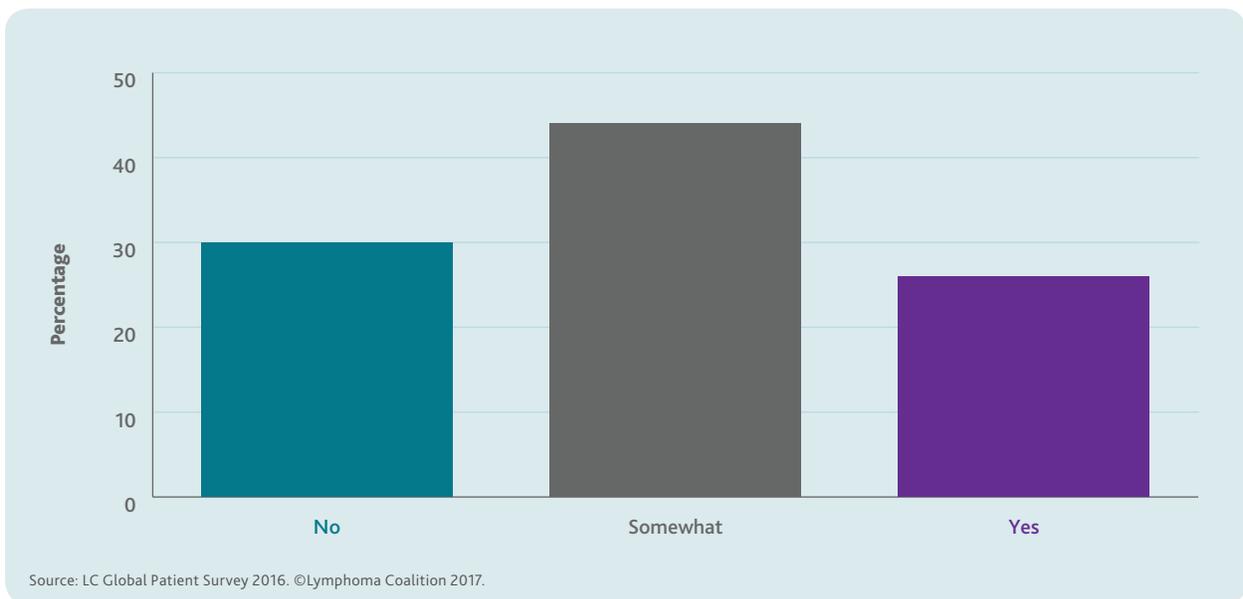
FIGURE 10. RESPONDENTS COMMUNICATING EMOTIONAL/PHYSICAL CONCERNS WITH DOCTOR, %



When asked if the doctor was helpful in addressing their concerns, 44% of respondents felt the doctor helped somewhat while 30% came away with no support at all. In essence a staggering 74% of patients received insufficient support from their healthcare professionals.

The gap between patient care and patient support needs a closer look and better working relationships between healthcare professionals and patient organisations that will create a more robust support structure for patients.

FIGURE 11. PATIENTS PHYSICAL/EMOTIONAL CONCERNS HELPED BY DOCTOR, %



Living with Psychosocial Effects

The emotional and physical concerns that patients face are often a result of their treatment side effects and these concerns can last a number of years as we can see from Figure 12. Patients need to be informed of the long-term risks of their treatment as well as measures on how to manage them.

In the 2016 GPS respondents were asked to indicate which physical and medical conditions affected them the most. Tingling, numbness, issues with other organs and heart-related issues were of the greatest concern for patients with BL. This can be linked to the fact that many BL therapies, as mentioned before, can be toxic and the physical and medical conditions that arise due to it can be varied and numerous.

As is the case for most lymphomas, fatigue was the top most physical concern for patients with BL at 71%. This is followed by hair loss, muscle weakness, mucositis and changes in taste and smell. All the physical conditions, including loss of appetite, trouble concentrating and bowel changes can have a huge impact of an individual's lifestyle leading to other psychosocial effects such as isolation and depression.

FIGURE 12. TIME LENGTH OF ISSUES

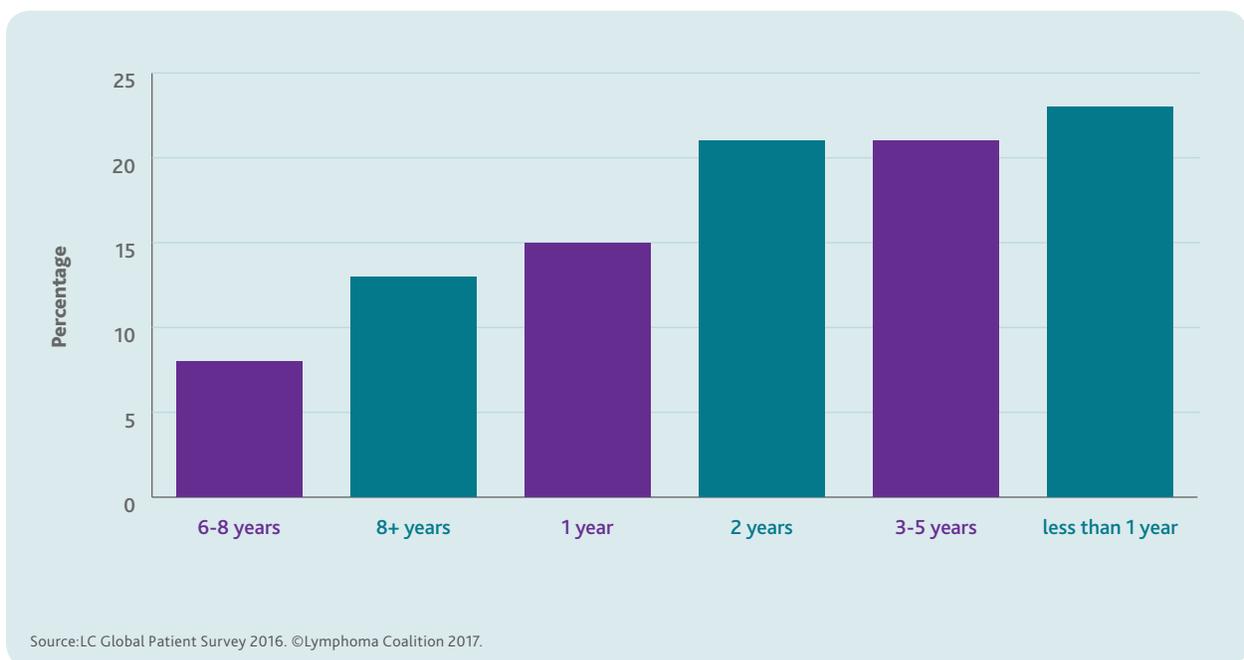


FIGURE 13. TOP MEDICAL CONCERNS, %

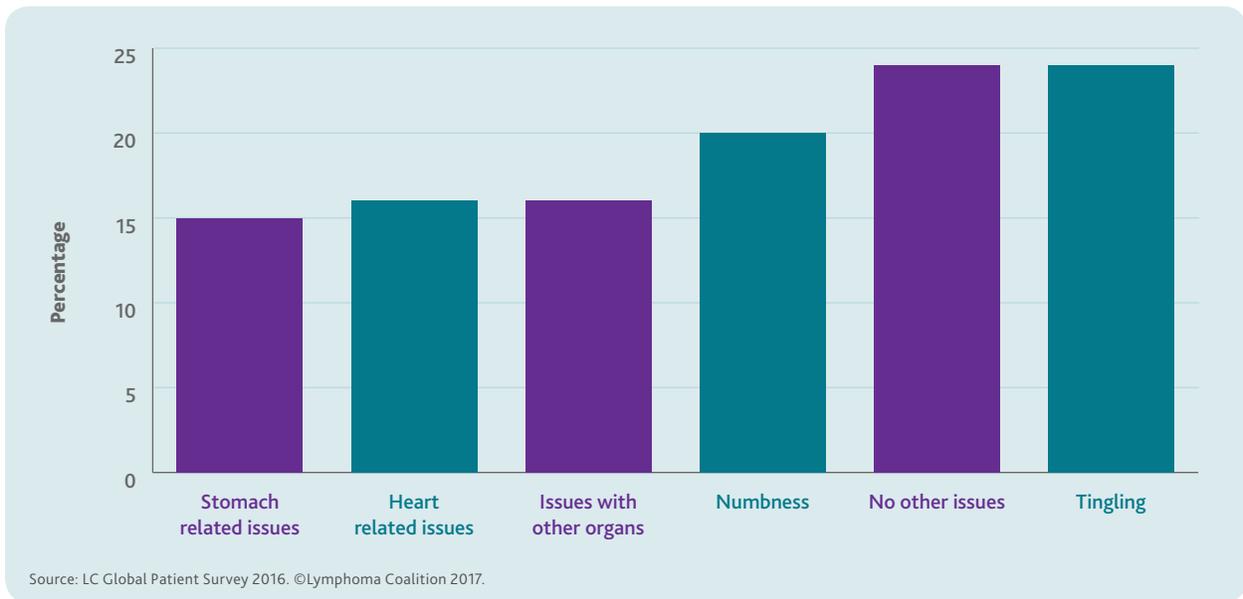
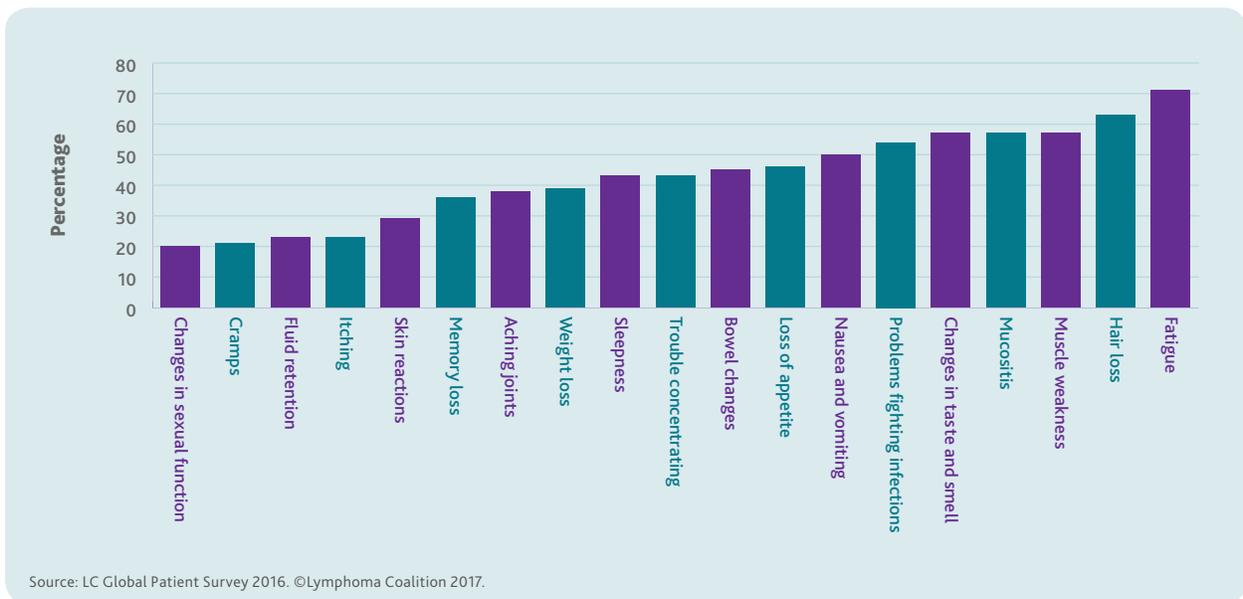


FIGURE 14. TOP PHYSICAL CONCERNS, %



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

Conclusion

Burkitt lymphoma is a rare but highly aggressive B-cell lymphoma. It has one of the fastest tumour growth rates of any known cancer and therefore it is essential to diagnose and treat as soon as possible. Intensive chemotherapy can achieve long-term survival in patients but if a diagnosis is not made in time the therapy may be too toxic for patients with advanced disease.

The unique geography of BL signals other challenges that need to be addressed. In equatorial Africa and other underdeveloped nations, access to specialists, treatment and financial support can be a huge barrier in receiving any kind of healthcare. Most patients who are diagnosed with BL in Africa are children – cure rates for children who live in developing nations is significantly lower. This statistic needs to urgently change. It is absolutely necessary that more work is done to provide better access to treatment and care for these children.

More work also needs to be done to improve survivorship among patients with relapsed/refractory disease. Patients are encouraged to enrol in clinical trials because it is the best way to gain access to latest therapies, but there are few available trials for patients outside of the USA.

BL therapies are high intensity and can be very toxic for many people. Side effects such as tingling and numbness as well as fatigue and muscle weakness are common. Communication between healthcare practitioners and patients needs to improve and include all aspects of care such as psychological and emotional as well as physical well-being. As is the case with any aggressive illness the psychological burden can be overwhelming for patients. A key element in treating patients and improving the patient experience is improving knowledge and awareness. Long term disease burden can be alleviated if healthcare providers work together with patient groups to provide ongoing patient support.

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Acronyms

AIDS	acquired immunodeficiency syndrome
BL	Burkitt lymphoma
C	cyclophosphamide, prednisone, ifosfamide, methotrexate, leucovorin, vincristine
CALGB 10002	dexamethasone, doxorubicin or etoposide or cytarabine; or intrathecal tripletherapy methotrexate, cytarabine, and hydrocortisone and rituximab
CHOEP	cyclophosphamide, vincristine, doxorubicin, etoposide, prednisone
CHOEP-R	cyclophosphamide, vincristine, doxorubicin, etoposide, prednisone, rituximab
CHOP	cyclophosphamide, vincristine, doxorubicin, prednisone
CHOP-R	cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab
CNS	central nervous system
CODOX-M	cyclophosphamide, vincristine, doxorubicin, methotrexate (high dose)
CODOX-M/IVAC	cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate / ifosfamide, etoposide, cytarabine (high dose)
CODOX-MR	cyclophosphamide, vincristine, doxorubicin, methotrexate (high dose), rituximab
CVP	cyclophosphamide, vincristine, prednisone
DHAP	dexamethasone, cisplatin, cytarabine
DHAP-R	dexamethasone, cisplatin, cytarabine, rituximab
DLBCL	diffuse large B cell lymphoma
EBV	Epstein Barr virus
EPOCH	etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
EPOCH-R	etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab
ESHAP	etoposide, methylprednisolone, cytarabine, cisplatin
ESHAP-R	etoposide, methylprednisolone, cytarabine, cisplatin, rituximab
ESMO	European Society for Medical Oncology
GC	germinal centre
GDP	gemcitabine, dexamethasone, cisplatin
GDP-R	gemcitabine, dexamethasone, cisplatin, rituximab
GPS	global patient survey
HDAC	histone deacetylase inhibitors
HIV	human immunodeficiency virus
HyperCVAD	cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high dose methotrexate and cytarabine
HyperCVAD-R	cyclophosphamide, vincristine, doxorubicin, rituximab and dexamethasone alternating with high dose methotrexate and cytarabine
ICE	ifosfamide, carboplatin, etoposide
ICE-R	ifosfamide, carboplatin, etoposide, rituximab
IGEV	ifosfamide, gemcitabine, vinorelbine
IT	intrathecal methotrexate, cytarabine
IVAC (ara-c)	ifosfamide, etoposide, cytarabine
IVAC-R	ifosfamide, etoposide, cytarabine, rituximab
NCCN	National Comprehensive Cancer Network
RBC	red blood cell
RT	radiation therapy
SIOP	International Society of Pediatric Oncology
SCT	stem cell transplant
TLS	tumour lysis syndrome
USA	United States of America

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