LYMPHOMA RESEARCH • FOUNDATION

Understanding Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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

CLL and SLL are essentially the same disease, with the only difference being the location where the cancer primarily occurs. When most of the cancer cells are located in the bloodstream and the bone marrow, the disease is referred to as CLL. When the cancer cells are located mostly in the lymph nodes and are rare in the blood, the disease is called SLL.

Patients with CLL/SLL do not have any obvious symptoms of the disease and many will live for years without symptoms. Their doctors might detect the disease during routine blood tests and/or a physical examination. For others, the disease is detected when symptoms occur and the patient sees a doctor because he or she is worried, uncomfortable, or does not feel well. Symptoms tend to be mild at first and get worse slowly. The symptoms depend on the location of the tumor in the body, and may include *fatigue* (extreme tiredness), shortness of breath, *anemia* (low red blood cell count), bleeding or bruising easily, bone pain, night sweats, weight loss and frequent infections. Other symptoms can include swollen glands or abdomen and feeling full even after eating only a small amount.

TREATMENT OPTIONS

Treatment is based on the severity of associated symptoms as well as the rate of cancer growth. If patients show no or few symptoms, doctors may decide not to treat the disease right away, an approach referred to as *active surveillance*, also known as *watchful waiting* (observation with no treatment). With this strategy, patients' overall health and disease are monitored through regular check-up visits and various evaluation procedures, such as laboratory and imaging tests. Active treatment is started if the patient begins to develop CLL/SLL-related symptoms or there are signs that the disease is progressing. Studies have shown that patients with less-advanced disease managed with an active surveillance approach have outcomes similar to those who are treated early in the course of the disease.

There are many current *frontline* (initial) treatment options for CLL/SLL. The choice of treatment might depend on the presence of certain chromosome (DNA) abnormalities, the patient's age and overall health, and the benefits versus side effects of treatment. Treatment may also depend on genetic alterations (called mutations). Newer drugs and combinations have shown excellent activity in patients with all sorts of disease characteristics. Common drugs or drug combinations used as initial treatments for CLL/SLL include targeted therapy and immunotherapy:

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

Occasionally patients might also be treated with chemotherapy, or other nonchemotherapy combinations. Chemotherapy plays a very limited role in the management of CLL nowadays. These decisions are dictated by specific patient factors, and their choice should be discussed extensively with the patient's oncologist or hematologist and ideally one that specializes in CLL. Other therapeutic regimens include: CG (chlorambucil [Leukeran] and obinutuzumab [Gazyva])

- C (chlorambucil)
- FCR (fludarabine [Fludara], cyclophosphamide [Cytoxan], rituximab [Rituxan])
- Ofatumumab (Arzerra) and chlorambucil (Leukeran)
- Rituximab (Rituxan) and chlorambucil (Leukeran)
- Bendamustine hydrochloride (Belrapzo/Bendeka/Treanda)
- Corticosteroids such as dexamethasone and prednisone

Ofatumumab (Arzerra), rituximab (Rituxan), and lenalidomide (Revlimid) have been used as *maintenance therapy* (ongoing treatment of patients whose disease has responded well to treatment) to prevent relapse in patients who achieve full or partial *remission* (disappearance of signs and symptoms) after at least two other therapies for CLL.

For patients whose disease becomes *refractory* (does not respond to treatment) or *relapses* (disease returns after treatment), subsequent therapies may be successful in providing another remission. Patients seeking information about relapsed/refractory disease should view the *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Relapsed/Refractory* fact sheet on LRF's website (click **here**).

Common therapeutic regimens for relapsed/refractory CLL and SLL include:

- Ibrutinib (Imbruvica) +/- rituximab (Rituxan) or obinutuzumab (Gazyva)
- Venetoclax (Venclexta) +/- rituximab (Rituxan) or obinutuzumab (Gazyva)
- Idelalisib (Zydelig) and rituximab (Rituxan) or obinutuzumab (Gazyva)
- Acalabrutinib (Calquence) +/- rituximab (Rituxan) or obinutuzumab (Gazyva)
- Duvelisib (Copiktra)
- Lenalidomide (Revlimid +/- rituximab.

Multiple other agents are available, and discussion with a CLL specialist is needed for appropriate selection. An allogeneic stem cell transplant (cells donated from a living donor) is a potentially curative option, but most patients will do well with newer treatments that avoid the risks of complications of transplants.

TREATMENTS UNDER INVESTIGATION

Many treatment strategies testing new agents and combinations are currently in clinical trials for patients with newly diagnosed or previously treated CLL/SLL (Table 1). Researchers are also investigating ways to improve stem cell transplantation in patients with CLL/SLL. In addition, a special type of immunotherapy called chimeric antigen receptor (CAR) T cell therapy, uses patients' own immune cells to treat their cancer. Several CAR T cell therapies are in development for patients with CLL/SLL. For more information on CAR T cell therapy, view the CAR T Cell Therapy for Lymphoma publication on the Lymphoma Research Foundation's (LRF's) website at lymphoma.org/publications.

It is critical to remember that today's scientific research is continuously 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 LRF for any treatment updates that may have recently emerged. It is also very important that all patients with CLL consult with a CLL specialist as early as possible.

Table 1. Investigational drugs for newly diagnosed CLL/SLL

AGENT	CLASS
Lenalidomide (Revlimid)	Immunomodulator
Ublituximab (TG-1101)	Immunotherapy; anti-CD20 antibody
Umbralisib (Ukoniq)	Targeted therapy; PI3K delta and CK1-epsilon inhibitor
ABP-798	Rituximab biosimilar; anti-CD20 antibody
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor
Cirmtuzumab (UC-961)	Targeted therapy; ROR1 antagonist
Orelabrutinib (ICP-022)	Targeted therapy; BTK inhibitor
Pirtobrutinib (LOXO-305)	Targeted therapy; BTK inhibitor
Umbralisib plus ublituximab	Targeted therapy and immunotherapy

BTK, Bruton's tyrosine kinase; CK, casein kinase; PI3K, phosphatidylinositol 3-kinase; ROR1, receptor-tyrosine kinase-like orphan receptor 1.

CLINICAL TRIALS

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

MINIMAL RESIDUAL DISEASE

Testing for *minimal residual disease* (MRD, or measurable residual disease) is often done in clinical trials to detect cancer cells that remain in the blood or bone marrow after the completion of treatment. Using very sensitive laboratory techniques, one abnormal cell can be detected among 10,000 healthy blood cells. Studies have found that patients with lower levels of MRD (fewer cancer cells remaining after the completion of treatment) may have a longer remission. Studies are underway to investigate whether MRD testing may be used to shorten the course of treatment for patients with undetectable levels of cancer cells in their blood before they have completed a full course of therapy.

FOLLOW-UP

Because multiple disease relapses are frequent in CLL/SLL, patients in remission should have regular visits with a physician who is familiar with their medical history and the treatments they have received.

Medical tests (such as blood tests, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term side effects or late side effects, which can vary based on the duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Patients and their caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any side effects resulting from treatment or potential disease recurrences. LRF's award-winning *Focus On Lymphoma* mobile app (lymphoma.org/mobileapp) can help patients manage this documentation.

LRF'S HELPLINE AND LYMPHOMA SUPPORT NETWORK

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. The LRF Helpline staff members are available to answer your general questions about a lymphoma diagnosis 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. A part of the Helpline is LRF's one-to-one peer support programs, Lymphoma Support Network. This program connects patients and caregivers with volunteers who have experience with CLL, similar treatments, or challenges, for mutual emotional support and encouragement. Patients and loved ones may find this useful whether the patient is newly diagnosed, in treatment, or in remission.

MOBILE APP

Focus On Lymphoma is the first mobile application (app) that provides patients and caregivers comprehensive content based on their lymphoma subtype, including CLL, and tools to help manage their lymphoma such as, keep track of medications and blood work, track symptoms, and document treatment side effects. The *Focus On Lymphoma* mobile app is available for download for iOS and Android devices in the Apple App Store and Google Play. For additional information on the mobile app, visit FocusOnLymphoma.org. To learn more about any of these resources, visit our website at lymphoma.org, or contact the LRF Helpline at 800-500-9976 or helpline@lymphoma.org.

Resources

LRF offers a wide range of free resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and CLL. LRF also provides many educational activities, including our in- person meetings, podcasts, and webinars for people with lymphoma. For more information about any of these resources, visit our websites at lymphoma.org/CLL or lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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Supported through grants from: Bristol Myers Squibb, Genentech | Biogen, Adaptive, AstraZeneca, BeiGene, pharmacyclics

Last updated 2022

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