Cancer Association of South Africa (CANSA)

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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]

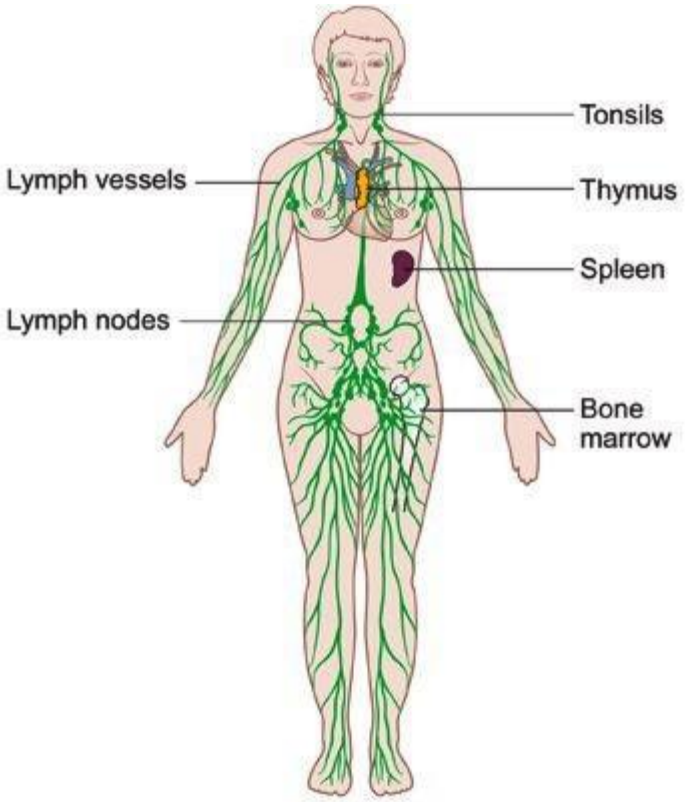

Diagram of the lymphatic system
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The Lymphatic System

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

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 immodeficiency 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.
- 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.

The International Classicification of Disease 10th Version (ICD-10)

The International Classification of Diseases (ICD) is designed to promote international comparability in the collection, processing, classification, and presentation of mortality statistics. This includes providing a format for reporting causes of death on the death certificate.

ICD serves a broad range of uses globally and provides critical knowledge on the extent, causes and consequences of human disease and death worldwide via data that is reported and coded with the ICD. Clinical terms coded with ICD are the main basis for health recording and statistics on disease in primary, secondary and tertiary care, as well as on cause of death certificates. These data and statistics support payment systems, service planning, administration of quality and safety, and health services research. Diagnostic guidance linked to categories of ICD also standardizes data collection and enables large scale research.

For more than a century, the International Classification of Diseases (ICD) has been the basis for comparable statistics on causes of mortality and morbidity between places and over time. Originating

in the 19th century, the latest version of the ICD, ICD-11, was adopted by the 72nd World Health Assembly in 2019 and came into effect on 1st January 2022.

The ICD-10 Code for Non-Hodgkin lymphoma, unspecified, unspecified site – C85.9.

Incidence of Non-Hodgkin's Lymphoma in South Africa

According to the outdated National Cancer Registry (2019), known for under reporting, the following number of Non-Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2019:

Group - Males 2019	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	1 330	1:176	3,20%
Asian males	44	1:178	4,00%
Black males	754	1:249	5,20%
Coloured males	138	1:148	2,80%
White males	394	1:95	1,85%

Group - Females 2019	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	1 123	1:265	2,55%
Asian females	38	1:200	2,71%
Black females	621	1:401	3,08%
Coloured females	118	1:234	2,41%
White females	346	1:122	1,94%

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma in South Africa for 2019 was as follows (National Cancer Registry, 2019):

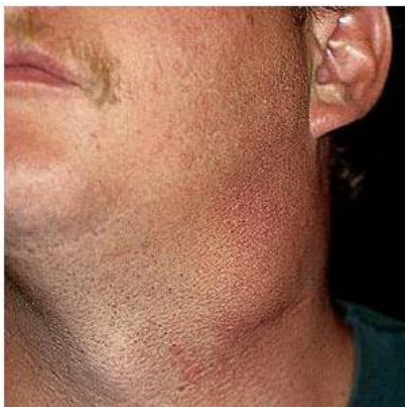
Group - Males 2019	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	56	73	192	307	274	206	160	62
Asian males	1	4	2	8	9	13	5	2
Black males	15	53	148	225	163	71	34	9
Coloured males	1	8	14	21	27	27	22	8
White males	3	8	28	43	75	95	99	43

Group - Females 2019	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	40	63	107	213	203	174	173	70
Asian females	1	0	1	1	9	11	11	4
Black females	32	49	154	171	118	61	24	12
Coloured females	4	8	16	14	24	21	23	8
White females	3	6	16	27	52	81	115	46

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
- PET (positron emission tomography) scan

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

Moleti, M.L., Testi, A.M. & Foà, R. 2022.

"In high-income countries (HICs) paediatric aggressive B-cell lymphomas are curable in about 90% of cases. Much worse results, with cure rates ranging from less than 30% to about 70%, are achieved in low- and middle-income countries (LMICs), where 90% of paediatric non-Hodgkin lymphomas occur. Low socio-economic and cultural conditions, the lack of optimal diagnostic procedures, laboratory facilities and adequate supportive care exert a strong negative impact on compliance, treatment delivery, toxicity and, consequently, on the clinical outcome. Published data are scarce, generally originating from single institutions, and are difficult to compare. National and international cooperation projects have been undertaken to reduce the unacceptable gap between HICs and LMICs in the management of children with cancer, by promoting the sharing of knowledge and by implementing adequate local healthcare facilities, with initial promising results. In the present review, we will summarize the results so far obtained in the management of paediatric aggressive B-cell NHL in LMICs."

Treatment - General

Bock, A.M., Nowakowski, G.S. & Wang, Y. 2022.

"While there have been numerous advances in the field of non-Hodgkin lymphoma (NHL) over the last decade, relapsed and/or refractory (R/R) NHL remains a challenge and an area with unmet needs. T-cell redirecting immunotherapeutic approaches including chimeric antigen receptor (CAR) T-cells and bispecific antibodies (BsAbs) have the potential to revolutionize NHL therapy. BsAbs target CD3 on T-cells and CD19 or CD20 on malignant B-cells and have shown promises as a novel immunotherapy for NHL. The development of CD19 × CD3 BsAbs such as blinatumomab was met with significant challenges due to dose-limiting neurologic side effects. However, several CD20 × CD3 BsAbs including odronextamab, mosunetuzumab, glofitamab, and epcoritamab emerged recently. They have favorable toxicity profiles, with reduced cytokine release syndrome and neurotoxicity. In addition, all these BsAbs have demonstrated very promising efficacy in R/R NHL. With expansion and registrational studies actively ongoing, approvals of these agents for R/R NHL are anticipated in the near future.

Some important questions pertinent to future clinical development of BsAbs include when and how to best utilize BsAbs in the management of R/R NHL, whether there is a role of BsAbs in treatment-naïve NHL, and how to combine BsAbs with other therapies. For example, whether BsAbs can be combined with cytotoxic chemotherapy effectively remains to be seen. A plethora of clinical studies will be needed to help address these questions, some of which are already ongoing. In addition, how do BsAbs compare to CAR T-cell therapy and how to choose and sequence between BsAbs and CAR T-cell therapy need to be addressed. While many of these critical questions remain to be answered in clinical studies, we believe the future of BsAbs in the NHL is very bright."

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.

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 enlarge3ment. 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.

For additional information, please visit: https://pactr.samrc.ac.za/

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"Glofitamab, a novel CD20xCD3, T-cell-engaging bispecific antibody, exhibited single-agent activity in Study NP30179, a first-in-human, phase 1 trial in relapsed/refractory B-cell non-Hodgkin lymphoma. Preclinical studies showed that glofitamab leads to T-cell activation, proliferation, and tumor cell killing upon binding to CD20 on malignant cells. Here, we provide evidence of glofitamab's clinical activity, including pharmacodynamic profile, mode of action, and factors associated with clinical response, by evaluating biomarkers in patient samples from the dose-escalation part of this trial. Patients enrolled in Study NP30179 received single-dose obinutuzumab pretreatment (1000 mg) 7 days before IV glofitamab (5 µg-25 mg). Glofitamab treatment lasted ≤12 cycles once every 2 or 3 weeks. Blood samples were collected at predefined time points per the clinical protocol; T-cell populations were evaluated centrally by flow cytometry, and cytokine profiles were analyzed. Immunohistochemical and genomic biomarker analyses were performed on tumor biopsy samples. Pharmacodynamic modulation was observed with glofitamab treatment, including dose-dependent induction of cytokines, and T-cell margination, proliferation, and activation in peripheral blood. Gene expression analysis of pretreatment tumor biopsy samples indicated that tumor cell intrinsic factors such as TP53 signaling are associated with resistance to glofitamab, but they may also be interlinked with a diminished effector T-cell profile in resistant tumors and thus represent a poor prognostic factor per se. This integrative biomarker data analysis provides clinical evidence regarding glofitamab's mode of action, supports optimal biological dose selection, and will further guide clinical development. This trial was registered at www.clinicaltrials.gov as #NCT03075696."

Medical Disclaimer

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Lymph Node
http://www.google.co.za/imgres?hl=en&sa=X&rlz=1T4LENN_enZA490ZA490&biw=1366&bih=613&tbm=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]

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