

Cancer Association of South Africa (CANSA)



Fact Sheet on Diffuse Large B-Cell Lymphoma

Introduction

Lymphoma is a cancer of the lymphatic system. It affects a type of white blood cells known as lymphocytes. These help fight disease in the body. They play an important role in the immune system.

This type of cancer starts in the white blood cells, or lymphocytes. As it is present in the bloodstream, it can spread, or metastasize, to different parts of the body.

Lymphoma can occur at any age, but it is one of the most common causes of cancer in children and young adults aged 15 to 24 years. It is more common in men.

DLBCL is often treatable.



Diffuse Large B-cell Lymphoma

There are two types of lymphoma: Hodgkin's and non-Hodgkin's. They behave, grow, and respond to treatment differently. DLBCL is the most common non-Hodgkin's lymphoma. And there are several types of DLBCL.

Diffuse large B-cell lymphoma, or DLBCL, is a cancer that starts in white blood cells called lymphocytes. It usually grows in lymph nodes -- the pea-sized glands in one's neck, groin, armpits, and elsewhere that are part of the immune system. It can also show up in other areas of the body.

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL) worldwide, accounting for about 22 percent of newly diagnosed cases of B-cell NHL and about 20 to 40 percent of non-Hodgkin's lymphoma cases.

DLBCL is an aggressive (fast-growing) NHL that affects B-lymphocytes. Lymphocytes are one type of white blood cell. B-cells are lymphocytes that make antibodies to fight infections and are an important part of the lymphatic system.

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Although it can occur in childhood, the occurrence of DLBCL generally increases with age, and most patients are over the age of 60 at diagnosis.

DLBCL can develop in the lymph nodes or in “extranodal sites” (areas outside the lymph nodes) such as the gastrointestinal tract, testes, thyroid, skin, breast, bone, brain, or essentially any organ of the body. It may be localised (in one spot) or generalised (spread throughout the body). Despite being an aggressive lymphoma, DLBCL is considered potentially curable.

Sub-types of Diffuse Large B-Cell Lymphoma

A number of DLBCLs have been categorized into subtypes which differ with respect to certain characteristics:

- T-cell/histiocyte-rich B-cell lymphoma: When viewed under a microscope, this form of DLBCL looks like a few scattered large and atypical B-cells in a background of many normal T cells and histiocytes, which are cells that migrate from bone marrow into tissues.
- Primary DLBCL of the Central Nervous System (CNS): This refers to all DLBCLs that originate in either the brain or the eye. Occasionally, patients who do not have this subtype may still develop secondary DLBCL of the CNS, which occurs when the lymphoma moves into the brain or spinal cord at a later time.
- Primary cutaneous DLBCL, leg type: This type of DLBCL consists of large transformed B-cells that typically appear as red or bluish-red tumours. Despite its name, the disease can involve the trunk, arms, legs, buttocks, or anywhere on the body. These lymphomas can also spread to areas other than just the skin.
- Epstein-Barr virus (EBV)-positive DLBCL of the elderly: This form of DLBCL usually occurs in patients who are age 50 or older and test positive for EBV.
- DLBCL not otherwise specified (NOS): When DLBCL doesn't fall into one of the subtypes listed above, it is classified as DLBCL not otherwise specified (NOS). A large number of diagnoses fall into this category. In western countries, about 25 to 30 percent of NHL cases diagnosed in adults are DLBCL-NOS, and this percentage is higher in developing countries. There are other ways of categorizing cases of DLBCL-NOS into molecular subgroups based on their genetic and immunophenotypic characteristics.

Sukswai, N., Lyapichev, K., Khoury, J.D. & Jeffrey Medeiros, L. 2020.

“Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma, representing approximately one-third of all cases worldwide. In the World Health Organization (WHO) classification of lymphomas, most cases of DLBCL are designated as not otherwise specified (NOS). About 20% of cases, however, are designated as specific variants of DLBCL. These variants, 13 in total, are specified on the basis of distinctive morphological or immunophenotypic findings or distinctive biological or clinical issues associated with their diagnoses. In this review we discuss the following variants: T-cell/histiocyte-rich large B-cell lymphoma; ALK-positive large B-cell lymphoma; plasmablastic lymphoma; intravascular large B-cell lymphoma; large B-cell lymphoma with IRF4 rearrangement; primary mediastinal large B-cell lymphoma; primary cutaneous diffuse large B-cell lymphoma, leg type; primary diffuse large B-cell lymphoma of the central nervous system; diffuse large B-cell lymphoma associated with chronic inflammation; lymphomatoid granulomatosis; primary effusion lymphoma; and HHV8-positive diffuse large B-cell lymphoma, NOS. Two additional variants recognised in the WHO classification, EBV-positive diffuse large B-cell lymphoma and EBV-positive mucocutaneous ulcer are discussed elsewhere in another review within this issue of Pathology. Although not recognised as a specific variant in the current WHO classification, primary testicular diffuse large B-cell lymphoma also has unique biological features and requires some modification of the standard treatment approach for patients with DLBCL. Therefore, we suggest that

primary testicular diffuse large B-cell lymphoma also should be recognised as a specific variant of DLBCL in a future version of the WHO classification.”

Pirzada, U.A., Kumar, K. Tariq, H., Niazi, M. & Makker, J. 2019.

“The gastrointestinal (GI) tract is the predominant site of extra nodal lymphoma involvement. In the United States (US), gastric lymphoma is the most common extra nodal site of lymphoma. Most of these lesions are either extra nodal marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT) type or diffuse large B cell lymphoma (DLBCL). We report a case of diffuse large B-Cell Gastric Lymphoma who initially presented with sore throat, dysphagia and hiccups for a few months. Esophagogastroduodenoscopy showed lower esophageal stenosis and a large, infiltrative, ulcerated, circumferential mass at the gastro esophageal junction and cardia. Histopathology showed diffuse large B cell lymphoma. Positron emission tomography scan showed advanced disease with presence of lymph nodes on both sides of the diaphragm. The patient was considered to have Stage IV gastric lymphoma. Subsequently, he was treated with R-CHOP regimen (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine), and prednisone).”

Costa, S.F.D.S., Silva, A.M.B., Amaral-Silva, G.K., Pontes, H.A.R., Pontes, F.S.C., Fonseca, F.P. & Almeida, O.P. 2019.

“Lymphomas of the oral cavity are rare and the most frequent type is diffuse large B-cell lymphoma (DLBCL). Epstein-Barr virus (EBV) is known to be associated with the development of different lymphomas. In 2008, the World Health Organization provisionally included the EBV-positive DLBCL of the elderly in the classification of hematopoietic and lymphoid tumors as a lymphoma occurring in older individuals without any known immunodeficiency. However, it has since been recognized that this entity may occur in younger individuals and present similar clinical parameters in both age groups. As a result, the 2017 revision has declined the term elderly and modified it to EBV-positive DLBCL, not otherwise specified (NOS). In this report, we describe a rare case of EBV-positive DLBCL, NOS, presenting as a painless swelling in the oral cavity. This entity shows a more aggressive clinical course than EBV-negative DLBCL, and other lymphoproliferative disorders should be considered in the differential diagnosis.”

Incidence of Diffuse Large B-cell Lymphoma

The National Cancer Registry (2016) does not provide any information regarding the incidence of Diffuse Large B-Cell Lymphoma.

Risk Factors for Diffuse Large B-cell Lymphoma

The exact causes of DLBCL are unknown. People who have a compromised immune system (e.g. HIV/Aids) may be more susceptible to developing DLBCL. This may include people who have previously been treated for other forms of cancer including a low-grade lymphoma, or people who have an autoimmune disorder.

Other risk factors that may affect a person’s likelihood of developing Diffuse Large B-Cell Lymphoma include:

- Age
- Gender
- Ethnicity
- Autoimmune disorders like rheumatoid arthritis and systemic lupus erythematosus
- Organ transplantation patients

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Although DLBCL has been found in people of all age groups, it is found most commonly in people who are middle-aged or elderly. The average age at the time of diagnosis is 64 years. Men are slightly more likely to develop DLBCL than women. In the United States, white people are more likely to develop this type of lymphoma than are Asians or Blacks.

DLBCL is not an inherited disease. Siblings and children of patients with DLBCL do not have a substantially increased risk of developing DLBCL. The majority of patients have no family history, but approximately 9 percent of patients have a first degree relative (e.g., parent or sibling) with lymphoma or chronic lymphocytic leukaemia.

Lamure, S., Carles, C., Aquereburu, Q., Quittet, P., Tchernonog, E., Paul, F., Jourdan, E., Waultier, A., Defez, C., Belhadj, I., Sanhes, L., Burcheri, S., Donadio, D., Exbrayat, C., Saad, A., Labourey, J.L., Baldi, I., Cartron, G. & Fabbro-Peray, P. 2019.

IMPORTANCE: Professional use of pesticides is a risk factor for non-Hodgkin lymphoma. The main biological mechanisms of pesticides and chemotherapy are genotoxicity and reactive oxygen species generation. Cellular adaptation among patients exposed to low doses of genotoxic and oxidative compounds might hinder chemotherapy efficiency in patients with lymphoma.

OBJECTIVE: To examine the association of occupational exposure to pesticides with immunochemotherapy response and survival among patients treated for diffuse large B-cell lymphoma.

DESIGN, SETTING, AND PARTICIPANTS: This retrospective cohort study assessed patients treated from July 1, 2010, to May 31, 2015, for diffuse large B-cell lymphoma, with a 2-year follow-up. The study took place at 6 university and nonuniversity hospitals in Languedoc-Roussillon, France. A total of 404 patients with newly diagnosed diffuse large B-cell lymphoma treated with anthracycline-based immunochemotherapy were included before the study began. Occupational history was reconstructed for 244 patients and analyzed with the PESTIPOP French job-exposure matrix to determine likelihood of occupational exposure to pesticides. Analysis of the data was performed from July 15, 2017, to July 15, 2018.

MAIN OUTCOMES AND MEASURES: Treatment failure (ie, partial response, stable disease, disease progression, or interruption for toxic effects) rate, 2-year event-free survival, and overall survival between exposed and nonexposed patients after adjustment for confounding factors.

RESULTS: A total of 244 patients (mean [SD] age, 61.3 [15.2] years; 153 [62.7%] male) had complete occupational data. Of these patients, 67 (27.4%) had occupational exposure to pesticides, with 38 exposed through agricultural occupations. Occupational exposure was not associated with clinical and biological characteristics at diagnosis. Occupationally exposed patients had a significantly higher treatment failure rate (22.4% vs 11.3%; $P = .03$; adjusted odds ratio [AOR] for confounding factors, 3.0; 95% CI, 1.3-6.9); this difference was higher among patients with exposing agricultural occupations compared with other patients (29.0% vs 11.7%; AOR, 5.1; 95% CI, 2.0-12.8). Two-year event-free survival was 70% in the occupationally exposed group vs 82% in the unexposed group (adjusted hazard ratio [AHR] for confounding factors, 2.2; 95% CI, 1.3-3.9). Among patients with exposing agricultural occupations compared with other patients, the difference was more pronounced (2-year event-free survival, 56% vs 83%; AHR, 3.5; 95% CI, 1.9-6.5). Similarly, 2-year overall survival was lower in the group of patients with exposing agricultural occupations compared with other patients (81% vs 92%; AHR, 3.9; 95% CI, 1.5-10.0).

CONCLUSIONS AND RELEVANCE: This retrospective study showed that agricultural occupational exposure to pesticides was associated with treatment failure, event-free survival, and overall survival among patients with diffuse large B-cell lymphoma.

Signs and Symptoms of Diffuse Large B-cell Lymphoma

Most people with DLBCL may first notice painless lumps, often in their neck, armpit or groin. These are enlarged lymph nodes (swollen glands). They can grow quite quickly, over just a few weeks.

DLBCL can develop in lymph nodes deep inside the body where they cannot be felt from the outside. It is quite common for people with DLBCL to have lymphoma in extranodal sites (areas outside the lymph node). Large lumps can form – this is known as ‘bulky disease’.

DLBCL can be hard to diagnose as people have different symptoms depending what organs and tissues the lymphoma is affecting, for example:

- DLBCL in the stomach or bowel can cause abdominal (tummy) discomfort or pain, diarrhoea or bleeding
- DLBCL in the chest can cause a cough or breathlessness.

Some people with DLBCL experience fevers, night sweats and unexplained weight loss. These are known as ‘B symptoms’. They may also experience the following:

- Swollen lymph glands
- Low-grade fever
- Anorexia (loss of appetite)
- Generalised pruritus (itching skin)
- Pedal oedema (accumulation of fluid in the feet and lower legs)

Fatigue and loss of appetite are also quite common, and some people experience severe itching.

Diagnosis of Diffuse Large B-cell Lymphoma

The following may be used in the diagnosis of Diffuse Large B-Cell Lymphoma:

Laboratory tests which may include the following:

- Complete blood count: To evaluate involvement of the bone marrow, which may result in anaemia, thrombocytopenia, and/or leukopenia
- Serum electrolyte levels: Electrolyte abnormalities may occur from renal involvement with lymphoma
- Lactate dehydrogenase and uric acid levels: Elevated levels correspond with the tumour burden
- Hepatitis B testing: Performed in patients undergoing combination chemoimmunotherapy with rituximab (risk of activation)
- Flow cytometry: Helps in determining a clonal cell population and in differentiating between B- and T-cell origins

Imaging studies

Imaging studies used in the diagnosis and assessment of Diffuse Large Cell Lymphoma include the following:

- Gastrointestinal imaging: Upper and lower gastrointestinal series indicated in patients with gastrointestinal symptoms, but these studies ^[1]
- Central nervous system imaging: Patients with CNS symptoms require brain evaluation with CT scanning with contrast or MRI with gadolinium
- Bone imaging: Bone scan for patients with unexplained bone pain or elevated alkaline phosphatase levels

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- CT scanning of the neck, chest, abdomen, and pelvis: To help identify degree of lymphadenopathy, presence of extranodal disease, or visceral involvement
- Gallium-67 scanning - Valuable in staging diffuse large cell lymphomas
- Multigated acquisition scanning: To evaluate the patient's ejection fraction before chemotherapy
- Positron emission tomography: To stage disease using fluorodeoxyglucose

Biopsy and lumbar puncture

Bone marrow aspiration and biopsy are performed as part of the staging process to help rule out involvement with lymphoma. Lymph node biopsy is required to establish a definitive diagnosis of NHL. The diagnosis of diffuse large cell lymphoma is usually confirmed after positive findings are obtained from a lymph node biopsy specimen.

In patients with advanced-stage disease, a lumbar puncture for cytologic and chemical analysis of the CSF may be necessary.

Jiang, X.Y., Shen, H.R., Ge, C.W., Li, J. & Zhou, D.B. 2019.

OBJECTIVE: To determine the significance of morphology of bone marrow smear for diagnosis of bone marrow involvement in patients with diffuse large B-cell lymphoma (DLBCL), and to study the morphological characteristics of DLBCL cells involved in bone marrow.

METHODS: Four hundred and twenty cases of DLBCL diagnosed at Peking Union Hospital from 2006 to 2016 were analyzed and identified.

RESULTS: Blinded analysis of bone marrow smear and bone marrow biopsy data showed involvement in 42 cases on smears (S), in 47 cases by biopsy (B) and the in 49 cases by (S+B). There was an excellent correlation between 2 methods diagnosing the bone marrow infiltration of DLBCL independently ($\kappa=0.889$). The morphological features of DLBCL cells involved in bone marrow were of medium sizes, round or irregular nuclear. The chromatin presented dark purple ream and coarse granular, and most of them had 1-5 nucleoli. The amount of cytoplasm was moderate with the color of dark blue or greyish blue. Vacuoles and pseudopodia were common.

CONCLUSION: The morphological examination of bone marrow cells has a certain role in the diagnosing bone marrow involvement in patients with DLBCL, and the atypical lymphoid cells making up $\geq 1\%$ of the total nucleated cells highly suggests the bone marrow involvement in the patients with DLBCL.

Treatment of Diffuse Large B-cell Lymphoma

Most people diagnosed with Diffuse Large B-Cell Lymphoma are treated with:

- targeted therapy
- chemotherapy
- steroids

Some individuals also have radiotherapy to treat an area of the lymphoma.

These treatments may make all signs of the DLBCL disappear (called remission). Many patients who go into remission are cured, but sometimes DLBCL comes back. If this happens, chemotherapy can be used again. Some people will then have high-dose chemotherapy and stem cell support.

Chemotherapeutic regimens used in the treatment of diffuse large cell lymphoma include the following:

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- CHOP: Cyclophosphamide, doxorubicin (Adriamycin), vincristine, and prednisone; standard treatment for early-stage diffuse large cell lymphoma; current data suggest that either 6 cycles of CHOP or 3-4 cycles of CHOP followed by involved-field radiation therapy (IFRT) is reasonable treatment for early-stage, nonbulky diffuse large cell lymphoma (stage IA or IIA, nonbulky)
- R-CHOP: Rituximab plus CHOP; standard therapy for patients with advanced diffuse large cell lymphoma
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine [Oncovin], cyclophosphamide, doxorubicin), plus rituximab

Salvage chemotherapeutic regimens used in relapse therapy include the following:

- DHAP - Dexamethasone, high-dose cytarabine, and cisplatin
- ESHAP - Etoposide, methylprednisolone, high-dose cytarabine, and cisplatin
- MIME - Mesna, ifosfamide, methotrexate, and etoposide
- IMVP-16 - Ifosfamide, methotrexate, and etoposide

After the first relapse, however, the duration of the second complete response to treatment is frequently shorter than 1 year. Patients whose condition relapses and who have chemoresponsive disease, as evaluated after salvage therapy, should be considered for high-dose chemotherapy followed by stem cell rescue.

Semira, S. & Kuruvilla, J. 2019.

Introduction: Pembrolizumab is a novel monoclonal antibody that targets the interaction between programmed cell death protein 1 (PD-1) and its ligand (PD-L1). Pembrolizumab has shown significant clinical efficacy in Hodgkin Lymphoma (HL), but results in non Hodgkin Lymphoma (NHL) are mixed. Some NHL subtypes, which share certain genetic features with HL, such as alterations in chromosome 9p24.1 and expression of PD-L1, have shown promising responses in early phase trials.

Areas covered: In this review, we provide an overview of pembrolizumab as a compound, and present the available clinical efficacy and safety data in the treatment of diffuse large B cell lymphomas.

Expert opinion: Current early phase data suggest that single agent pembrolizumab in NHL demonstrates both efficacy and a favorable safety profile. However, it is anticipated that future treatment strategies will be biomarker-driven and incorporate pembrolizumab into combination therapies with chemotherapy and/or immunotherapy agents.

Flinn, I.W., Erter, J., Daniel, D.B., Mace, J.R. & Berdela, J.G. 2019.

LESSONS LEARNED: The combination of ofatumumab and bendamustine in elderly patients with diffuse large B-cell lymphoma demonstrated modest efficacy compared with standard of care. The poor response may have been due to patient age and the high rate of treatment discontinuation.

BACKGROUND: This phase II trial evaluated the efficacy of bendamustine and ofatumumab in elderly patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) who were not candidates for rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

METHODS: Patients received IV 90 mg/m² bendamustine on days 1 and 2 of cycles 1 through 6 and IV 1,000 mg ofatumumab on days 1 and 8 of cycle 1 and on day 1 of cycles 2 through 6. Both drugs were administered at the U.S. Food and Drug Administration-approved dose for combination therapy. All patients received premedications before each infusion of ofatumumab and hematopoietic growth factors. Treatment was administered in 21-day cycles, with restaging after cycle 3 and cycle 6. The primary endpoint was complete response rate (CRR).

RESULTS: Twelve of 21 enrolled patients completed treatment; median age was 83 years. The most common reasons for treatment discontinuation were disease progression (three patients), intercurrent illness (two patients), and death (one patient due to drug-related sepsis and bowel necrosis and one patient due to unknown cause). Thrombocytopenia (14%), neutropenia (10%), diarrhea (10%), vomiting (10%), and

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dehydration (10%) were the most common grade ≥ 3 treatment-related adverse events. The overall response rate was 90.5% and the CRR was 33.3%. Median progression-free survival (PFS) and overall survival (OS) were 8.6 and 12.0 months, respectively.

CONCLUSION: The combination of ofatumumab and bendamustine is feasible in elderly patients with DLBCL.

Hu, K., Gao, J.J., Li, Q.H., Tian, L., Wan, W., Zhao, W., Wang, J.J. & Fu, L. 2019. "Myc-positive diffuse large B-cell lymphoma has lower curative efficacy and long-term survival than its negative counterpart, even when treated with R-CHOP regimen. The present study aims to determine whether the use of autologous hematopoietic stem cell transplantation as a consolidation therapy can improve the curative efficacy in this type of patients after achieving the best effect of chemotherapy for the first time. The data of 50 patients with Myc-positive diffuse large B-cell lymphoma were retrospectively analyzed. Autologous transplantation was performed for 23 patients, while transplantation was not performed for 27 patients. The clinicopathological features and survival conditions were compared. The 1-year and 3-year progression-free survival (PFS) rates were $66.7\% \pm 0.9\%$ and $57.7\% \pm 1.0\%$, respectively, in the non transplantation group, and 100% and $82.1\% \pm 0.1\%$, respectively, in the transplantation group ($P = .021$). The 1-year overall survival (OS) rate for these two groups was $88.7\% \pm 0.6\%$ vs 100% , respectively, while the 3-year OS rates for these two groups was $78.6\% \pm 0.1\%$ vs $91.3\% \pm 0.1\%$, respectively ($P = .176$). Hematopoietic stem cell transplantation performed after chemotherapy is a risk factor for OS. Autologous hematopoietic stem cell transplantation as a consolidation therapy in the early stage can improve the prognosis of patients with Myc-positive diffuse large B-cell lymphoma."

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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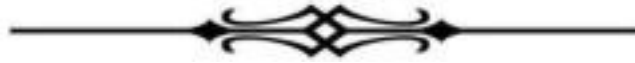
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Diffuse Large B-Cell Lymphoma

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