Understanding Lymphoma and
Chronic Lymphocytic Leukemia (CLL)

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Lymphoma Research Foundation

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are forms of *low-grade* (slow growing) non-Hodgkin lymphoma that develop from white blood cells called lymphocytes.

CLL and SLL are basically the same disease, with the only difference being the location of the primary cancer. In CLL, cancer cells are located in the bloodstream and the bone marrow (the spongy tissue inside the bone). In SLL, the cancer cells are located mainly in the lymph nodes (small bean-shaped structures that help the body fight disease, **Figure 1**). In many cases of CLL/SLL, cancer cells are located in the bloodstream, bone marrow, and lymph nodes.

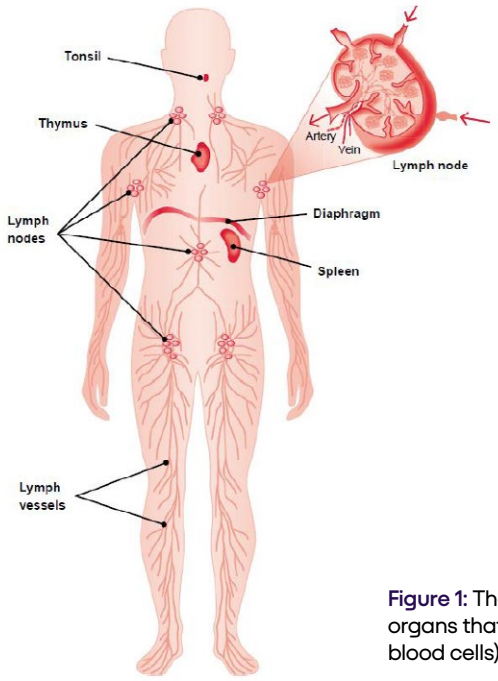

Figure 1: The lymphatic system (tissues and organs that produce, store, and carry white blood cells) and lymph nodes.

Many patients with CLL/SLL will live for years without any obvious symptoms. The disease might be detected during routine blood tests and/or a physical examination. Other patients may have symptoms that cause them to seek care from a doctor, and testing may lead to the diagnosis of CLL/SLL. Symptoms depend on the tumor location and may be mild.

The most common symptoms are:

- *fatigue* (extreme tiredness)
- shortness of breath
- bleeding or bruising easily
- bone pain
- night sweats
- weight loss
- frequent infections

Less frequent symptoms are often related to enlarged lymph nodes or spleen and may be discomfort and a feeling of fullness after eating small amounts.

Treatment Options

Treatment is based on the severity of symptoms. When patients show no or few symptoms, doctors may decide to monitor the patient without treating the disease. This approach is called *active surveillance*, or *watchful waiting*. In this case, patients' overall health and disease are monitored through regular check-up visits that may include laboratory tests (like a complete blood cell count) and physical examinations (like checking for any swelling). Sometimes, patients experience symptoms due to low red blood cell count (anemia). If patients begin to have symptoms or signs of disease progression, treatment is then prescribed.

There are many current *frontline* (initial) treatment options for CLL/SLL. Treatments might differ in the presence of certain *mutations* (permanent changes in the DNA [deoxyribonucleic acid, the molecule that carries genetic information inside the cell]). An oncologist (doctor who specializes in treating cancer) or hematologist (doctor who specializes in treating blood cancers and other blood disorders) will run a variety of tests to confirm a person's diagnosis and decide the appropriate treatment, if needed. The patient's age, health status, and the benefits versus side effects of treatment are also considered for treatment decision. To learn more about how doctors establish a treatment plan for CLL/SLL, please view the *Understanding Lymphoma and CLL guide* on the Foundations website (lymphoma.org/publications).

Newer drugs and combinations have shown excellent activity in patients with all sorts of disease characteristics. Treatments for newly diagnosed CLL/SLL include:

- Targeted therapies (drugs that target molecules that cancer cells use to grow and spread). These include inhibitors of proteins involved in cell signaling and growth like kinases (such as acalabrutinib, zanubrutinib, and ibrutinib) and B-cell lymphoma-2 (venetoclax). Patients seeking information about targeted therapy and immunotherapy should view the *Immunotherapy and Other Targeted Therapies* fact sheet on the Foundation's website (lymphoma.org/publications).
- Immunotherapy (drugs that help the body's immune system fight cancer), including monoclonal antibodies (a protein made in the laboratory that binds to cancer cells and helps the immune system destroy them) such as obinutuzumab (Gazyva) and rituximab (Rituxan).
- Chemotherapy (drugs that stop the growth of or kill cancer cells).
- Chemoimmunotherapy which is a combination of chemotherapy (drugs that stop the growth of or kill cancer cells) with immunotherapy (drugs that use the body's immune system to fight cancer), such as FCR (fludarabine [Fludara], cyclophosphamide [Cytoxan], rituximab [Rituxan]), GC (obinutuzumab [Gazyva] and chlorambucil [Leukeran]), and BR (bendamustine [Belrapzo/Bendeka/Treanda], and rituximab [Rituxan]).

Common drugs or drug combinations for newly diagnosed CLL/SLL include:

- Venetoclax (Venclexta) +/- obinutuzumab (Gazyva)
- Acalabrutinib (Calquence) +/- obinutuzumab (Gazyva)
- Zanubrutinib (Brukinsa)
- Ibrutinib (Imbruvica) +/- rituximab (Rituxan)
- Ibrutinib (Imbruvica) and obinutuzumab (Gazyva)

Occasionally, patients might also be treated with chemotherapy. Chemotherapy plays a limited role in the treatment of CLL nowadays. Treatment decisions depend on specific patient factors, like the ones mentioned above, and should be discussed extensively with the patient's physician, ideally one that specializes in CLL. There are other combinations of treatments that may be suggested. These include chemoimmunotherapy and/or immunotherapy regimens, like the ones listed below:

- FCR (fludarabine [Fludara], cyclophosphamide [Cytoxan], rituximab [Rituxan])
- GC (obinutuzumab [Gazyva] and chlorambucil [Leukeran])
- BR (bendamustine[Belrapzo/Bendeka/Treanda] and rituximab [Rituxan])
- Rituximab (Rituxan) or obinutuzumab (Gazyva) with corticosteroids such as dexamethasone and prednisone
- Obinutuzumab (Gazyva)

For patients who *relapse* (disease returns after treatment) or patients whose disease becomes *refractory* (does not respond to treatment), different therapies may result in improved treatment outcomes. Patients seeking information about relapsed/refractory disease should view the *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Relapsed/Refractory* fact sheet on the Foundation's website (lymphoma.org/publications).

The following are common therapeutic regimens for relapsed/refractory CLL and SLL:

- Targeted therapies that can be combined with the monoclonal antibody Rituximab (Rituxan):
  - Ibrutinib (Imbruvica)
  - Acalabrutinib (Calquence)
  - Venetoclax (Venclexta) +/- rituximab (Rituxan)
  - Zanubrutinib (Brukinsa)
  - Pirtobrutinib (Jaypirca)
  - Idelalisib (Zydelig) and rituximab (Rituxan)
  - Duvelisib (Copiktra)
- Stem cell transplantation (SCT, the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells)
  - Allogeneic SCT (cells donated from a living donor)

An allogeneic SCT is a potentially curative option. However, most patients will do well with newer treatments that avoid the risk of complications of transplants. For more information on allogeneic SCT, view the *Understanding Cellular Therapy* publication on the Lymphoma Research Foundation's website at lymphoma.org/publications.

In addition, a special type of immunotherapy called chimeric antigen receptor (CAR) T cell therapy, uses patients' own immune cells to treat their cancer. In 2024, a CAR T-cell therapy called lisocabtagene maraleucel (Breyanzi) was approved by the FDA for treatment of CLL/SLL. Several other CAR T cell therapies are in development for patients with CLL/SLL. For more information on CAR T cell therapy, view the *Understanding Cellular Therapy* guide on the Lymphoma Research Foundation's website at lymphoma.org/publications.

Various other treatments are available or in development and should be discussed with your physician and/or a physician specialized in CLL.

Treatments Under Investigation

Many new treatments (also referred to as investigational drugs) and combinations are currently being tested in clinical trials for patients with newly diagnosed or previously treated CLL/SLL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). Table 1 (below) lists some of these investigational drugs that can be accessed through a clinical trial. For more information on clinical trials, view the *Understanding Clinical Trials* publication on the Lymphoma Research Foundation's website at **lymphoma.org/publication** (**Table 1**).

It is important to remember that scientific research is always evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared. It is also very important that all patients with CLL consult with a CLL specialist to clear up any questions.

Table 1: Investigational drugs for newly diagnosed CLL/SLL

Agent (drug)	Class (type of treatment)
Cirmtuzumab (UC-961)	Immunotherapy; anti-ROR1 antibody
Lisaftoclax (APG-2575)	Targeted therapy; BCL2 inhibitor
Sonrotoclax (BGB-11417)	Targeted therapy; BCL2 inhibitor
Orelabrutinib (ICP-022)	Targeted therapy; BTK inhibitor
Nemtabrutinib (MK-1026, ARQ 531)	Targeted therapy; BTK inhibitor
BGB-16673	Targeted therapy; BTK inhibitor
MB-106	Immunotherapy; CAR T-cell
NX-5948	Targeted therapy, BTK degrader
NX-2127	Targeted therapy, BTK degrader

BCL2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR T-cell, chimeric antigen receptor T-cell; ROR1, receptor-tyrosine kinase-like orphan receptor 1.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and optimal treatment doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (**lymphoma.org/publications**), talk to their physician, or contact the Foundation's Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

Minimal Residual Disease

Minimal residual disease (MRD) refers to the small number of cancer cells in the body after completion of treatment. Typically, MRD tests detect cancer cells that remain in the blood or bone marrow. Testing for MRD is often done in clinical trials. Using very sensitive laboratory methods, one cancer cell can be detected among 1,000,000 healthy blood cells. An MRD-negative test means that there are no cancer cells detected within the sensitivity of the method used. Testing for MRD is mostly used as a prognostic marker (predicts the likely course of the disease) that provides useful information about long-term outcome after treatment. The prognostic value of MRD may be dependent on the treatment the patient is receiving.

With certain CLL therapies, studies have found that patients with lower levels of MRD (fewer cancer cells remaining after the completion of treatment) have a longer remission. Patients receiving treatment with Bruton's tyrosine kinase (BTK) inhibitors may not reach a negative MRD status. However, the response to treatment can still last for a long period and maintain disease control for many years. For this reason, having detectable MRD does not necessarily mean the disease has relapsed or become refractory. This will help to make individualized decisions for your case. More recent studies are investigating whether undetectable MRD may result in a shorter course of treatment for patients. Patients should be encouraged to discuss MRD with their physician or a physician specialized in CLL/SLL. If your doctor decides to test for MRD, it is important to discuss what your MRD status is and what does it mean.

Follow-up

Because disease relapses are frequent in CLL/SLL, patients in remission should have regular visits with their physician. During these visits, medical tests (such as blood tests and computed tomography [CT] scans) may be recommended to evaluate the need for additional treatment.

Some treatments can cause long-term side effects (occur **during** treatment and continue for months or years) or late side effects (appear only months, years or decades **after** treatment has ended). These side effects can vary depending on the following factors:

- duration of treatment (how long the treatment lasted)
- frequency of treatment (how often was the treatment was administered
- type of treatment given
- age and gender of the patient
- patient overall health at the time of their treatment

A physician and their care team will check for these side effects during follow-up care. Visits may become less frequent the longer the patient stays in remission.

Patients and their care partners are encouraged to keep copies of all medical records. This includes test results as well as information on the type, amount, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundation's award-winning *Focus On Lymphoma* mobile app can help patients manage this documentation.

Lymphoma Care Plan

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. The Foundation's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting **lymphoma.org/publications**.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

Helpline

The Foundation's Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at **lymphoma.org**, or contact the Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Para información en Español, por favor visite **lymphoma.org/es**. (For Information in Spanish please visit **lymphoma.org/es**).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at **lymphoma.org/mobileapp**, or contact the Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

Research. Community. Cure.

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