

Understanding Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma: Relapsed/Refractory

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.

The outlook for patients with CLL/SLL has improved in recent years, but the disease course still varies widely. Many patients with CLL do not require treatment at diagnosis and perhaps for months to years thereafter. Other patients with CLL/SLL respond to initial treatment and go into remission (disappearance of signs and symptoms). Others experience a *refractory* (does not respond to treatment) disease course, and their cancer stops responding to *frontline* (initial) therapy or *relapses* (disease returns after treatment).¹ For patients whose disease becomes refractory or relapses, subsequent therapies may be successful in providing another remission.

TREATMENT OPTIONS

Chemotherapy plays a very limited role in the management of CLL. Most patients are now treated initially with either targeted therapy or immunotherapy. Preferred regimens for frontline treatment include Ibrutinib (Imbruvica) alone or in combination with rituximab (Rituxan), a therapy that targets survival signals around cancer cells, or the combination of venetoclax (Venclexta) and obinutuzumab (Gazyva), which helps the immune system fight cancer cells. As with frontline treatment, treatment for relapsed/refractory disease is based on the patient's age and overall health, and the extent and location of disease. Additionally, the type of previous therapies received and the length of response to previous therapies should be considered.² If chemotherapy is being considered, the patient's physician may want to test the cancer again.³ Treatment may depend on the identification of markers found on cancer cells and whether the patient's lymphoma cells have certain genetic alterations.⁴

Some common agents that are used either alone or in combinations as initial treatment or for relapsed/refractory CLL and SLL include:

- Ibrutinib +/- rituximab (Rituxan)
- Venetoclax +/- rituximab (Rituxan) or obinutuzumab
- Idelalisib (Zydelig) and rituximab
- Duvelisib (Copiktra)

- Chlorambucil plus obinutuzumab
- Bendamustine (Treanda) + rituximab
- Acalabrutinib (Calquence) +/- obinutuzumab

Biosimilar therapies (drugs that are modeled after an existing biologic therapy) may be an option for patients who are taking rituximab. These include rituximab-abbs and rituximab-pvvr. For more information on biosimilar therapies visit lymphoma.org/publications for our *Biosimilar Therapies* factsheet. Multiple other agents are available and treatment selection is often dictated by specific patient factors. Options should be discussed with the patient's oncologist or hematologist, and ideally one that specializes in CLL.

Ofatumumab (Arzerra), rituximab, 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 after at least two other therapies for CLL. However, maintenance therapy is not often used in the relapsed setting. 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.

¹ NCCN Guidelines for Patients CLL p.22 Relapsed or refractory CLL; Kipps 2017

² LRF18204 CLLSLL Booklet_D3v3 p.70 What is relapsed or refractory CLL/SLL?

³ NCCN Patient Guidelines p.24 Relapse or refractory CLL

⁴ NCCN Patient Guidelines p.24 Relapse or refractory CLL

TREATMENTS UNDER INVESTIGATION

Many treatments are currently being tested in clinical trials for patients with both newly diagnosed and relapsed/refractory CLL/SLL. The efficacy and safety of agents such as, ME-401, SNX-5422, DTRMWXHS-12, XmAb13676, pembrolizumab (Keytruda), ublituximab, umbralisib, nivolumab (Opdivo), tafasitamab, 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 for 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 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.

Contact LRF:

Helpline: (800) 500-9976

Email: helpline@lymphoma.org

www.lymphoma.org

Medical reviewers:

Bruce D. Cheson, MD, FACP, FAAAS, FASCO
LRF Scientific Advisory Board Member
Georgetown University Hospital
Lombardi Comprehensive Cancer Center

Anthony Mato, MD, MSCE
Memorial Sloan Kettering Cancer Center

Supported through grants from:

 Bristol Myers Squibb

 Genentech
A Member of the Roche Group

 Biogen

 Kite
A Division of Amgen

 abbvie

 pharmacyclics

 TG Therapeutics

 AstraZeneca

 Adaptive
BIOMEDICINES

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.

© 2020 Lymphoma Research Foundation

Last updated 2020