UNDERSTANDING
Double-Hit Lymphoma (DHL)

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 double-hit lymphoma (DHL) 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)

DHL is a type of NHL. NHLs are approximately eight times more common than HL – 85% of all lymphomas are NHLs. 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.

NHLs are further sub-categorized by 'grade':

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

DHL is an aggressive lymphoma. Aggressive lymphomas develop more rapidly than indolent lymphomas. Patients with aggressive lymphoma usually experience symptoms from the onset of their disease and often require immediate, intensive treatment. Indolent lymphomas, however, develop more slowly than 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.

Genes are created from the combination of DNA and function as a unit of heredity. There are many genes that make up a chromosome. A gene mutation can be caused by abnormal changes of the DNA within a gene or between genes. A type of mutation called a rearrangement causes part of one gene to switch with a part of another gene. Double-hit lymphoma describes patients whose lymphoma cells have rearrangements in two specific genes (*MYC, BCL2* and/or *BCL6* genes). If rearrangements are present in all three genes (*MYC, BCL2,* and *BCL6*) the condition is called "triple-hit lymphoma."

In regards to gene mutations, DHL shares many features with diffuse large B-cell lymphoma (DLBCL). These lymphomas share similar rearrangements of the *MYC, BCL2* or *BCL6* genes. Approximately 5-8% of DLBCLs are double- or triple-hit lymphomas. However, DHL cells do differ in shape and form (morphology) from DLBCL cells, and not all DLBCL cells have both gene rearrangements. Identifying DHLs from other B cell lymphomas can be difficult and testing is often complex.

DHL 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 DHL?

DHL is a relatively rare type of lymphoma. DHL usually affects older adults but it can also affect any age group including young adults and children. It occurs both in men and women, although it is slightly more common in men.

People who have a compromised immune system due to either an autoimmune disorder or disease, such as the Epstein Barr virus or HIV/AIDS, or an organ transplant, may have a higher risk of developing DHL than the general population. However, the risk is still low. Most people with these conditions will not develop lymphoma and most cases of DHL are not related to an underlying immune disorder.

Symptoms

You may experience other symptoms depending on where the lymphoma cells are located. For instance, if the lymphoma is present within your chest, you may experience a cough or breathlessness and difficulty swallowing. If it develops in your abdominal region, you may experience abdominal pain, gastrointestinal bleeding, nausea and/or diarrhea. If the bone marrow is affected, this may cause symptoms associated with anemia (low red blood cell levels) or thrombocytopenia (low platelet levels). If the DHL spreads to the central nervous system (CNS), you may experience confusion, difficulty remembering, and hearing or visual impairment.

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.

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 DHL. A tissue biopsy is needed to confirm your diagnosis of DHL. 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). Molecular tests (such as fluorescence in situ hybridization [FISH] or immunohistochemistry [IHC]) may be performed on the tissue sample, allowing doctors to check for gene rearrangements in chromosomes. This type of biopsy procedure can usually be performed under local anesthetic.

Other tests may also be performed to help you and your doctor understand all aspects of your diagnosis. Because DHL 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 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. DHL is staged based on the findings from your clinical examinations. Knowing the stage of your lymphoma helps your doctor determine the extent of your disease and monitor its progression over time.

Your DHL 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 extranodal 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)

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 DHL. 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.

INTERNATIONAL PROGNOSTIC INDEX (IPI)

If you have DHL, 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 their 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 DHL can grow quickly, it usually requires immediate treatment. The purpose of DHL treatment is usually to cure the lymphoma. The most common treatment for DHL is intensive chemotherapy, which often involves the combination of multiple chemotherapy drugs. Chemotherapy is additionally used in combination with an antibody therapy, specifically with the monoclonal antibody rituximab in many cases.

Some commonly used chemotherapy regimens include:

- **DA-EPOCH-R** (dose-adjusted etoposide, prednisone, vincristine [Oncovin], cyclophosphamide, doxorubicin [Hydroxydaunorubicin], plus rituximab [Rituxan])
- **R-Hyper-CVAD (**rituximab [Rituxan] plus hyperfractionated cyclophosphamide, vincristine [Oncovin], doxorubicin [Hydroxydaunorubicin], and dexamethasone, methotrexate, cytarabine)
- **R-CODOX-M/R-IVAC** (rituximab plus cyclophosphamide, vincristine [Oncovin], doxorubicin [Hydroxydaunorubicin], methotrexate, alternating with rituximab [Rituxan] plus ifosfamide [Ifex], etoposide, and cytarabine)
- **R-CHOP** (rituximab plus cyclophosphamide, doxorubicin [Hydroxydaunorubicin], 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, may 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 treatment days followed by a period of rest and healing. The number of cycles you receive (called the 'course' or 'regimen') depends on the recommendation of your medical team based on your test results. Many patients will be able to receive their treatment as an out-patient, which means you will not have to stay in the hospital overnight.

After your course of chemotherapy, you may have radiation therapy to the area(s) affected by the lymphoma. In some patients, chemotherapy may be followed by either an autologous stem-cell transplant (infusion of the patient's own stem-cells) or an allogeneic stem-cell transplant (infusion of stem-cells from a healthy donor).

Patients with DHL have a higher risk of extranodal involvement including the spread of lymphoma cells to the central nervous system (CNS). To reduce this risk, patients may receive CNS prophylaxis, which is a preventative treatment. Intrathecal chemotherapy which is a therapy given directly to the brain and spinal cord through the cerebrospinal fluid (CSF) in your spine, is a type of prophylaxis that may be used to treat or prevent the spread of lymphoma cells to the CNS. The chemotherapy is injected directly into the CSF through a lumbar puncture (spinal tap).

For some patients with DHL, the initial treatment may be effective at curing your lymphoma. 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 include supportive care, conventional salvage chemotherapies, and stem-cell transplantation. Chimeric Antigen Receptor T-cell therapy, or CAR-T therapy, is another treatment that may be used to treat DHL. CAR-T therapy is a type of immunotherapy that uses genetic engineering to alter a patient's own T cells to better detect and destroy the lymphoma. The choice of therapy will depend on your age and other health factors. 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 DHL 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 drug, 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 DHL 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, such as a swelling of the lymph nodes and/or "B symptoms". Relapse is most likely to happen within two years following the end of your first treatment. As time goes on, your lymphoma is less likely to relapse. Doctors may perform additional testing including blood tests and imaging 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.