

Cancer Association of South Africa (CANSA)



Fact Sheet On Non-Hodgkin's Lymphoma

Introduction

Lymphoma is a type of cancer involving cells of the immune system, called lymphocytes. Just as cancer represents many different diseases, lymphoma represents many different cancers of lymphocytes -- about 35 different subtypes. Lymphoma is a group of cancers that affect the cells that play a role in the immune system and primarily represents cells involved in the lymphatic system of the body.

[Picture Credit: Lymphatic System]

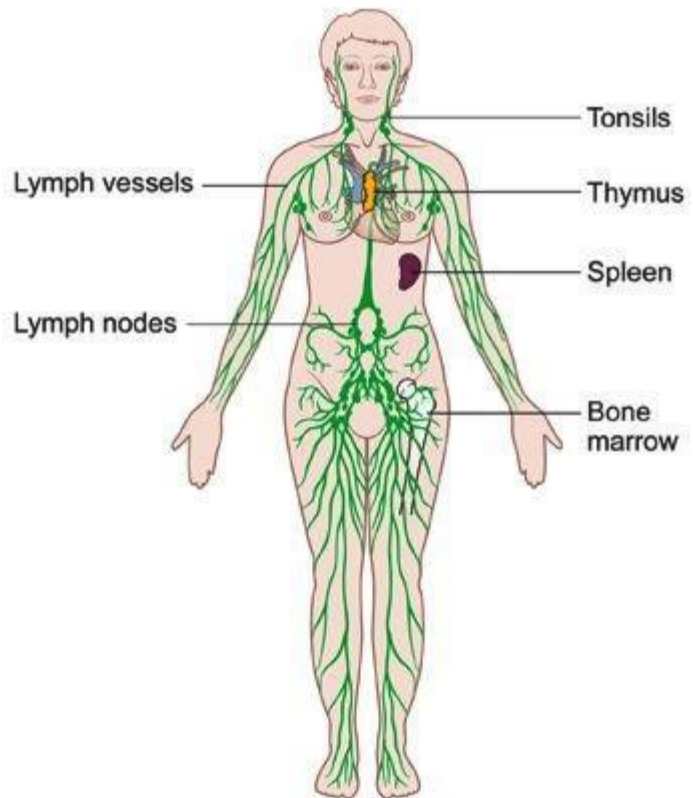


Diagram of the lymphatic system
Copyright © CancerHelp UK

The Lymphatic System

The lymphatic system is an extensive drainage network that helps keep bodily fluid levels in balance and defends the body against infections. It is made up of a network of lymphatic vessels that carry lymph - a clear, watery fluid that contains protein molecules, salts, glucose, urea, and other substances - throughout the body.

Types of Lymphoma

Lymphomas fall into one of two major categories:

- Hodgkin's lymphoma (HL, previously called Hodgkin's disease)
- Non-Hodgkin's Lymphoma (NHL, all other lymphomas)

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These two types occur in the same places, may be associated with the same symptoms, and often have similar appearance on physical examination. However, they are readily distinguishable via microscopic examination.

Many of the NHL subtypes look similar, but they are functionally quite different and respond to different therapies with different probabilities of cure. HL subtypes are microscopically distinct, and typing is based upon the microscopic differences as well as extent of disease.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma is cancer of the lymphoid tissue, which includes the lymph nodes, spleen, and other organs of the immune system.

There are many different types of non-Hodgkin lymphoma (NHL), so classifying it can be quite confusing (even for doctors). Several different systems have been used, but the most recent system is the World Health Organization (WHO) classification. The WHO system groups lymphomas based on:

- The type of lymphocyte the lymphoma starts in
- How the lymphoma looks under a microscope
- The chromosome features of the lymphoma cells
- The presence of certain proteins on the surface of the cancer cells

Sapkota, S. & Shaikh, H. 2020.

"Non-Hodgkin lymphoma (NHL) is a neoplasm of the lymphoid tissues originating from B cell precursors, mature B cells, T cell precursors, and mature T cells.

Non-Hodgkin lymphoma comprises various subtypes, each with different epidemiologies, etiologies, immunophenotypic, genetic, clinical features, and response to therapy. It can be divided into two groups, 'indolent' and 'aggressive,' based on the disease's prognosis.

The most common mature B cell neoplasms are Follicular lymphoma, Burkitt lymphoma, diffuse large B cell lymphoma, Mantle cell lymphoma, marginal zone lymphoma, primary CNS lymphoma. The most common mature T cell lymphomas are Adult T cell lymphoma, Mycosis fungoides.

The treatment of NHL varies greatly, depending on tumor stage, grade, and type of lymphoma, and various patient factors (e.g., symptoms, age, performance status).

The natural history of these tumors shows significant variation. Indolent lymphomas present with waxing and waning lymphadenopathy for many years, whereas aggressive lymphomas have specific B symptoms such as weight loss, night sweats, fever and can result in deaths within a few weeks if untreated. Lymphomas that usually have indolent presentations include follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and splenic marginal zone lymphoma. Aggressive lymphomas include diffuse large B cell lymphoma, Burkitt lymphoma, precursor B and T cell lymphoblastic leukemia/lymphoma, and adult T cell leukemia/lymphoma, and certain other peripheral T cell lymphomas.

Up to two-thirds of patients present with peripheral lymphadenopathy. Rashes on the skin, increased hypersensitivity reactions to insect bites, generalized fatigue, pruritus, malaise, fever of unknown origin, ascites, and effusions are less common presenting features. Approximately half of the patients develop the extranodal disease (secondary extranodal disease) during the course of their disease, while between 10 and 35 percent of patients have primary extranodal lymphoma at diagnosis. Primary gastrointestinal (GI) tract lymphoma may present with nausea and vomiting,

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aversion to food, weight loss, fullness of abdomen, early satiety, visceral obstruction related symptoms. Patients may even present with features of acute perforation and gastrointestinal bleeding, and at times with features of malabsorption syndrome. Primary central nervous system (CNS) lymphoma may present with headaches, spinal cord compression features, lethargy, focal neurologic deficits, seizures, and paralysis.”

Causes, Incidence, and Risk Factors for Non-Hodgkin’s Lymphoma

White blood cells called lymphocytes are found in lymph tissues. They help prevent infections. Most Non-Hodgkin’s Lymphomas (NHL) start in a type of white blood cells called B lymphocytes, or B cells.

Some of the Known Risk Factors for Non-Hodgkin’s Lymphoma include:

- Age - Non-Hodgkin's lymphoma can develop in people of all ages, including children, it is most common in adults. The most common types of NHL usually appear in people in their 60s and 70s.
- Sex - In general, NHL is more common in men than in women.
- Race - Overall, the risk for NHL is slightly higher in Caucasians than in African-Americans and Asian Americans.
- Family History - People who have close family relatives who have developed NHL may be at increased risk for this cancer. However, no definitive hereditary or genetic link has been established.
- Infections - Viral or bacterial infections may play a role in some lymphomas. These include:
 - Epstein-Barr virus (EBV), the cause of mononucleosis, is highly associated with Burkitt's lymphoma and NHLs associated with immunodeficiency diseases. It is also a risk factor for Hodgkin's disease.
 - The human immunodeficiency virus (HIV), which causes AIDS, increases the risk for Burkitt lymphoma and diffuse large B-cell lymphoma
 - The hepatitis C virus (HCV) may increase the risk for certain types of lymphomas.
 - The *Helicobacter pylori* bacterium, which causes stomach ulcers, is associated with increased risk for mucosa-associated lymphoid tissue lymphomas (MALT). (The use of antibiotics to get rid of the bacteria may cause remission in some patients who have an early stage form of lymphoma in an early stage.)
- Immune System Deficiency Disorders - Patients with diseases or conditions that affect the immune system may be at higher risk for lymphomas:
 - HIV-positive patients and those with full-blown AIDS are at higher risk for NHL, and the disease is more likely to be widespread in these patients than in those without the immune disease. Most AIDS-related NHLs are high-grade lymphomas.
 - People who have organ transplants are at higher risk for NHL, probably due to multiple factors, including the drugs used to suppress the immune system and the transplanted organ itself.
 - Patients who have had high-dose chemotherapy with stem-cell transplantation are at higher risk.
- Other immunodeficiency syndromes that put people at risk for NHL include Chediak-Higashi syndrome, ataxia-telangiectasia, B-cell lymphoproliferative syndrome, Bruton agammaglobulinemia, common variable immunodeficiency, and Wiskott-Aldrich syndrome.

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- Autoimmune Disorders - Patients with a history of autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus, Hashimoto's thyroiditis, Crohn's disease, and Sjogren syndrome, are at an increased risk for certain NHLs, such as marginal zone lymphomas.
- Chemical Exposure - Overexposure to a number of industrial and agricultural chemicals (such as pesticides, herbicides, and petrochemicals) has been frequently linked to an increased risk for lymphomas. The data, however, are not consistent.
- Lifestyle Factors - Lifestyle does not seem to be a major risk factor for NHL. Some studies have suggested that obesity may increase risk, but this association is not definite. Other studies have investigated the role of diet. Although some research has indicated an increased risk for diets high in consumption of red meat and lower risk for diets high in vegetables, for the most part a strong association remains speculative. There is no evidence that smoking increases the risk for NHL itself, although it has been linked with high-grade and follicular NHLs in people with lymphoma.

Incidence of Non-Hodgkin's Lymphoma in South Africa

According to the outdated National Cancer Registry (2016), known for under reporting, the following number of Non-Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	1 381	1:158	3,45%
Asian males	35	1:222	3,60%
Black males	804	1:223	6,13%
Coloured males	130	1:152	2,77%
White males	412	1:85	1,94%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	1 129	1:238	2,71%
Asian females	33	1:274	2,58%
Black females	658	1:343	3,51%
Coloured females	110	1:194	2,42%
White females	328	1:120	1,94%

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

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	51	60	214	343	280	216	153	64
Asian males	0	0	5	11	3	12	3	1
Black males	45	37	172	270	167	61	29	13
Coloured males	4	5	16	19	29	33	17	7
White males	2	8	21	43	81	110	104	43

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Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	29	62	207	224	217	169	159	63
Asian females	1	2	2	6	10	3	8	1
Black females	23	51	180	181	123	53	32	15
Coloured females	2	2	6	15	24	30	23	8
White females	3	7	19	21	50	83	96	39

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 males' and 'all females', however, always reflect the correct totals.

Symptoms of Non-Hodgkin's Lymphoma

Symptoms depend on what area of the body is affected by the cancer and how fast the cancer is growing. Symptoms may include:

[Picture Credit: Non-Hodgkin's Lymphoma]



- Night sweats (soaking the bedsheets and pyjamas even though the room temperature is not too hot)
- Fever and chills that come and go
- Itching
- Swollen lymph nodes in the neck, underarms, groin, or other areas
- Weight loss
- Coughing or shortness of breath may occur if the cancer affects the thymus gland or lymph nodes in the chest, which may put pressure on the windpipe (trachea) or other airways.
- Some patients may have abdominal pain or swelling, which may lead to a loss of appetite, constipation, nausea, and vomiting.
- If the cancer affects cells in the brain, the person may have a headache, concentration problems, personality changes, or seizures.

Signs and Tests for Non-Hodgkin's Lymphoma

The doctor will perform a physical exam and check body areas with lymph nodes to feel if they are swollen.

The disease may be diagnosed after:

- Biopsy of suspected tissue, usually a lymph node biopsy
- Bone marrow biopsy

Other tests that may be done include:

- Blood test to check protein levels, liver function, kidney function, and uric acid level
- Complete blood count (CBC)
- CT scans of the chest, abdomen and pelvis
- Gallium scan

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- PET (positron emission tomography) scan

Diagnosis of non_Hodgkin's Lymphoma

Melani, C., Wilson, W.H. & Roschewski, M. 2019

"ctDNA provides an important new strategy that will aid in the treatment of non-Hodgkin's lymphoma. Immunoglobulin sequencing provides a tumor specific marker for disease activity with a sensitivity equivalent to one tumor cell per 10⁶. Furthermore, it can provide an estimate of tumor bulk and tumor response dynamics during treatment. Interim monitoring can identify patients at high risk of treatment failure and surveillance monitoring can identify patients months before radiographic disease progression. Tumor specific mutations can also be detected in ctDNA and may reflect an averaging of mutations present within multiple tumor masses. Such analysis may aid in the molecular characterization of tumors and selection of targeted treatments for precision medicine."

Treatment of Non-Hodgkin's Lymphoma

Treatment depends on:

- The type of lymphoma
- The stage of the cancer when you are first diagnosed
- Your age and overall health
- Symptoms, including weight loss, fever, and night sweats

Common treatments may include:

- Radiation therapy may be used for disease that is confined to one body area.
- Chemotherapy is the main type of treatment. Most often, multiple different drugs are used in combination together.
- Another drug, called rituximab (Rituxan), is often used to treat B-cell non-Hodgkin's lymphoma.
- Radioimmunotherapy may be used in some cases. This involves linking a radioactive substance to an antibody that targets the cancerous cells and injecting the substance into the body.
- People with lymphoma that returns after treatment or does not respond to treatment may receive high-dose chemotherapy followed by a bone marrow transplant (using stem cells from the patient).

Additional treatments depend on other symptoms. They may include:

- Transfusion of blood products, such as platelets or red blood cells
- Antibiotics to fight infection, especially if a fever occurs

Treatment in Children

Minard-Colin, V., Aupérin, A., Pillon, M., Burke, G.A.A., Barkauskas, D.A., Wheatley, K., Delgado, R.F., Alexander, S., Uyttebroeck, A., Bollard, C.M., Zsiros, J., Csoka, M., Kazanowska, B., Chiang, A.K., Miles, R.R., Wotherspoon, A., Adamson, P.C., Vassal, G., Patte, C., Gross, T.G.. European Intergroup for Childhood Non-Hodgkin Lymphoma, & Children's Oncology Group. 2020.

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Background: Rituximab added to chemotherapy prolongs survival among adults with B-cell cancer. Data on its efficacy and safety in children with high-grade, mature B-cell non-Hodgkin's lymphoma are limited.

Methods: We conducted an open-label, international, randomized, phase 3 trial involving patients younger than 18 years of age with high-risk, mature B-cell non-Hodgkin's lymphoma (stage III with an elevated lactate dehydrogenase level or stage IV) or acute leukemia to compare the addition of six doses of rituximab to standard lymphomas malins B (LMB) chemotherapy with standard LMB chemotherapy alone. The primary end point was event-free survival. Overall survival and toxic effects were also assessed.

Results: Analyses were based on 328 patients who underwent randomization (164 patients per group); 85.7% of the patients had Burkitt's lymphoma. The median follow-up was 39.9 months. Events were observed in 10 patients in the rituximab-chemotherapy group and in 28 in the chemotherapy group. Event-free survival at 3 years was 93.9% (95% confidence interval [CI], 89.1 to 96.7) in the rituximab-chemotherapy group and 82.3% (95% CI, 75.7 to 87.5) in the chemotherapy group (hazard ratio for primary refractory disease or first occurrence of progression, relapse after response, death from any cause, or second cancer, 0.32; 95% CI, 0.15 to 0.66; one-sided P = 0.00096, which reached the significance level required for this analysis). Eight patients in the rituximab-chemotherapy group died (4 deaths were disease-related, 3 were treatment-related, and 1 was from a second cancer), as did 20 in the chemotherapy group (17 deaths were disease-related, and 3 were treatment-related) (hazard ratio, 0.36; 95% CI, 0.16 to 0.82). The incidence of acute adverse events of grade 4 or higher after prephase treatment was 33.3% in the rituximab-chemotherapy group and 24.2% in the chemotherapy group (P = 0.07); events were related mainly to febrile neutropenia and infection. Approximately twice as many patients in the rituximab-chemotherapy group as in the chemotherapy group had a low IgG level 1 year after trial inclusion.

Conclusions: Rituximab added to standard LMB chemotherapy markedly prolonged event-free survival and overall survival among children and adolescents with high-grade, high-risk, mature B-cell non-Hodgkin's lymphoma and was associated with a higher incidence of hypogammaglobulinemia and, potentially, more episodes of infection. (Funded by the Clinical Research Hospital Program of the French Ministry of Health and others; ClinicalTrials.gov number, [NCT01516580](#).)

Moleti, M.L., Testi, A.M. & Foá R. 2020.

“Aggressive B-cell non-Hodgkin lymphoma (B-NHL) accounts for ≈60% of NHL in children/adolescents. In newly diagnosed Burkitt lymphoma and diffuse large B-cell lymphoma, short intensive multiagent chemotherapy is associated with a five-year event-free survival of around 90%. Very few children/adolescents with aggressive B-NHL show a relapsed/refractory (r/r) disease. The outcome is poor, with cure rates <30%, and there is no standard of care. Rituximab-containing salvage regimens may provide a complete/partial response in 60-70% of cases. However, long-term survival is <10% for non-transplanted patients. Autologous or allogeneic haematopoietic stem cell transplant is, nowadays, the best option for responding patients, with survival rates around 50%. The benefit of autologous versus allogeneic HSCT is not clear. Numerous novel therapies for r/r B-NHL are currently being tested in adults, including next-generation monoclonal antibodies, novel cellular therapy strategies and therapies directed against new targets. Some are under investigation also in children/adolescents, with promising preliminary results.”

Treatment - General

Barrington, S.F. & Trotman, J. 2021.

“This Review focuses on the use of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET in the assessment of diffuse large B-cell lymphoma, follicular lymphoma, and peripheral T-cell lymphoma. PET is important for staging and prognostication with stage migration compared with CT. Better outcomes for patients with early stage diffuse large B-cell lymphoma and follicular lymphoma suggests better delineation of disease has translated to improved outcomes in such patients beyond simple stage migration. The aim of treatment of diffuse large B-cell lymphoma and peripheral T-cell lymphoma is potential cure, during which PET is mainly used to assess remission. Interim PET can assess chemosensitivity in these lymphomas, but it does not predict treatment success sufficiently well to enable treatment modification, particularly in the absence of more effective therapies for patients who remain PET-positive on interim scanning. In follicular lymphoma, traditionally viewed as an incurable lymphoma, the aim of treatment is to control disease for several years, while maintaining quality of life. PET can predict prognosis for patients with follicular lymphoma with high tumour burden at the end of induction chemotherapy, and it is being evaluated as a platform for response-adapted treatment of follicular lymphoma.”

Fuertes, T., Ramiro, A.R. & de Yebenes, F.G. 2020.

“Non-Hodgkin lymphoma (NHL) is a diverse class of hematological cancers, many of which arise from germinal center (GC)-experienced B cells. Thus GCs, the sites of antibody affinity maturation triggered during immune responses, also provide an environment that facilitates B cell oncogenic transformation. miRNAs provide attractive and mechanistically different strategies to treat these malignancies based on their potential for simultaneous modulation of multiple targets. Here, we discuss the scientific rationale for miRNA-based therapeutics in B cell neoplasias and review recent advances that may help establish a basis for novel candidate miRNA-based therapies for B cell-NHL (B-NHL).”

Tun, A.M. & Ansell, S.M. 2020.

“Since the clinical introduction of anti-CD20 monoclonal antibodies into lymphoma treatment, immunologic approaches in lymphoma have made substantial progress. Advances in our understanding of tumor immunology have led to the development of strategies to overcome immunologic barriers responsible for an ineffective immune response. Specifically, therapeutic agents have been developed and tested against molecules that are responsible for T-cell exhaustion. The use of monoclonal antibodies against immune checkpoints in the adaptive immune system, such as programmed cell death-1 and cytotoxic T-lymphocyte-associated protein 4, has changed the landscape of cancer therapy including the treatment of lymphoma. This achievement has recently been accompanied by the development of novel immune checkpoint inhibitors targeting the innate immune system, including the CD47-SIRP α signaling pathway, and this approach has yielded promising results. To overcome impaired antigen presentation, antibody-based cytotoxic strategies, namely antibody-drug conjugates (polatuzumab vedotin and brentuximab vedotin) and bispecific T-cell or NK-cell engagers (blinatumomab, REGN1979, RG6206, and AFM13), have rapidly evolved with promising clinical activity. As additional tools become available for lymphoma treatment, formulation of safe, rational combination strategies to combine them with standard therapy will be of paramount importance. A successful approach to the treatment of lymphoma may require both an optimized anti-tumor immune response as well as effective depletion of malignant lymphoid cells.”

Abramson, J.S., Ghosh, N. & Smith, S.M. 2020.

“Novel immunotherapies and small molecular inhibitors are transforming our approach to previously treated and newly diagnosed patients across the spectrum of non-Hodgkin lymphomas (NHLs). Anti-CD19 CAR T cells are now indicated for the treatment of relapsed/refractory aggressive B-cell lymphomas after at least two previous lines of therapy in which durable remissions are achieved in approximately 40% of previously incurable patients. Second-line chemoimmunotherapy remains the standard of care at first relapse, but poor outcomes with conventional treatment in this setting creates an appealing rationale for earlier use of CAR T cells, which is currently under investigation, along with even earlier use in selected high-risk patients in the frontline setting. Other emerging immunotherapies include antibody-drug conjugates (ADCs), such as polatuzumab vedotin for multiple-relapsed diffuse large B-cell lymphoma (DLBCL) in combination with bendamustine-rituximab. Multiple bispecific antibodies that bring malignant B cells in contact with effector T cells appear promising in early clinical trials and will likely emerge as off-the-shelf immunotherapy options. Chemotherapy-free small molecule-based regimens are increasingly available for mantle cell (MCLs) and follicular lymphomas (FLs). Bruton tyrosine kinase inhibitors (BTKi) now represent standard second-line therapy for MCL and are being investigated in combination and as initial therapy. Lenalidomide-rituximab is an active regimen in both FL and MCL and may be used in either relapsed/refractory or previously untreated disease. Three PI3K inhibitors are approved for multiple-relapsed FL and can induce durable remissions in patients with chemotherapy- and rituximab-refractory disease. Additional emerging targeted therapies include BCL2 inhibition in MCL and EZH2 inhibition in FL.”

Makita, S., Hosoba, R. & Tobinai, K. 2020.

Introduction: B-cell non-Hodgkin lymphomas (B-NHLs) are the most frequent hematologic malignant cancers. Molecular targeted therapy is an important aspect of B-NHL treatment alongside cytotoxic chemotherapy, radiotherapy, and immunotherapy.

Areas covered: Molecular targeted therapies have changed the landscape of treatment strategies for B-NHLs since the approval of rituximab, an anti-CD20 monoclonal antibody, by the US Food and Drug Administration in 1997. Currently, several targeted therapies have been approved or are in the later-phase of clinical trials including naked antibodies, antibody-drug conjugates, and small molecules, such as Bruton's tyrosine kinase (BTK) inhibitors, phosphatidylinositol 3-kinase (PI3 K) inhibitors, enhancer of zeste homolog 2 (EZH2) inhibitors, and B-cell lymphoma 2 (Bcl-2) inhibitors. These drugs have various toxicities because of their unique mechanisms of action. In this review, the available toxicity data of the targeted therapies for B-NHLs have been summarized.

Expert opinion: Recent clinical developments of targeted therapies for B-NHLs have provided several useful effective therapeutic options for patients. However, there are unique toxicities that need to be resolved. It is necessary to find out the toxicity mechanism; optimal treatment strategy for these toxicities; and novel targeted therapies that might potentially overcome the toxicities of previously approved targeted therapies.

Expectations (Prognosis) of Non-Hodgkin's Lymphoma

Low-grade non-Hodgkin's lymphoma usually cannot be cured by chemotherapy alone. However, the low-grade form of this cancer progresses slowly, and it may take many years before the disease gets worse or even requires any treatment. Chemotherapy can often cure many types of high-grade lymphoma. However, if the cancer does not respond to chemotherapy drugs, the disease can cause rapid death.

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Complications of Non-Hodgkin's Lymphoma

Complications may include:

- Autoimmune haemolytic anaemia
- Infection
- Side effects of chemotherapy drugs

Relationship of Staging Systems – Hodgkin Lymphoma and Non-Hodgkin Lymphomas

Description of Extent (Based on Ann Arbor Staging Systems)	Summary Stage	Ann Arbor Staging*	AJCC Staging Stage**
Involvement of a single lymph node region	Localised	I	I
A single extralymphatic organ or site	Localised	Ie	Ie
Involvement of more than one lymphatic region on only one side of the diaphragm	Regional NOS	II	II
Localised involvement of one extralymphatic organ or site and its regional lymph nodes with or without other nodes on the same side of the diaphragm	Regional NOS	IIE	IIE
Involvement of more than one lymphatic region on only one side of the diaphragm plus involvement of the spleen	Distant	IIs	IIs
Involvement of lymph node regions on both sides of the diaphragm	Distant	III	III
Involvement of lymph node regions on both sides of the diaphragm plus localised involvement of an extralymphatic organ or site	Distant	IIIE	IIIE
Involvement of lymph node regions on both sides of the diaphragm plus involvement of the spleen	Distant	IIIs	IIIs
Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Organs considered distant include liver, bone, bone marrow, lung and/or pleura and kidney	Distant	IV	IV
Isolated extralymphatic organ involvement with distant (non-regional) nodal involvement	Distant	IV	IV

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.

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

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Sources and References Consulted or Utilised

Abramson, J.S., Ghosh, N. & Smith, S.M. 2020. ADCs, BiTEs, CARs, and Small Molecules: A New Era of Targeted Therapy in Non-Hodgkin Lymphoma. *Am Soc Clin Oncol Educ Book*. 2020 May;40:302-313.

American Cancer Society

<http://www.cancer.org/Cancer/Non-HodgkinLymphoma/DetailedGuide/non-hodgkin-lymphoma-risk-factors>
<https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/what-is-non-hodgkin-lymphoma.html>

Armitage, J.O., Gascoyne, R.D., Lunning, M.A. & Cavalli, F. 2017. Non-Hodgkin lymphoma. *Lancet*. 2017 Jul 15;390(10091):298-310. doi: 10.1016/S0140-6736(16)32407-2. Epub 2017 Jan 31.

Autologous Transplant

<http://multiple-sclerosis-research.blogspot.com/p/grand-challenges-in-ms.html>

Barrington, S.F. & Trotman, J. 2021. The role of PET in the first-line treatment of the most common subtypes of non-Hodgkin lymphoma. *Lancet Haematol*. 2021 Jan;8(1):e80-e93.

Boston Children's Hospital

<http://childrenshospital.org/az/Site2182/mainpageS2182P1.html>

Bruni, L., Albero, G., Serrano, B., Mena, M., Gómez, D., Muñoz, J., Bosch, F.X. & de Sanjosé, S. 2019. ICO/IARC Information Centre on HPV and Cancer (*HPV Information Centre*). Human Papillomavirus and Related Diseases in South Africa. Summary Report 17 June 2019. [Date Accessed]

Cancer Research UK

<http://www.cancerresearchuk.org/cancer-info/cancerstats/types/hodgkinslymphoma/riskfactors/hodgkins-lymphoma-risk-factors#genetics>

Cells of the Immune System

http://www.alohamedicinals.com/how-your-immune-system-works.html#.VBvpG_mSySo

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Chu, Y., Gardenswartz, A., Termuhlen, A.M. & Cairo, M.S. 2019. Advances in cellular and humoral immunotherapy - implications for the treatment of poor risk childhood, adolescent, and young adult B-cell non-Hodgkin lymphoma. *Br J Haematol.* 2019 Jan 6. doi: 10.1111/bjh.15753. [Epub ahead of print]

eMedicineHealth. Lymphoma. http://www.emedicinehealth.com/lymphoma/article_em.htm

Fuertes, T., Ramiro, A.R. & de Yebenes, F.G. 2020. miRNA-Based Therapies in B Cell Non-Hodgkin Lymphoma. *Trends Immunol.* 2020 Oct;41(10):932-947.

Hodgkin's Lymphoma

https://www.google.co.za/search?q=hodgkin%27s+lymphoma&source=lnms&tbn=isch&sa=X&ei=Kl-ZU_bUJaeV7Ab_q4CwCA&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=wrUKxr_raB8ehM%3A%3B3MTF6fAZjSVIEM%3BwrUKxr_raB8ehM%3A&imgrc=wrUKxr_raB8ehM%253A%3ByWB-1qzXMW4rDM%3Bhttp%253A%252F%252Fs2.hubimg.com%252Fu%252F6438913_f260.jpg%3Bhttp%253A%252F%252Fki.mhdimino.blogspot.com%252F2013%252F03%252Fhodgkins-disease-overview.html%3B260%3B195

Hüttmann, A., Rekowski, J., Müller, S.P., Hertenstein, B., Franzius, C., Mesters, R., Weckesser, M., Kroschinsky, F., Kotzerke, J., Ganser, A., Bengel, F.M., La Rosée, P., Freesmeyer, M., Höffkes, H.G., Hertel, A., Behringer, D., Prange-Krex, G., Grieshammer, M., Holzinger, J., Wilop, S., Krohn, T., Raghavachar, A., Maschmeyer, G., Brink, I., Schroers, R., Gaska, T., Bernhard, H., Giagounidis, A., Schütte, J., Dienst, A., Hautzel, H., Naumann, R., Klein, A., Hahn, D., Pöpperl, G., Grube, M., Marienhagen, J., Schwarzer, A., Kurch, L., Höhler, T., Steiniger, H., Nüchel, H., Südhoff, T., Römer, W., Brinkmann, M., Ose, C., Alashkar, F., Schmitz, C., Dürig, J., Hoelzer, D., Jöckel, K.H., Klapper, W. & Dührsen, U. 2019. Six versus eight doses of rituximab in patients with aggressive B cell lymphomareceiving six cycles of CHOP: results from the "Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas" (PETAL) trial. *Ann Hematol.* 2019 Jan 4. doi: 10.1007/s00277-018-3578-0. [Epub ahead of print]

Kanate, A., Kumar, A., Dreger, P., Drevling, M. Le Gouill, S., Corradini, P., Baredeson, C., Fenske, T.S., Smith, S.M., Sureda, A., Moskowitz, A., Friedberg, J.W., Inwards, D.J., Herrera, A.F., Kharfan-Dbaja, A.K., Reddy, N., Montoto, S., Robinson, S.P., Abutalib, S.A., Gisselbrecht, C., Vose, J., Gopal, A., Shadman, M., Perales, M.-A., Carpenter, P., Savani, N. & Hamadani, M. 2019. Maintenance therapies for Hodgkin and non-Hodgkin lymphomas after autologous transplantation: a consensus project of ASBMT, CIBMTR, and the Lymphoma Working Party of EBMT. *JAMA Oncol.* (5), 715-722, 2019 May 1.

KidsHealth. The Lymphatic System. http://kidshealth.org/parent/general/body_basics/spleen_lymphatic.html

Lymphatic System

http://www.google.co.za/imgres?start=83&hl=en&sa=X&rlz=1T4LENN_enZA490ZA490&biw=1366&bih=613&tbn=isch&prmd=imvns&tbnid=flgwTmsqqhLNM:&imgrefurl=http://cancerhelp.cancerresearchuk.org/type/hodgkins-lymphoma/about/what-is-hodgkins-lymphoma&docid=sUKIP6oPMYIj-M&imgurl=http://cancerhelp.cancerresearchuk.org/prod_consump/groups/cr_common/%2540cah/%2540gen/documents/image/crukimg_1000img-12066.jpg&w=350&h=431&ei=YdRSUOCpMOSx0QXWr4DABQ&zoom=1&iact=hc&vpx=1106&vpy=249&dur=2671&hovh=249&hovw=202&tx=127&ty=114&sig=107310304455409594391&page=4&tbnh=129&tbnw=105&ndsp=30&ved=1t:429,r:29,s:83,i:96

Lymph Node

http://www.google.co.za/imgres?hl=en&sa=X&rlz=1T4LENN_enZA490ZA490&biw=1366&bih=613&tbn=isch&prmd=imvns&tbnid=y5UPisMY6d3v2M:&imgrefurl=http://www.smartdraw.com/examples/view/non-hodgkin%2Blymphoma%2B-%2Bcell/&docid=r4nBtXE1dXFrEM&imgurl=http://wc1.smartdraw.com/examples/content/Examples/10_Healthcare/Cancer_Illustrations/Non-Hodgkin_Lymphoma_-_Cell_L.jpg&w=842&h=627&ei=RNRSUM_6O9DY0QX1vYDABQ&zoom=1&iact=rc&dur=527&sig=107310304455409594391&page=2&tbnh=131&tbnw=175&start=23&ndsp=29&ved=1t:429,r:19,s:23,i:206&tx=110&ty=82

Lymphoma Association UK

<http://www.lymphomas.org.uk/sites/default/files/pdfs/Angioimmunoblastic-T-cell-lymphoma.pdf>

Lymphomainfo.net

<http://www.lymphomainfo.net/nhl/classify.html>

<http://www.lymphomainfo.net/nhl/types/t-ail.html>

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Lymphoma Research Foundation

<http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300145>

MacMillan Cancer support

<http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Lymphomanon-Hodgkin/TypesofNHL/Burkitt.aspx>

Makita, S., Hosoba, R. & Tobinai, K. 2020. Safety considerations with targeted therapy drugs for B-cell non-Hodgkin lymphoma. *Expert Opin Drug Saf.* 2020 Sep;19(9):1105-1120.

Mayo Clinic

<http://www.mayoclinic.com/health/hodgkins-disease/DS00186/DSECTION=risk-factors>

Medscape

<http://emedicine.medscape.com/article/1099386-overview#aw2aab6b4>

Medline Plus

<http://www.nlm.nih.gov/medlineplus/ency/article/001308.htm>

Melani, C., Wilson, W.H. & Roschewski, M. 2019. Liquid biopsy in non-Hodgkin's Lymphoma. *Hematol Oncol*, 37 Suppl 1, 70-74, Jun 2019.

Merseyside & Cheshire Cancer Network

<http://www.mccn.nhs.uk/userfiles/documents/Guidelines%20for%20treatment%20of%20Burkitts%20Lymphoma%20DEC%202010.pdf>

Minard-Colin, V., Aupérin, A., Pilon, M., Burke, G.A.A., Barkauskas, D.A., Wheatley, K., Delgado, R.F., Alexander, S., Uyttebroeck, A., Bollard, C.M., Zsiros, J., Csoka, M., Kazanowska, B., Chiang, A.K., Miles, R.R., Wotherspoon, A., Adamson, P.C., Vassal, G., Patte, C., Gross, T.G.. European Intergroup for Childhood Non-Hodgkin Lymphoma, & Children's Oncology Group. Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children. *N Engl J Med.* 2020 Jun 4;382(23):2207-2219.

Moleti, M.L., Testi, A.M. & Foá R. 2020. Treatment of relapsed/refractory paediatric aggressive B-cell non-Hodgkin lymphoma. *Br J Haematol.* 2020 Jun;189(5):826-843.

MPR

http://www.empr.com/news/rituxan-hycela-hyaluronidase-human-subcutaneous-injection/article/670580/?DCMP=EMC-MPR_DailyDose_cp20170622&cpn=hemonc_all&hmSubId=i7VmYKZCM_41&hmEmail=OdsiBxRYPdkldpZ00Ap-a5dX4uYlpfYu0&NID=&c_id=&dl=0&spMailingID=17512615&spUserID=MzMyODk3NTcxNTcS1&spJobID=1041709197&spReportId=MTA0MTcwOTE5NwS2

Munshi, P.M. & Ujjani, C. 2019. The acceleration of CAT-T therapy in non-Hodgkin Lymphoma. *Hematol Oncol*, 37 (3), 233-239, Aug 2019.

National Cancer Institute

<http://www.training.seer.cancer.gov/lymphoma/abstract-code-stage/>
<http://www.cancer.gov/clinicaltrials/learningabout/what-are-clinical-trials>

Non-Hodgkin's Lymphoma

https://www.google.co.za/search?q=non-hodgkin%27s+lymphoma&source=lnms&tbn=isch&sa=X&ei=AGCZU8q1KsLD7Aax9IH4Aw&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=kKB9P4GyA_Fu3M%3A%3B2h1pJ-GD7YW-PM%3BkKB9P4GyA_Fu3M%3A&imgsrc=kKB9P4GyA_Fu3M%253A%3BNDhAy5EHR6ijXM%3Bhttp%253A%252F%252Fwww.cixip.com%252Fpublic%252Fkindeditor%252Fattached%252Fimage%252F20120925%252F20120925100954_31690.jpg%3Bhttp%253A%252F%252Fwww.cixip.com%252Findex.php%252Fpage%252Fcontent%252Fid%252F613%3B537%3B600

PubMed Health. Hodgkin's Lymphoma.

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001606/>
<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001607/>
<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002285/>

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Rodriguez-Justo, M., Attygalle, A.D., Munson, P., Roncador, G, Maragioti, T. & Pirisw, M.A. 2009. Antioimmunoblastic T-Cell lymphoma with hyperplastic germinal centres: a neoplasia with origin in the outer zone of the germinal centre? Clinicopathological and immunohistochemical study of 10 cases with follicular T-cell markers. *Modern Pathology*, 22:753-761. doi:10.1038/modpathol.2009.12; published online 27 March 2009

Sapkota, S. & Shaikh, H. 2020. Non-Hodgkin lymphoma. *In*: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2020 Dec 14.

The Burkitt's Lymphoma Society

<http://burkittslymphomasociety.com/>

The Immune System

<http://www.humanvitaminhealth.com/yourimmunesystem.html>

Tun, A.M. & Ansell, S.M. 2020. Immunotherapy in Hodgkin and non-Hodgkin lymphoma: Innate, adaptive and targeted immunological strategies. *Cancer Treat Rev*. 2020 Aug;88:102042.

University of Maryland Medical Center

http://www.umm.edu/patiented/articles/what_risk_factors_non-hodgkins_lymphomas_000084_2.htm

WebMD

<http://www.webmd.com/cancer/burkitt-lymphoma-prognosis-diagnosis-treatments>