UNDERSTANDING
Follicular Lymphoma (FL)

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 follicular lymphoma (FL) 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)

FL is a 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.

NHLs are further sub-categorized by 'grade':

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

FL is an indolent lymphoma. Indolent lymphomas develop more slowly than aggressive lymphomas. Patients with indolent lymphoma usually do not show symptoms until later, often as the disease progresses, and may therefore not require immediate treatment. Aggressive lymphomas on the other hand develop much more rapidly. Patients with aggressive lymphomas will usually experience symptoms from the onset of the disease and may require immediate and more intensive treatment.

Follicular lymphoma gets its name because the cancerous lymphocytes often collect in lymph nodes forming circular clusters and creating a growth pattern that looks like follicles. These circular clusters are made up of centrocytes (small to medium sized cells) and centroblasts (large cells). The aggressiveness of your FL will increase when there is a higher number of centroblasts present.

FL usually develops in the lymph nodes and can often spread to other lymph nodes throughout the body or to the bone marrow by the time it is diagnosed. It is less common for it to spread to other organs. Some patients may experience a waxing and waning (on and off) of lymphadenopathy (swelling of the lymph nodes) for many years before a diagnosis is made.

FL can transform (change) into a more aggressive form of NHL, usually a diffuse large B-cell lymphoma (DLBCL). This type of transformation can be caused by a type of genetic mutation (abnormal change in genes, a unit of heredity) called a translocation. A translocation is a switch of genetic material between two different chromosomes. This leads to an abnormal change in the function a protein (BCL2), preventing cell death and causing an accumulation of abnormal cells. This specific mutation is found in about 85% of FL patients that experience a transformation.

Who gets FL?

Follicular lymphoma is the most common subtype of indolent NHL, accounting for 20% to 30% of all NHLs. FL typically affects middle-aged or older adults, and usually occurs in people aged 50 years or older. It is rarely diagnosed in very young people. FL is slightly more common in women than in men.

Symptoms

Since FL is an indolent lymphoma, symptoms develop gradually as the disease progresses. Patients with FL may experience very few symptoms or none at all. The most common symptom of FL is a painless swelling in the neck, armpit or groin region(s) caused by enlarged lymph nodes. Patients may also experience fatigue, loss of appetite, or itchy skin.

Patients with lymphoma may also experience what are called **B symptoms**, however this is less common in FL. 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

A diagnosis of follicular lymphoma 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 FL 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, and sometimes a spinal tap (lumbar puncture) may be performed to determine if there are lymphoma cells in the spinal fluid.

If a transformation to a more aggressive form of NHL is suspected, you may undergo additional testing such as a lymph node biopsy to confirm.

Staging

Staging describes a cancer based on how much cancer is in the body and where it is located when first diagnosed. FL 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 FL 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. Most people have advanced stage FL when they are first diagnosed.

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)

Follicular lymphoma may also be given a grade based on the amount of centroblasts (large cells) per high power field (HPF) are present within FL tumours. Tumours with more centroblasts may have a more aggressive clinical behaviour. Grade 1 (0–5 centroblasts per HPF) and grade 2 (6–15 centroblasts per HPF) tumours are considered to be low grade. Grade 3 (>15 centroblasts) can be further subdivided into grade 3A (centrocytes (small cells) are present) and grade 3B (follicles consist almost entirely of centroblasts). Grade 3A FL can behave as a low-grade lymphoma, but grade 3B often behaves as an aggressive lymphoma.

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 FL. 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.

FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI)

Your doctor may also give you a prognostic score using the Follicular Lymphoma International Prognostic Index (FLIPI). The FLIPI is a clinical tool developed by oncologists to aid in predicting the prognosis (outcome and survival) of patients with FL.

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

- Age 60 years and older;
- Ann Arbor stage III/IV;
- More than four nodal sites affected;
- Serum lactate dehydrogenase (LDH) level above normal;
- Hemoglobin level <120 g/L.

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

Treatment for follicular lymphoma depends on the stage of the lymphoma. Patients who are diagnosed at an early stage (stage I or II) may not require immediate treatment and will instead undergo a 'watch and wait' approach where treatment is not required until the disease progresses and certain symptoms develop. If a patient requires treatment, they may receive radiation therapy or chemotherapy. Local radiation therapy often produces excellent results in stage I patients, with remission lasting longer than 10 years in 50% of patients.

Patients who are at a later disease stage (stage III or IV) at the time of diagnosis, but who are not experiencing symptoms, can also undergo the 'watch and wait' approach with very close monitoring.

WHAT IS 'WATCH & WAIT'?

Many people newly diagnosed with FL may not require immediate anti-cancer treatment. FL often progresses slowly and may not cause any problems for a period of time. Therefore, instead of receiving immediate treatment, patients will be regularly monitored by their oncologist for months or years until the cancer changes and treatment is considered necessary. This approach is called 'watch and wait', 'watchful waiting' or 'active surveillance'. Watch and wait is a standard treatment approach for those who have no symptoms, and additionally lets you avoid harmful treatment related side effects when treatment may not be necessary.

Once a patient has been treated, the watch and wait phase will start again, and their oncologist will begin to monitor them for a potential return of their cancer. Throughout the watch and wait period, your doctor will ask you whether you notice any changes in your current symptoms or if you are experiencing any new symptoms. They may also perform a physical examination, blood tests, and imaging scans to assess your response to treatment.

Some patients are concerned about the watch and wait approach and would rather receive immediate treatment following their diagnosis. Clinical trials for early-stage or slow-growing stable cancers have compared the watch and wait approach with immediate treatment. These trials have shown that patients that are monitored through watch and wait do as well or better than those given treatment immediately when treatment is likely to not improve outcomes or survival, and instead cause harmful or toxic side effects.

Once symptoms (such as B symptoms) begin to occur, the most common treatments include:

- Combination chemotherapy such as **CVP** (cyclophosphamide, vincristine [Oncovin], prednisone) or **CHOP** (cyclophosphamide, doxorubicin, vincristine [Oncovin], prednisone)
- Combination chemotherapy with **Bendamustine** and **Rituximab (Rituxan)**
- Single-agent chemotherapy such as **Chlorambucil**
- Radiation therapy

Some patients who have responded to their initial treatment may receive prolonged treatment with rituximab, called rituximab **maintenance therapy**. This means that patients who have received treatment for FL and have achieved remission (complete or partial disease response to treatment) may benefit from a longer remission by receiving rituximab monotherapy (generally administered every three months for a period of two years). Maintenance therapy has been shown to sustain the response obtained from the initial therapy and can improve survival for patients with FL.

Follicular lymphoma tends to be very sensitive to both chemotherapy and radiation, leading to a positive and long-lasting disease response. However, for patients in whom the disease becomes refractory (does not respond to treatment) or relapses (returns after treatment), further therapies may be required. Therapies may include the monoclonal antibody obinutuzumab in combination with chemotherapy, autologous stem-cell transplant (infusion of a patient's own stem-cells), or newer drugs available through a clinical trial. 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 FL 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.

Transformation

Some patients with follicular lymphoma can have their lymphoma change into a more aggressive lymphoma, often referred to as a **histologic transformation**. A transformed lymphoma is one that was initially diagnosed as indolent (slow-growing), such as FL, but then later develops into an aggressive (fast-growing) disease. There are certain signs and symptoms that may suggest that your FL is undergoing a transformation to a more aggressive NHL. These include fast growing lymph nodes, new extranodal sites (such as in the central nervous system, liver, bone), presence of B symptoms, or high blood levels of calcium or lactate dehydrogenase (LDH). If you experience any of these signs or symptoms, consult with your doctor. As transformed lymphomas are more aggressive in their behavior, they can require different treatments than what you may have received previously for your FL.

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 FL 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.

During follow-up, your doctor will tell you to watch for specific signs or symptoms of relapse, recurrence or transformation.

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.

YOU DON'T HAVE TO FACE LYMPHOMA ALONE.

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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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