

Chronic Lymphocytic Leukemia



Revised **2021**

Support for this publication
provided by

abbvie

AstraZeneca 

Genentech
A Member of the Roche Group

 **Biogen.**

 **pharmacyclics**
An AbbVie Company

janssen
A Division of Janssen Pharmaceutica


A six-word narrative about living with blood cancer from patients in our LLS Community

Stay strong and keep moving forward. Find the positive in every day. Be your own best patient advocate. Changed my life for the better. Accept, learn and focus on present. Learning to live a different life. Sudden and life changing—be positive. Waiting, worrying, anxiousness/happy I'm alive! Embrace a new normal each day. 5 years, 41 infusions, constant fatigue. Patience, positive attitude, hope and faith. Test to test, I will survive! Treatment, fatigue, treatment, fatigue and survival. Love life, live better every day. I don't look back only forward. So far, so good, live life. Meditation, mindfulness, wellness, faith, nutrition and optimism. Finding the joy while living with uncertainty. Watch, wait, treat, regroup, rest, re-energize. Blessed to be doing so well! Eye opening needed learning and healing. Feel great: uncertain travel plans annoying. Renewed faith, meditation, diet, mindfulness, gratitude. Watchful waiting can be watchful worrying. Scary, expensive, grateful, blessings, hope, faith. Thank god for stem cell transplants! Do not know what to expect. Extraordinarily grateful, I love my life. Diagnosed; frightened; tested; treating; waiting; hoping. I'm more generous, impatient less often. Embrace your treatment day after day. Live today, accept tomorrow, forget yesterday. Strength you never realized you had. Challenging to our hearts and minds. Life is what we make it. Live life in a beautiful way.



Discover what thousands already have at
www.LLS.org/Community

Join our online social network for people who are living with or supporting someone who has a blood cancer. Members will find

- Thousands of patients and caregivers sharing experiences and information, with support from knowledgeable staff
- Accurate and cutting-edge disease updates
- The opportunity to participate in surveys that will help improve care.

Inside This Booklet

- 2** Introduction
- 2** Chronic Lymphocytic Leukemia Basics
- 4** Signs and Symptoms
- 4** Diagnosis
- 5** Treatment Planning
- 13** Treatment Options
- 26** Treatment Options for Relapsed and Refractory Cases
- 28** Financial Concerns
- 28** Research and Clinical Trials
- 31** Disease and Treatment-Related Complications
- 35** Treatment Response and Follow-Up Care
- 38** Related Diseases
- 38** Incidence, Causes and Risk Factors
- 40** Normal Blood and Bone Marrow
- 42** The Lymphatic System
- 43** Resources and Information
- 47** Health Terms
- 54** References

Acknowledgement

The Leukemia & Lymphoma Society (LLS) appreciates the review of this material by:

Steven Coutre, MD

Professor of Medicine (Hematology)
Stanford University School of Medicine
Stanford Cancer Institute
Stanford, CA

New treatments may have been approved since this book was printed.
Check www.LLS.org/DrugUpdates or call (800) 955-4572.

This publication is designed to provide accurate and authoritative information about the subject matter covered. It is distributed as a public service by The Leukemia & Lymphoma Society (LLS), with the understanding that LLS is not engaged in rendering medical or other professional services. LLS carefully reviews content for accuracy and confirms that all diagnostic and therapeutic options are presented in a fair and balanced manner without particular bias to any one option.

Introduction

This booklet provides information about chronic lymphocytic leukemia (CLL) for patients and their families. It also includes brief descriptions of blood, bone marrow and the lymphatic system in normal conditions, as well as definitions of health terms related to CLL.

Approximately 21,250 new cases of CLL are expected to be diagnosed in 2021. As of 2017, the latest year for which statistics are available, an estimated 181,666 people are either living with or are in remission from CLL.¹

Doctors have learned a great deal about CLL in the last few decades. Advances in the treatment of CLL have resulted in improved remission rates, quality of life and survival for patients. This is due to the large number of approved therapies and new drug combinations. New therapies are under study in clinical trials.

All LLS publications mentioned in this booklet are free and can be viewed, downloaded or ordered online at www.LLS.org/booklets.

Feedback. Visit www.LLS.org/PublicationFeedback to give suggestions about this booklet.

¹ Source: Facts 2020-2021. The Leukemia and Lymphoma Society. April 2021.

New treatments may have been approved since this book was printed.
Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Chronic Lymphocytic Leukemia Basics

Leukemia is a cancer of the blood and bone marrow. The four major types of leukemia are chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The different types of leukemia are identified based on the type of cell that is involved in the disease, as well as the rate of disease progression.

Leukemia is classified as “lymphocytic” or “lymphoblastic” if the cancerous change (mutation) takes place in a mature blood stem cell in the bone marrow that normally develops into a type of white blood cell called a “lymphocyte.” If the mutation occurs in a bone marrow cell that would normally develop into a red blood cell, white blood cell (other than a lymphocyte) or a platelet, it is classified as a “myeloid” or “myelogenous” leukemia.

Acute leukemias progress rapidly and affect cells that are not fully developed. These cells cannot carry out their normal functions. Chronic leukemias usually progress more slowly than acute types of leukemia, and patients have greater numbers of mature cells. In general, these more mature cells can carry out some of their normal functions. (See *Normal Blood and Bone Marrow* on page 40 of this booklet and *Where Do Blood Cancers Develop?* at www.LLS.org/booklets).

The four main types of leukemia are often further classified into subtypes based on specific features of the leukemia cells. It is important to know the subtype of your disease because the treatment approach depends on the specific diagnosis.

Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL).

According to the World Health Organization (WHO), CLL and SLL are considered different manifestations of the same disease. Both are the result of one or more changes (mutations) in a developing cell that was supposed to become a healthy lymphocyte. As a result of the change, the abnormal (leukemic) lymphocyte begins to multiply uncontrollably, causing leukemia cells to accumulate in the blood, bone marrow and lymphoid tissues. These abnormal cells are able to survive and live longer than normal cells.

Whether the diagnosis is CLL or SLL depends on where the abnormal B cells are located in the body. The leukemic lymphocytes in people with SLL are identical to those in people with CLL, but they are mostly present in lymphoid tissues. In CLL, there are significant accumulations of abnormal lymphocytes in the blood and bone marrow, and often in the spleen and lymph nodes. Although each diagnosis differs, the same treatments are used for both conditions. Talk to your doctor if you have questions about your specific diagnosis and treatment.

How Chronic Lymphocytic Leukemia (CLL) Develops. CLL results from one or more acquired mutations to the genetic material, called DNA, of a single bone marrow cell that would otherwise develop into a healthy lymphocyte. (“Acquired” means that the change in the cell occurs after birth; it is not inherited from a parent.) The altered cell multiplies, resulting in an accumulation of types of leukemia cells called “CLL cells,” in the blood, bone marrow, spleen and lymph nodes. CLL cells grow and survive better than normal cells and so, over time, they crowd out the healthy cells.

Leukemia cells do not function like normal blood cells; healthy white blood cells fight infection much more effectively than leukemia cells. However, CLL cells do not prevent normal blood cell production as extensively as diseased cells in people with acute leukemia. In some people with CLL, the disease progresses slowly and, if there are minimal changes in their blood cell counts, CLL may remain stable for years. Other people have a faster-growing form of the disease, in which the CLL cells accumulate in the bone marrow and blood, and there is a significant decrease in the numbers of red blood cells and platelets.

Signs and Symptoms

Many people with CLL are diagnosed with the disease before they have any symptoms. A doctor may suspect that a person has CLL based on abnormal results of blood tests done for an annual checkup or a medical examination for an unrelated condition. An unexplained elevated white blood cell (lymphocyte) count is the most common finding that leads a doctor to suspect a diagnosis of CLL.

Generally, CLL symptoms develop over time. As the disease progresses, a person may experience symptoms such as:

- Fatigue
- Shortness of breath during normal physical activity
- Lymph node enlargement (particularly in the neck)
- Low-grade fever
- Unexplained weight loss
- Night sweats
- Feeling of fullness (due to an enlarged spleen or liver)
- Infection of the skin, lungs, or sinuses

Diagnosis

It is important to get an accurate diagnosis of your type of leukemia. The exact diagnosis helps the doctor to:

- Estimate how the disease will progress
- Determine the appropriate treatment

Blood Cell Count and Examination. A diagnosis of CLL is usually based on the results of blood cell counts and an examination of blood cells in a sample. People with CLL have an increased number of lymphocytes. They may also have low platelet and red blood cell counts, but these are usually normal or only slightly decreased in the early stage of the disease.

Immunophenotyping. Lymphocyte immunophenotyping is an important test used to diagnose CLL and other types of leukemia and lymphoma, by comparing the cancer cells to normal cells. The test results indicate whether the person's abnormal lymphocytes developed from a single cancer (leukemia) cell, or are the result of another, non-cancerous condition. This test is especially important if the number of lymphocytes in the blood is only slightly elevated.

Immunophenotyping also determines whether the abnormal cells originated from a B cell or a T cell, which is also a factor in the diagnosis.

Immunophenotyping is done with an instrument called a “flow cytometer.” A flow cytometry test can measure the number of cells in a sample, as well as specific characteristics of the cells, including their size and shape, and identify specific markers on the cell surface. A sample of cells from blood or bone marrow is tagged with a panel of antibodies that are specific to areas on the cell surface. The cells are stained with a light-sensitive dye and are passed through a laser beam in the flow cytometer. If they have an antibody-specific surface marker, the cells light up and are counted. A test result showing the presence of 5,000 or more abnormal B-cells per microliter of blood (5,000/ μ L), with a specific pattern of markers on their surfaces, is required for a diagnosis of CLL.

Quantitative Immunoglobulin Test. This important test measures the concentration of immunoglobulins in the blood. Immunoglobulins are a type of protein called “antibodies” that are made by B cells in healthy individuals to protect the body from infections. There are three major types of antibodies in the blood: IgG, IgA and IgM. A blood test can be used to measure the amount of each type of antibody.

CLL cells do not make effective antibodies and they also interfere with the ability of normal lymphocytes to make antibodies. As a result, people with CLL often have low immunoglobulin levels, which result in immune deficiency and increase the risk of infections.

Bone Marrow Examination. It usually is not necessary for doctors to do a bone marrow aspiration or biopsy to diagnose CLL. So, for most patients, this procedure is not recommended. Occasionally, bone marrow aspiration and biopsy may be recommended before treatment begins. The results of bone marrow tests can help rule out other diseases, if the diagnosis is uncertain. These tests can also be used during treatment to evaluate its effectiveness.

Treatment Planning

In some cases, treatment for CLL needs to start immediately after diagnosis. In others, treatment does not need to start right away (see Watch and Wait on page 14). Healthcare teams monitor patients to determine when the disease becomes symptomatic, which can happen quickly or take many years. Treatment needs to start when the disease becomes symptomatic, so ongoing follow up with the healthcare team is essential.

A diagnosis of CLL is associated with a wide range of outcomes. For the best outcome, patients are encouraged to seek treatment in a center with specialized doctors, called hematologist-oncologists, who have specific experience in the diagnosis and care of patients with chronic leukemia.

Treatment options for CLL change often based on new therapies and research findings emerging from clinical trials. The outlook for people with CLL is improving. New treatment approaches for CLL are being studied in clinical trials for patients of all ages and at every stage of the disease.

The tests described below may be done at the time of diagnosis, but if they are not, they will be done when a patient starts to have symptoms of CLL. The test results help guide treatment planning and decisions. These tests are not essential to diagnose CLL, but may help predict the patient's prognosis (likely outcome). They are also done to assess the extent of the disease, check for specific mutations, and determine the best treatment approach.

Fluorescence in situ Hybridization (FISH). This test looks for chromosome abnormalities using DNA probes tagged with fluorescent molecules that emit light of different colors. The DNA-tagged probes bind to specific genes or areas in the chromosomes within the leukemia cells and light up when viewed under a microscope. It is very common for CLL cells to have abnormal chromosomes. Typical abnormalities involve chromosomes 11, 12, 13 and 17 (see **Table 1** on page 8). A FISH test can be done with samples of either blood or bone marrow cells.

About 80 percent of CLL patients who undergo FISH testing have chromosome abnormalities in their leukemia cells. Based on the specific abnormalities that are found, doctors can identify patients who will likely need to start treatment sooner, as well as those who may benefit most from certain types of drug therapy.

Karyotyping. This test provides a snapshot of the chromosomes by pairing and arranging all the chromosomes of a cell in order. It can provide more complete information about chromosomes than the FISH test. A blood or bone marrow sample from the patient can be used. In CLL, a “complex karyotype” is defined by the presence of three or more unrelated defects in chromosomes that occur in more than one cell, and is associated with a poorer prognosis. Patients with CLL who have the del(17p) abnormality or a complex karyotype have a higher risk of relapse than those with other genetic abnormalities.

DNA Sequencing. This lab test uses blood or marrow samples to look for mutations in genes. In CLL, DNA sequencing is used to test for mutations in the immunoglobulin heavy chain variable (*IGHV*) region and *NOTCH1*, *SF3B1* and *TP53* genes. Normal immunoglobulins (antibodies) are made of two heavy chain proteins and two light chain proteins. The *IGHV* region genes in B cells give instructions for making the heavy chain component. These genes may or may not be mutated in individuals with CLL; the patient's prognosis is better if the *IGHV* gene is mutated, and this is currently the strongest predictor of prognosis. The *TP53* gene makes a protein that signals for either the repair or the destruction of abnormal cells. It helps prevent tumors from forming. In CLL, mutated *TP53* is associated with a poor prognosis. See **Table 2** on pages 9-10 for more information about these factors.

During the last decade, numerous markers have been discovered that can help identify patients who have different rates of disease progression that require treatment. Examples of these markers include:

- Serum markers, such as beta-2 microglobulin
- Genetic markers, including immunoglobulin heavy chain variable (*IGHV*) region and *TP53* gene mutational status
- Genetic abnormalities detected by fluorescence in situ hybridization (FISH) or cytogenetic analysis
- Protein markers, such as zeta-chain-associated protein kinase 70 (ZAP-70), cluster designation 38 (CD38) or CD49d

For more information on these factors, see **Table 2** on pages 9-10, **Tables 3A and 3B** on page 11 and in *Health Terms* starting on page 47.

Hepatitis B Screening. It is important for your treatment team to know if you have ever been infected with hepatitis B. This is because CLL and some of its treatments can cause the hepatitis B virus to reactivate. Testing for evidence of hepatitis B is often done before treatment.

Beta-2 Microglobulin Level. This small protein is made by many types of cells, including CLL cells, and can be measured through a blood chemistry test. High levels of beta-2 microglobulin (B2M) are associated with earlier progression of CLL.

Lactate Dehydrogenase (LDH) Level. This protein is present in most cells and gets into the bloodstream when a cell becomes damaged. A high level of LDH in the blood indicates cell damage and may also indicate the presence of cancer or other health conditions. When related to cancer, it may be a sign that the disease will progress sooner.

Table 1. Common Cytogenetic Abnormalities in CLL

Abnormality	Feature(s)	Frequency	Associated Risk/ Outcomes
Del(13q)	Deletion in the long arm of chromosome 13	55%	<p>If no other abnormality is present, it indicates:</p> <ul style="list-style-type: none"> • Favorable outcome • Indolent (slow-growing) disease (in greater than 50% of patients)
Trisomy 12	Three copies of chromosome 12	10%-20%	<ul style="list-style-type: none"> • If by itself, associated with intermediate-risk CLL (about 30% of patients) • If in conjunction with other abnormalities, associated with higher-risk CLL
Del(11q)	<ul style="list-style-type: none"> • Deletion in the long arm of chromosome 11 • Often associated with extensive lymph node involvement 	<p>10% of patients with early-stage disease</p> <p>25% of untreated patients with advanced-stage disease</p>	High-risk and more aggressive disease (about 20% of patients)
Del(17p)	<ul style="list-style-type: none"> • Deletion in short arm of chromosome 17 • Critical <i>TP53</i> gene in the region is deleted • Does not respond well to chemotherapy or chemoimmunotherapy 	<ul style="list-style-type: none"> • Less than 10% at diagnosis • Up to 30% in relapsed/refractory cases 	<ul style="list-style-type: none"> • High-risk and more aggressive disease • Accompanied by other mutations about 80% of the time

Source: Hallek M. *American Journal of Hematology*. 2019. (See References.)

Table 2 lists factors that may be signs of faster-growing (higher-risk) CLL and indicate the need for closer monitoring of the patient.

Table 2. Some Factors Associated with Higher-Risk CLL

Factor	Features and Associated Outcomes
<i>TP53</i> gene mutations	<ul style="list-style-type: none"> • The <i>TP53</i> gene is considered the gatekeeper that protects cell DNA from damage. • In cancer cells, this mutation leads to increased cancer cell growth and resistance to chemotherapy. • <i>TP53</i> mutation is seen in about 10%-15% of patients at time of diagnosis. • It is very commonly seen in patients who also have deletion 17p, abbreviated del(17p). • CLL patients who have this mutation may have a faster disease progression. • These mutations are resistant to traditional therapy and indicate a less favorable outcome.
<i>NOTCH1</i> gene mutations	<ul style="list-style-type: none"> • <i>NOTCH1</i> is a gene involved in the development of different types of blood cells. • Approximately 10%-15% of CLL patients have this mutation. • CLL patients who have <i>NOTCH1</i> gene mutations may have a faster disease progression and a less favorable outcome. • <i>NOTCH1</i> is associated with increased risk of transformation to diffuse large B-cell lymphoma (Richter transformation).
<i>SF3B1</i> gene mutations	<ul style="list-style-type: none"> • The <i>SF3B1</i> gene is involved in the formation of certain proteins in CLL and other blood cancers. • Approximately 10%-15% of CLL patients have this mutation, which results in dysfunctional protein processing. • CLL patients who have <i>SF3B1</i> gene mutations may have a faster disease progression and a less favorable outcome.
<i>IGHV</i>	<ul style="list-style-type: none"> • The unmutated immunoglobulin heavy chain variable (<i>IGHV</i>) region gene is associated with higher-risk CLL. • About 40% of CLL patients have unmutated <i>IGHV</i> status at diagnosis, while the other 60% have a more favorable <i>IGHV</i>-mutated form of the disease. • Testing for <i>IGHV</i> mutational status is necessary for treatment planning when considering chemoimmunotherapy. • <i>IGHV</i> is a stable marker (does not tend to change over time), so testing for this mutation should only need to be done once.
Blood lymphocyte doubling	<ul style="list-style-type: none"> • People with CLL whose lymphocyte count doubles in a period of one year have higher-risk CLL and may need closer monitoring. • A lymphocyte count that remains stable generally indicates a relatively lower risk.

(continued on pg. 10)

Table 2. Some Factors Associated with Higher-Risk CLL (continued)

Factor	Features and Associated Outcomes
CD38	<ul style="list-style-type: none">• CD38 expression is an indicator of higher-risk CLL^a
Beta-2 microglobulin (B2M)	<ul style="list-style-type: none">• Beta-2 microglobulin (B2M) is a protein that is released by CLL cells.• It is associated with a greater extent of disease.
CD49d	<ul style="list-style-type: none">• CD49d expression is an indicator of higher-risk CLL^a
ZAP-70	<ul style="list-style-type: none">• ZAP-70 is the abbreviation for zeta-chain-associated protein kinase 70.• It is a protein expressed near the surface membrane of T cells.• It plays a key role in T-cell signaling.• Increased expression of ZAP-70 may be associated with higher-risk CLL.

^aAbbreviation: CD, cluster designation; denotes a specific molecule on the surface of an immune cell.

For more information see the free LLS books *Understanding Genetics* and *Cancer Molecular Profiling*.

Commonly Used Staging Systems for CLL. Staging helps doctors assess how the disease is expected to progress over time and then develop a treatment plan. Two staging systems, the Rai system and the Binet system, have been used throughout the world in both clinical practice and in clinical trial settings. In 2016, a prognostic model called the CLL International Prognostic Index (CLL-IPI) was released, allowing for a more targeted management of CLL.

The Rai and Binet staging systems for CLL are based on the following factors:

- Lymphocytosis (abnormal increase in number of lymphocytes)
- Enlarged lymph nodes
- Enlarged spleen and/or liver
- Anemia (abnormal decrease in the number of red blood cells)
- Thrombocytopenia (abnormal decrease in the number of platelets)

The Rai staging system categorizes patients into three separate risk groups, as shown in **Table 3A** on page 11.

Table 3A. Rai Staging System

Stage	Characteristics
Low Risk (Stage 0)	<ul style="list-style-type: none"> Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood
Intermediate Risk (Stages I & II)	<ul style="list-style-type: none"> Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood Enlarged lymph nodes <p>OR</p> <ul style="list-style-type: none"> Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood Enlarged spleen and/or liver
High Risk (Stages III & IV)	<ul style="list-style-type: none"> Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood Anemia (hemoglobin < 11 g/dL) <p>OR</p> <ul style="list-style-type: none"> Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood Thrombocytopenia (platelet count < 100,000/μL)

The Binet system is based on the number of areas of involved lymph nodes (defined as lymph nodes larger than 1 cm), the enlargement of the liver and spleen, and whether there are reduced numbers of red blood cells and/or platelets. See **Table 3B** below.

Table 3B. Binet Staging System

Stage	Characteristics
A	<ul style="list-style-type: none"> No anemia (hemoglobin \geq 10 g/dL) No thrombocytopenia (platelet count \geq 100,000/μL) Less than 3 areas of lymphoid tissue enlargement
B	<ul style="list-style-type: none"> No anemia (hemoglobin \geq 10 g/dL) No thrombocytopenia (platelet count \geq 100,000/μL) 3 or more areas of lymphoid tissue enlargement
C	<ul style="list-style-type: none"> Anemia (hemoglobin < 10 g/dL) Thrombocytopenia (platelet count < 100,000/μL) Any number of areas of lymphoid tissue enlargement

Although the Rai and Binet staging systems are still widely used, they have certain limitations. These include limited ability to predict which patients will have a more aggressive disease progression, and those who will have less favorable responses to treatment. These staging systems were developed before the discovery of the genetic and molecular prognostic features of CLL. Therefore, they cannot be used to estimate the risk of disease progression in patients with early-stage CLL, or to predict how patients will respond to therapy.

To create a more comprehensive prognostic system, some of these genetic features have been integrated into the CLL International Prognostic Index (CLL-IPI). The CLL-IPI combines genetic, biochemical and clinical parameters into a prognostic model, categorizing patients into four subgroups: low, intermediate, high and very high risk. Five independent prognostic factors were identified and are scored as follows:

- *TP53* deleted or mutated = 4 points
- Unmutated *IGHV* = 2 points
- Serum beta-2 microglobulin concentration > 3.5 mg/L = 2 points
- Rai Stage I - IV or Binet Stage B - C = 1 point
- Patient age > 65 years = 1 point

The CLL-IPI also provides treatment recommendations for the different patient risk groups (see **Table 4** below).

Table 4. CLL International Prognostic Index (CLL-IPI) Categories

CLL-IPI Category	Risk Score	Treatment Recommendations
Low Risk	0 - 1	Do not treat (Watch and Wait)
Intermediate Risk	2 - 3	Do not treat unless the disease is highly symptomatic
High Risk	4 - 6	Treat unless the patient is asymptomatic (has no symptoms)
Very High Risk	7 - 10	If the decision is made to treat, use novel (new) agents or treatment in a clinical trial rather than chemotherapy

Treatment Options

New treatments may have been approved since this book was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all of your treatment options, including clinical trials, you will be taking an active role in a very important decision that affects you.

Speak with your doctor about treatment sequencing. This refers to the determination of the best first-line therapy and the order of additional therapies once treatment begins. Note that current recommendations for this are likely to change as new treatments/drug combinations are approved.

Also talk to your doctor or healthcare team about the cost of treatment and how long treatment will last. Once these factors are understood, you can begin to plan how to pay for your treatment.

Treatment options for CLL have evolved during the last several decades. The development of targeted therapies has led to new and more effective treatment regimens, resulting in better outcomes for patients. The field of CLL treatment is moving away from the use of chemotherapy to these newer targeted therapies.

Although current therapies do not offer a cure for CLL, there are now many treatment options that have the potential to give patients longer remissions and a better quality of life. Treatment options for CLL include:

- The Watch and Wait approach or Active Surveillance
- Single or combination drug therapy
- Chemoimmunotherapy (chemotherapy combined with immunotherapy)
- Targeted therapies
- Monoclonal antibody therapies
- A clinical trial (to be considered at any point treatment is being discussed; see *Research and Clinical Trials* on page 28)
- Radiation therapy (rarely used for CLL)
- Splenectomy (removal of the spleen, rarely used for CLL)
- Allogeneic stem cell transplantation

The goals of CLL treatments are to:

- Stop the CLL cells from multiplying

- Activate programmed cell death (apoptosis) in the CLL cells
- Provide long periods of remission (when there are no signs or symptoms of CLL)
- Improve survival
- Help people manage symptoms and complications of the disease

People with CLL are treated by a hematologist-oncologist. Patients are advised to consult with a doctor who specializes in CLL and to discuss their most appropriate treatment options, including whether participation in a clinical trial is recommended.

Watch and Wait. In this approach, also called “active surveillance,” people with CLL are observed regularly by their hematologist-oncologist. This approach includes:

- Routine medical exams (to check the size of lymph nodes, spleen, etc)
- Routine blood tests to determine whether the disease is stable or beginning to progress

Patients are not treated with drugs or other therapies during the Watch and Wait period. When people receive a diagnosis of CLL and then learn that they will not begin treatment right away, they are often concerned. However, the Watch and Wait approach is the current standard of care when there are minimal changes in red blood cell and platelet counts and no symptoms of CLL. It is important to note that a rapidly rising lymphocyte count in patients who have no other symptoms may not be a cause to start treatment.

Are you concerned that you will not begin treatment right away? Speak to your doctor to get more information about the Watch and Wait approach.

This approach may seem scary and counterintuitive. Many people who are diagnosed with cancer begin drug treatment right away. But CLL can be a very slow-progressing disease, and in many patients the disease will not be serious enough at the time of diagnosis to warrant drug treatment. In addition, a small number of patients never need to receive treatment for CLL.

Many studies have compared the Watch and Wait approach to an early treatment approach for people with low-risk CLL. Studies have led to the following findings:

- To date, clinical trials have not shown that there are any benefits of early treatment in terms of survival.

- Several studies have confirmed that patients with early-stage CLL do not benefit from the use of alkylating agents (see **Table 6** on page 19) or aggressive chemotherapy, and these treatments do not prolong survival.
- There are risks associated with early treatment, including potential side effects and treatment complications.
- Patients may develop resistance to the drugs used in early treatment, meaning that these drugs could no longer be options once disease progression makes treatment essential.

This topic will remain of interest to doctors and will continue to be studied in clinical trials.

For more information see the free LLS fact sheet *Watch and Wait*.

When to Start Treatment. Some people with CLL can be managed with a Watch-and-Wait approach for years before their disease progresses. The decision to treat a person with CLL is based on a number of factors that indicate the disease is progressing. According to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Guidelines, the following conditions define active disease. The patient should meet at least one of these criteria in order to start CLL treatment:

- Disease involvement that is extranodal (outside of the lymph nodes), in the skin, kidneys, lungs and spine
- Enlarging lymph nodes (at least 10 cm) noted over a series of clinical exams
- Enlarging spleen noted over a series of clinical exams
- Evidence of progressive marrow failure based on the development or worsening of
 - Anemia (hemoglobin level of less than 10 g/dL), and/or
 - Thrombocytopenia (platelet count of less than 100,000/ μ L)
- Autoimmune anemia and/or thrombocytopenia with poor response to corticosteroids
- Doubling of lymphocyte count in less than 6 months, or progressive lymphocytosis with an increase of more than 50 percent over a 2 month period
- Presence of specific CLL symptoms
 - Significant fatigue
 - Night sweats (more than once per month with no evidence of infection)
 - Unexplained weight loss (10% or more of baseline weight within the previous 6 months)
 - Fever (higher than 100.5° F for 2 or more weeks) without other evidence of infection

Table 5, below, summarizes the tests that need to be done before a patient begins treatment.

Table 5. Baseline Evaluation of Patients with CLL

Diagnostic Test	General Practice ^a	Clinical Trial
To establish the diagnosis:		
Complete blood count with differential	Always	Always
Immunophenotyping of peripheral blood lymphocytes	Always	Always
Prior to treatment:		
Medical history and physical exam; performance status ^b	Always	Always
Complete blood count with differential	Always	Always
Bone marrow aspiration and biopsy	When clinically indicated	Desirable
Serum chemistry, serum immunoglobulin and direct antiglobulin test	Always	Always
Chest x-ray	Always	Always
Infectious disease status	Always	Always
Additional tests prior to treatment:		
Molecular cytogenetics (FISH) test to check for del(13q), del(11q), del(17p) and add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping of peripheral blood lymphocytes (with specific stimulation)	NGI (not generally indicated)	Desirable
<i>TP53</i> gene mutation	Always	Always
<i>IGHV</i> mutational status	Always	Always
Serum beta-2 microglobulin	Desirable	Always
CT scan of chest, abdomen and pelvis	NGI	Desirable
MRI and PET scans	NGI	NGI
Abdominal ultrasound	Possibly	NGI

^aGeneral practice” is defined as the use of accepted treatment options for CLL patients not enrolled in a clinical trial.

^bPerformance status helps to quantify a cancer patient’s general well-being and activities of daily life.

Abbreviations: FISH, fluorescence in situ hybridization; del, deletion or removal of a piece of DNA; add, addition/extra copy of a chromosome; *IGHV*, immunoglobulin heavy chain variable; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; NGI, not generally indicated.

Source: Hallek M et al. *Blood*. 2018.

Initial Treatment of Symptomatic CLL. Treatment for CLL needs to start when symptoms that are associated with active disease progression develop. It is important that you speak to the healthcare team about the sequence, or order, of your treatments for CLL. Talk to them about long-term treatment, versus a fixed-duration treatment (6-12 months) and the specific side effects of each treatment option.

Before beginning treatment, it is important for patients to have the following tests:

- Cytogenetic (FISH) test to determine if del(17p) or del(11q) is present
 - If this test was not done at the time of the initial diagnosis, it should be done at this time for treatment planning.
 - If previous testing was done months or years ago, this test should be repeated at this time.
- Assessment of *IGHV* and *TP53* gene mutational status
- Screening for prior hepatitis B exposure
- Direct antibody test (DAT, also known as the “direct Coombs test”); if anemia is present, evaluate for possible hemolysis (red blood cell destruction)

Because CLL is more prevalent in older people, evaluation of a patient’s fitness and identification of other medical conditions or problems (comorbidities) that may affect CLL treatment is very important. (The median age at diagnosis is 70 years, although CLL has been diagnosed in people as young as age 30). CLL treatment options are impacted by the patient’s age, fitness and health.

Another important factor in the treatment choice is the patient’s genetic risk profile. For instance, the deletion of the short arm of chromosome 17, abbreviated del(17p), is associated with a less favorable prognosis and resistance to chemotherapy. The presence or absence of del(17p) is essential information that must be taken into account when determining which treatment option to use. Testing for *IGHV* mutational status is also necessary when considering chemoimmunotherapy.

After all these tests are completed, CLL patients are typically classified into one of two categories based on mutation status.

Patients Without del(17p) or *TP53* Mutations. The following are preferred first-line treatment regimens for this group of patients, which includes patients 65 years and younger without comorbidities and also those who are older than 65 years with comorbidities:

- Ibrutinib (Imbruvica®)
- Acalabrutinib (Calquence®), with or without obinutuzumab (Gazyva®)

- Venetoclax (Venclexta®) in combination with obinutuzumab

Other treatment options for these patients include:

- Ibrutinib in combination with obinutuzumab
- FCR—Fludarabine (Fludara®), cyclophosphamide (Cytosan®), and rituximab (Rituxan®)
- FR—Fludarabine (Fludara®) and rituximab (Rituxan®)

The first treatments prescribed to many patients in this category include ibrutinib or acalabrutinib or venetoclax in combination with obinutuzumab. However, some patients may be candidates for intensive chemoimmunotherapy; these patients are generally treated with a combination called FCR (see *Chemoimmunotherapy* on page 25 and *Monoclonal Antibody Therapies* on page 23). This therapy is very effective at reducing the extent of the disease and, for most patients, is well tolerated. Studies have shown that this combination is most effective in patients with the *IGHV* gene mutation but without the del(17p) or *TP53* mutations.

Results from studies with long-term follow-up periods have shown that some patients who received FCR continue to have no detectable disease 10 years after the end of treatment. However, there can be complications associated with this therapy. Some studies have indicated a higher incidence of neutropenia and a more frequent occurrence of viral and bacterial infections for up to 2 years after the completion of this treatment. (Neutropenia is a decrease in the number of neutrophils, a type a white blood cell, in the blood.) Recent research has also indicated that up to 5 percent of patients treated with FCR develop treatment-related myelodysplastic syndrome or acute myeloid leukemia. Despite the potential complications, FCR remains an option given the achievement of long-term remission in some patients. See *Treatment Response and Follow-Up Care* on page 35. Nonetheless, most CLL patients are increasingly being treated with ibrutinib or acalabrutinib or venetoclax in combination with obinutuzumab. A large, randomized study demonstrated that an ibrutinib-based therapy offers a better chance of survival than treatment with FCR.

Venetoclax, given in combination with obinutuzumab, is a chemotherapy-free combination and is given for a fixed period of 12 months. Results showed that patients achieved durable, progression-free survival after 12 months of treatment and a higher rate of minimal residual disease (MRD) negativity compared to obinutuzumab plus chlorambucil. See *Minimal/Measurable Residual Disease* on page 35.

Patients With del(17p) or TP53 Mutations. Patients with del(17p) or TP53 mutations, whether younger or older, either do not respond well to treatment or are likely to have early relapses if the first-line therapy is any type of chemoimmunotherapy. The following treatments are approved for patients with del(17p) and should be used as a first option, unless there are contraindications:

- Ibrutinib (Imbruvica®)
- Acalabrutinib (Calquence®), with or without obinutuzumab (Gazyva®)
- Venetoclax (Venclexta®) in combination with obinutuzumab

Less effective regimens include rituximab (Rituxan®) plus high-dose methylprednisolone or alemtuzumab (Campath®).

Clinical trials should always be considered. Allogeneic stem cell transplantation may also be an option for this patient group (see page 27).

Table 6. Some Drugs Approved or in Clinical Trials for the Treatment of CLL

<p>Targeted Therapies</p> <ul style="list-style-type: none"> • Acalabrutinib (Calquence®) • Duvelisib (Copiktra®) • Ibrutinib (Imbruvica®) • Idelalisib (Zydelig®) • Venetoclax (Venclexta®) <p>Monoclonal Antibodies</p> <ul style="list-style-type: none"> • Alemtuzumab (Campath®) • Obinutuzumab (Gazyva®) • Ofatumumab (Arzerra®) 	<ul style="list-style-type: none"> • Rituximab (Rituxan®)^a • Rituximab and hyaluronidase human (Rituxan Hycela®) <p>Alkylating Agents</p> <ul style="list-style-type: none"> • Bendamustine hydrochloride (Bendeke®) • Chlorambucil (Leukeran®) <p>Antitumor Antibiotics</p> <ul style="list-style-type: none"> • Doxorubicin (Adriamycin®) 	<p>DNA-Damaging Agent</p> <ul style="list-style-type: none"> • Cyclophosphamide (Cytosan®) <p>Antimetabolites</p> <ul style="list-style-type: none"> • Cladribine (2-CdA; Leustatin®) • Fludarabine (Fludara®) • Pentostatin (Nipent®) <p>Corticosteroids</p> <ul style="list-style-type: none"> • Prednisone • Dexamethasone
--	---	--

^aAfter the first dose of Rituxan, patients may be switched to Rituxan Hycela. It is possible for a patient to be treated with drugs that are not listed in this table and still receive appropriate and effective treatment for CLL.

New treatments may have been approved since this book was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Targeted Therapies. These drugs generally have an impact on specific features of cancer cells. In most cases, targeted therapies are given orally and are generally better tolerated than chemotherapy agents.

Kinase Inhibitors. Kinases are enzymes that are found in both normal cells and cancer cells. Kinases move chemicals called phosphates from one molecule to another. Kinase inhibitors stop the phosphates from being moved and block growth signals and pathways within cancer cells. These drugs are associated with fewer side effects than chemotherapy agents. There are many different kinases in CLL cells, including phosphatidylinositol 3-kinase (PI3-kinase) and Bruton tyrosine kinase (BTK), which are the focus of several targeted therapies. These are summarized below.

○ **Acalabrutinib (Calquence®)**

- This oral medication is taken twice a day, every 12 hours.
- It is a targeted therapy that blocks the kinase protein known as BTK.
- It is FDA-approved for the treatment of adult patients with CLL/SLL.
 - As a single agent
 - In combination with obinutuzumab
- Symptomatic patients with CLL take acalabrutinib continuously until it does not work anymore, or until side effects occur that require them to stop taking it.
- The common side effects are anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain. These symptoms generally subside over time.
- Serious but uncommon side effects include infection, bleeding and decrease in blood cell counts.
- Patients should tell their healthcare team about all the medicines they take, including prescription and over-the-counter medicines including antacids and blood thinners, vitamins, and herbal supplements. Taking acalabrutinib with certain other medications may affect how acalabrutinib works and can cause side effects.

○ **Duvelisib (Copiktra®)**

- This is an oral medication taken twice a day.
- It is a dual inhibitor of the kinase called PI3K-delta and PI3K-gamma.
- It is FDA-approved for the treatment of relapsed or refractory chronic CLL or small lymphocytic lymphoma (SLL) after at least two prior therapies.
- Common side effects include diarrhea, neutropenia, rash, fatigue, fever, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain and anemia.

○ **Ibrutinib (Imbruvica®)**

- This is an oral medication that is taken once a day.
- It is an inhibitor of the Bruton's tyrosine kinase (BTK).
- It is FDA-approved for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.
 - As a single agent
 - In combination with bendamustine and rituximab
 - In combination with rituximab or obinutuzumab
- Symptomatic patients with CLL take ibrutinib continuously until it does not work anymore, or until side effects occur that require them to stop taking it.
- Thus far, patients have taken ibrutinib for up to more than 7 years without any long-term side effects.
- Unlike chemotherapy, ibrutinib initially causes the number of leukemia cells to increase as lymph nodes shrink, due to the lymphocytes being released into the blood.
- In most patients, this is followed by a decline in the number of leukemia cells in the blood, which may take several months.
- The common side effects of ibrutinib are rashes, diarrhea, fatigue, thrombocytopenia, musculoskeletal pain, neutropenia, anemia and bruising. These symptoms generally subside over time.
- Serious but uncommon side effects include bleeding, atrial fibrillation and high blood pressure.
- The risks and benefits of ibrutinib use should be considered when used with other medicines that may also increase the risk of bleeding, including aspirin and anti-inflammatory drugs, blood thinners and supplements such as fish oil, vitamin E and flaxseed oil.
- Because of the risk of bleeding, ibrutinib should be stopped for 3 days before and 3 days after any minor surgery. For major surgeries, ibrutinib should be stopped for 7 days before and 7 days after surgery.

○ **Idelalisib (Zydelig®)**

- This oral medication is taken twice a day.
- A targeted therapy, it blocks the kinase protein known as PI3K.
- It is FDA-approved for the treatment of relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities. It is also approved for relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

- Idelalisib is not indicated or recommended for first-line treatment.
- The most common side effects of idelalisib are diarrhea, fatigue, nausea, cough, fever, abdominal pain, pneumonia, and rashes.
- Symptomatic patients with relapsed CLL are given idelalisib twice daily continuously until it does not work anymore, or until side effects occur that require them to stop taking it.
- Similar to ibrutinib, idelalisib initially causes the leukemia blood cell count to increase as lymph node size decreases. In most patients, this is followed by a decline in the number of leukemia blood cells over time.
- The most common side effects are fatigue, liver function abnormalities, diarrhea, pneumonia, nausea, cough, fever, abdominal pain and infection. Liver function abnormalities can be very serious, and it is important to monitor liver function with blood tests during the first several months of therapy.
- Idelalisib can cause an immune-related colitis associated with diarrhea that often shows up after 9 to 12 months (or longer) on therapy. Patients should be seen by the doctor if diarrhea develops.
- Idelalisib is not known to cause any excess bleeding and it can be given together with blood thinners. This treatment is a good choice for patients with relapsed CLL who are at risk for significant excessive bleeding (for example, hemophilia).
- It increases the risk for tumor lysis syndrome (see page 34). Talk to your doctor about what this means for you.

BCL2 Proteins and Cell Death. B-cell lymphoma 2 (BCL2) proteins are a family of proteins that regulate the growth and death of cells. In CLL, abnormal function of BCL2 proteins prevents normal cell death, resulting in the uncontrolled growth of cancer cells.

- **Venetoclax (Venclexta®)**
 - This targeted therapy is an oral medication taken once a day.
 - It is a small-molecule inhibitor that targets the BCL2 protein, a protein overexpressed in CLL.
 - It is FDA-approved:
 - For the treatment of adult patients with CLL or small lymphocytic lymphoma (SLL).
 - In combination with obinutuzumab (Gazyva®) for the treatment of people with previously untreated CLL or SLL. This treatment combination allows patients to stop treatment after 12 months. Results of studies showed durable progression-free survival after 12 months

and a higher rate of MRD negativity compared to obinutuzumab plus chlorambucil.

- In combination with rituximab (Rituxan®) for the treatment of patients whose cancer has progressed after at least one prior treatment, regardless of whether their cancer cells have del(17p). This treatment combination allows patients to stop treatment after approximately 2 years.
- Venetoclax is not a type of chemotherapy. It is a pill that works differently from other treatments to help restore apoptosis, a natural process of cell death that is disrupted when you have cancer. Through apoptosis, your body kills cancer cells.
- Common side effects include low blood cell counts, diarrhea, nausea, upper respiratory infection and fatigue.
- There is a risk of tumor lysis syndrome, but this can be prevented through appropriate monitoring and prophylactic measures (see page 34). Talk to your doctor about what this means in your case.

Monoclonal Antibody Therapies. Monoclonal antibodies are proteins produced in the laboratory that either react with or attach to specific antigens on the target cells. Examples of antibody therapies that target CD20 and CD52 include the following:

Monoclonal antibodies that target CD20

- **Alemtuzumab (Campath®)**
 - This drug targets the CD52 antigen found on the surface of CLL cells.
 - It is indicated as a single agent for the treatment of B-cell CLL.
 - It is administered intravenously (IV) over a 2-hour period.
- **Obinutuzumab (Gazyva®)**
 - This drug is approved in combination with venetoclax (Venclexta®) for the treatment of people with previously untreated CLL or small lymphocytic lymphoma (SLL). This treatment combination allows patients to stop treatment after 12 months.
 - It is also approved in combination with chlorambucil for the treatment of patients with previously untreated CLL.
 - It is a liquid that is administered by slow injection via IV infusion over a period of a few hours.
- **Ofatumumab (Arzerra®)**
 - This drug is generally used if CLL does not respond to other treatments, such as other monoclonal antibodies or chemotherapy.

- It is administered via IV infusion. It takes about 6 hours to receive the first dose.
- Ofatumumab is approved
 - In combination with chlorambucil for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate
 - In combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL
 - For extended treatment of patients who have had complete or partial response after at least two lines of therapy for recurrent or progressive CLL
 - For the treatment of patients with CLL that is refractory to fludarabine and alemtuzumab (Campath®)
- **Rituximab (Rituxan®)**
 - This drug is approved for adult patients with previously untreated and previously treated CD20-positive CLL in combination with fludarabine (Fludara®) and cyclophosphamide.
 - It is a liquid that is slowly administered via intravenous (IV) infusion.
 - It has become one of the standard treatments for CLL.
- **Rituximab and hyaluronidase human (Rituxan Hycela®)**
 - This drug is given subcutaneously (under the skin)
 - It is approved for adult patients with previously untreated or previously treated CLL in combination with fludarabine and cyclophosphamide (FC). This drug should be used only after patients have received at least one full dose of a rituximab product intravenously.

Chemotherapy. Chemotherapy drugs are designed to kill cancer cells. Some do so by damaging the DNA of the cancer cells or by disrupting the process of making DNA. Others interfere with cell components that are needed for making new cells. Chemotherapy is typically given in cycles, with each period of treatment followed by a rest period. There are many types of chemotherapeutic agents, including anti-metabolites, alkylating agents, and corticosteroids as listed below.

Anti-metabolites:

- Cladribine (Leustatin®)
- Fludarabine (Fludara®)
- Pentostatin (Nipent®)

Alkylating agents:

- Bendamustine hydrochloride (Bendeka®)
- Chlorambucil (Leukeran®)
- Cyclophosphamide (Cytoxan®)

Corticosteroids may also be given with chemotherapy. Examples of corticosteroids include:

- Prednisone
- Dexamethasone

Chemoimmunotherapy. After the introduction of the anti-CD20 monoclonal antibody rituximab (Rituxan®), chemoimmunotherapy regimens combining chemotherapy drugs with rituximab were established. Examples of these are:

- **FCR: fludarabine (Fludara), cyclophosphamide and rituximab (Rituxan)**
- **BR: bendamustine (Bendeka®) and rituximab**

Before the introduction of newer targeted agents, younger patients with CLL who needed to receive treatment were given a chemo-immunotherapy regimen, provided they were in good health and had no major comorbidities. The goal of these higher-intensity treatments was to induce deep and durable remissions for patients. With the advent and approval of these targeted agents, there are additional treatment options for patients. Currently, first-line chemoimmunotherapy is considered an option for young, fit patients with low-risk disease—patients with mutated *IGHV* but without *del(17p)* or *TP53* mutations—given the excellent long-term outcomes for these patients.

Radiation Therapy. This treatment uses high-energy rays to destroy cancer cells. It is not part of standard treatment for CLL but is used in rare circumstances to shrink an enlarged spleen, enlarged lymph node masses, or masses in locations that interfere with the function of a neighboring body part, such as the kidneys, gastrointestinal tract or throat. It can be helpful in treating pain from bone damage caused by leukemia cells growing in the marrow.

Splenectomy. In some patients, CLL cells can accumulate in the spleen. Sometimes the spleen becomes so enlarged that it starts pressing on nearby organs, causing discomfort. If it is enlarged, surgical removal of the spleen (splenectomy) may improve blood cell counts and reduce the need for transfusions. This approach is used selectively for patients who have severe recurrent bouts of autoimmune diseases that target either the red blood cells—causing autoimmune hemolytic anemia (AIHA)—or the platelets, causing immune thrombocytopenic purpura (ITP). In such cases, removal of the spleen can help reduce the severity of the anemia (in AIHA) or low platelet count (in ITP). See *Disease and Treatment-related Complications* on page 31.

Treatment Options for Relapsed or Refractory Cases

The term “relapsed” is used to refer to cases in which the CLL responds to therapy, but after 6 or more months, becomes active again. “Refractory” is the term used when treatment does not result in a remission (although it may remain stable), or the disease gets worse within 6 months of the last treatment.

Patients with relapsed or refractory CLL often have good quality of life for years after receiving additional treatment. **Patients should be re-tested to find out if their mutation profile has changed before planning their next treatment.** If symptoms return, treatments similar to those used initially can be considered again, if a patient’s initial length of response has been prolonged.

Abnormalities that involve the short arm of chromosome 17 are found in about 5 percent of patients at the time of diagnosis. In cases of relapsed and refractory CLL, the prevalence can increase to as high as 30 to 40 percent of patients. This can happen as a result of disease progression or the effects of past treatments.

The following are some drugs and treatments that can be used for relapsed or refractory CLL:

- Ibrutinib (Imbruvica®)
- Venetoclax (Venclexta®), alone or with rituximab (Rituxan®)
- Acalabrutinib (Calquence®)
- Duvelisib (Copiktra®)
- Idelalisib (Zydelig®) in combination with rituximab
- Ofatumumab (Arzerra®)
- Combinations of ibrutinib or venetoclax with anti-CD20 antibodies
- Allogeneic stem cell transplantation
- Alemtuzumab (Campath®), alone or in combination with other treatments

There is no role for chemoimmunotherapy in cases of relapsed or refractory CLL. See pages 20-24 for more information about the treatments listed above.

Idelalisib, ibrutinib, duvelisib and acalabrutinib are given for as long as there is a good treatment response, which can be indefinitely. Venetoclax, which is given for a period of two years, can be combined with rituximab. Patients who have signs of disease progression while they are taking any of these medications should keep taking them until a new therapy is started. Patients should never stop taking their medication unless directed to do so by their doctor.

In order to decide whether to treat with ibrutinib, acalabrutinib, idelalisib, venetoclax or duvelisib, doctors will consider the side effects of these medications and tailor the treatment to each individual patient.

Patients with relapsed CLL are advised to speak to their doctors about whether treatment in a clinical trial is a good option. Clinical trials involving new drug therapies, or allogeneic stem cell transplantation, may offer more appropriate treatment options (see *Research and Clinical Trials* starting on page 28).

Stem Cell Transplantation. Allogeneic stem cell transplantation is a treatment option for people with relapsed or refractory CLL categorized as high-risk. This type of stem cell transplant requires a matched donor. It may be an appropriate therapy for carefully selected younger people with CLL who can be matched with a stem cell donor. Talk to your doctor to see if this is a treatment option for you.

A modified form of allogeneic stem cell transplantation called a “reduced-intensity conditioning” or “nonmyeloablative” allogeneic stem cell transplantation may be another transplant option for CLL patients who do not respond to other treatments. This type of transplant is generally done in high-risk CLL patients with del(17p) or *TP53* gene mutations identified early in the course of their disease. It is also done in patients with relapsed CLL who have received multiple prior therapies. Even if a decision is made later not to go forward with the transplant, it is important for patients with high-risk CLL who require treatment, as well as for patients with relapsed CLL, to be evaluated for potential transplantation relatively early in the course of the disease.

For more information see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

CAR T-Cell Therapy. This is a type of immunotherapy in which a patient’s own immune system cells are collected and modified, so that when they are reintroduced into the patient’s body, they will recognize and then attack cancer cells. This approach has shown very promising results in patients with blood cancers. The T cells are genetically engineered to produce receptors on their surfaces, called “chimeric antigen receptors” (CARs), which recognize and bind to a specific target on the cancer cells. Clinical trials are in progress to study the use of CD19-directed CAR T-cell therapy in the treatment of chemotherapy-resistant, relapsed CLL, or CLL that has not responded to treatment with ibrutinib. The results of recent trials have demonstrated that this new approach can induce long-term, disease-free remissions in CLL patients.

For more information see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts*.

Please call (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials.

Financial Concerns

In the past few years there have been significant advances in the treatment of CLL. New targeted therapies, such as **ibrutinib (Imbruvica®)**, **idelalisib (Zydelig®)**, **acalabrutinib (Calquence®)**, **venetoclax (Venclexta®)** and **duvelisib (Copiktra®)**, have been shown to provide remarkable outcomes for patients with CLL, improving their survival and quality of life. However, the cost of these medications is significantly higher than the standard treatments used previously, which raises concerns for both patients and healthcare providers.

All four of these medications are expensive. In addition, ibrutinib, idelalisib and duvelisib require continuous daily use until they stop working or the disease progresses. Treatment with venetoclax can be completed in a set amount of time, but the treatment period is still significant: 1 year for first-line (initial) treatment and 2 years for relapsed and refractory cases. The financial impact can be a burden for patients. It can also limit access to these medications and lower treatment adherence when patients are unable to afford them.

Speak to your doctor if you have any concerns about being able to afford your CLL medication. A member of your treatment team may be able to provide information and resources that can help. Health insurance plans may not cover all the costs of cancer care, but there are many resources available for prescription drug payment assistance. In addition, several major pharmaceutical manufacturers currently provide patient assistance or prescription assistance programs. These programs can provide both insured and uninsured patients with free or reduced-cost medications.

For more assistance, call an LLS Information Specialist at (800) 955-4572 for information about prescription assistance programs, co-pay programs and LLS financial programs for patients.

For more information and resources to cope with the financial aspects of cancer care see the free LLS booklet *Cancer and Your Finances*.

Research and Clinical Trials

New approaches to CLL treatment are being studied in clinical trials. This research holds the promise of increasing the rate of remission and duration of the treatment response, finding additional chemotherapy-free treatment options and eventually finding a cure for CLL. Many of these clinical trials are being supported by LLS research programs.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called “clinical trials” before it becomes part of the standard treatment for a disease. Clinical trials are carefully designed and reviewed by expert clinicians

and researchers as well as patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time treatment is discussed with the doctor. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option for them. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Research on Treatment Approaches. A number of approaches are under study in clinical trials for the treatment of patients with CLL.

New Targeted Treatments. Specific new drug therapies under study in clinical trials for people with CLL include:

- **Kinase Inhibitor Therapy.** Some types of cancer can be treated with kinase inhibitor drugs that target specific enzymes within the cancer cells that are involved in cell growth and death. These drugs, listed below, may be associated with fewer side effects than traditional chemotherapy agents:
 - Ibrutinib (Imbruvica®)
 - Acalabrutinib (Calquence®)
 - Zanubrutinib (Brukinsa®)
 - Tirabrutinib (ONO-4059 or GS-4059)
 - Duvelisib (Copiktra®)
 - Umbralisib (TGR-1202)
- **Monoclonal Antibodies**
 - Ofatumumab (Arzerra®)
 - Cirmtuzumab (UC-961)
 - Obinutuzumab (Gazyva®)
 - Ublituximab (TG-1101)
- **Combinations of Antibodies and Other Targeted Drugs**
 - Combination regimens with venetoclax (Venclexta®)
 - Combination regimens with immunomodulatory drugs
 - Multidrug combination regimens consisting of 3 or 4 drugs

Immunomodulatory Drug Therapy. The oral drug lenalidomide (Revlimid®) is a targeted treatment used in patients with myeloma and is now being studied for use in CLL patients. It stimulates a person's own immune system to attack cancer cells. It also interferes with a wide range of the components of the CLL microenvironment, the network of cells and molecules that allow CLL cells to survive and grow.

Early Treatment of CLL. Several ongoing trials are investigating the potential benefit of early treatment interventions, particularly in patients with high-risk CLL, using new drugs in development that are less toxic than current standard CLL treatments.

National Veteran Affairs Tumor Registry Study. Exposure to Agent Orange, the herbicide used for deforestation during the Vietnam War, has been associated with the development of CLL. This multi-center, retrospective study focused on assessing the impact of Agent Orange exposure on prognosis and management in patients with CLL, using data from the National Veteran Affairs Tumor Registry. According to the study's findings, exposure to Agent Orange was not associated with unfavorable prognostic factors or shortened survival in CLL patients from the large veteran population examined.

CLL Natural History Study. This study helps researchers understand how CLL cells behave in the body, which should ultimately help to develop new and better treatments for CLL patients. Applying new technologies to investigate the molecular basis and clinical indicators of CLL and small lymphocytic lymphoma (SLL) can clarify processes involved in disease progression and possibly lead to the discovery of new targeted treatments. Patients with CLL may qualify for this clinical trial if they have not yet received treatment for the disease.

CAR T-Cell Therapy. This type of immunotherapy consists of collecting and modifying a patient's own immune system cells, so that when they are reintroduced into the patient's body, they will recognize and attack cancer cells. This approach has shown very promising results in patients with blood cancers. The T cells are genetically engineered to produce receptors on their surfaces, called "chimeric antigen receptors" (CARs), which recognize and bind to a specific target on the cancer cells.

For more information see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts*.

PD-1 Checkpoint Inhibitors. A vital part of the immune system is its ability to distinguish healthy cells in the body from those that it recognizes as foreign or harmful. The immune system depends on multiple checkpoints—molecules on certain immune cells that must either be activated or deactivated to start an immune response. Cancer cells sometimes take advantage of these checkpoints to escape detection by active immune cells. Programmed cell death 1 (PD-1) is

a checkpoint protein found on the surface of T cells. It normally acts as a kind of “off switch” that helps keep immune cells from attacking healthy cells in the body. It does this by attaching to PD-L1, a protein found on some normal cells as well as some cancer cells. When PD-1 binds to PD-L1, a message is sent to the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1 receptors, which help them avoid being attacked by the immune system.

Checkpoint inhibitors are drugs created to target PD-1 or PD-L1. By blocking the activity of these proteins, they allow the immune system to recognize and eliminate cancer cells. Two examples are:

- Nivolumab (Opdivo®)
- Pembrolizumab (Keytruda®)

We encourage you to contact an LLS Information Specialist and to visit www.LLS.org/CTSC for more information about finding a clinical trial.

Disease and Treatment-Related Complications

Infections. People with CLL may be more susceptible to infections caused by the disease itself and/or its treatment. A higher risk of infection is caused by:

- The inability of leukemia cells to make antibodies needed to fight infections
- The effect of treatment, which reduces the number of two types of infection-fighting white blood cells in the blood, called neutrophils and monocytes

Because of the increased risk of infections, vaccination every 5 years for pneumococcal pneumonia and a yearly flu vaccine are recommended. CLL patients should never receive live vaccines, such as Zostavax (a live shingles vaccine), but they can receive Shingrix® because it is an inactivated shingles vaccine. Current COVID-19 vaccines are also recommended, although they have not been specifically tested in patients with CLL as of this printing. Speak to your doctor for more information.

Antibiotic therapy is usually required to treat bacterial or fungal infections that may occur during the course of the disease. People who get recurrent infections may also receive injections of immunoglobulin (gamma globulin) on a regular basis to correct the immune deficiency. This treatment is expensive, but it can help decrease the frequency of infections in CLL patients who have low levels of immunoglobulin in their blood.

Cytomegalovirus (CMV) reactivation occurs in about 10 to 25 percent of patients with relapsed or refractory CLL who are treated with alemtuzumab. Rates of reactivation as high as 6 percent have also been reported in patients treated

with idelalisib (Zydelig®). It is important to monitor for this potential problem during alemtuzumab or idelalisib therapy. In addition, appropriate preventive, anti-infection measures and routine monitoring for early signs of infection should be considered for patients who receive these drug therapies.

Hepatitis B virus (HBV) reactivation has been reported in patients treated with chemotherapy, with or without immunotherapy agents. HBV reactivation has also been reported in patients treated with alemtuzumab, ibrutinib, acalabrutinib and idelalisib. Prophylactic antiviral care and continuous monitoring for HBV are recommended for patients receiving therapy with anti-CD20 monoclonal antibodies, alemtuzumab, ibrutinib, acalabrutinib and/or idelalisib, who are at high risk for this complication.

Low Blood Cell Counts. Supportive (palliative) care for CLL may include administering blood cell growth factors to improve low blood cell counts. The use of white blood cell growth factors may benefit patients who have prolonged low white blood cell counts after treatment. Examples of white blood cell growth factors are:

- Granulocyte-colony stimulating factors (G-CSF), under the names filgrastim (Neupogen®) and pegfilgrastim (Neulasta®), can increase the number of neutrophils
- Granulocyte macrophage-colony stimulating growth factor (GM-CSF) sargramostim (Leukine®) can increase the number of neutrophils and monocytes

Richter Transformation. In about 2 to 10 percent of people with CLL, the disease transforms into a more complex type of blood cancer. The vast majority (95 percent) of this relatively small group of people develop diffuse large B-cell lymphoma (DLBCL), and the other 5 percent develop Hodgkin lymphoma (HL), during the course of their disease and treatment. This complication, known as “Richter transformation” or “Richter’s syndrome,” is much more common in patients with high-risk factors. These include advanced stage CLL according to the Rai system assessment; del(17p), trisomy 12, *TP53* or *NOTCH1* mutations; and *IGHV*-unmutated CLL.

Richter transformation generally occurs between 2 and 6 years after a diagnosis of CLL. Patients may have significantly enlarged lymph nodes and experience fevers and weight loss. Lymphocyte masses may also develop in parts of the body other than the lymph nodes. This transformation appears to be much less common in patients who do not receive chemoimmunotherapy for treatment of their CLL.

Patients with Richter transformation of CLL into DLBCL are typically treated with regimens designed for DLBCL treatment. Allogeneic stem cell transplantation may be considered following a response to initial therapy. Standard treatment

for HL is used for patients with Richter transformation of CLL into HL. With aggressive therapy, these patients tend to do better and may be cured of the lymphoma, although they will not be cured of the underlying CLL.

Some treatment responses have been reported in recent studies with the use of checkpoint inhibitors and CAR T-cell therapy for CLL patients with Richter transformation. Treatment in a clinical trial should be considered for these patients. If remission is achieved, these patients should consider an allogeneic stem cell transplant, which is the only curative option.

Call (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials.

Autoimmune Cytopenias. The most frequent autoimmune cytopenias in CLL patients are autoimmune hemolytic anemia (AIHA), immune-mediated thrombocytopenia (also known as “immune thrombocytopenic purpura” or ITP) and pure red blood cell aplasia (PRCA). Autoimmune cytopenias occur in 4 to 10 percent of patients with CLL. Bone marrow tests may be used to confirm the presence of these conditions.

AIHA is the most common form of autoimmune cytopenia. People with AIHA produce antibodies that work against their red blood cells, causing them to be eliminated rapidly from the blood. The loss of red blood cells due to these “autoantibodies” can worsen the effects of already low red blood cell counts.

The direct antiglobulin test (DAT, also known as the “direct Coombs test”) is used to identify the autoantibodies; however, most patients with AIHA have a negative DAT test result. In these cases, additional serum markers, such as low haptoglobin (a blood protein) and elevated reticulocyte (immature red blood cell) levels, are required to make the diagnosis. Other patients who are also more likely to develop AIHA include those with advanced disease and high-risk factors such as unmutated *IGHV* gene status, increased serum beta-2 microglobulin levels, and high expression of ZAP-70. Less often, the antibody works against the platelets. This condition, called “immune thrombocytopenic purpura” (ITP), results in significantly decreased platelet counts.

The drugs prednisone, rituximab (Rituxan®) and cyclosporine are sometimes used to treat AIHA and ITP. Splenectomy should be considered if the patient does not respond to steroid therapy. The drugs romiplostim (Nplate®) and eltrombopag (Promacta®) are both FDA-approved for the treatment of ITP that is resistant to other treatments. There is now significant clinical experience with the use of ibrutinib (Imbruvica®) to treat the underlying CLL, which often resolves these autoimmune complications as well.

Tumor Flare Reactions. This drug-related complication is a painful enlargement of the lymph nodes that may be accompanied by an elevated lymphocyte count, enlarged spleen, low-grade fever, rashes and bone pain. These reactions are

commonly seen in CLL patients treated with lenalidomide (Revlimid®). Use of steroid medications to control the inflammation, and antihistamines to manage the rash are recommended.

Tumor Lysis Syndrome (TLS). This is a potentially life-threatening condition that occurs when large amounts of tumor cells are killed all at once by the cancer therapy, releasing their content into the bloodstream. Patients with very enlarged, “bulky” lymph nodes are considered at high risk for developing TLS, which is best managed if it can be anticipated and treatment is given for it before chemotherapy begins.

Treatment for TLS includes increased hydration, monitoring and management of electrolyte imbalances and abnormal uric acid levels, as well as therapy with the drug rasburicase (Elitek®), as needed. When starting venetoclax (Venclexta®), it is important to monitor for TLS. Detailed guidelines for prevention and monitoring of TLS when using venetoclax are readily available to doctors.

Second Cancer Risk. People with CLL have a high risk of developing a second cancer. This may be due to abnormalities in immune system function associated with the disease or caused by the use of chemotherapy drugs, which can induce potentially long-lasting remission but are also associated with prolonged immunosuppression. The types of cancer that are seen most frequently as a second cancer in CLL patients are acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), melanoma, gastrointestinal cancer, breast cancer, lung cancer, non-melanoma skin cancer, prostate cancer, kidney cancer, bladder cancer, and head and neck cancers.

People diagnosed with CLL can develop AML or MDS whether they receive treatment or not. These complications are more common after treatment with FC: fludarabine (Fludara®) and cyclophosphamide or with FCR: fludarabine, cyclophosphamide and rituximab (Rituxan®).

Although all CLL patients should be advised about their increased risk for developing a second cancer, studies indicate there are certain factors that may help predict increase risk for these other cancers. These factors include:

- Age (higher risk in patients older than 60 years)
- Sex (higher risk in males)

It is important to have follow-up appointments with your hematologist-oncologist on a regular basis due to the increased second cancer risk associated with CLL. An annual comprehensive skin exam is also strongly recommended.

For more information about long-term and late effects see the free LLS booklet *Long-Term and Late Effects of Treatment in Adults Facts*.

Treatment Response and Follow-Up Care

Treatment Outcomes. Treatment outcomes for people with CLL vary widely. The expected outcomes for each patient depend on the stage of the disease, whether or not they have certain factors associated with higher-risk CLL, their overall health and other considerations. Current research suggests that the newer treatment combinations and approaches for CLL may improve the length of survival, compared to previous treatment options for the disease. People with CLL should consult with their doctors to discuss the potential outcomes in their specific case.

Minimal/Measurable Residual Disease. Some people with CLL have such a low level of CLL cells remaining in their bodies after treatment that the cancer cannot be detected by standard blood tests or bone marrow examinations. In this situation, called "minimal/measurable residual disease" (MRD), more sensitive tests may be performed to detect these abnormal cells. The methods generally used to detect MRD in people with CLL are four-color flow cytometry and allele-specific polymerase chain reaction (AS-PCR). These tests are reliably sensitive to a level of less than one CLL cell in a sample of 10,000 leukocytes.

When patients have less than one CLL cell per 10,000 leukocytes in blood or bone marrow cell samples based on these sensitive tests, the disease is in a deep state of remission classified as MRD undetectable or MRD-negative (abbreviated MRD–). Blood samples can generally be used to make this determination. However, because some therapies eliminate CLL cells more effectively from the blood than from the bone marrow, in some circumstances it may be necessary to confirm that the bone marrow aspirate also has an undetectable level of MRD. This is often the case when anti-CD20 monoclonal antibody treatment is used.

Having undetectable MRD (U-MRD) status after treatment with some drug regimens for CLL is becoming an important factor for predicting prolonged effectiveness of the treatment. Another proposed goal of MRD assessment is to eventually develop risk-adapted treatment strategies for CLL patients. Patients who have a detectable level of MRD after the end of treatment could be candidates for treatment intensification, consolidation and maintenance strategies. Those who achieve U-MRD status early in the course of treatment may be candidates for treatment de-escalation strategies. However, to achieve this long-term goal, highly sensitive methods specific to MRD detection must be available, and further study on the predictive capacity of these testing methods will be necessary. Some patients may only achieve a partial response with a targeted therapy, but may do very well for a long period of time without the disease progressing, even without achieving U-MRD status. At present, MRD assessment is primarily used in clinical trials, including clinical trials being conducted to find the most effective way to deepen treatment responses in patients with CLL.

For more information see the free LLS booklet *Minimal Residual Disease*.

Table 7 describes the criteria for various types of CLL treatment responses. Stable disease means absence of progressive disease (PD) and failure to achieve at least a partial response (PR).

Table 7. Responses to CLL Treatment

Group	Parameter	CR (Complete Response)	PR (Partial Response)	PD (Progressive Disease)
A	Lymph nodes	None ≥ 1.5 cm	Decrease $\geq 50\%$ from baseline	Increase $\geq 50\%$ from baseline or response assessment
	Liver and/or spleen size (spleen size considered normal if < 13 cm)	Spleen size < 13 cm; liver size normal	Decrease $\geq 50\%$ from baseline	Increase $\geq 50\%$ from baseline or response assessment
	Constitutional symptoms ^a	None	Any	Any
	Circulating lymphocyte count	Normal	Decrease $\geq 50\%$ from baseline	Increase $\geq 50\%$ from baseline
B	Platelet count	$\geq 100,000/\mu\text{L}$	$\geq 100,000/\mu\text{L}$ or increase $\geq 50\%$ from baseline	Decrease $\geq 50\%$ from baseline secondary to CLL ^b
	Hemoglobin	≥ 11.0 g/dL (without transfusion or erythropoietin)	≥ 11.0 g/dL or increase $\geq 50\%$ from baseline	Decrease ≥ 2 g/dL from baseline secondary to CLL ^b
	Bone marrow	Normal cell count, no CLL cells, no B-lymphoid nodules	Presence of CLL cells or B-lymphoid nodules, or test was not done	Increase $\geq 50\%$ in CLL cells based on successive biopsies

Abbreviations and qualifications: CR, complete response (all of the criteria have to be met); PR, partial response (at least 1 of the parameters of group A and 1 of group B needs to improve if previously abnormal; if only 1 parameter of both groups A and B are abnormal prior to therapy, only 1 needs to improve); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met; constitutional symptoms alone do not indicate PD).

^aConstitutional symptoms are general, indicate a system wide effect of a disease, and can be associated with many conditions. They can include fever, night sweats, extreme fatigue and weight loss.

^bSecondary to CLL means that this decrease in platelets or hemoglobin is due to the CLL and not from something else (for example, autoimmune disorder, treatment, etc).

Source: Hallek M et al. *Blood*. 2018. (See references.)

Follow-Up Care. After treatment, patients who are in remission and have completed treatment continue to be examined regularly by their doctors. Careful periodic assessment of the patient's health, blood cell counts and, if indicated, other testing may be required to assess the full effect of treatment, as well as to identify signs of disease relapse. Patients need to keep their doctors informed of any changes they notice (for example, infections, lymph node changes, etc). These assessments may become less frequent over time.

People who have been treated for CLL are encouraged to:

- Maintain regular follow-up appointments with their hematologist-oncologists. Their doctors will monitor them for signs of relapse and also be able to detect any side effects from treatment or the onset of other medical problems.
- Keep a record of your cancer diagnosis, treatment, and follow-up care needs. This is often called a “survivorship care plan.” Ask your doctor for a written survivorship care plan. Share this information with any new healthcare providers you see. The plan should include the following information:
 - List of all healthcare providers
 - Diagnosis summary with specifics such as subtype and/or genetic markers
 - Treatment summary with specifics such as the names, dates, and dosages of chemotherapy or other drugs, site of radiation treatment, surgery and/or transplantation information, response to treatment, and side effects
 - Maintenance treatment information, if applicable
 - List of possible late effects
 - Schedule for ongoing monitoring with recommended tests, frequency and coordinating provider
 - Health and wellness recommendations such as nutrition, exercise or other disease screenings
- Receive periodic screening and monitoring for skin, gastrointestinal, kidney, blood, bladder, prostate, breast, lung, head and neck and other types of cancer because of the increased risk of a second cancer associated with CLL (see *Second Cancer Risk* on page 34).
- Seek medical and psychosocial support for fatigue, depression and other long-term effects, if needed.
- Consider cancer risk-reduction strategies, such as smoking cessation, skin protection against prolonged sun exposure, healthy eating and exercising.

For additional information, including the risks of specific treatments, see the free LLS booklet *Long-Term and Late Effects of Treatment in Adults Facts*.

Related Diseases

Diseases related to CLL, such as prolymphocytic leukemia, result from the cancerous transformation of a type of lymphocyte. The accumulation of these cancer cells occurs primarily in the bone marrow, the blood and the spleen.

There are distinguishing characteristics that enable the hematologist-oncologist to identify each type of disease, including: the appearance and the immunophenotype of the cancer cells; the varying effects of the cancer cells on normal bone marrow and blood cell development and also on other parts of the body, such as the kidneys, bowels and nervous system.

The CLL-related diseases listed in **Table 8** have a range of clinical severity. At one end of the range are the diseases that may be stable and may not progress for some months or years or, in occasional cases, indefinitely. At the other end of the range are diseases associated with complications that may be present at diagnosis and that can possibly get worse without rapid intervention, therefore requiring immediate treatment and frequent observation.

Table 8. Diseases Related to CLL

Slower progression	Faster progression	Fastest progression
<ul style="list-style-type: none">• Hairy cell leukemia^a• Large granular lymphocytic leukemia (LGL)^b• Waldenström macroglobulinemia^a	<ul style="list-style-type: none">• Prolymphocytic leukemia• Mantle cell lymphoma^a	<ul style="list-style-type: none">• Acute lymphoblastic leukemia^a

^aFor more information, please see the free LLS booklet or factsheet about this disease.

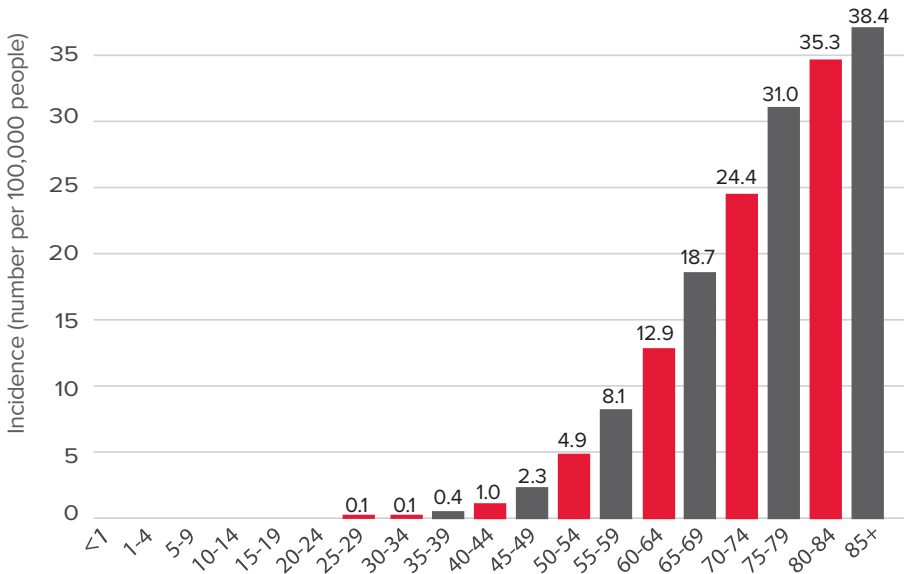
^bFor more information, please visit the webpage www.LLS.org/LGL.

Incidence, Causes and Risk Factors

Incidence. CLL is the most common type of leukemia in Western countries, accounting for over 45% of all cases of leukemia. The disease generally affects older individuals; more than 70% of patients with CLL are older than 65 years (see **Figure 1** on page 39). The median age at diagnosis is 72 years.

CLL affects more males than females. CLL incidence is substantially lower among Asian individuals and higher among Ashkenazi Jews. The reason for these differences is not known.

**Figure 1. Chronic Lymphocytic Leukemia (CLL):
Age-Specific Incidence Rates 2013-2017**



The frequency of new cases of CLL per 100,000 people, by 5-year age groups.

Source: National Institutes of Health; National Cancer Institute. Table 13.1 Leukemia; Age-specific incidence rates. Trends in SEER (Surveillance, Epidemiology, and End Results Program) SEER Cancer Statistics Review 1974-2017.

Causes and Risk Factors. There are few known risk factors for CLL. Some studies have associated exposure to Agent Orange, an herbicide used during the Vietnam War, with an increased risk of CLL. The Health and Medicine Division (formerly known as the Institute of Medicine) of the National Academy of Sciences, Engineering and Medicine issued a report titled *Veterans and Agent Orange: Update 2008*, which concluded that there was “sufficient evidence of an association” between herbicides used in Vietnam and CLL, hairy cell leukemia and other chronic B-cell leukemias. A recent study focused on investigating the impact of Agent Orange exposure on the prognosis and treatment of patients with CLL. Veterans who were exposed to Agent Orange may be eligible for additional US Department of Veteran Affairs (VA) benefits. If you are a Vietnam Veteran with CLL, it is worth getting a formal evaluation at the VA. Visit www.publichealth.va.gov/exposures/agentorange/ for more information.

Other studies suggest that exposure to benzene in the workplace increases the risk of CLL. However, the evidence is not as strong for CLL as with other blood cancers.

Genetic factors likely play a role in the development of CLL, as some families have more than one family member with the disease. First-degree relatives of patients with CLL are approximately four times more likely to develop CLL than people who do not have first-degree relatives with the disease. However, the risk

is small. For example, the 60-year-old sibling or child of someone with CLL would have three to four chances in 10,000 of developing the disease, compared with one chance in 10,000 for a 60-year-old person without a family history of the disease.

Visit www.LLS.org/DiseaseRegistries for information on studies about the occurrence of the same type of blood cancer in two or more blood relatives.

Normal Blood and Bone Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

Plasma. Plasma is largely made up of water, in which many chemicals are dissolved. These chemicals each have a special role. They include:

- Proteins
 - Albumin, the most common blood protein
 - Blood-clotting proteins (coagulation factors) made by the liver
 - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
 - Immunoglobulins, proteins that help the body fight infection
- Hormones, such as thyroid hormone and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B₁₂
- Electrolytes, such as calcium, potassium and sodium

Blood Cells. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." The blood cells are suspended in the plasma. See **Figure 2** on page 41.

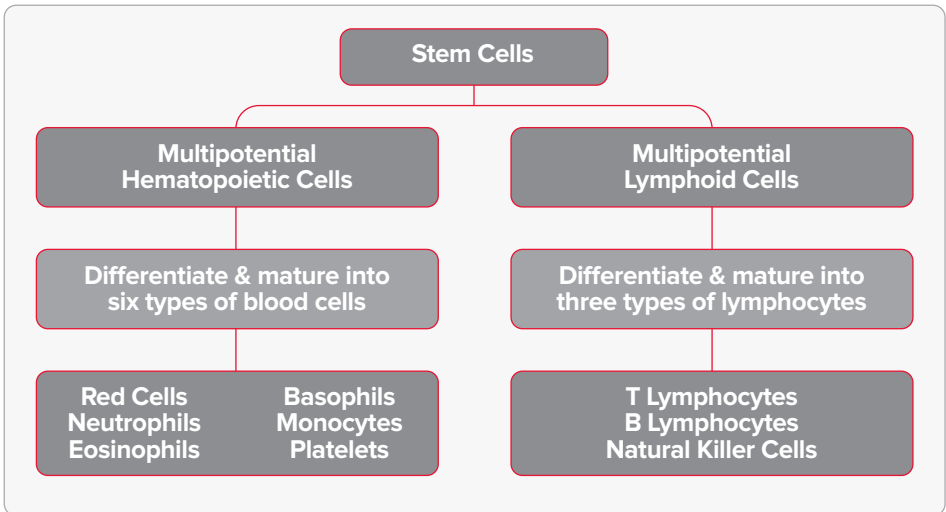
Once the stem cell is created, it will develop into one of the three types of blood cells:

1. Red blood cells (the cells that carry oxygen)
 - These make up a little less than half of the body's total blood volume.
 - They are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO₂) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO₂ is removed from the lungs.

2. Platelets (the cells that help blood to clot)
 - These are small cells (one-tenth the size of red blood cells).
 - They help stop bleeding from an injury or cut.
 - They stick to the torn surface of the vessel, clump together and plug up the bleeding site. They form a clot with the help of proteins, such as fibrin, and electrolytes, such as calcium.

3. White blood cells (WBCs). These are the cells that fight infections. They include:
 - Neutrophils and monocytes. These cells, called “phagocytes,” ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
 - Eosinophils and basophils. These WBCs respond to allergens or parasites.
 - Lymphocytes. These WBCs, found mostly in the lymph nodes, spleen and lymphatic channels, are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
 - T lymphocytes (T cells)
 - B lymphocytes (B cells)
 - Natural killer cells (NK cells)

Figure 2 . Blood Cell & Lymphocyte Development



Stem cells develop into blood cells (hematopoiesis) and lymphocytic cells.

Bone Marrow. In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as it passes through the marrow and then circulate throughout the body.

In babies, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have blood-forming marrow. In adults, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be used for transplants. Some stem cells enter the bloodstream and circulate. Doctors know how to stimulate the growth of these cells in the marrow and make them migrate into the bloodstream. Then a special technique called “apheresis” is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

The Lymphatic System

The marrow is really two organs in one. It is (1) the organ that forms blood cells, and it is (2) the organ that forms lymphocytes, which make up part of the immune system.

The marrow produces three main types of lymphocytes. They are:

- B lymphocytes (B cells), which make antibodies in response to foreign antigens, especially microbes
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for other white blood cells to recognize the antibody and pull it into the cell (ingest it) along with its attached microbe. The white blood cell then kills and ingests the microbe.
- Natural killer (NK) cells, which attack virus-infected cells or tumor cells without requiring an antibody or other mediation. T cells and NK cells have other functions as well, and are important elements in research efforts to design immunotherapies to treat lymphoma and other cancers.

The lymphocytes circulate through channels called “lymphatics,” which connect the lymph nodes to each other throughout the body. The lymphatic channels collect into large ducts that empty into blood vessels. Lymphocytes enter the

blood via these ducts. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system, such as the skin, spleen, tonsils and adenoids, intestinal lining, and (in young people) the thymus.

Resources and Information

LLS offers free information and services to patients and families affected by blood cancers. This section of the booklet lists various resources available to you. Use this information to learn more, to ask questions and to make the most of the knowledge and skills of the members of your healthcare team.

For Help and Information

Consult With an Information Specialist. Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date disease, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information.

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm ET)
- Email and Live Chat: www.LLS.org/InformationSpecialists

Clinical Trial Support Center. Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find a clinical trial according to their needs and personally assist them throughout the entire clinical-trial process. Please visit www.LLS.org/CTSC for more information.

Free Information Booklets. LLS offers free education and support booklets that can be either read online or ordered. Please visit www.LLS.org/booklets for more information.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.

Financial Assistance. LLS offers financial assistance to individuals with blood cancer. Please visit www.LLS.org/finances for more information.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. Please call or visit our website for more information.

- Call: (877) 557-2672
- Visit: www.LLS.org/copay

Free Mobile Apps

- LLS Coloring For Kids™ – Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.
- LLS Health Manager™ – Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian with experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or for more information.

Podcast. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Please visit www.LLS.org/TheBloodline for more information and to subscribe.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

Continuing Education. LLS offers free continuing education programs for healthcare professionals. Please visit www.LLS.org/ProfessionalEd for more information.

Community Resources and Networking

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Please visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients reach out and share information. Please visit www.LLS.org/chat to join.

LLS Chapters. LLS offers community support and services in the United States and Canada, including the *Patti Robinson Kaufmann First Connection® Program* (a peer-to-peer support program), local support groups and other great resources. For more information about these programs or to contact the nearest chapter, please call or visit our website.

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to obtain our directory.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. Please call or visit our website for more information.

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

Additional Help for Specific Populations

Información en español (LLS Information in Spanish). Please visit www.LLS.org/espanol for more information.

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs (VA). For more information, please call the VA or visit the website.

- Call: (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks who were subsequently diagnosed with a blood cancer may be eligible for help from the WTC Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were either in the NYC disaster area, or who lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please call the WTC Health Program or visit their website.

- Call: (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a 2-week period. For more information, please call the National Institute of Mental Health (NIMH) or visit their website.

- Call: (866) 615-6464
- Visit: www.nimh.nih.gov and enter “depression” in the search box

Health Terms

Allogeneic Stem Cell Transplantation. A treatment that uses stem cells from a healthy donor to restore a patient's bone marrow and blood cells. It uses high doses of chemotherapy and sometimes radiation to "turn off" a patient's immune system so that the donor cells are not rejected.

See the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Anemia. A health condition that occurs when a person has a low number of red blood cells and therefore a low hemoglobin concentration. When this happens, it is hard for the blood to carry oxygen. People with severe anemia can be pale, weak, tired and easily become short of breath.

Antibodies. A type of protein created by blood cells when they are invaded by bacteria, viruses or other harmful foreign substances called "antigens." Antibodies help the body fight against invaders that cause illness. They can also be produced in the lab and are used to help detect certain types of cancer and to treat other cancer/diseases.

Antigen. Any substance that causes the body to make an immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses or other substances that come from outside the body.

Basophil. A type of white blood cell present in certain allergic reactions.

Beta-2 microglobulin (B2M). A small protein normally found on the surface of many cells, including lymphocytes, and in small amounts in the blood and urine. An increased amount in the blood or urine may be a signal of certain diseases, including some types of cancer, such as multiple myeloma or lymphoma. The degree of elevation of the serum B2M level appears to correlate with *IGHV* mutation status and ZAP-70 protein expression. Patients with a high level of ZAP-70 expression or an unmutated *IGHV* gene status are more likely to have a high B2M level. The test to measure B2M is available in most laboratories in the United States.

Bone Marrow. A spongy tissue in the hollow central cavity of the bones where blood cells are made. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In adults, the bones of the hands, feet, legs and arms no longer contain blood-forming marrow, and these bones are instead filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried in the bloodstream throughout the body.

Bone Marrow Aspiration. A test done to look for abnormal marrow cells in a bone marrow sample. The area around the hip bone is numbed, a special needle is inserted, and a fluid sample is drawn out of the marrow. Usually, this test is done at the same time as a bone marrow biopsy.

Bone Marrow Biopsy. A test done to look for abnormal marrow cells. The area around the hip bone is numbed, a special needle is inserted, and a sample of bone containing marrow is removed. Usually, this test is done at the same time as a bone marrow aspiration.

Bone Marrow Transplantation. See Allogeneic Stem Cell Transplantation.

CD38. An antigen on CLL cells and other cells. The expression of CD38 may be a marker for predicting CLL progression. See Cluster Designation.

Chemotherapy. A treatment that uses chemical agents (medications) to kill cancer cells.

Chromosome. Thread-like structures within cells that carry genes in a linear order. Human cells have 23 pairs of chromosomes: the chromosome pairs numbered 1 to 22 and a 23rd pair that contains the sex chromosomes (XX for females and XY for males).

Clonal. The designation for a population of cells derived from a single transformed parent cell. Virtually all cancers are derived from a single cell with an injury (mutation) to its DNA and therefore are monoclonal. Leukemia, lymphoma, myeloma and myelodysplastic syndromes are examples of clonal cancers, meaning they are derived from a single abnormal cell.

Cluster Designation (CD). A term used in conjunction with a number to identify a specific molecule on the surface of an immune cell. It is commonly used in its abbreviated form, for example: “CD20”—the target of the monoclonal antibody therapy rituximab (Rituxan®)—and “CD52,” the target of the monoclonal antibody therapy alemtuzumab (Campath®).

Colony-Stimulating Factor. See Growth Factor.

Eosinophil. A type of white blood cell that helps fight some parasitic infections and participates in allergic responses.

Erythrocytes. See Red Blood Cells.

Fluorescence In Situ Hybridization (FISH). A technique to study chromosomes in cells and tissues. It uses probes with fluorescent molecules that emit light of different wavelengths and colors. The probes bind to the chromosomes within the cells, and the chromosomes emit fluorescent color. A FISH test can be helpful in assessing the risk profile and treatment needs of patients, and for monitoring treatment effectiveness by detecting cell abnormalities, such as 17p deletion.

Flow Cytometry. A test that identifies specific types of cells in a sample. During this test, cells flow through an instrument called a “flow cytometer.” When the cells with the antibody-specific features pass through its laser beam, they light up and can be counted. This test may be used to examine blood cells, bone marrow cells or cells from a tissue biopsy.

G-Banding Karyotyping. A testing method that makes a certain characteristic of chromosomes easier to see. A “karyotype” is the systematic arrangement, using images, of the 46 human chromosomes of a cell. Karyotypes are examined for deviations from the expected arrangement, number, size, shape or other characteristics of the chromosomes. Each chromosome pair has a characteristic banding pattern. To make the banding pattern easier to see, a dye called “Giemsa” may be used as a stain. This process is also referred to as “G-banding.” This type of karyotyping and other cytogenetic tests provide doctors with information that contributes to determining the best treatment approach for individual patients. It takes longer than the FISH test but has the advantage of being able to detect any changes that are visible because it does not rely on specific probes. Usually, both tests are done on samples from the bone marrow, especially at the time of diagnosis. See karyotype.

Gene. A small section of DNA that is passed from parent to child. Most genes provide instructions for making specific proteins that are used in one or more types of cells in the body. These proteins perform many important roles in the body, including breaking down food, carrying oxygen and detecting and destroying bacteria and viruses.

Granulocyte. A type of white blood cell with many particles (granules) in the cell body. Neutrophils, eosinophils and basophils are the three types of granulocytes.

Growth Factor. A substance used to increase the numbers of neutrophils after chemotherapy. Granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) are growth factors that can be produced in the lab.

Hematologist. A doctor who specializes in blood cell diseases. A hematologist-oncologist specializes in blood cancers.

Hematopoiesis. The formation of all types of blood cells that starts in the bone marrow. For the blood cell development process, see *Normal Blood and Bone Marrow* on page 40.

Immunoglobulin Heavy Chain Variable (*IGHV*) Region Gene Status. A marker that can distinguish between CLL subtypes (unmutated vs mutated *IGHV*). CLL patients with unmutated *IGHV* gene status may have more rapid disease progression.

Immunophenotyping. A process used to find specific types of cells within a blood sample. It looks at antigens or markers on the surface of the cells to identify antibodies.

Karyotype. The order, number and appearance of chromosomes within a cell. There are 46 human chromosomes: 22 pairs called “autosomes” and a 23rd pair, shown separately, with the sex chromosomes (either XX or XY). See Fluorescence In Situ Hybridization (FISH) and G-banding Karyotyping.

Lymph Nodes. Small structures, the size of beans, which contain large numbers of lymphocytes and are connected with each other by small channels called “lymphatics.” Lymph nodes are distributed throughout the body. In patients with lymphoma and some types of lymphocytic leukemia, the malignant lymphocytes grow inside the lymph nodes and they become enlarged.

Lymphatic System. System of the body consisting of the lymph nodes, thymus gland (in the first several decades of life), lymphatic channels, lymphatic tissue of the bone marrow, gastrointestinal tract, skin and spleen, along with the T lymphocytes, B lymphocytes and natural killer (NK) lymphocytes contained in those sites. (These different types of lymphocytes are also referred to B cells, T cells and NK cells.)

Lymphocyte. A type of white blood cell that is important to the body's immune system. There are three major types of lymphocytes: 1) B lymphocytes (B cells), which produce antibodies to help combat infectious agents, such as bacteria, viruses and fungi; 2) T lymphocytes (T cells), which have several functions, including assisting B lymphocytes in making antibodies; and 3) natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Lymphocytosis. An increase in the number of lymphocytes in the blood.

Macrophage. Type of white blood cell, referred to as a “scavenger cell,” that surrounds and kills microorganisms, removes dead cells and stimulates the action of other immune system cells. See Monocyte.

Minimal Residual Disease (MRD). The small amount of cancer cells that may remain in the body after treatment. These cells can only be identified by sensitive molecular testing techniques. Also referred to as “measurable residual disease.”

Monoclonal. See Clonal.

Monocyte. A type of white blood cell that is made in the bone marrow and travels through the blood to tissues in the body, where it becomes a macrophage. See Macrophage.

Mutation. A change in the DNA that makes up a gene.

Neutropenia. An abnormal decrease in the number of neutrophils, a type of white blood cell, in the blood. See Neutrophil.

Neutrophil. A kind of white blood cell, and the main type that works to fight infection. People with certain types of blood cancer, or those who have received treatment (such as chemotherapy) for cancer, often have low neutrophil counts. People with low neutrophil counts are very susceptible to infections.

Oncologist. A doctor who specializes in treatment of cancer. A hematologist-oncologist specializes in cancers of the blood. See Hematologist.

Peripheral Blood. Blood circulating throughout the body.

Platelets. Small, colorless blood cell fragments that travel to and clump together at the site of a wound. Once there, the platelets' sticky surface helps them form clots and stop bleeding. Platelets make up about one-tenth of the volume of red blood cells. Also called “thrombocytes.”

Polymerase Chain Reaction (PCR). A technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be studied.

Red Blood Cells. These blood cells contain a substance called hemoglobin, which carries oxygen from the lungs to the tissues of the body. They make up about 40 to 45 percent of blood volume in healthy people. Also called “erythrocytes.”

Refractory. The term used to describe a disease that does not go away and/or improves after treatment.

Relapse. A return of the disease after it has been in remission following treatment. Also called “recurrence.”

Remission. When signs of a disease disappear, or diminish significantly, usually after treatment. Complete remission means that all evidence of the disease is gone. Partial remission means that the disease is significantly improved by treatment, but residual evidence of the disease is still present.

Resistance to Treatment. When cancer cells continue to grow even after administration of strong drugs and/or treatments, the disease is said to be “treatment resistant.”

Richter Transformation. In a small number of patients, CLL takes on the characteristics of an aggressive lymphoma. This change is not a second cancer, but rather a transformation of the CLL cells.

Spleen. This organ, in the left upper portion of the abdomen just under the left side of the diaphragm, acts as a blood filter. Enlargement of the spleen is called “splenomegaly.” Surgical removal of the spleen is known as “splenectomy.”

Stem Cell Transplantation. See Allogeneic Stem Cell Transplantation.

Stem Cells. Immature (undeveloped) cells that mature into red blood cells, white blood cells and blood platelets. Stem cells are mostly found in the bone marrow, but some leave the marrow and circulate in the bloodstream. Stem cells can be collected, preserved and used for stem cell therapy. See Hematopoiesis.

Thrombocytopenia. A disorder characterized by having too few platelets in the blood.

White Blood Cells. The five types of infection-fighting cells in the blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes. Also called “leukocytes.”

ZAP-70. Abbreviation for the cell protein called “zeta-chain associated protein kinase 70.” A high level of ZAP-70 expression on the leukemia cells of patients with B-cell CLL is one of several factors that may predict more rapid disease progression. Outside of a research laboratory, this test is generally not very reliable and should not be used.

References

- Brander D, Islam P, Barrientos JC. Tailored treatment strategies for chronic lymphocytic leukemia in a rapidly changing era. *American Society of Clinical Oncology Educational Book*. 2019; 39:487-498. doi:10.1200/EDBK_238735.
- Burger JA, O'Brien S. Evolution of CLL treatment – from chemoimmunotherapy to targeted and individualized therapy [review]. *Nature Reviews: Clinical Oncology*. 2018;15(8):510-527. doi:10.1038/s41571-018-0037-8.
- Chen Q, Jain N, Ayer T, et al. Economic burden of chronic lymphocytic leukemia in the era of oral targeted therapies in the United States. *Journal of Clinical Oncology*. 2017;35(2):166-175.
- Coutre SE. Is ibrutinib-based therapy the preferred initial treatment for all patients with CLL? Heallo web site; HemOnc PharmAnalysis [online]. Issue April 10, 2019. <https://www.heallo.com/news/hematology-oncology/20190328/is-ibrutinibbased-therapy-the-preferred-initial-treatment-for-all-patients-with-ll#:~:text=Yes.,most%20common%20leukemia%20among%20adults>. Accessed October 26, 2020.
- Furman R. Frontline management of chronic lymphocytic leukemia. *Clinical Advances in Hematology & Oncology*. 2017; suppl 10(8):1-20.
- Furstenau M, DeSilva N, Eichhorst B, et al. Minimal residual disease assessment in CLL: ready for use in clinical routine? *HemaSphere*. 2019;3:1-9.
- Goodman A., Helwick C. Treating patients with chronic lymphocytic leukemia in 2020. *The ASCO Post* [online]. March 10, 2020. <https://ascopost.com/issues/march-10-2020/treating-patients-with-chronic-lymphocytic-leukemia-in-2020/>. Accessed October 26, 2020.
- Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;31(25):2745-2760.
- Hallek M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification and treatment. *American Journal of Hematology*. 2017;92:946-965.
- Hallek M. Role and timing of new drugs in CLL. *Hematological Oncology*. 2017;35(suppl 1):30-32.
- Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. *American Journal of Hematology*. 2019;94:1266-1287.
- Hilal T, Betcher JA, Leis JF. Economic impact of oral therapies for chronic lymphocytic leukemia—the burden of novelty. *Current Hematologic Malignancy Reports*. 2018;13(4):237-243. doi:10.1007/s11899-018-0461-y.

Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2017. Bethesda, MD: National Cancer Institute; 2020. Based on November 2019 SEER data submission, posted to the SEER website April 15, 2020. https://seer.cancer.gov/csr/1975_2017/. Accessed October 28, 2020.

Jain N, Thompson P, Ferrajoli A, et al. Approaches to chronic lymphocytic leukemia therapy in the era of new agents: the conundrum of many options. *ASCO Educational Book* (American Society of Clinical Oncology Educational Book online). ascopubs.org/doi/full/10.1200/EDBK_200691. Accessed February 28, 2019.

Lazarian G, Guieze R, Wu CJ. Clinical implications of novel genomic discoveries in chronic lymphocytic leukemia. *Journal of Clinical Oncology*. 2017;35(9):984-993.

Liu Y, Wang Y, Yang J, et al. Zap-70 in chronic lymphocytic leukemia: a meta-analysis. *Clinica Chimica Acta*. 2018;483:82-88.

Mato A, Nabhan C, Lamanna N, et al. The connect CLL registry: final analysis of 1494 patients with chronic lymphocytic leukemia across 199 US sites. *Blood Advances*. 2020;4(7):1407-1418.

Mescher C. The impact of Agent Orange exposure on prognosis and management in patients with chronic lymphocytic leukemia: a National Veteran Affairs Tumor Registry Study. *Leukemia & Lymphoma*. 2017;59(6). doi:10.1080/10428194/2017.1375109.

National Cancer Institute. Drug combination improves outlook for some patients with chronic lymphocytic leukemia [news & events]. Published January 5, 2018. <https://www.cancer.gov/news-events/cancer-currents-blog/2018/venetoclaxrituximab-cll>. Accessed October 28, 2020.

National Comprehensive Cancer Network. NCCN Guidelines Version 1.2021. Chronic lymphocytic leukemia/Small lymphocytic lymphoma. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed October 29, 2020.

National Comprehensive Cancer Network. NCCN Guidelines for Patients. Chronic lymphocytic leukemia, 2019. <https://www.nccn.org/patients/guidelines/content/PDF/cll-patient.pdf>. Accessed October 29, 2020.

Primeau ASB. Genetic prognostic factors in CLL treated with novel compounds. *Cancer Therapy Advisor*. July 28, 2020. <https://www.cancertherapyadvisor.com/home/cancer-topics/chronic-lymphocytic-leukemia/chronic-leukemia-cll-genetic-prognostic-factors-novel-compounds/>. Accessed October 26, 2020.

Shustik C, Bence-Bruckler I, Delage R, et al. Advances in the treatment of relapsed/refractory chronic lymphocytic leukemia. *Annals of Hematology*. 2017;96:1185-1196.

Strati P, Jain N, O'Brien S. Chronic lymphocytic leukemia: diagnosis and treatment. *Mayo Clinic Proceedings*. 2018;93(5):651-664.

Tausch E, Schneider C, Robrecht S, et al. Prognostic and predictive impact of genetic markers in patients with CLL treated with obinutuzumab and venetoclax. *Blood*. 2020; 135(25):2402-2412. <https://doi.org/10.1182/blood.2019004492>.

Teh BW, Tam CS, Handunnetti S, Worth LJ, Slavin MA. Infections in patients with chronic lymphocytic leukaemia: mitigating risk in the era of targeted therapies [review]. *Blood Reviews*. 2018;52(6):499-507. doi:10.1016/j.blre.2018.04.007.

The Leukemia & Lymphoma Society. Chronic lymphocytic leukemia (CLL): what are my treatment options? May 21, 2020.

<https://www.lls.org/patient-education- webcasts/ chronic-lymphocytic-leukemia-cll-what-are-my-treatment-options>.

Vitale C, Ferrajoli A. Richter syndrome in chronic lymphocytic leukemia. *Current Hematologic Malignancy Reports*. 2016;11(1):43-51.

Wanner D, Steurer M. Chronic lymphocytic leukemia at ASH 2017. *Magazine of European Medical Oncology (MEMO)*. 2018.11(2):105-108. doi:10.1007/s12254-018-0414-0.



Get support. Reach out to our **INFORMATION SPECIALISTS**

The Leukemia & Lymphoma Society team consists of highly trained oncology social workers, nurses and health educators who are available by phone Monday through Friday, 9 a.m. to 9 p.m. (ET).

- Get one-on-one personalized support and information about blood cancers
- Know the questions to ask your doctor
- Discuss financial resources
- Receive individualized clinical-trial searches

Contact us at
800-955-4572 or
**www.LLS.org/
InformationSpecialists**

(Language interpreters can be requested)





For more information, please
contact our Information Specialists
800.955.4572 (Language interpreters
available upon request).

**BEATING
CANCER
IS IN
OUR BLOOD.**

National Office 3 International Drive, Suite 200 Rye Brook, NY 10573

The mission of The Leukemia & Lymphoma Society (LLS) is to cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families. Find out more at www.LLS.org.