

Understanding Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are forms of non-Hodgkin lymphoma (NHL) that arise from B 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, although the lymph nodes and spleen are often involved. When the cancer cells are located mostly in the lymph nodes and are less frequent in the blood, the disease is called SLL.

Many patients with CLL/SLL do not have any obvious symptoms of the disease. 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 goes to the doctor because he or she is worried, uncomfortable, or does not feel well. CLL/SLL may cause different symptoms depending on the location of the tumor in the body, including fatigue (extreme tiredness), shortness of breath, anemia (low red blood cell count), bruising easily, night sweats, weight loss, frequent infections. Other symptoms can include a swollen abdomen and feeling full even after eating only a small amount. However, many patients with CLL/SLL will live for years without symptoms.



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 [drug therapy, radiation therapy, or stem cell transplantation] given). 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 based on testing during follow-up visits. 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 chromosome (DNA) abnormalities, the patient's age and overall health, and the benefits versus side effects of treatment. Treatment may also depend on whether the patient's cancer cells are missing parts of certain chromosomes (called deletions) or 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:

- Acalabrutinib (Calquence)
- Ibrutinib (Imbruvica) +/- rituximab (Rituxan)
- Ibrutinib (Imbruvica) and obinutuzumab (Gazyva)

- Chlorambucil (Leukeran) and obinutuzumab (Gazyva)
- Venetoclax (Venclexta) and obinutuzumab (Gazyva)

Occasionally patients might also be treated with chemotherapy, or other nonchemotherapy combinations. 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.

- CG (chlorambucil [Leukeran] and obinutuzumab [Gazyva])
- FCR (fludarabine [Fludara], cyclophosphamide [Cytoxan], rituximab [Rituxan])
- Ofatumumab (Arzerra) and chlorambucil (Leukeran)
- Rituximab (Rituxan) and chlorambucil (Leukeran)

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. Some common agents that may be used either alone or in combination for relapsed/refractory CLL and SLL include:

- Ibrutinib (Imbruvica)
- Venetoclax (Venclexta) +/- rituximab (Rituxan)
- Idelalisib (Zydelig) and rituximab (Rituxan)
- Bendamustine (Bendeka, Treanda) and rituximab (Rituxan)

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 is rarely utilized since most patients will do well with newer treatments, and the transplant procedure is associated with substantial risk of complications. For more information on stem cell transplants, view the *Understanding the Stem Cell Transplantation Process* publication on the Lymphoma Research Foundation's (LRF's) website at lymphoma.org/publications.

TREATMENTS UNDER INVESTIGATION

Many treatments are currently being tested in clinical trials for patients with both newly diagnosed and relapsed/refractory CLL/SLL. Several chemoimmunotherapy agents are being explored as induction therapy in newly diagnosed patients. In addition, the efficacy and safety of agents such as lenalidomide (Revlimid), ME-401, SNX-5422, DTRMWXHS-12, XmAb13676, pembrolizumab (Keytruda), ublituximab, umbralisib, nivolumab (Opdivo), MOR208, cerdulatinib, and multiple other drugs are being investigated alone or as part of combination therapy regimens in patients with relapsed/refractory disease. Another area of research for treating CLL is genetically engineering patients' own T cells to recognize and kill CLL cells, referred to as chimeric antigen receptor (CAR) T-cell therapy. Finally, researchers are also investigating ways to improve stem cell transplantation in patients with CLL/SLL. 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 early in their disease journey.

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 at lymphoma.org/publications, 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 during and after the completion of treatment. Using very sensitive laboratory techniques one

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The *Understanding Lymphoma* series is published by the Lymphoma Research Foundation (LRF) for the purpose of informing and educating readers. Facts and statistics were obtained using published information, including data from the Surveillance, Epidemiology, and End Results (SEER) Program. Because each person's body and response to treatment is different, no individual should self-diagnose or embark upon any course of medical treatment without first consulting with his or her physician. The medical reviewer, the medical reviewer's institution, and LRF are not responsible for the medical care or treatment of any individual.

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Last updated 2020

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 CLL/SLL is generally characterized by multiple disease relapses after responses to a variety of treatments, 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.

Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and CLL/SLL, including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to webinars for people with lymphoma, as well as an *Understanding Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma* patient guide and CLL/SLL e-Updates that provide the latest disease-specific news and treatment options. To learn more 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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