Cancer Association of South Africa (CANSA)

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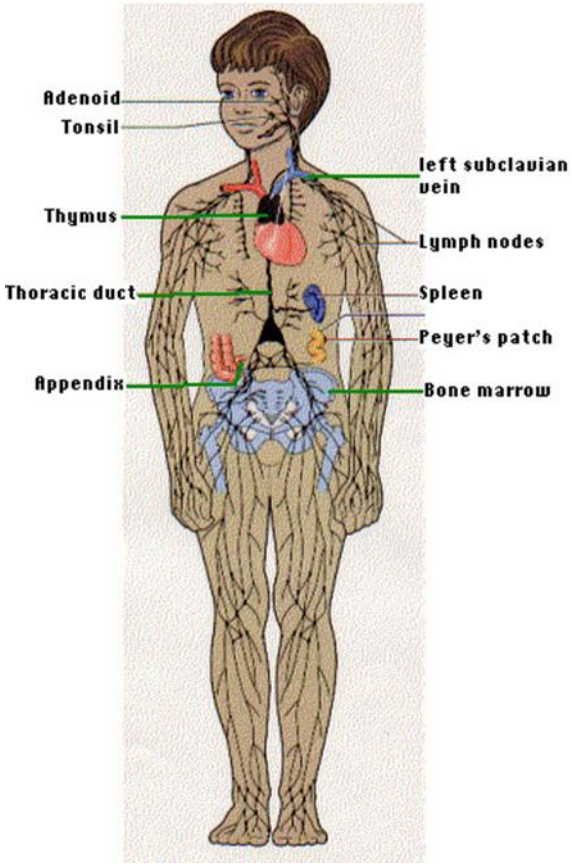
Fact Sheet on Childhood Burkitt's Lymphoma

Introduction

The term 'lymphoma' refers to cancers that originate in the body's lymphatic tissues. Lymphatic tissues include the lymph nodes (also called lymph glands), thymus, spleen, tonsils, adenoids, and bone marrow, as well as the channels (called lymphatics or lymph vessels) that connect them. Although many types of cancer eventually spread to parts of the lymphatic system, lymphomas are distinct because they actually originate there.



[Picture Credit: Lymphatic System of a Child]

It is said that about 150 children younger than 19 years old are diagnosed with lymphoma each year in South Africa. Lymphomas are divided into three broad categories, depending on the appearance of their cancerous (malignant) cells. These are known as Hodgkin's lymphoma (HL), non-Hodgkin lymphoma (NHL), and Burkitt Lymphoma (BL). Together, they are one of the most common types of cancer in children.

Part of the body's immune system, the lymphatic system is a network of vessels and nodes that normally filters the fluid found within all tissues. Lymph nodes remove bacteria and other disease-causing organisms from the lymph fluid, and produce lymphocytes and antibodies needed to fight off infections caused by these organisms. An increase in the size of a lymph node (lymphadenopathy) indicates increased activity within the node, due to inflammation, infection, or cancer.

Malignancy (cancer) occurs when a cell's genetic code mutates, or changes, resulting in abnormal cells that grow rapidly and in uncontrolled fashion. Lymphomas are a group of cancers originating from

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lymphocytes, which are white blood cells whose normal function is to fight off infections within the body.

Molyneux, E.M., Rochford, R., Griffin, B., Newton, R., Jackson, G., Menon, G., Harrison, C.J., Israels, T. & Bailey, S. 2012.
Burkitt's lymphoma is a highly aggressive B-cell non-Hodgkin lymphoma and is the fastest growing human tumour. The disease is associated with Epstein-Barr virus and was one of the first tumours shown to have a chromosomal translocation that activates an oncogene (c-MYC). Burkitt's lymphoma is the most common childhood cancer in areas where malaria is holoendemic. The incidence is very high in immunosuppressed patients in non-endemic areas, especially when associated with HIV infection. Outcome with intensive chemotherapy has improved and is now excellent in children, but the prognosis is poor in elderly adults. The success of intensive treatment relies on good supportive care. The therapy offered in oncology units in low-income countries is not as aggressive as in centres in high-income countries and outcomes are less successful. Adjuvant monoclonal antibody therapy with rituximab shows promise for improved outcomes and reduced toxic effects in the future.

Symptoms of Lymphoma in Children
Warning signs for lymphoma are similar in children and adolescents as well as in adults. Symptoms include:

- One or more enlarged lymph nodes in the neck, underarm, or groin, which are usually painless
- Chills
- Swelling of the lymph nodes, which may or may not be painless
- Abdominal swelling (lymphomas in the chest or abdomen can grow to a very large size before symptoms appear)
- Unexplained fever
- Night sweats
- Loss of appetite
- Unexplained weight loss
- Lack of energy
- Coughing
- Difficulty in breathing\
- Itchiness

If a child has a lymph node that becomes enlarged without explanation or remains enlarged for a prolonged period of time, a paediatrician should be consulted. He/she may prescribe a course of antibiotics to treat a possible infection before performing a more extensive.

Causes and Risk Factors of Lymphoma in Children
Although the causes of lymphoma remain unknown, the following may increase the risk of childhood or adolescent lymphomas:

- Family history (though no hereditary pattern has been firmly established)

- Presence or history of an autoimmune disease
- Receipt of an organ transplant
- Exposure to chemicals such as pesticides, fertilizers or solvents
- Infection with viruses such as Epstein-Barr, human T-lymphotropic virus type 1, HIV, hepatitis C, or certain bacteria such as *Helicobacter pylori*

The cause of lymphoma is not known, but there is a genetic component. Incidence rates are higher for those who have a family member diagnosed with lymphoma, especially a sibling. While environmental and lifestyle factors are known to play a role in the development of cancer among adults, these factors have less of an impact on the development of childhood cancer.

Childhood Burkitt's Lymphoma

Burkitt's lymphoma is an aggressive form of non-Hodgkin lymphoma involving B cells. It occurs as the result of chromosome translocation involving the Myc gene. Translocation disrupts Myc expression leading to abnormal cell growth and proliferation. The rate of cell division in Burkitt's lymphoma is one of the highest among human tumours. It was first described by Dr Denis Burkitt in 1958 while he was working in Uganda. Burkitt's lymphoma was later discovered to be highly associated with the Epstein-Barr virus; this was the first time a virus was linked to a form of cancer.

[Picture Credit: Burkitt's Lymphoma]

The World Health Organization describes three clinical variants of Burkitt's lymphoma: endemic, sporadic, and immunodeficiency-associated.

- *Endemic Burkitt's lymphoma* - primarily refers to cases occurring in African children. This type usually involves the facial bones, especially the jaw, maxilla, and orbit. The Epstein-Barr virus (EBV) is associated with over 90% of endemic Burkitt's lymphoma.
- *Sporadic Burkitt's lymphoma* - refers to cases occurring in no specific geographic or climatic region. This type usually involves the abdomen. Unlike endemic lymphoma, infection with EBV is found in only about 20% of sporadic lymphoma. It accounts for 40-50% of childhood non-Hodgkin lymphoma.
- *Immunodeficiency-associated Burkitt's lymphoma* - refers to cases occurring in patients infected with HIV, transplant patients (most often solid organ), or individuals with other immune system disorders. BL accounts for 30-40% of non-Hodgkin lymphomas diagnosed in HIV infected individuals. However, HIV is not directly related to cancer formation. EBV is found in 30-40% of these cases of Burkitt's lymphoma.

Peprah S, Ogwang MD, Kerchan P, Reynolds SJ, Tenge CN, Were PA, Kuremu RT, Wekesa WN, Sumba PO, Masalu N, Kawira E, Magatti J, Kinyera T, Otim I, Legason ID, Nabalende H, Dhudha H, Ally H, Genga IO, Mumia M, Ayers LW, Pfeiffer RM, Biggar RJ, Bhatia K, Goedert JJ, Mbulaiteye SM. 2019. "Endemic Burkitt lymphoma (eBL) is the most common childhood cancer in sub-Saharan African countries, however, few epidemiologic studies have been undertaken and none attempted enrolling cases from multiple countries. We therefore conducted a population-based case-control study of eBL

in children aged 0-15 years old in six regions in Northern Uganda, Northern Tanzania and Western Kenya, enrolling 862 suspected cases and 2,934 population controls (response rates 98.5-100%), and processing ~40,000 vials of samples using standardized protocols. Risk factor questionnaires were administered, and malaria period prevalence was measured using rapid diagnostic tests (RDTs). A total of 80.9% of the recruited cases were diagnosed as eBL; 61.4% confirmed by histology. Associations with eBL risk were computed using logistic regression models adjusted for relevant confounders. Associations common in at least two countries were emphasized. eBL risk was decreased with higher maternal income and paternal education and elevated with history of inpatient malaria treatment >12 months before enrollment. Reporting malaria-attributed fever up to 6 months before enrollment and malaria-RDT positivity at enrollment were associated with decreased eBL risk. Conversely, reporting exposure to mass malaria suppression programs (e.g., indoor residual insecticide) was associated with elevated risk. HIV seropositivity was associated with elevated eBL risk, but the relative impact was small. The study shows that it is feasible to conduct networked, multisite population-based studies of eBL in Africa. eBL was inversely associated with socioeconomic status, positively associated with inpatient malaria treatment 12 months ago and with living in areas targeted for malaria suppression, which support a role of malaria in eBL."

Incidence of Childhood Burkitt's Lymphoma in South Africa

According to the National Cancer Registry (2017) the following number of Burkitt's Lymphoma cases was histologically diagnosed in South Africa during 2017:

Group Boys: 0 to 19 Years 2017	Actual No of Cases
All boys	6
Asian boys	0
Black boys	4
Coloured boys	2
White boys	0

Group Girls: 0 to 19 Years 2017	Actual No of Cases
All girls	9
Asian girls	0
Black girls	8
Coloured girls	0
White girls	1

The frequency of histologically diagnosed cases of Burkitt's Lymphoma in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group Boys: 0 to 19 Years 2017	0 – 4 Years	5 – 9 Years	10 – 14 Years	15 – 19 Years
All boys	0	2	1	3
Asian boys	0	0	0	0
Black boys	0	1	1	2
Coloured boys	0	1	0	1
White boys	0	0	0	0

Group Girls: 0 to 19 Years 2017	0 – 4 Years	5 – 9 Years	10 – 14 Years	15 – 19 Years
All girls	1	4	3	1
Asian girls	0	0	0	0
Black girls	1	4	3	0
Coloured girls	0	0	0	0
White girls	0	0	0	1

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all boys' and 'all girls', however, always reflect the correct totals.

Diagnosis of Burkitt's Lymphoma (BL)

A diagnosis of Burkitt's lymphoma begins with a medical history and physical examination. A biopsy of tumours confirms the diagnosis. The bone marrow and central nervous system are often involved. Bone marrow and spinal fluid are usually examined to see how far the cancer has spread.

Burkitt's lymphoma is staged according to lymph node and organ involvement. The involvement of bone marrow or the central nervous system means you have stage 4. A CT scan and MRI can help pinpoint which organs and lymph nodes are involved.

Zhang, J., Meng, L., Jiang, W., Zhang, H., Zhou, A. & Zeng, N. 2020.

"Burkitt lymphoma (BL) is a malignant tumor in children. Although BL is generally curable, early relapse and refractoriness may occur. Some molecular indicators have been recently suggested for BL diagnosis, but large heterogeneity still exists. This study aimed at providing clinical molecular targets and methods that may help improve diagnosis and treatment of childhood BL. Only children patients were included in the study, and targeted gene sequencing was conducted to identify tumor specific mutations. The mRNA and protein level expression of potential target genes were measured by real-time PCR and immunohistochemistry. The relationship between BL specific gene mutation and differential expression with clinical features was analyzed. The results showed that i) detailed analysis of c-MYC/BCL2/BCL6 gene loci alteration and gene expression would help in accurate diagnosis and treatment determination of childhood BL; ii) loss-of-function mutations in SOCS1 or CIITA gene might be used as malignant markers for BL diagnosis and prognosis; iii) specific mutations of CD79A, MYD88, KLF2, DNMT3A and NFKBIE genes often concurrently existed in BL and showed association with benign clinical outcomes; iv) the high expression of MYC, TCF3 and loss-of-function ID3 genes in tumor may be potential therapeutic targets and could be used for treatment monitoring; and v) four MYC-translocation negative cases were re-defined as high-grade B-cell lymphoma-not otherwise specified (HGBL-NOS) but showed similar clinical outcomes and molecular features to other BL cases in the study, suggesting more studies needed to explore the molecular mechanisms and clinical significance of this provisional tumor entity."

Treatment of Childhood Lymphoma

Treatment of childhood lymphoma is largely determined by staging. Staging is a way to categorise or classify patients according to how extensive the disease is at the time of diagnosis.

Chemotherapy (the use of highly potent medical drugs to kill cancer cells) is the primary form of treatment for all types of lymphoma.

In certain cases, radiation therapy (the use of high-energy rays to shrink tumours and keep cancer cells from growing), may also be used.

Short-term and long-term side effects - Intensive lymphoma chemotherapy affects the bone marrow, causing anaemia and bleeding problems, and increasing the risk for serious infections. Chemotherapy and radiation treatments have many other side effects — some short-term (such as hair loss, changes in skin colour, increased infection risk, and nausea and vomiting) and some long-term (such heart and kidney damage, reproductive problems, thyroid problems, or the development of another cancer later in life) — that parents should discuss with their doctor.

Relapses - Although most kids do recover from lymphoma, some with severe disease will have a relapse (reoccurrence of the cancer). For these children, bone marrow transplants and stem-cell transplants are often among the newest treatment options.

During a bone marrow/stem cell transplant, intensive chemotherapy with or without radiation therapy is given to kill residual cancerous cells. Then, healthy bone marrow/stem cells are introduced into the body in the hopes that it will begin producing white blood cells that will help the child fight infections.

New Treatments - Promising new treatments being developed for childhood lymphomas include several different types of immunotherapy, specifically the use of antibodies to deliver chemotherapy medicines or radioactive chemicals directly to lymphoma cells. This direct targeting of lymphoma cells may avoid the toxic side effects that occur when today's chemotherapy and radiation treatments damage normal, noncancerous body tissues.

Woessmann, W., Zimmermann, M., Meinhardt, A., Müller, S., Hauch, H., Knörr, F., Oschlies, I., Klapper, W., Niggli, F., Kabickova, E., Attarbaschi, A., Reiter, A. & Burkhardt, B. 2020.
"Children with refractory or relapsed Burkitt lymphoma (BL) or Burkitt leukemia (B-AL) have a poor chance to survive. We describe characteristics, outcome, reinduction, and transplantation approaches and evaluate risk factors among children with progression of a BL/B-AL included in Non-Hodgkin's Lymphoma-Berlin-Frankfurt-Münster studies between 1986 and 2016. Treatment recommendation was reinduction including rituximab from the early 2000s followed by blood stem cell transplantation. The 3-year survival of the 157 children was 18.5 ± 3%. Survival significantly improved from 11 ± 3% before to 27 ± 5% after 2000 (P < .001), allowing for risk factor analyses among the latter 75 patients. Survival of 14 patients with relapse after initial therapy for low-risk disease (R1/R2) was 50 ± 13% compared with 21 ± 5% for 61 patients progressing after R3/R4 therapy (P < .02). A total of 25 of 28 patients with progression during first-line therapy, 31 of 32 with progression during reinduction, 15 of 16 not reaching a complete remission (CR) before transplantation, 9 of 10 treated with rituximab front-line, and all 13 patients not receiving rituximab during reinduction died. Forty-six patients received stem cell transplantation (20 autologous, 26 allogeneic). Survival after a regimen combining rituximab with continuous-infusion chemotherapy followed by allogeneic transplantation was 67 ± 12% compared with 18 ± 5% for all other regimen and transplantations (P = .003). Patients with relapsed BL/B-AL have a poor chance to survive after current effective front-line therapies. Progression during initial or reinduction chemotherapy and initial high-risk disease are risk factors in relapse. Time-condensed continuous-infusion reinduction followed by stem cell transplantation forms the basis for testing new drugs."

Du, J. & Zhang, Y. 2020.

Purpose: Burkitt lymphoma (BL) is one of the most frequent subtypes of non-Hodgkin lymphoma (NHL) in children. Currently, short, intensive chemotherapy is used internationally and has greatly improved survival in children with BL. However, 5-10% of patients suffer recurrence after intensive chemotherapy, and the prognosis of these patients remains poor. The overall survival rate is only approximately 10%. Innovative therapies are needed to attain a higher rate of remission, such as immunotherapy for relapsed refractory (r/r) BL patients.

Methods: An 8-year-old boy with BL was studied. He suffered a relapse after treatment with standard chemotherapy. Then, we treated this patient using autologous chimeric antigen receptor T-cell (CAR-T) therapies, sequentially targeting antigens CD19, CD22, and CD20. A review of the current literature on CAR-T treatment for lymphoma is presented.

Results: The patient had no discernible response to anti-CD19 CAR-T treatment and exhibited progressive disease (PD). Following CD-22-directed CAR-T treatment, the patient underwent a partial remission (PR), but unfortunately a relapse rapidly occurred. Finally, after administering the anti-CD20 CAR-T cell therapy, the child went into complete remission (CR). The young boy has currently achieved 16-month event-free survival (EFS) so far. During administration of the CD19 and CD20 CAR-T cells, the patient appeared to experience mild (Grade I) cytokine release syndrome (CRS). However, during the CD22 CAR-T therapy, he appeared to experience grade III CRS.

Conclusion: Autologous anti-CD19, anti-CD22, and anti-CD20 CAR-T cell therapies targeting multiple tumor antigens could be an innovative and sound treatment for children with r/r BL, provided that they are closely monitored during treatment.

McGoldrick, S.M., Mutyaba, I., Adams, S.V., Larsen, A., Krantz, E.M., Namirembe, C., Mooka, P., Nabakooza, S., Ndagire, M., Mubiru, K., Nabwana, M., Nankinga, R., Gerdts, S., Gordon-Maclean, C., Geriga, F., Omoding, A., Sessle, E., Kambugu, J., Uldrick, T.S., Orem, J. & Casper. C. 2019.

PURPOSE: "Endemic" Burkitt lymphoma (BL) is a common childhood cancer in Africa. Social and treatment factors may contribute to poor survival. With the aim of improving BL outcomes in Uganda, we undertook a comprehensive project (BL Project) that provided diagnostic support, access to standard chemotherapy, nutritional evaluations, and case management. We evaluated survival of children with BL in the context of the project.

PATIENTS AND METHODS: Patients followed by the BL Project who consented to research were enrolled in this study. Children with a pathology diagnosis consistent with BL were eligible. Data were collected prospectively. First-line chemotherapy generally consisted of six cycles of cyclophosphamide, vincristine, low-dose methotrexate (COM). We used Kaplan-Meier and Cox regression analyses to evaluate factors associated with overall survival (OS).

RESULTS: Between July 2012 and June 2017, 341 patients with suspected BL presented to the BL Project. One hundred eighty patients with a pathology-based diagnosis were included in this study. The median age was seven years (interquartile range, 5-9), 74% lived ≥100 km from the Uganda Cancer Institute, 61% had late-stage disease, 84% had ECOG performance status < 3, 63% reported B-symptoms, and 22% showed neurologic symptoms. Fewer than 10% abandoned therapy. The four-year OS rate was 44% (95% CI, 36%-53%). In a multivariate model, ECOG status was significantly associated with mortality.

CONCLUSION: The BL Project reduced effects of lacking supportive care and oncology resources, and allowed patients from Uganda to receive curative intent therapy with minimal loss to follow-up. Nonetheless, OS remains unacceptably low. Improved therapeutic approaches to endemic BL are urgently needed in Africa.

Kalisz, K., Alessandrino, F., Beck, R., Smith, D., Kikano, E., Ramaiya, N.H. & Tirumani, S.H. 2019. "Burkitt lymphoma (BL) is a highly aggressive, rapidly growing B cell non-Hodgkin lymphoma, which manifests in several subtypes including sporadic, endemic, and immunodeficiency-associated forms. Pathologically, BL is classically characterized by translocations of chromosomes 8 and 14 resulting in upregulation of the c-myc protein transcription factor with upregulation of cell proliferation. BL affects nearly every organ system, most commonly the abdomen and pelvis in the sporadic form. Imaging using a multimodality approach plays a crucial role in the management of BL from diagnosis, staging, and evaluation of treatment response to therapy-related complications with ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography playing roles. In this article, we review the pathobiology and classification of BL, illustrate a multimodality imaging approach in evaluating common and uncommon sites of involvement within the trunk and head and neck, and review common therapies and treatment-related complications."

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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