

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Overview

Lymphoma is the most common blood cancer. The main forms of lymphoma are classified as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL), which includes several B-cell lymphomas and T-cell lymphomas. Lymphoma is the most common blood cancer. Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, uncontrollably grow and multiply. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and can form a mass called a tumor. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells).

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are forms of 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 rare 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, bruising easily, night sweats, weight loss, and 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” or “careful observation”). With this strategy, patients’ overall health and disease are monitored through regular checkup 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 will depend on the presence of chromosome (DNA) abnormalities, the patient’s age and overall health of the patient, and the benefits versus side effects of treatment. Treatment may also depend on whether the patient’s lymphoma cells are missing parts of certain chromosomes (called deletions). Common drugs or drug combinations used as initial treatments for CLL/SLL include:

- BR (bendamustine [Treanda] and rituximab [Rituxan])
- CG (chlorambucil [Leukeran] and obinutuzumab [Gazyva])
- FCR (fludarabine [Fludara], cyclophosphamide [Cytoxan, Neosar], and rituximab)
- FR (fludarabine and rituximab)
- Ibrutinib (Imbruvica)
- Ofatumumab (Arzerra) and chlorambucil
- Rituximab and chlorambucil
- PCR (pentostatin, cyclophosphamide, and rituximab)

In 2017, a subcutaneous form of rituximab (Rituxan Hycela or “rituximab and hyaluronidase human”) was approved for patients with CLL when combined with fludarabine and cyclophosphamide. Rituxan Hycela is given as injection under the skin (subcutaneously) in the stomach area rather than as an infusion into a vein. Before patients can receive rituximab and hyaluronidase human (Rituxan Hycela), they must receive at least one intravenous infusion of rituximab.

For patients whose disease becomes *refractory* (no longer responds to treatment) or *relapses* (returns after treatment), subsequent therapies may be successful in providing another remission. Some common agents that are used either alone or in pairs for relapsed/refractory CLL and SLL include:

- Bendamustine (Treanda)
- Chlorambucil (Leukeran)
- Fludarabine (Fludara)
- Ibrutinib (Imbruvica)
- Idelalisib (Zydelig) and rituximab (Rituxan)
- Alemtuzumab (Campath; provided only through Campath Distribution Program; no longer commercially available)
- Obinutuzumab (Gazyva)
- Ofatumumab (Arzerra)
- Rituximab (Rituxan)
- Venetoclax (Venclexta)

Other combination treatment regimens occasionally used in the relapsed/refractory setting include:

- HDMP (high-dose methylprednisolone) and rituximab (Rituxan)
- OFAR (oxaliplatin [Eloxatin], fludarabine [Fludara], cytarabine [Cytosar-U], and rituximab)

Ofatumumab (Arzerra), rituximab (Rituxan), and lenalidomide (Revlimid) have also 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 after at least two other therapies for CLL. It is not yet clear whether stem cell transplantation is helpful for patients with CLL/SLL. Stem cell transplants are usually done as part of a clinical trial in patients with high-risk or relapsed/refractory disease. Typically, stem cells from a donor are used. 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), acalabrutinib (Calquence), ME-401, SNX-5422, DTRMWXHS-12, XmAb13676, pembrolizumab (Keytruda), ublituximab, umbralisib, nivolumab (Opdivo), MOR208, and cerdulatinib 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 engineered T cells designed 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.

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.

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* (disappearance of signs and symptoms) 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 teleconferences and webcasts 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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