UNDERSTANDING
Lymphoplasmacytic Lymphoma (LPL)/ Waldenstrom Macroglobulinemia (WM)

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 Lymphoplasmacytic Lymphoma (LPL)/ Waldenstrom Macroglubulinemia (WM) 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)

LPL/WM are 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.

NHL is further sub-categorized by 'grade':

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

LPL/WM are indolent lymphomas. 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.

Who gets LPL/WM?

LPL/WM is a rare form of B-cell lymphoma, making up 1% to 2% of all NHL cases. It typically affects older adults, with the average age at diagnosis being 60 years. LPL/WM incidence is highest amongst Caucasians.

Symptoms

LPL/WM lymphoma normally develops over a long period of time. You may experience no symptoms prior to diagnosis or at diagnosis, or the symptoms may not be obvious. As such, the disease is often found by chance when undergoing routine blood tests or clinical examinations for another reason.

Since LPL/WM lymphoma cells mainly develop and grow within the bone marrow, they can crowd out and disrupt the production of normal, healthy cells. Many of the symptoms that occur from your LPL/WM are a result of altered blood cell levels. Low levels of healthy red blood cells can lead to a condition called anemia, causing weakness and fatigue. Low levels of white blood cells (neutropenia) can make it difficult for the body to fight infection and can lead to a higher infection rate. A low platelet count, called thrombocytopenia, can cause increased bleeding and bruising.

Lymph nodes may also be enlarged as a result of LPL/WM. Enlargement of the spleen (splenomegaly) or liver (hepatomegaly) is also relatively common. This may cause the patient to experience bloating or fullness after eating only small amounts of food. It can also cause abdominal pain, diarrhea, and vomiting. Most patients with LPL/WM do not experience "B symptoms" which are a group of symptoms including fever, drenching night sweats and unexplained weight loss.

There are additional symptoms that may occur due to the high immunoglobulin (IgM) antibody level which is a defining feature of WM. There may be a thickening (hyperviscosity) of the blood when there is a high concentration of IgM antibody which can lead to problems with circulation and other symptoms such as visual impairment (blurred vision), dizziness, headaches, peripheral neuropathy (numbness or tingling in the feet, legs or hands), shortness of breath, hearing loss or confusion. High IgM levels can also lead to the development of a condition called cryoglobulinemia where blood proteins will clump together at decreased temperatures. The temperature of blood is warmest near the heart and decreases as it moves away from the heart to the limbs, reaching the lowest temperatures in the fingers and toes. With cryoglobulinemia, the blood temperature in the fingers and toes may be low enough to cause clumping which will reduce circulation and cause a bluish tinge or discoloration to these regions.

Diagnosis

Doctors will need the results of different tests to confirm if you have LPL/WM. This type of NHL may be initially suspected after an abnormal blood test. Other tests that will help to confirm the diagnosis can include a bone marrow biopsy, an ultrasound to determine whether the spleen or liver are enlarged and imaging scans such as a computed tomography (CT) scan to accurately visualize the cancer in the body. If a bone marrow biopsy is performed, 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.

IgM antibody levels can also be tested from a blood sample through a special blood test called "serum protein electrophoresis." This test can identify if all the IgM molecules are different (which is normal) or if they are all the same (also called "clonal", which is found in the case of WM).

Staging

Staging describes a cancer based on how much of the cancer is in the body and where it is located when first diagnosed. LPL/WM 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 LPL/WM can sometimes 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. Bone marrow involvement is common in LPL/WM, which would make the patient stage IV.

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 LPL/WM. 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 SCORING SYSTEM FOR WALDENSTROM MACROGLOBULINEMIA (IPSSWM)

Your doctor may give you a prognostic score using the International Prognostic Scoring System for Waldenstrom Macroglobulinemia (IPSSWM). The IPSSWM is a clinical tool developed by oncologists to aid in predicting the prognosis (outcome and survival) of patients with WM.

Except for age, one point is assigned for each of the following IPSSWM risk factors:

- Age 65 years and over;
- Hemoglobin level of 11.5 g/dL or less;
- Platelet count of 100,000 platelets/mcL or less;
- Beta-2 microglobulin (B2M) greater than 3 mg/L;
- Serum monoclonal protein concentration greater than 70 g/L.

These risk factors help identify if the patient is:

- Low-risk (under 65 and 0-1 factors);
- Intermediate-risk (age 65+ and/or 2 factors);
- High-risk (3+ factors).

Treatment Options

Treatment for LPL/WM can depend on whether you experience any symptoms. Asymptomatic patients (patients that do not experience any symptoms) may undergo a 'watch & wait' approach, where the patient does not receive immediate treatment but are closely monitored.

WHAT IS 'WATCH & WAIT'?

Many people newly diagnosed with LPL/WM may not require immediate anti-cancer treatment. LPL/WM 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.

Patients that experience symptoms or have high IgM levels and hyperviscosity of the blood, will usually require immediate treatment. Treatment options for LPL/WM patients can include:

- **Single agent chemotherapy** (e.g., chlorambucil, bendamustine, etc.), or combination chemotherapy (e.g., CVP [cyclophosphamide, vincristine, prednisone]).
- Combination of monoclonal antibody **rituximab (Rituxan)** and chemotherapy drugs (listed above).
- **Steroids** such as dexamethasone and prednisone.

Most of these drugs are 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 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.

LPL/WM is an incurable disease, however with treatment you can minimize the abnormal cells to make its presence almost non-existent within the body and limit the number of symptoms experienced. Most patients will relapse after initial therapy. For those 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 response to your first therapy, the length of time between your first therapy and your relapse, and your disease features. Autologous stem-cell transplant is an option for patients that are transplant eligible. For non-transplant eligible patients, options can include bendamustine and rituximab, bortezomib based therapies, ibrutinib or zanubrutinib, or dexamethasone, rituximab and cyclophosphamide. 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 LPL/WM 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 treatment. You might 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 may change your treatment to one that does not cause as many, or any, side effects.

Transformation

About 10% of patients with LPL/WM may have their lymphoma change into a more aggressive lymphoma, often referred to as histologic transformation. A transformed lymphoma is one that was initially diagnosed as indolent (slow-growing), such as LPL/WM, but then later develops into an aggressive (fast-growing) disease. Transformation will typically occur between 3-6 years after the lymphoma was initially diagnosed, however it can occur at any time. It is unlikely that a transformation will occur after 15 years from initial diagnosis. As transformed lymphomas are more aggressive in their behavior, they can require different treatments than what you may have received previously for your LPL/WM.

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 LPL/WM lymphoma 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 transformation. These signs and symptoms may include symptoms associated with altered blood cell levels and counts, swelling of the lymph nodes, and problems with circulation. If you begin experiencing B symptoms (fever, unexplained weight loss, and drenching night sweats), that may be a sign that your lymphoma has relapsed. Doctors may perform additional testing including blood tests and imaging scans to confirm if your lymphoma has relapsed or transformed.

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.