UNDERSTANDING
Diffuse Large B-cell Lymphoma (DLBCL)

LYMPHOMA CANADA

Overview

Lymphoma is the most common form of blood cancer. Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably.

WHAT ARE LYMPHOCYTES?

Lymphocytes are a type of white blood cell and are a major part of the lymphatic system. Together with other cells of the immune system, they work to fight infection and prevent disease. Lymphocytes can be found in the blood and bone marrow; however, most of them are normally circulating in the lymphatic system.

There are two main types of lymphocytes that can develop into lymphomas: B lymphocytes and T lymphocytes. The types of cells that become cancerous in diffuse large B-cell lymphoma (DLBCL) are B lymphocytes (B cells). B lymphocytes make antibodies to fight infections. They are called B cells because they mature in the bone marrow.

There are over 80 different subtypes of lymphoma. They fall into two main categories:

- Hodgkin lymphoma (HL)
- Non-Hodgkin lymphoma (NHL)

DLBCL is the most common type of NHL. NHLs are approximately eight times more common than HL – 85% of all lymphomas are NHL. One of the main differences between HL and NHL is the presence of Reed-Sternberg cells which are large abnormal lymphocytes that can be detected under a microscope. Reed-Sternberg cells are typically present in Hodgkin lymphoma and are absent in Non-Hodgkin lymphoma.

NHL is further sub-categorized by 'grade':

- Low-grade: indolent (or slow-growing) NHLs
- Intermediate or high-grade: aggressive (or fast-growing) NHLs

DLBCL is an aggressive lymphoma. Aggressive lymphomas usually develop more rapidly than indolent lymphomas. Patients with aggressive lymphoma often experience symptoms from the onset of their disease and may require immediate, intensive treatment. Indolent lymphomas, however, develop more slowly then aggressive lymphomas. Patients with indolent lymphomas usually do not show symptoms until later, often as the disease progresses, and may therefore not require immediate treatment. DLBCL can affect lymph nodes (nodal sites) as well as organs or tissues other than the lymph nodes (called extranodal sites) including the gastrointestinal tract, testes, adrenal gland, thyroid, skin, breast, bone, or brain/spinal cord.

Who gets DLBCL?

The risk of developing DLBCL increases as you age. The average age range at diagnosis is 60-70 years of age, however this cancer can affect patients at any age including young adults and children. DLBCL occurs both in men and women, although it is slightly more common in men.

DLBCL can develop as a first-time lymphoma (called de novo) or it can develop in people who have been diagnosed with an indolent lymphoma whereby their original lymphoma transforms (changes) into DLBCL. If this happens, the lymphoma is treated as a DLBCL, and will no longer be treated for the type of indolent lymphoma the patient had prior to the transformation.

Types of DLBCL

There are several subtypes of DLBCL. These subtypes are generally named according to the cell where the cancer originated from within the body. Each subtype can have a different prognosis (outcome and survival) and different treatment options.

DLBCL subtypes include:

PRIMARY MEDIASTINAL B-CELL LYMPHOMA (PMBL)

PMBL arises from a thymic B cell. Thymic B cells are a unique population of B lymphocytes that are found in the thymus, an organ where T lymphocyte development occurs. There is often fibrous (scar-like) lymph tissue present in this lymphoma. It grows rapidly in the mediastinum (the central area of the upper chest located behind the breastbone containing the heart and blood vessels). It accounts for about 2-4% of all lymphomas and occurs predominantly in young patients; it is seen more commonly in women than in men.

This lymphoma may press on the trachea and cause coughing, abnormal voice changes (hoarseness), or trouble breathing. It can also block the large vein that returns blood to the heart from the arms and head (the superior vena cava), which can make the arms, neck and face swell. Other symptoms include difficulty swallowing (dysphagia), dizziness and headaches.

PRIMARY CENTRAL NERVOUS SYSTEM (CNS)

CNS lymphoma only affects the brain and/or spinal column and rarely spreads outside the nervous system. It can also start in the eye (called ocular lymphoma). People with a weakened immune system such as those diagnosed with HIV/AIDS or who have had an organ transplant, are at an increased risk of developing primary CNS lymphoma. However, this type of lymphoma can also develop in individuals with healthy immune systems. CNS lymphoma is mostly commonly diagnosed in patients between 50-60 years of age, but it can develop at any age. Symptoms can include headaches, changes in thinking/confusion, vision problems, dizziness, numbness, stroke-like events, pain throughout the body, and seizures.

EBV-POSITIVE DLBCL

EBV-positive DLBCL of the elderly accounts for less than 5% of DLBCL cases and is often diagnosed in patients aged 50 years and older, especially in those of East Asian descent (due to genetic factors). While the disease name includes the term 'elderly' it can develop in people younger than 50 years of age as well.

EBV-positive refers to patients who are positive for the Epstein-Barr virus (EBV), a virus that causes infectious mononucleosis (more commonly known as "mono"). Many people carry the Epstein-Barr virus but do not show symptoms and therefore do not know they are infected. It is thought that the virus infects and stays in the B lymphocytes of the body, causing lymphoma in a small percentage of people. The reason as to why some people who are EBV-positive develop lymphoma and others do not is not known.

This lymphoma is often extranodal (for example it can be found in the skin, lungs, tonsils or stomach) and may or may not involve the lymph nodes. Patients with EBV-positive DLBCL do not respond to treatment as well as those who have EBV-negative DLBCL.

T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA

T-cell/histiocyte-rich large B-cell lymphoma is more common in men aged 50 years and older but can be diagnosed in people of any age. Fewer than 10% of people with DLBCL will have this subtype. T cells, histiocytes (another type of immune cell that breaks down toxic cells) and large B cells are affected with this subtype.

Symptoms can include swollen lymph nodes, a group of symptoms called "B symptoms" (fever, night sweats, unexplained weight loss) and swelling of the liver or spleen. People with this type of DLBCL will feel generally unwell and experience abdominal swelling and discomfort.

PRIMARY EFFUSION LYMPHOMA (PEL)

Primary effusion lymphoma (PEL) is a rare subtype of DLBCL that may also be called body cavity–based lymphoma. It causes an abnormal buildup of fluid in the cavity (space) around the heart, the cavity around the lungs, or the cavities within the abdomen. Lymphoma cells are found within the fluid that builds up in these body cavities. This fluid buildup is caused by a herpes virus. People with a weakened immune system (for instance those who have HIV/AIDS or who have received an organ transplant) are also at an increased risk of developing this type of lymphoma.

INTRAVASCULAR LARGE B-CELL LYMPHOMA (ILCL)

ILCL is a rare subtype where the lymphoma cells are only found inside small blood vessels (called capillaries), and usually not within the lymph nodes or bone marrow. ILCL can block these small blood vessels in just about any part of the body and can affect organs such as the brain, bone marrow, liver, lungs or skin. It occurs more often in older adults with the average age at diagnosis in the mid-sixties.

Symptoms vary depending on which small blood vessels are affected, but 75% of people with this form of DLBCL experience stroke-like symptoms such as confusion, weakness, numbness or paralysis, difficulty speaking, loss of balance or unexplained falls, changes in vision, and severe headaches due to the effect of the lymphoma on the nervous system. Some people may also develop reddened patches or lumps on their skin or experience a group of symptoms called "B symptoms" (fevers, night sweats and unexplained weight loss).

ALK-POSITIVE LARGE B-CELL LYMPHOMA

ALK-positive large B-cell lymphoma is a very rare subtype of DLBCL that affects people of all ages, mainly affecting men. The lymphoma cells in this subtype express a protein called 'anaplastic large-cell kinase (ALK) on their surface. Most people diagnosed with this subtype experience enlarged lymph nodes, often impacting the cervical lymph nodes and mediastinum (centre of the chest). These lymphoma cells have also been reported in extranodal sites (outside of the lymph nodes). This is an aggressive subtype with high relapse rates.

DOUBLE-HIT LYMPHOMAS (DHL) or TRIPLE-HIT LYMPHOMAS (THL)

DHL or THL affect approximately 5% to 10% of patients diagnosed with DLBCL. DHL and THL describe patients whose lymphoma cells have a type of mutation called a rearrangement in two (DHL) or three (THL) significant genes (*MYC, BCL2* and/or *BCL6*). Genes are made up of DNA and are a unit of heredity found within chromosomes. Generally, these lymphomas are aggressive, developing rapidly and requiring early treatment. Patients often have advanced disease when diagnosed and many have extranodal involvement, including central nervous system (CNS) involvement. These lymphomas are difficult to treat, and outcomes are significantly worse with treatment compared to DLBCLs without these genetic changes. **For more information about DHL, please review the DHL subtype fact sheet.**

DOUBLE-EXPRESSOR LYMPHOMAS (DEL)

DEL have a high percentage of expression of the MYC and BCL2 protein. However, unlike other subtypes, double-expressor lymphomas do not involve gene translocations (change in genetic material between chromosomes). These are primarily activated B cell DLBCLs which means they have a poorer prognosis.

For cases of DLBCL that do not fall within any one of these subtypes, these are called DLBCL not otherwise specified (NOS). DLBCL-NOS can be categorized by molecular subtype for most patients into:

- **Germinal centre B-cell (GCB):** DLBCLs are thought to develop from lymphoid cells that incorrectly stay in the germinal centre of the lymph node (the region of the lymph node where B cells normally grow and mature). Patients with GCB DLBCL disease generally have better outcomes.
- **Activated B-cell (ABC):** DLBCLs develops in activated B cells due to errors in the normal development of plasma cells (cells that produce antibodies in response to a foreign agent) from germinal B cells. ABC DLBCL is associated with a poorer outcome than GCB DLBC.

Newer molecular classifications are being developed, breaking down DLBCL-NOS into more categories, and these may become a standard way in which we describe and further categorize DLBCL in the next few years.

Symptoms

The most common symptom of DLBCL is a painless swelling in the neck, armpit, abdomen or groin region(s), caused by an enlarged lymph node or multiple enlarged lymph nodes. Often, lymph nodes in more than one area of the body are affected. DLBCL can also develop deep within the body where you may not be able to feel it. You may also have other symptoms depending on where the DLBCL is located. For instance, if it develops within your chest, you may experience a cough or difficulty swallowing. If it develops within your intestines, you may experience stomach pain or diarrhea.

Patients may also experience a group of symptoms called **B symptoms**. In the case of lymphoma, B symptoms refer to a specific set of symptoms that may help to predict how your lymphoma will progress. These usually appear alongside other symptoms such as significant swelling throughout the body, fatigue, cough, difficulty breathing, or significant pain in different areas of the body.

B SYMPTOMS ARE:

- Fever with temperatures above 38˚C (100.4˚F), without any sign of an infection;
- Night sweats, enough to drench your pajamas or bedding;
- Weight loss without trying (at least 10% of your body weight over 6 months).

Diagnosis

Doctors will need the results of different tests to determine if you have DLBCL. A biopsy is needed for a diagnosis. A biopsy involves removing a sample of tissue (cells) from an affected lymph node or other abnormal tissue region. The removed tissue is then sent to a lab where it is examined under a microscope by a hematopathologist (a doctor who specializes in diagnosing diseases of the blood and bone marrow). This type of biopsy procedure can usually be performed after the administration of local anesthetic.

Other tests may also be performed to confirm your diagnosis. Because DLBCL is a blood cancer, it is important to look at the entire body to find all of the lymphoma. This is usually done with blood tests and imaging scans which can include a whole-body computed tomography (CT) scan or positron emission tomography (PET) scan. A bone marrow biopsy may also be performed to look for the presence of lymphoma cells in the bone, and sometimes a spinal tap (lumbar puncture) may be performed to determine if there are lymphoma cells in the brain and spinal cord.

Staging

Staging describes a cancer based on how much cancer is in the body and where it is located when first diagnosed. DLBCL is staged based on the findings from your clinical examinations. Knowing the stage of your lymphoma will help your doctor determine the extent of your disease and monitor its progression over time.

Your DLBCL may be staged using the Ann Arbor Staging System. The stage is determined by the number and location of lymph nodes affected, whether the affected lymph nodes are above, below or on both sides of the diaphragm (the large, dome-shaped muscle under the ribcage that separates the chest from the abdomen), and whether the disease has spread to the bone marrow or to other organs such as the liver.

THERE ARE FOUR MAIN STAGES:

- **Stage I** The lymphoma is in one group of lymph nodes or one extranodal site
- **Stage II** The lymphoma is in two or more groups of lymph nodes on the same side of the diaphragm
- **Stage III** The lymphoma is in nodes both above and below the diaphragm
- **Stage IV** The lymphoma is widespread and found in multiple areas throughout the body including nodal and extra nodal sites

Stages I and II are considered early stages. Stages III and IV are considered advanced stages.

YOUR DOCTOR MAY ALSO ADD A SINGLE LETTER TO THE STAGE:

- **A** generally means the patient has not experienced any troublesome symptoms
- **B** means the patient has experienced B symptoms (fever, night sweats, weight loss)
- **X** means the patient has bulky disease (large tumours)
- **E** means the patient has extranodal disease (disease outside of the lymph nodes)

Staging is needed to choose an appropriate course of treatment. It is common for patients with DLBCL to have advanced-stage disease, and treatment can still be very effective in this scenario.

Prognosis

WHAT IS PROGNOSIS?

Prognosis is the medical term used to describe how the disease will progress, how well the patient will respond to treatment, and the likelihood of recovery. It is usually based on information gathered from thousands of other patients who have had the same disease which provides a general idea of what to expect when a patient is diagnosed with DLBCL. However, it is important to remember that no two patients are alike and that it is not possible to accurately predict what will happen to a specific patient.

THE INTERNATIONAL PROGNOSTIC INDEX (IPI)

If you have DLBCL, your doctor may give you a prognostic score using the International Prognostic Index (IPI). The IPI is a clinical tool developed by oncologists to aid in predicting the prognosis (outcome and survival) of patients with aggressive NHL.

One point is assigned for each of the following IPI risk factors:

- Age 60 years and over;
- Ann Arbor stage III/IV;
- More than one extranodal site;
- Serum lactate dehydrogenase (LDH) level above normal;
- Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 (looks at a patient's ability to care for themselves and daily activity level).

These risk factors help identify if the patient is:

- Low-risk (0-1 factors);
- Low/intermediate-risk (2 factors);
- Intermediate/high-risk (3 factors);
- High-risk (4-5 factors).

Treatment Options

Since DLBCL can grow quickly, it usually requires immediate treatment. Certain prognostic factors such as IPI factors (age, LDH, and Ann Arbor stage), along with tumor size and extranodal involvement, can be used to determine the best treatment option.

Overall, DLBCL is very sensitive to chemotherapy, so it is used as the first-line of treatment, and it is often successful. A combination of chemotherapy and the antibody therapy drug rituximab, with or without radiation therapy, can be curative for a good proportion of patients.

The standard of care therapy for first-line treatment for DLBCL patients is:

- **R-CHOP** (rituximab [Rituxan], cyclophosphamide, doxorubicin [Hydroxydaunorubicin], vincristine [Oncovin], prednisone)

Other options based on the stage of disease and patient factors can include:

- **R-EPOCH** (rituximab [Rituxan], etoposide, cyclophosphamide, doxorubicin [Hydroxydaunorubicin], vincristine [Oncovin], prednisone)
- **R-CEOP** (rituximab [Rituxan], cyclophosphamide, epirubicin, vincristine [Oncovin], prednisone).

These drugs are typically administered intravenously (into a vein) which is performed in the hospital. A central-line, which is a catheter placed in a large vein, can be used to administer chemotherapy drugs and draw blood for testing. The chemotherapy is usually given in cycles of 2 to 4 weeks. A cycle includes the treatment days and a period of rest and healing. The number of cycles you receive (called the 'course' or 'regimen') depends on your disease and the recommendation of your medical team based on your test results. Most patients will be able to receive their treatment as an out-patient, which means you will not have to stay in the hospital overnight.

If you have a DLBCL subtype that is more difficult to treat, your doctor may recommend a more intensive chemotherapy regimen using other drugs like methotrexate, etoposide and cytarabine. Your chemotherapy regimen may also be changed by your doctor if they feel you are not well enough to tolerate the side effects of the drugs, or if you have other conditions that may further compromise your health.

After your course of chemotherapy, you may receive radiation therapy to the areas affected by the lymphoma. This is often used following treatment with R-CHOP chemotherapy. In some cases, radiation therapy without chemotherapy is used, but this is rare.

For some types of DLBCL, intrathecal chemotherapy may be used to try to destroy lymphoma cells that may have spread to the brain and spinal cord. Intrathecal chemotherapy involves an injection of CNS prophylaxis, a preventative drug, directly into the cerebrospinal fluid (CSF) in your spine. The chemotherapy is injected directly into the CSF through a lumbar puncture (spinal tap). The drug often used for intrathecal chemotherapy is methotrexate.

For some patients, the initial treatment is effective and the DLBCL does not return after treatment; however, for patients in whom the disease becomes refractory (does not respond to treatment) or relapses (returns after treatment), further therapies may be required. These therapies can range depending on your age and other health factors. The standard of care for patients in the relapsed/refractory setting is to receive an autologous stem-cell transplant, where you are treated with high-dose chemotherapy followed by an infusion of your own stem-cells. **Chimeric Antigen T-Cell Therapy (CAR-T)** is a type of immunotherapy given in the relapsed/refractory setting. This treatment involves the extraction of a patient's immune cells (in particular the T cells) that are then changed in a laboratory so that they will specifically attack the patient's lymphoma cells when re-infused. Other therapies can include supportive care and conventional salvage therapy. Salvage therapies may include singe-agent therapies such as bendamustine [Treanda] or gemcitabine [Gemzar]), multi-agent therapies such as **DHAP** (dexamethasone, cisplatin, cytarabine), **ICE** (ifosfamide, carboplatin, etoposide), **GDP** (gemcitabine, dexamethasone, cisplatin), **CEPP** (cyclophosphamide, etoposide, prednisone, procarbazine) and **MEP** (mitomycin C, etoposide, cisplatin), and targeted drug therapies (such as polatuzumab vedotin [Polivy]). A patient may require multiple lines of therapy if their lymphoma relapses or is refractory to their previous treatment(s).

Patients with relapsed or refractory DLBCL are often encouraged to participate in clinical trials so that they can receive newer treatments that are not yet on the market. Clinical trials are crucial for establishing more effective, less toxic treatments for patients. You should consult your medical team for more information on whether a clinical trial is an appropriate treatment option for you.

Treatment Side Effects

Many people may be frightened to learn that there can be side effects associated with the therapies they may take to treat their lymphoma. However, it is important to understand that:

- Not all patients who receive therapy experience side effects;
- Side effects are not always severe, they can be mild;
- Different therapies have different side effects;
- There are many effective treatments that can reduce side effects or prevent them from happening altogether.

Some of the most common side effects of chemotherapy include decreased blood cell production (myelosuppression), fatigue, vomiting, diarrhea, loss of appetite, change in taste, hair loss, "chemo-brain" (cognitive impairment(s) that cause difficulties with concentrating and remembering) and peripheral neuropathy (affects nerve endings causing tingling and numbness).

Most side effects are short-lived, but some can last for a few weeks or months after treatment has finished. Occasionally, side effects can be permanent. Some side effects can start long after treatment has finished. These are called late side effects. Your doctor will talk to you about any potential side effects before you start treatment.

Depending on the side effects you experience and how strongly you feel them, you might not be able to maintain your usual level of activity during and following treatment. You may need to set aside more time for rest and healing. Additionally, depending on the severity of your side effects related to a therapy, your doctor may suggest to stop your treatment and can change your treatment to one that may not cause as many, or any, side effects.

Follow-Up Care

Once you have completed active treatment, you will likely be given a follow-up care plan to monitor your response and recovery as well as to watch for late effects (side effects that develop months or years after treatment) or a potential recurrence. Follow-up care for your DLBCL is often shared between your cancer specialists and your family doctor. Your medical team will work with you to decide on the correct follow-up care plan to meet your needs.

Follow-up care after treatment is an important part of your cancer care. It is very important to go to all of your follow-up appointments. Your schedule of visits and the tests and procedures that you will undergo during your follow-up are tailored to your individual lymphoma.

Your doctor will also tell you to watch for specific signs or symptoms of relapse or recurrence. Relapse is most likely to happen within two years following the completion of your first treatment. As time goes on, your lymphoma is less likely to relapse. Doctors may perform additional testing including blood tests and scans to check if your lymphoma has relapsed.

Use the time during your follow-up appointments to talk to your medical team about any changes or problems you notice and any questions or concerns you may have about your health after treatment. If you notice any change in your signs and symptoms between follow-up appointments, be sure to contact your medical team right away.

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For more information please visit lymphoma.ca or call 1-866-659-5556, or email us at info@lymphoma.ca.

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