UNDERSTANDING
Chronic Lymphocytic Leukemia (CLL) & Small Lymphocytic Lymphoma (SLL)

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. Although chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are called leukemias, you can think of CLL and SLL as types of lymphoma rather than as types of leukemia because they behave and are treated like other lymphomas.

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.

CLL is very similar to SLL and the two are generally considered the same disease. The difference between CLL and SLL is where the cancer cells are located within the body. When most of the cancer cells are found in the blood stream and the bone marrow, it is called CLL. When the cancer cells are mostly found in the lymph nodes, it is called SLL. Both CLL and SLL are usually treated the same way.

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 CLL and SLL are B lymphocytes (B cells). B lymphocytes make antibodies to fight infections. They are called B cells because they mature in the bone marrow. With CLL and SLL, your body makes an abnormally high number of lymphocytes that do not work correctly.

CLL and SLL usually progress slowly. In many cases, it causes few, if any problems in its early stages. Some people may have CLL/SLL that is slow-growing (indolent) and can have stable disease for years with few or no symptoms. Other people with CLL may have a faster-growing (aggressive) form of the disease that may cause more symptoms and require treatment sooner.

You may be diagnosed with SLL first, but doctors may later start calling your condition CLL if the number of lymphocytes in your blood (white cell count) rises. This is nothing to be alarmed about and does not necessarily mean the disease has 'transformed' or changed to become more aggressive , but that the location of where the lymphoma cells are in your body has changed.

Who gets CLL?

CLL/SLL most commonly affects people over the age of 60 years, with the average age at diagnosis in the early seventies. It is rarely diagnosed in young people. CLL/SLL affects nearly twice as many men as women.

Although there is no known cause of CLL/SLL, those with a close relative with CLL/SLL are at an increased risk of developing this type of lymphoma. However, it is not an inherited disease and the risk of developing CLL is still low.

Some studies have also suggested that certain environmental factors might play a role in the development of CLL, including exposure to some chemicals (herbicides and insecticides), however more research is required to confirm this association.

Symptoms

Many patients with CLL/SLL have no symptoms when they are first diagnosed. CLL/SLL is often detected by chance during a routine blood test. As cancerous cells begin to build up in the body, patients will usually begin to experience more symptoms. Symptoms usually start off as mild and begin to worsen as more abnormal cells accumulate.

Patients with CLL/SLL often experience fatigue and a lack of energy as well as 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 appear in 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).

High numbers of cancer cells can gather in the lymph nodes or spleen, causing swelling in these areas. As the lymph nodes increase in size, they can become tender or uncomfortable. Often, lymph nodes in more than one area of the body, including the neck, armpit or groin regions, are affected. An enlarged spleen (splenomegaly) may cause patients to experience bloating or fullness after eating only small amounts of food. It can also cause abdominal pain, diarrhea, and vomiting.

Cancerous cells can also build up in your bone marrow. As the cancerous cells overpopulate and crowd out the normal healthy blood cells, this can cause anemia (low red blood cell levels), thrombocytopenia (low platelet counts) and/or neutropenia (low white blood cell counts). You may experience different symptoms related to these changes in blood count levels.

Since the immune system is also affected by this type of cancer, patients with CLL/SLL may be more prone to infection and/or have a difficult time fighting off infections.

Diagnosis

CLL is usually diagnosed after examining the results of various blood tests. A **complete blood count (CBC)** is a test that measures the total number of each type of blood cell within your blood. If there are a large number of lymphocytes in the blood, then CLL may be suspected. A **blood smear** examination, which looks at the shape of your blood cells, may then be performed to diagnose CLL. Another type of test called **flow cytometry**, which uses a machine to identify specific markers on cells, can also be used to see if the lymphocytes in your blood sample contain "CLL cells" which are large abnormally shaped lymphocytes.

For SLL, a diagnosis 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.

Doctors will additionally perform **molecular testing** to find out what type of chromosome abnormalities and genetic mutations (abnormal changes in genes which are units of heredity) are present in your CLL/SLL cells. The results of these tests help doctors to determine the best course of treatment. These tests can usually be performed with a blood sample. However, a bone marrow sample can also be used.

There are three types of molecular testing:

- **The FISH Test (fluorescent in situ hybridization):** The FISH test helps identify changes in the chromosomes of cancer cells by making them "fluoresce" or glow.
- **TP53 Test:** Results of this test show if the TP53 gene has a mutation.
- **IGHV Test:** This test determines if your IGHV (immunoglobulin heavy-chain variable region) gene is mutated or unmutated. People with unmutated IGHV status may have a more aggressive form of CLL.

For more information about molecular testing and what the results of these tests mean for your future treatment, please review the **Lymphoma Canada Molecular Testing Infographic**. Speak to your doctor about molecular testing to see if it is an option for you and to discuss when you should receive this test.

Other tests may also be performed to confirm your diagnosis. These can include a bone marrow aspiration (removal of a small amount of fluid and cells from the bone marrow), bone marrow biopsy (removal of a small amount of bone along with the fluid and cells from the bone marrow) 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.

Staging

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

Most doctors in North America use a system called the Rai Staging System to stage CLL. Either the classic or the modified version can be used. There is another staging system called the Binet Staging System, which is used in Europe.

Both systems categorize CLL patients into risk categories based on the:

- Number of lymphocytes found in the blood;
- Enlargement of the lymph nodes, liver and spleen;
- Number of platelets found in the blood;
- Number of red blood cells found in the blood.

CLASSIC RAI (Stage)	**MODIFIED RAI** (Risk Level)	**SIGNS AND SYMPTOMS**
0	**LOW**	• Too many lymphocytes in the blood; • Lymph nodes and spleen are not enlarged; • Normal numbers of red blood cells and platelets.
1	**INTERMEDIATE**	• Too many lymphocytes in the blood; • Lymph nodes are enlarged, liver and spleen are normal; • Normal number of red blood cells and platelets.
2	**INTERMEDIATE**	• Too many lymphocytes in the blood; • Lymph nodes may be enlarged, spleen and/or liver are enlarged; • Normal number of red blood cells and platelets.
3	**HIGH**	• Too many lymphocytes in the blood; • Lymph nodes, spleen or liver might be enlarged; • Low number of red blood cells (anemia); • Normal number of platelets.
4	**HIGH**	• Too many lymphocytes in the blood; • Lymph nodes, spleen or liver might be enlarged; • Normal or low numbers of red blood cells (anemia); • Low number of platelets (thrombocytopenia).

Your SLL 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 patients have advanced stage disease at diagnosis.

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 and provides a general idea of what to expect when a patient is diagnosed with CLL/SLL. 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.

CHRONIC LYMPHOCYTIC LEUKEMIA INTERNATIONAL PROGNOSTIC INDEX (CLL-IPI)

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

Points are assigned for each of the following CLL-IPI risk factors:

- Age 65 years and over (+1 point);
- Rai stage 1-4 (+1 point);
- Serum 2 microglobulin > 3.5 mg/L (+2 points);
- Unmutated IGHV genes (+2 points);
- Deletion 17p (FISH) and/or TP53 mutation (+4 points).

These risk factors help identify if the patient is:

- Low-risk (0-1 points);
- Intermediate-risk (2-3 points);
- High-risk (4-6 points);
- Very high-risk (7-10 points).

Treatment Options

CLL/SLL is not curable, and a person can live with it for many years. As such, it is often referred to as a chronic blood cancer. Treatment aims to keep the lymphoma under control for as long as possible and to reduce any symptoms that the patient may experience. Since CLL/SLL is typically slow-growing, many people will have stable disease for years with few or no symptoms. If this is the case, your doctors may suggest the 'watch and wait' approach. In this approach, instead of immediate treatment, patients will be regularly monitored by their oncologist or hematologist for months or years until symptoms develop and treatment is considered necessary.

WHAT IS 'WATCH & WAIT'?

Many people newly diagnosed with CLL/SLL may not require immediate anti-cancer treatment. CLL/SLL 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.

The decision to start treatment depends on whether you have signs and symptoms that are associated with progression of disease. Treatment indications can include the presence or worsening of B symptoms, an increased number or enlargement of existing lymph nodes, spleen enlargement, and/or worsening of blood cell counts. If your doctor decides that treatment is necessary, many factors are taken into consideration when deciding on a treatment option, including your age, overall health, molecular markers (important markers for CLL/SLL include del17p, TP53 mutation and IGHV mutation) and your personal preferences.

There are several different treatment options for CLL/SLL. Chemotherapy used in combination with antibody therapy is a common first-line treatment for CLL/SLL. Antibody therapies are drugs that restore, increase, or mimic the body's natural immune system to attack cancer cells. Most of these drugs are administered orally or intravenously (into a vein). The chemotherapy is usually given in cycles of 3-4 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 medical tests. Many patients will be able to get their treatment as an out-patient, which means you will not have to stay in the hospital overnight.

Various first-line treatment options are listed below. It is important for you and your medical team to discuss your treatment options together and determine the best option available for you. The level of fitness and health of the patient, as well as their molecular marker status, play an important role in determining the optimal treatment for a patient's CLL.

1. **For FIT Patients WITHOUT del17p or TP53 mutation, treatment options include:**
   - Fludarabine + cyclophosphamide + rituximab (FCR) (for patients with mutated IGHV)
   - Bendamustine + rituximab (BR) (for patients with mutated IGHV)
   - Ibrutinib (for patients with umutated IGHV)
2. **For UNFIT Patients WITHOUT del17p or TP53 mutation, treatment options include:**
   - Ibrutinib
   - Acalabrutinib with or without obinutuzumab
   - Chlorambucil with or without obinutuzumab
   - Bendamustine + rituximab
   - Venetoclax with obinutuzumab
3. **For All Patients WITH del17p or TP53 mutation, treatment options include:**
   - Ibrutinib
   - Acalabrutinib with or without obinutuzumab

For some patients with CLL/SLL, the initial treatment may be effective at controlling your CLL/SLL symptoms and you may not require further treatment. However, for patients where their disease becomes refractory (does not respond to treatment) or relapses (returns after treatment), further therapies may be required. In the same way that a first-line treatment is decided upon, doctors will take many factors into consideration when deciding an appropriate second-line or later line treatment. This can include your age, overall health, molecular markers and previous therapies used to treat your CLL. Your doctor may want to test your CLL again before starting your next round of treatment. Some treatment options for relapsed or refractory CLL/SLL may include:

1. **For Patients WITHOUT del17p or TP53 mutation, treatment options include:**
   - Venetoclax with or without rituximab
   - Ibrutinib
   - Idelalisib + rituximab
   - Chemoimmunotherapy (eg. FCR [fludarabine + cyclophosphamide + rituximab], BR [bendamustine + rituximab] or chlorambucil + obinutuzumab)
   - Clinical trial
2. **For Patients WITH del17p or TP53 mutation, treatment options include:**
   - Venetoclax with or without rituximab
   - Ibrutinib
   - Idelalisib + rituximab
   - Allogeneic stem-cell transplant (infusion of stem-cells from another person)
   - Clinical trial
   - Acalabrutinib

Other treatment options may include radiation therapy, or supportive therapies including antibiotics, antivirals, blood transfusions, infusions of immunoglobulins (IVIG), growth factors and more.

Patients with relapsed or refractory CLL/SLL 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 CLL/SLL. 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, infections, vomiting, diarrhea, loss of appetite, change in taste, hair loss, and "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 may 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.

Secondary Cancers and Transformation

A secondary cancer is a new cancer that is different from the CLL/SLL you were initially diagnosed with and treated for, and can develop after treatment for CLL/SLL. CLL/SLL patients are at a higher risk for developing other kinds of cancer. The most common secondary cancer among CLL/SLL patients is non-melanoma skin cancer, along with cancers of the digestive organs, prostate, breast, and lung. There is also a possibility of developing another type of blood cancer such as myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML).

Some patients with CLL/SLL may develop a **transformed lymphoma. Richter's Syndrome (RS)**, also known as Richter's Transformation, is a rare condition where your CLL/SLL will transform into a significantly more aggressive form of large cell lymphoma. It occurs in approximately 2-10% of all CLL/SLL patients and can occur at any point throughout the course of their disease. RS typically presents as a rapidly growing mass that is changing more quickly than the remaining indolent disease. A biopsy is required to confirm transformation. In most cases, the normally slow growing or indolent CLL/SLL transforms into a common type of Non-Hodgkin lymphoma known as diffuse large B-cell lymphoma (DLBCL). Rarer cases transform into Hodgkin lymphoma, and some types of T-cell lymphomas have also been reported. As transformed lymphomas are more aggressive in their behavior, they can require different treatments than what was previously used prior to the transformation.

It is very important to remain vigilant and attend all of your follow-up appointments during and after CLL/SLL treatment to monitor for the development of secondary cancers or transformed lymphoma.

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 CLL/SLL 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. CLL/SLL will relapse (come back) after treatment in most people. Your doctor will tell you to watch for specific signs or symptoms of relapse or recurrence such as "B symptoms", fatigue and swelling of the lymph nodes. 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.

YOU DON'T HAVE TO FACE LYMPHOMA ALONE.

Lymphoma Canada connects patients, their family and friends, medical professionals, researchers, volunteers and donors, to build a strong lymphoma community.

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

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