UNDERSTANDING
Hodgkin Lymphoma (HL)

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 Hodgkin lymphoma (HL) 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)

One of the main differences between HL and NHL is the presence of Reed-Sternberg (R-S) cells, detected under a microscope. R-S cells are typically present in Hodgkin lymphoma and are absent in Non-Hodgkin lymphoma. R-S cells are formed when abnormal B cells double some of their genetic material (units of heredity), but fail to divide properly into two cells. R-S cells are therefore abnormally large cells that do not function properly. Having R-S cells alone does not necessarily mean that a person has HL. To confirm a diagnosis, the lymphatic tissue must also contain other cells and features that are characteristic of HL.

Hodgkin lymphomas are less common than NHL – approximately 15% of all lymphomas are HL. In Canada, about 1000 people are diagnosed with HL each year.

HL originates in the lymph nodes (nodal sites) and can spread through lymphatic vessels to other lymph node regions throughout the body. Organs or tissues other than the lymph nodes (called extranodal sites) can also be affected.

Who gets HL?

People at any age can get Hodgkin Lymphoma. However, those between the ages of 15-35 years and 55 years and older, are more likely to develop HL. It is more commonly observed in males than in females.

Individuals with a weakened immune system caused by an inherited condition or those that are using immunosuppressive drugs (such as those taken to prevent organ transplant rejection) are at a greater risk of developing HL. Additionally, there are certain viruses, such as the Epstein-Barr virus, that can increase the risk for developing HL. However, most people with these risk factors do not develop HL, while others without these risk factors can develop this type of lymphoma.

Types of HL

There are two main types of HL which are classified based on what the cells look like under a microscope:

1. CLASSICAL HODGKIN LYMPHOMA (CHL)

cHL is the most common type of HL. About 95% of all HL cases are classical HL which can be further subdivided into four subtypes:

- **Nodular Sclerosis:** This is the most common subtype making up about 60-70% of all HL cases. It develops most frequently in young adults aged 15-35 years. This lymphoma mostly affects lymph nodes of the neck and chest, and the lymph nodes often contain scar tissue. Patients commonly present with bulky nodes. Nodular sclerosis is highly curable.
- **Mixed cellularity:** About 25% of patients have this subtype of HL. This type of HL most often develops in those with existing infections or viruses. In this subtype, lymph nodes contain many Reed-Sternberg cells mixed with other types of cells. It primarily affects those over the age of 55 years. It is commonly found within the abdomen.
- **Lymphocyte-Rich:** About 4% of patients have this subtype of HL. Normal lymphocytes are abundant in this subtype and there are very few abnormal cells and Reed-Sternberg cells. It is usually diagnosed at an early stage in adults aged 40 to 50 years. It mostly affects lymph nodes of the neck and armpits. This disease has a low rate of relapse or recurrence.
- **Lymphocyte-Depleted:** This is the least common subtype making up about 1% of all HL cases. It occurs most frequently in the elderly or those affected by HIV/AIDS. In this subtype, there are very few normal lymphocytes and many Reed-Sternberg cells. It mainly affects lymph nodes within the abdomen and tends to be a more aggressive subtype of cHL.

2. NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA

Nodular lymphocyte-predominant Hodgkin lymphoma is rare, affecting about 5% of patients diagnosed with HL. It is usually diagnosed at an early stage in people aged under 35 years. This subtype is often found in the lymph nodes of the neck, and it is typically not very aggressive (i.e. grows slowly). Most of the lymphocytes in the lymph nodes are not cancerous and typical Reed-Sternberg cells are absent; however, abnormal B cells (sometimes called 'popcorn cells') can be found.

There are also some patients where their test results reveal cancer cells that do not fit into either of these subtype categories of HL. In these cases, a patient's HL is then described as **Hodgkin lymphoma unclassifiable.**

Symptoms

The most common symptom of Hodgkin lymphoma is a painless swelling in the neck, armpit 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. These nodes may grow or change shape over time. Sometimes, lymph nodes may become painful for a few minutes after the consumption of alcohol.

Often, lymph nodes in the chest will swell. These may not be visible in appearance from the surface of the body but can cause symptoms such as coughing and breathlessness. Other more common regions where lymph node swelling can occur includes lymph nodes of the abdomen and spleen.

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).

Patients can also experience other symptoms including fatigue, itchy skin and loss of appetite. Depending on where the HL is located throughout the body, there may be additional symptoms. For instance, if it develops within your chest, you may experience a cough, breathlessness and/or difficulty swallowing. If it develops within your abdominal region, you may experience abdominal pain, gastrointestinal bleeding, nausea and/or diarrhea. It is important to note however, that many patients with HL do not experience any symptoms.

Diagnosis

A diagnosis of HL is typically confirmed by a lymph node biopsy. This type of biopsy involves removing a sample of tissue (cells) from the lymph node. 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 under local anesthetic.

Other tests may also be performed to confirm your diagnosis. Because HL 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, positron emission tomography (PET) scan, and/or magnetic resonance imaging (MRI) scan. A bone marrow biopsy may also be performed to look for the presence of lymphoma cells in the bone.

Staging

Staging describes a cancer based on how much cancer is in the body and where it is located when first diagnosed. HL 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 HL 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 HL. 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.

Your doctor may determine your prognosis (outcome and survival) based on several risk factors and the stage of your disease.

Early stage HL (stages I & II) is classified as favourable or unfavourable based on the following factors:

- B symptoms;
- Presence of a large mediastinal (chest) mass;
- Spread of lymphoma to areas other than the lymph nodes (extranodal);
- Spread of lymphoma to several lymph node areas;
- Erythrocyte sedimentation rate (ESR) of 50mm/h or higher in people who do not have B symptoms, or an ESR of 30 mm/h or higher in people who have B symptoms. Normally the ESR is slow; a higher than normal ESR may indicate inflammation.

Some International Prognostic Score (IPS) factors used for advanced HL may also be used to determine the prognosis of a patient with early-stage HL. If a patient does not have any of the above factors, their HL is considered favourable. If they have one or more of these factors, their HL is considered less favourable and can impact your prognosis.

Advanced stage HL (stages III & IV) is classified using the International Prognostic Score (IPS), which is a clinical tool developed by oncologists to aid in predicting the prognosis (outcome and survival) of patients with this type of lymphoma. Points are assigned to each of the following IPI risk factors:

- Ann Arbor Stage IV;
- Age 45 years or older;
- Male sex;
- Hemoglobin levels ≤ 105 g/L;
- Albumin levels ≤ 40 g/L;
- White blood cell count ≥ 15,000/mm^3;
- Lymphocyte count ≤ 600/mm^3 or < 8% of the total white blood cell count.

The more of the above factors that you have, the less favourable your prognosis may be.

Treatment Options

Treatment for Hodgkin lymphoma is usually very successful; over 80% of HL patients are cured following their first line of therapy. Most patients respond well to treatment regardless of the type of Hodgkin lymphoma subtype they have. An important consideration in choosing the best treatment option for a patient is how widely the lymphoma has spread throughout their body (i.e., the stage of the disease) and the presence of the prognostic factors listed above. Patients with advanced stage or more unfavourable prognostic factors may require different therapy.

The most common first-line treatment for early-stage HL is chemotherapy, usually in combination with radiation. Radiation therapy can be used following a short course of chemotherapy to improve the chance having a complete and curative response to treatment, or in cases where there is a concern that the lymphoma will persist following chemotherapy. Patients with advanced disease are mainly treated with combination chemotherapy as their first-line treatment, which can include:

- **ABVD** (doxorubicin [Adriamycin], bleomycin, vinblastine [Velbe], dacarbazine [DTIC]) with or without brentuximab vedotin (Adcentris).
- **BEACOPP** (bleomycin, etoposide, doxorubicin [Adriamycin], cyclophosphamide, vincristine [Oncovin], procarbazine, prednsione).

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.

For most patients with HL, the initial treatment is effective. 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 chemotherapies or other drug treatments such as brentuximab vedotin (Adcentris) or pembrolizumab (Keytruda), autologous stem-cell transplantation (infusion of your own stem-cells), radiation therapy, or newer drugs available through a clinical trial. The choice of therapy will depend on your stage of disease 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 HL 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 to treatment 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 HL 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.

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.