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FOR PATIENTS & CAREGIVERS

# Chronic Lymphocytic Leukemia



Revised **2023**

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

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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.



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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.

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### Acknowledgement

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# Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. 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. But more work needs to be done. Researchers continue to study and develop new therapies in clinical trials to treat CLL.

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

While this booklet focuses on CLL, there is a type of non-Hodgkin lymphoma, called “small lymphocytic lymphoma (SLL),” which most experts consider essentially the same disease as CLL. This type of lymphoma starts in the same kind of cells that cause CLL but, at diagnosis, it is more localized in lymph nodes. Patients with SLL generally benefit from treatment with CLL-like regimens, rather than traditional lymphoma therapy. So, if you have been diagnosed with SLL, this booklet may also have helpful information for you.

We trust that this booklet will provide you with a good working knowledge about CLL or that it reinforces what you already know. We hope you will keep this booklet handy and, should you ever feel alone when confronting problems, you will turn to it for information and guidance to locate the support and resources you need. You can also contact us directly at (800) 955-4572.

We are here to help.

**All LLS publications mentioned in this booklet are free and can be viewed, downloaded or ordered online at [www.LLS.org/booklets](http://www.LLS.org/booklets).**

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# Leukemia Basics

Leukemia is a type of cancer. “Cancer” is a term for diseases in which abnormal cells grow uncontrollably and can spread to other parts of the body. Cancer can start almost anywhere in the body. Leukemia is a cancer of the blood and bone marrow.

There are three main types of blood cells: red blood cells, white blood cells and platelets. Red blood cells carry oxygen throughout the body. White blood cells help fight infections. Platelets help stop bleeding by clotting (clumping together) at the site of an injury.

Blood cells are made in the bone marrow, the spongy tissue in the center of most bones. The bone marrow contains immature cells that eventually develop into blood cells. Leukemia begins in one of the blood cells in the bone marrow. One or more mutations (changes) occur in the DNA (deoxyribonucleic acid) of the cell, and it becomes a type of cancer cell called a “leukemia cell.”

Leukemia cells do not mature into healthy functioning blood cells. They grow more quickly and live longer than normal blood cells. They divide and copy themselves making more and more leukemia cells. Over time, the leukemia cells crowd out and suppress the development of normal healthy blood cells in the bone marrow. As a result, the body does not have enough healthy red blood cells, white blood cells and platelets. When this happens, the body’s organs and tissues may not receive enough oxygen to work properly. Also, the body may not be able to fight infections or form blood clots when needed.

The four major types of leukemia are:

- Chronic lymphocytic leukemia (CLL)
- Acute lymphoblastic leukemia (ALL)
- Chronic myeloid leukemia (CML)
- Acute myeloid leukemia (AML)

Doctors classify leukemia based on:

- **The type of blood cell.** Leukemia is classified by the type of blood cell that becomes cancerous. The two primary types are lymphoid and myeloid. Lymphoid cells develop into a type of white blood cell called a “lymphocyte.” Myeloid cells can develop into red blood cells, platelets as well as certain other types of white blood cells (basophils, eosinophils, monocytes and neutrophils). Leukemia is classified as “lymphocytic” (or “lymphoblastic”) if the cancerous change starts in a lymphoid cell, or “myeloid” (or “myelogenous”) if the cancerous change originates in a myeloid cell. See **Figure 5** on page 45.

- **Disease progression (meaning either how quickly or how slowly the leukemia grows).** Leukemias can be “acute” or “chronic.” Acute leukemias develop and progress rapidly and usually get worse quickly if they are not treated. Acute leukemias affect cells that are not fully developed. These immature 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.

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

**How Chronic Lymphocytic Leukemia (CLL) Develops.** Lymphocytes are white blood cells that are part of the body’s immune system. There are three main types of lymphocytes: B cells, T cells and natural killer (NK) cells. CLL is a cancer that starts in B cells, (also called “B lymphocytes”). Healthy B cells produce special proteins called "antibodies." These antibodies bind to foreign substances such as bacteria and viruses, and mark them for destruction by other white blood cells.

CLL results from one or more mutations in the DNA (genetic material) of a single bone marrow cell that would otherwise develop into a healthy B cell. Genetic errors in the mutated cell cause the leukemia cell (also referred to as a “CLL cell”) to keep growing and dividing, whereas a healthy cell would stop dividing and eventually die. Every cell that arises from the initial leukemia cell also has the mutated DNA.

These leukemia cells do not function like normal B cells. As a result, people with CLL usually have weakened immune systems and are more vulnerable to infections because they lack sufficient numbers of healthy B cells and their antibodies.

In addition to being ineffective, the leukemia cells accumulate in the bone marrow and slow down normal blood cell production. As a result, people with CLL may not have enough mature, healthy red blood cells, other white blood cells and platelets. Having low levels of blood cells may result in anemia, infections and excessive bleeding or bruising.

Over time, the leukemia cells can spill out of the bone marrow into the bloodstream. This can cause the number of white blood cells in the blood to increase, but most of these are leukemia cells that do not protect against infection. Once in the blood, the leukemia cells can spread to the lymph nodes and other organs in the body.

**How Small Lymphocytic Lymphoma (SLL) Develops.** Small lymphocytic lymphoma (SLL) is a type of non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphoma is the term for different types of cancer that start in a lymphocyte in the lymphatic system, the network of organs and tissues that protect the body against disease and infection. The lymphatic system produces and releases lymphocytes that monitor and destroy bacteria, viruses and parasites that may enter the body.

In SLL, a genetic mutation causes abnormal B cells to build up and multiply, mostly in the lymph nodes. This causes the lymph nodes to swell and become larger than normal.

The abnormal lymphocytes in people with SLL are identical to those in people with CLL. According to the World Health Organization (WHO), CLL and SLL are considered the same cancer. They only differ by the location of the cancer cells. With CLL, the abnormal lymphocytes are found in the blood and bone marrow. They may also be in the lymph nodes and spleen. With SLL, there are few, if any abnormal lymphocytes in the blood. Instead, they are found mainly in the lymph nodes and spleen.

**Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS booklet *Non-Hodgkin Lymphoma* for more information about non-Hodgkin lymphoma.**

## Signs and Symptoms

Signs and symptoms are changes in the body that may indicate an illness or disease. A “sign” is a change that the doctor notices during an examination or notes in a laboratory test result. A “symptom” is a change that a patient can see and/or feel.

Many people with CLL are diagnosed with the disease before they have any symptoms. CLL is often detected during a routine blood test. A high number of lymphocytes, a type of white blood cell, is often the first sign of CLL.

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

- Infections
- Weakness or feeling tired
- Shortness of breath during normal physical activity
- Swelling of the lymph nodes in the neck, armpits, stomach or groin (top part of the inner thigh)
- Feeling of fullness below the ribs due to an enlarged spleen or liver
- Easy bruising or bleeding

- Petechiae (pinhead-sized red spots on the skin)
- B symptoms:
  - Fever when there is no infection
  - Heavy night sweats
  - Unexplained weight loss

## Medical Tests

While certain signs and/or symptoms may indicate that a person has CLL, laboratory tests are needed to confirm the diagnosis. It is important to have an accurate diagnosis because it helps the doctor to:

- Estimate how slowly or how quickly the disease will progress
- Determine the appropriate treatment

### Talk to your doctor about:

- The diagnostic tests that are being done
- What the results mean
- Getting copies of the results

**Medical History.** Your doctor will take a thorough medical history. The history may include information about past illnesses, injuries, treatments and medications. Some illnesses and cancers run in families, so the doctor may also ask about the health of your blood relatives. These include parents, grandparents, brothers and sisters. A family history of CLL or other blood cancers may increase your risk of developing CLL.

**Physical Examination.** The doctor will want to know about your current symptoms and will conduct a physical examination. During the examination, the doctor may listen to your lungs and heart and carefully examine your body for signs of infection and disease. To check the internal organs, the doctor may also feel different parts of your body. For example, the doctor may feel the abdomen to see if you have an enlarged spleen or liver. Because CLL can cause enlarged lymph nodes, the doctor may check the lymph nodes in your neck, armpits, stomach and groin.

**Complete Blood Count with Differential.** This test is used to measure the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin in the red blood cells. The complete blood count (CBC) should include a differential (diff), which measures the numbers of the different types of white blood cells—basophils, eosinophils, lymphocytes (B cells and T cells), monocytes and neutrophils.



A high number of B cells, one type of lymphocyte, may indicate CLL. People with CLL have "lymphocytosis" (a higher-than-normal number of lymphocytes) with more than 5000 B lymphocytes/microL ( $5 \times 10^9/L$ ) in the blood. Most of these lymphocytes are leukemia cells that do not protect against infection. In addition, these patients may also have a low number of red blood cells and platelets.

**Bone Marrow Aspiration and Biopsy.** Leukemia starts in the bone marrow, the spongy tissue inside the center of most bones. Bone marrow aspiration and bone marrow biopsy are procedures to collect and examine bone marrow.

- A bone marrow aspiration removes a small sample of liquid bone marrow for testing.
- A bone marrow biopsy removes a small sample of intact bone filled with bone marrow for testing.

For a bone marrow aspiration, a special, hollow needle is inserted through the hip bone and into the bone marrow and a liquid sample of cells is aspirated (removed). For a bone marrow biopsy, a wider needle is used to remove a sample of solid bone that contains bone marrow. Both samples are usually taken from the large hip bone in the lower back. The samples are then sent to the laboratory where they are examined under a microscope.

To diagnose CLL, it is usually not necessary for doctors to do a bone marrow aspiration or biopsy. 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.

**Lymph Node Biopsy.** Patients with enlarged lymph nodes may need to undergo a lymph node biopsy to determine whether their signs and/or symptoms are due to lymphoma, leukemia or some other condition. A lymph node biopsy is a procedure in which either all or part of a lymph node is removed and examined for signs of infection or disease such as cancer.

To ensure that there is enough tissue to make an accurate diagnosis, the preferred methods for the lymph node biopsy are often "excisional" or "incisional." In an excisional biopsy, the whole lymph node is removed. In an incisional biopsy, only part of the lymph node is removed. If the lymph node is just under the skin, the biopsy procedure is usually simple and can sometimes be done with a local anesthetic (numbing medication). If the lymph node is deep inside the chest or abdomen (stomach area), the patient may either be sedated or receive general anesthesia.

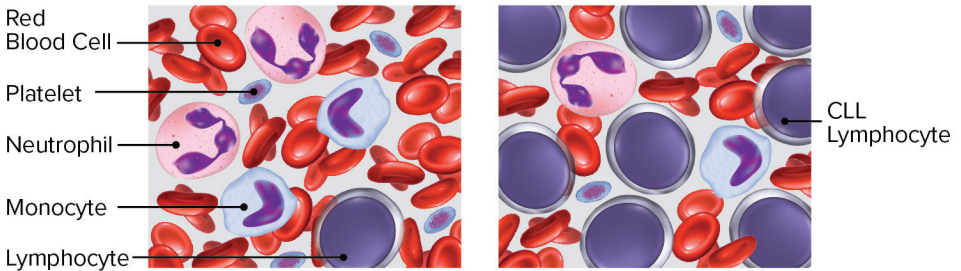
In certain situations, a "core needle biopsy" may be necessary if the lymph node is too difficult to reach. In this method, a wide needle is used to remove a column of tissue from the lymph node. This is done after the area has been numbed with

a local anesthetic. Another type of needle biopsy, called a “fine-needle aspiration biopsy,” is generally not suitable for diagnosing lymphoma. The fluid and cells drawn out through the long thin needle often does not provide enough cells to make an accurate diagnosis.

**Cell Assessment.** At the laboratory, a hematopathologist examines the blood, bone marrow and/or lymph node samples. A “hematopathologist” is a doctor who has special training in diagnosing diseases of the blood, bone marrow and lymphatic system.

The hematopathologist examines the cells under a microscope to determine their size, shape and type, and to identify other cell features. Normal blood contains many different blood cells including white blood cells and platelets, but most of the cells are red blood cells. In patients with CLL, there are too many CLL cells and not enough red blood cells, other healthy white blood cells and platelets (see **Figure 1** below).

**Figure 1. Normal Cells Versus CLL Cells**



**Left:** Normal blood contains red blood cells, white blood cells and platelets.

**Right:** The CLL cells multiply uncontrollably within the blood, bone marrow and lymphoid tissue, resulting in too many leukemia cells and too few healthy blood cells.

Additional tests are done on the samples to determine the type of leukemia or lymphoma.

**Immunophenotyping.** This laboratory test identifies the antigens, or proteins, on the surface of cells. This test is used to diagnose specific types of leukemia and lymphoma. Finding (or not finding) certain proteins on the surfaces of the cells can help the hematopathologist determine the type of leukemia or lymphoma. The pattern of the surface proteins is called the “immunophenotype.” In CLL, a blood sample is often used for this test, but it can also be done by using cells from the bone marrow, lymph nodes and other tissues. In SLL, a lymph node sample is often used.

Immunophenotyping is done with an instrument called a “flow cytometer.” A flow cytometer measures the number of cells in a sample, as well as specific characteristics of the cells, including their size and shape, and markers on the cell surface. A sample of cells 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.

Leukemia and lymphoma cells have different antigens on their surfaces. Certain antigens, called “cluster of differentiation (CD) proteins,” can help the hematopathologist determine the type of leukemia or lymphoma.

**Biomarker Testing.** Biomarker testing can be used to check for certain abnormal changes in genes or chromosomes in a person’s CLL cells. In the past, people with CLL all received the same treatment, but research has shown that not all CLL is the same. Doctors are now using biomarkers to gain more information about a patient’s CLL to predict the treatment that is most likely to work against their specific CLL. It is important to have biomarker testing and get a treatment plan specific for your CLL.

Biomarker testing should be done when the cancer is first diagnosed and may also be indicated before beginning treatment and after a relapse. This is because it is possible for the CLL cells to acquire additional genetic abnormalities.

The following tests are used to examine the chromosomes and genes in the leukemia cells:

**Cytogenetic Analysis (Karyotyping).** In this test, a hematopathologist uses a microscope to examine the chromosomes inside cells. In patients with CLL, cytogenetic analysis is used to look for abnormal changes in the chromosomes of the cancer cells.

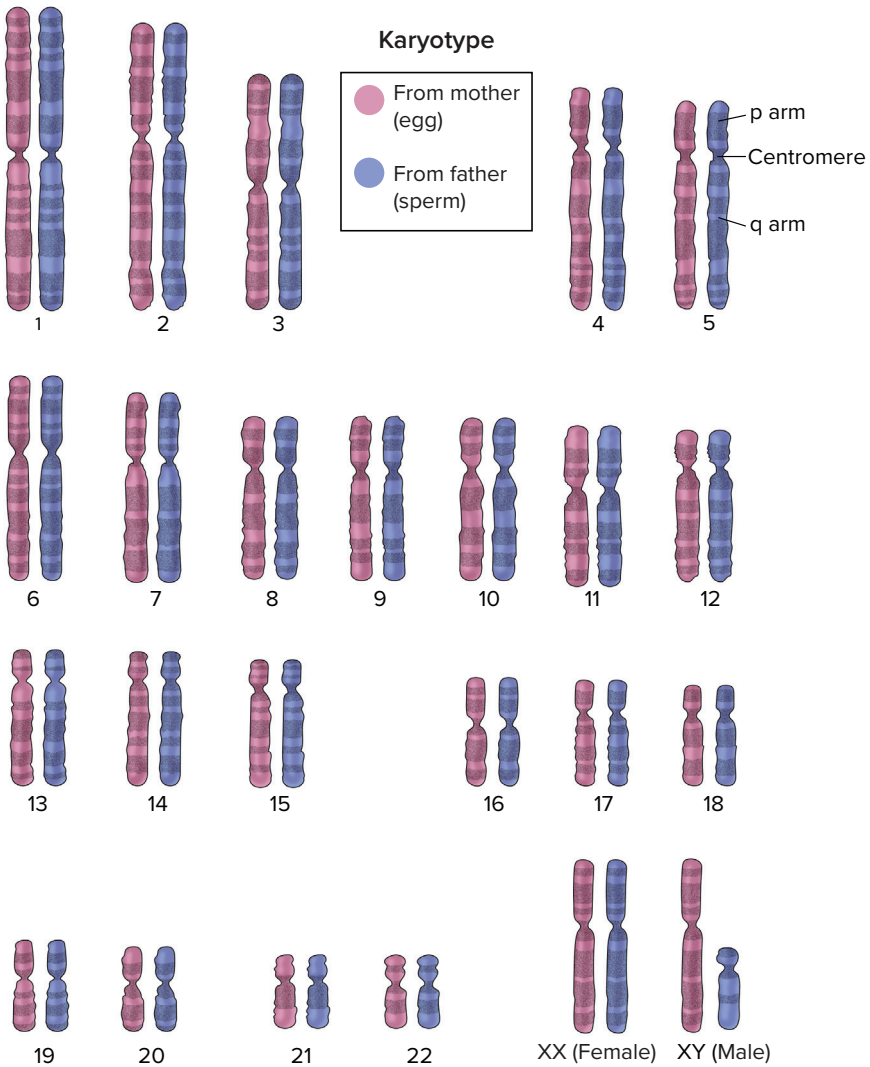
Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each pair of chromosomes is a certain size, shape and structure. In some cases of CLL, the chromosomes of the cancer cells have abnormal changes that can be seen under a microscope.

Chromosomes come in different lengths and striping patterns. Somewhere between one-third and two-thirds of the way down the chromosome is the centromere, a narrow region that divides the chromosome into two sections, or “arms.” The short arm of the chromosome is called the “p arm,” and the long arm of the chromosome is called the “q arm.” Geneticists use the names of the arms to describe the position of a specific section of the chromosome. For example, 13q describes the long arm of chromosome 13, while 17p describes the short arm of chromosome 17.

Cytogenetic testing is done with a blood, bone marrow or lymph node biopsy sample. The leukemia or lymphoma cells in the sample are allowed to grow in a laboratory and then are stained prior to examination. The sample is then examined under a microscope and photographed to show the arrangement of the chromosomes in the cells. This arrangement is called a “karyotype.” The karyotype shows if there are any abnormal changes in the size, shape, structure or number of chromosomes in the leukemia cells (see **Figure 2** on page 11).

Chromosomal abnormalities in CLL cells can be identified in many patients who have CLL. These abnormalities can be “numerical” or “structural.” A numerical abnormality is when there is a different number of chromosomes in the cells than the number that is usually found. For example, instead of the typical 46 chromosomes in each cell of the body, there may be 45 or 47 chromosomes. A structural abnormality means the chromosome’s structure has been altered. One common structural abnormality often found in CLL is a “deletion (del).” A deletion occurs when part of a chromosome is missing.

**Figure 2. Normal Karyotype**



**Fluorescence In Situ Hybridization (FISH).** This sensitive test is used to examine genes or chromosomes in cells and tissues. Doctors use FISH to detect certain abnormal changes in the chromosomes and genes of leukemia/lymphoma cells. Pieces of DNA that contain special fluorescent dyes are prepared in the laboratory and added to the leukemia/lymphoma cells on a glass slide. The pieces of DNA that bind to certain genes or areas of chromosomes light up when the slide is viewed under a specialized “fluorescence” microscope. FISH can be used to identify missing parts of chromosomes and extra chromosomes. In CLL, some patients may have leukemia cells with an extra copy of chromosome 12, or they may have 11q, 13q or 17p deletions.

**DNA Sequencing.** A laboratory method used to learn the exact sequence (order) of the DNA in the leukemia/lymphoma cells. Errors in the sequence of DNA can cause cancer cells to grow and spread.

There are targeted sequencing tests (also called “multigene panels”) that look for specific mutations in the cancer cells. The test focuses on specific sets of genes or areas of DNA. There are also broad DNA sequencing tests (genomic screening tests) that analyze the sequence of large regions of DNA, rather than looking for mutations of specific genes. Doctors may also order sequencing of all the DNA in your entire genome. This test is known as “whole genome sequencing.”

The term “next-generation sequencing (NGS)” is a catch-all term used to describe a number of different modern sequencing technologies. These technologies allow for sequencing of DNA and ribonucleic acid (RNA) much more quickly and cheaply than sequencing methods that were used previously.

In CLL patients, DNA sequencing is used to look for mutations in the *TP53* and *IGHV* genes.

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**Other Blood Tests.** Some people with CLL may get following blood tests before treatment begins:

- **Quantitative Immunoglobulin Test.** People with CLL usually have a weakened immune system and are more vulnerable to infections. Doctor use quantitative immunoglobulin tests to assess a patient's risk of infection. It measures the amount 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. This blood test measures 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, resulting in immune deficiency and an increased risk of infection.
- **Hepatitis Tests.** Hepatitis is a disease of the liver. It can be caused by the hepatitis C and B viruses. All patients should be tested for hepatitis C because the virus has been associated with B-cell lymphomas. Hepatitis B testing should be performed because some CLL treatments can cause the hepatitis B virus to reactivate.
- **Beta-2 Microglobulin Level.** Beta-2 microglobulin is a small protein found on the surface of many cells, including lymphocytes. It is a marker of how much CLL is in the body.

- **Lactate Dehydrogenase Level (LDH).** LDH is a protein found in most cells. When a cell is damaged, LDH is released into the bloodstream. A high level of LDH in the blood indicates cell damage, and it may also indicate the presence of cancer or other health conditions. When related to CLL, it indicates how much cancer is in the body and how fast it is growing.

## Treatment Planning

**Choosing a Hospital and a Doctor.** When you find out that you have cancer, you want to get the best possible medical care and treatment. So, it is essential to seek treatment in a center with hematologists-oncologists who have significant experience in the care of patients with CLL. A “hematologist” is a doctor who has special training in treating blood disorders. An “oncologist” is a doctor who has special training in treating cancer. A hematologist-oncologist specializes in treating blood cancers.

It is important to discuss all of your treatment options with your doctor to find a treatment that best fits your needs. It is also important to ask questions if there is any information that you do not understand. If time allows, you may want to seek a second opinion from another doctor, as it may help you feel more confident about the recommended treatment plan. The second opinion should come from another hematologist-oncologist, preferably one who treats CLL. This type of doctor will usually have the most knowledge and experience about the latest treatment options for CLL.

If you are unsure about getting a second opinion or feel uncomfortable about how to tell a doctor that you are seeking one, call our Information Specialists at (800) 955-4572, to discuss a way to do so that makes you feel comfortable. You may also want to check with your insurance company to be sure that your plan covers the cost of getting a second opinion.

**Fertility.** If you are of child-bearing age, you should be aware that some cancer treatments can affect your fertility (the ability to have children in the future). Before you begin treatment, it is important to talk with your doctor about whether your treatment could affect your fertility. You may also want to speak with a fertility specialist, a doctor who has special training helping people who have trouble conceiving or carrying a pregnancy to term. This specialist can talk to you about possible options for preserving your fertility. You may be able to take steps to preserve your fertility. However, delaying treatment to address fertility options may not always be recommended. You may need to start treatment right away.

**Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS booklet *Fertility and Cancer* for more information about fertility preservation.**

**Prognostic Factors.** Certain factors can affect a patient’s prognosis—the probable outcome of the patient’s cancer. These are called “prognostic factors.” Doctors use prognostic factors to help predict how a patient’s disease is likely to respond to treatment. These factors help doctors plan the most appropriate initial treatment regimen for each patient. See **Table 1**, below for prognostic factors for adults with CLL/SLL.

**Table 1. Prognostic Information for CLL/SLL**

Method of Detection	Genetic Abnormality	Risk Category
FISH	del(17p)	Unfavorable
	del(11q)	Unfavorable
	+12	Intermediate
	Normal	Intermediate
	del(13q) (as a sole abnormality)	Favorable
DNA Sequencing	<i>TP53</i>	Wild-type: Favorable Mutated: Unfavorable
	<i>IGHV</i>	>2% mutation: Favorable ≤2% mutation: Unfavorable
Cytogenetic Analysis (Karyotyping)	Complex karyotype (3 or more chromosome abnormalities in more than one cell on karyotype)	Unfavorable

Abbreviations: del, deletion; FISH, fluorescence in situ hybridization; p, the short arm of a chromosome (the upper half); q, the long arm of a chromosome (the lower half); +, an extra copy of a chromosome.

Source: NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. 2023.



**Staging of CLL.** When a person is diagnosed with CLL, tests are done to determine the stage of the disease. Staging helps doctors assess how the disease is expected to progress over time and then develop a treatment plan. Staging also helps doctors to determine whether to start treatment right away or delay treatment with regular monitoring to check for disease progression.

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, the CLL International Prognostic Index (CLL-IPI), was released, allowing for a more targeted management of CLL. In all of the scoring systems, lower numbers or letters indicate a lower level of risk. Higher numbers or letters indicate a higher level of risk.

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

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

The Rai staging system categorizes patients into three separate risk groups, see **Table 2** below.

**Table 2. Rai Staging System**

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

The Binet staging 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 3** below.

**Table 3. Binet Staging System**

Stage	Characteristics
A	<ul style="list-style-type: none"> <li>• No anemia (hemoglobin <math>\geq 10</math> g/dL)</li> <li>• No thrombocytopenia (platelet count <math>\geq 100,000/\mu\text{L}</math>)</li> <li>• Less than 3 areas of lymphoid tissue enlargement</li> </ul>
B	<ul style="list-style-type: none"> <li>• No anemia (hemoglobin <math>\geq 10</math> g/dL)</li> <li>• No thrombocytopenia (platelet count <math>\geq 100,000/\mu\text{L}</math>)</li> <li>• 3 or more areas of lymphoid tissue enlargement</li> </ul>
C	<ul style="list-style-type: none"> <li>• Anemia (hemoglobin <math>&lt; 10</math> g/dL) and/or</li> <li>• Thrombocytopenia (platelet count <math>&lt; 100,000/\mu\text{L}</math>)</li> <li>• Any number of areas of lymphoid tissue enlargement</li> </ul>

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 chromosomal biomarkers of CLL.

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 the following five prognostic factors to help predict a patient's outlook:

- Deletion 17p and/or *TP53* deleted or mutated = 4 points
- Unmutated *IGHV* = 2 points
- Serum beta-2 microglobulin concentration  $> 3.5$  mg/L = 2 points
- Rai stage III - IV or Binet stage B - C = 1 point
- Patient age  $> 65$  years = 1 point

Each factor has points—some factors have more points than others. When these points are added up, they provide the patient a score and a risk group. See **Table 4** on page 17 for the CLL-IPI risk groups.

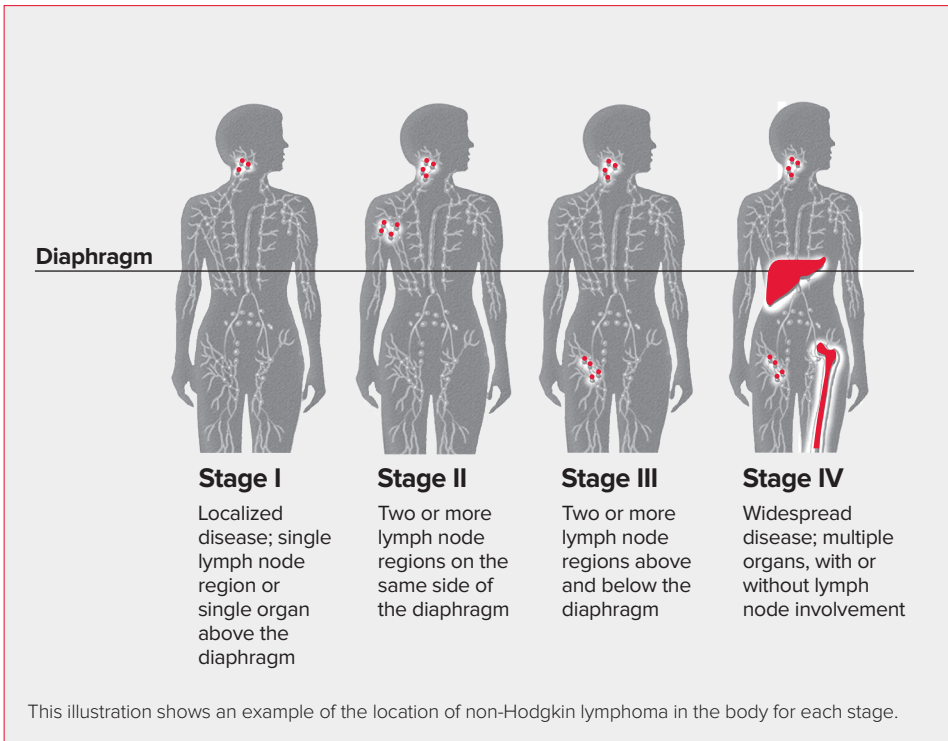
**Table 4. CLL International Prognostic Index (CLL-IPI) Categories**

CLL-IPI Category	Risk Score
Low Risk	0 - 1
Intermediate Risk	2 - 3
High Risk	4 - 6
Very High Risk	7 - 10

**Staging of SLL.** In staging of lymphoma, the Roman numerals I through IV (1 through 4) are used to represent the extent of cancer in the body. Stage I cancers are less advanced, and patients with stage I cancer often have a better prognosis. Higher-stage cancers are generally more widespread in the body and may require different or more intense treatment. Doctors use the findings from laboratory and imaging tests to determine the stage. Most people with SLL have disease in their bone marrow, which makes the disease stage IV, but this is not associated with an adverse prognosis.

The Lugano system, a modification of the older Ann Arbor system, is one of the more widely-used staging systems for non-Hodgkin lymphomas such as SLL. See **Figure 3** below for a description of NHL stages.

**Figure 3. Non-Hodgkin Lymphoma (NHL) Stages**



# Treatment Options

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

Not everyone with CLL receives the same type of treatment. Your doctor will tailor your treatment based on your CLL biomarkers, the stage of your CLL and other factors, such as your age and overall health, as well as your preferences.

Treatment options for CLL have evolved during the last 10 years. 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 newer targeted therapies. Most people with CLL do very well with newer targeted drugs and immunotherapies. For certain patients, however, chemotherapy remains an important treatment option.

For prescribing information for any of the following treatments, please see **Table 8** on page 40.

**Targeted Therapy.** Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells and their function but cause less harm to normal, healthy cells. Not all cancers have the same targets. Each type of targeted therapy works a little bit differently, but they all interfere with the growth and survival of cancer cells. In most cases, targeted therapies are given orally and are generally better tolerated than chemotherapy agents.

**Bruton Tyrosine Kinase (BTK) Inhibitors.** Human cells have many different kinases. Kinases are proteins in cells that normally relay signals that tell cells to grow, divide and survive. The BTK protein transmits important chemical signals that instruct B cells to mature and produce antibodies. This protein is central to B-cell receptor signaling. It is present in all B cells, and low-level activation is necessary for normal B-cell growth and survival. Certain B-cell cancers, including CLL and SLL, are dependent on BTK for survival. In CLL and SLL, the BTK protein is overactive resulting in the proliferation (multiplication or increase in number) of the cancer cells. Drugs that block this overactive pathway are called “BTK inhibitors.”

BTK inhibitors also help release the CLL/SLL cells from the bone marrow, lymph nodes, spleen or other areas in which they are hidden in a protective microenvironment where they can hide from the immune system. When CLL/SLL cells are released from the protective microenvironment the immune system can potentially find and destroy them.

BTK inhibitors are long-term therapies—a very different type of approach from chemotherapy.

○ **Acalabrutinib (Calquence®)**

- This oral medication is taken twice a day, every 12 hours.
- It can be taken as a single agent or in combination with obintuzumab
- Symptomatic patients with CLL either take acalabrutinib continuously until it does not work anymore or they have to stop taking it because of the side effects they are experiencing.
- The common side effects are anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and joint pain. These symptoms generally subside over time.
- Serious but uncommon side effects include infection and bleeding.
- 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.
- Patients should tell their healthcare provider of any planned medical, surgical or dental procedures. Depending on a patient's bleeding risk, acalabrutinib may need to be stopped for a short period of time before and after the procedure.

○ **Zanubrutinib (Brukinsa®)**

- This oral medication may be taken once or twice a day.
- Symptomatic patients with CLL either take zanubrutinib continuously until it does not work anymore or they have to stop taking it because of the side effects they are experiencing.
- Common side effects of zanubrutinib are decreased white blood cell count, infection, decreased platelet count, and muscle, bone or joint pain. These symptoms generally subside over time.
- Serious, but uncommon, side effects include low blood cell counts, infection and bleeding.
- Patients should tell their healthcare provider of any planned medical, surgical or dental procedures. Depending on a patient's bleeding risk, zanubrutinib may need to be stopped for a short period of time before and after the procedure.

○ **Ibrutinib (Imbruvica®)**

- This is an oral medication that is taken once a day.
- It can be taken
  - As a single agent
  - In combination with bendamustine and rituximab

- In combination with rituximab, obinutuzumab or venetoclax
- Symptomatic patients with CLL either take ibrutinib continuously until it does not work anymore or they have to stop taking it because of the side effects they are experiencing.
- Common side effects of ibrutinib are low blood cell counts, rashes, diarrhea, fatigue and musculoskeletal pain. These side effects generally subside over time.
- For some patients, ibrutinib may cause cardiac side effects including heart rhythm disorders. Due to these side effects, ibrutinib is no longer considered a preferred treatment regimen by the National Comprehensive Cancer Network (NCCN) since acalabrutinib and zanubrutinib have demonstrated fewer cardiac side effects in clinical trials to date.
- 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.
- Patients should tell their healthcare provider of any planned medical, surgical or dental procedures. 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.

**PI3K Inhibitors.** PI3Ks are a group of proteins that are an important part of the B-cell receptor pathway. They transmit signals in cells that help control cell growth. Some cancer cells have higher-than-normal levels of PI3K, which causes them to multiply. The following drugs are PI3K inhibitors that block the signaling pathways that cause the cancer cells to grow and divide:

- **Duvelisib (Copiktra®)**
  - This is an oral medication taken twice a day for relapsed or refractory CLL or SLL.
  - Common side effects include diarrhea, neutropenia, rash, fatigue, fever, cough, nausea, upper respiratory tract infection, pneumonia, musculoskeletal pain and anemia.
- **Idelalisib (Zydelig®)**
  - This oral medication is taken twice a day 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.
  - Idelalisib is not indicated or recommended for first-line treatment.

- Symptomatic patients with relapsed CLL are given idelalisib, either continuously until it does not work anymore or they have to stop taking it because of the side effects they are experiencing.
- Idelalisib may initially cause the leukemia cells in the blood to increase as lymph node size decreases. In most patients, this is followed by a decline in the number of leukemia cells in the blood.
- The most common side effects are fatigue, rashes, diarrhea, pneumonia, nausea, cough, fever, abdominal pain, infection and liver function abnormalities. 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).

**BCL2 Inhibitors.** BCL2 is a protein inside B cells that helps prevent cell death. In CLL, overexpression of the BCL2 protein allows cancer cells to evade “programmed cell death,” meaning it helps them live longer than they should. BCL2 inhibitors target the BCL2 protein. This helps restore what is called “apoptosis,” a process of natural cell death that is disrupted when you have cancer. It restores the body's natural ability to tell cancer cells to die. Once apoptosis is restored, your body can begin to kill cancer cells. With fewer cancer cells in the bone marrow, there is room for healthy blood cells to grow.

#### ○ **Venetoclax (Venclexta®)**

- This targeted therapy is an oral medication taken once a day.
- Treatment with venetoclax can be completed in a set time: 1 year for first-line (initial) treatment and 2 years for relapsed/refractory cases.
- It is taken as a single agent or with other drugs.
- Common side effects include low blood cell counts, diarrhea, nausea, upper respiratory tract infection and fatigue.
- There is a risk of tumor lysis syndrome, but this can be prevented through appropriate monitoring and prophylactic measures (see *Tumor Lysis Syndrome (TLS)* on page 37).

**Monoclonal Antibody Therapy.** Monoclonal antibody therapy is a type of immunotherapy. It helps stimulate the immune system. Monoclonal antibodies are proteins, made in the laboratory, that can bind to certain targets in the body, such as proteins on the surface of cancer cells. Monoclonal antibody therapy marks leukemia cells so that the immune system can find and destroy them.

CD20 is a protein found on the surface of B cells, the cells from which CLL starts. The following monoclonal antibodies bind to CD20 proteins on B cells including CLL cells:

- **Obinutuzumab (Gazyva®)**
  - Obinutuzumab is a liquid that is administered slowly, via intravenous (IV) infusion, over a period of a few hours.
  - This drug can be taken as a single agent or in combination with chlorambucil, acalbrutinib, venetoclax, or ibrutinib.
- **Rituximab (Rituxan®)**
  - Rituximab is a liquid that is administered slowly, via IV infusion.
  - This drug is used in the treatment of untreated and previously treated CD20-positive CLL in combination with other drugs.
  - Some side effects of rituximab include fever, chills, nausea, headache, cough, runny nose and shortness of breath.
- **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. 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. Typically, chemotherapy is given in cycles, with each period of treatment followed by a rest period. There are many types of chemotherapy drugs, including the following antimetabolites, alkylating agents, and corticosteroids:

Antimetabolite:

- **Fludarabine (Fludara®)**

Alkylating agents:

- **Bendamustine hydrochloride (Bendeka®)**
- **Chlorambucil (Leukeran®)**
- **Cyclophosphamide (Cytosan®)**



**Corticosteroid.** Corticosteroids are hormones made in the body. They can also be made in the laboratory and are used to treat certain leukemias and lymphomas. **Methylprednisolone** is a corticosteroid that may be used to treat CLL in combination with rituximab or obinutuzumab.

**Chemoimmunotherapy.** This type of therapy combines chemotherapy with immunotherapy. Immunotherapy is a type of treatment that uses a person's immune system to help fight cancer.

Rituximab, a type of monoclonal antibody therapy, can be used with chemotherapy to treat CLL. The following regimens use rituximab and chemotherapy to treat CLL:

- **FCR: fludarabine, cyclophosphamide and rituximab**
- **BR: bendamustine and rituximab**

Before the introduction of newer targeted agents, younger patients with CLL who needed treatment were given a chemoimmunotherapy 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 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.

**Splenectomy.** A splenectomy is an operation to remove the spleen. In some patients, CLL cells can accumulate in the spleen. Sometimes, the spleen becomes so enlarged that it presses on nearby organs, causing discomfort. In rare cases, if other treatments do not help shrink the spleen, the spleen may be surgically removed. This surgery cannot cure CLL, but it can help reduce symptoms. It may also improve blood cell counts and reduce the need for transfusions.

Splenectomy is also 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 *Autoimmune Cytopenias* on page 37.

# Treatment

New treatments may have been approved since this booklet was printed.  
Check [www.LLS.org/DrugUpdates](http://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. See *Clinical Trials for Blood Cancers* on page 32.

In most cases CLL cannot be cured, but there are now many treatment options that have the potential to give patients longer remissions and a better quality of life. Many people with CLL have normal life spans and go long periods without experiencing symptoms or health complications.

People may have treatment for CLL on and off for many years. 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.

**Watch and Wait.** “Watch and wait” is a treatment approach in which the doctor monitors a patient’s condition closely, over time, and sees the patient for regular check-ups. Active treatment is not started until signs and/or symptoms of CLL appear or change. CLL is a slow-growing type of leukemia, so many people with CLL do not need treatment when they are diagnosed, and they may not need treatment for several years; however, they will need to be monitored regularly.

At these check-ups, the doctor will:

- Check to see if the patient has developed any new symptoms
- Perform a physical examination to check the size of lymph nodes, spleen, liver, etc
- Order blood tests to determine whether the disease is stable or if it is beginning to progress

During watch and wait, low-risk or intermediate-risk patients may see the doctor every 6 to 12 months while high-risk patients may see the doctor every 3 to 6 months.

During watch and wait, patients are not treated with drugs or other therapies. This is the standard approach for patients with early-stage disease and no symptoms. When people receive a diagnosis of CLL and then learn that they will not begin treatment right away, they are often concerned. Current research has shown that delaying treatment is safe for many people.

**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 quarter 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 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. This means that these drugs are no longer options once disease progression makes treatment essential.

The watch-and-wait approach remains of interest to doctors, and it will continue to be studied in clinical trials.

**Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS fact sheet *Watch and Wait* for more information.**

**When to Start Treatment.** Some people with CLL can be managed with a watch-and-wait approach for years before their disease progresses. Treatment is recommended for people whose blood cell counts have gotten worse and have also developed symptoms.

The decision to treat 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, patients should meet at least one of the following criteria in order to start CLL treatment:

- An increase in the size of the lymph nodes
- An increase in the size of the liver and/or the spleen
- Presence of specific CLL symptoms
  - Severe fatigue
  - Night sweats for more than a month with no evidence of infection
  - Unexplained weight loss of at least 10 percent of body weight within 6 months
  - Fever higher than 100.5° F for 2 or more weeks without evidence of infection
- 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
- A decrease in the red blood cell count
- A decrease in the platelet count
- Disease involvement that is extranodal (outside of the lymph nodes), in the skin, kidneys, lungs and spine

**Testing Before Treatment.** Before you begin treatment, your doctor should test your cancer cells again for biomarkers (See *Biomarker Testing* on page 9). Biomarkers may change during watch and wait, and the changes may affect treatment decisions. In addition, the doctor will conduct other tests before treatment begins. **Table 5**, on page 27 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 <sup>a</sup>
<b>To establish the diagnosis:</b>	
Complete blood count with differential	Always
Immunophenotyping of peripheral blood lymphocytes	Always
<b>Prior to treatment:</b>	
Medical history and physical exam; performance status <sup>b</sup>	Always
Complete blood count with differential	Always
Bone marrow aspiration and biopsy	When clinically indicated
Serum chemistry, serum immunoglobulin and direct antiglobulin test	Always
Chest x-ray	Always
Infectious disease status	Always
<b>Additional tests prior to treatment:</b>	
Molecular cytogenetics (FISH) test to check for del(13q), del(11q), del(17p) and add(12) in peripheral blood lymphocytes	Always
Conventional karyotyping of peripheral blood lymphocytes (with specific stimulation)	NGI (not generally indicated)
<i>TP53</i> gene mutation	Always
<i>IGHV</i> mutational status	Always
Serum beta-2 microglobulin	Desirable
CT scan of chest, abdomen and pelvis	NGI
MRI and PET scans	NGI
Abdominal ultrasound	Possibly

<sup>a</sup> General practice is defined as the use of accepted treatment options for CLL patients not enrolled in a clinical trial.

<sup>b</sup> Performance status helps to quantify a cancer patient's general well-being and activities of daily life.

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

Source: Hallek M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018.

**Initial Treatment of Symptomatic CLL.** Therapy often begins when patients develop extremely low blood cell counts or when symptoms affect quality of life. It is important that you speak to your healthcare team about the sequence, or order, of your treatments for CLL. Talk to them about long-term treatment, versus a fixed-duration treatment and the specific side effects of each treatment option.

Because CLL is more prevalent in older people, evaluation of a patient’s fitness and comorbidities (other medical conditions) is very important. Treatment options for CLL are affected 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. 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.

**Patients Without del(17p)/TP53 Mutation.** The first treatments prescribed to many patients in this category include **acalabrutinib, zanubrutinib, or venetoclax** in combination with **obinutuzumab**. See **Table 6** below for a list of National Comprehensive Cancer Network (NCCN) preferred treatment regimens.

Patients who are prescribed a BTK inhibitor (acalabrutinib, zanubrutinib or ibrutinib) will take the drug until it no longer works, or until side effects occur that require them to stop taking it. If one BTK inhibitor causes severe side effects, a patient may be able to try a different BTK inhibitor. Venetoclax, given in combination with obinutuzumab, is a chemotherapy-free combination and is given for a fixed period of 12 months.

**Table 6. NCCN Suggested Treatment Regimens for CLL without del(17p)/TP53 Mutation**

FIRST-LINE THERAPY		
<u>Preferred regimens</u> <ul style="list-style-type: none"> <li>• Acalabrutinib ± obinutuzumab</li> <li>• Venetoclax + obinutuzumab</li> <li>• Zanubrutinib</li> </ul>	<u>Other recommended regimens</u> <ul style="list-style-type: none"> <li>• Ibrutinib</li> <li>• Bendamustine + anti-CD20 monoclonal antibody therapy</li> <li>• Chlorambucil + obinutuzumab</li> <li>• Obinutuzumab</li> <li>• High-dose methylprednisolone + rituximab or obinutuzumab</li> <li>• Ibrutinib + obinutuzumab</li> <li>• Ibrutinib + rituximab</li> <li>• Ibrutinib + venetoclax</li> </ul>	<u>Useful in certain circumstances</u> (consider for <i>IGHV</i> -mutated CLL in patients age <65 years without significant comorbidities) <ul style="list-style-type: none"> <li>• FCR (fludarabine cyclophosphamide, rituximab)</li> </ul>

Source: NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. 2023

**Patients With del(17p) or TP53 Mutation.** Patients with del(17p) or TP53 mutation (whether younger or older), typically, either do not respond well to treatment or are likely to have early relapses if the first-line therapy is any type of chemoimmunotherapy. Treatment with BTK inhibitors or monoclonal antibodies generally has better results. **Table 7** below, lists suggested treatment regimens for patients with del(17p)/TP53 mutation.

**Table 7. NCCN Suggested Treatment Regimens for CLL with del(17p)/TP53 Mutation**

FIRST-LINE THERAPY	
<u>Preferred regimens</u> <ul style="list-style-type: none"> <li>• Acalabrutinib ± obinutuzumab</li> <li>• Venetoclax + obinutuzumab</li> <li>• Zanubrutinib</li> </ul>	<u>Other recommended regimens</u> <ul style="list-style-type: none"> <li>• High-dose methylprednisolone + rituximab</li> <li>• Ibrutinib</li> <li>• Obinutuzumab</li> <li>• Ibrutinib + venetoclax</li> </ul>

Source: NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. 2023.

Clinical trials should always be considered as a treatment option. Allogeneic stem cell transplantation may also be an option for this patient group (see *Allogeneic Stem Cell Transplantation* on page 31).

**Treatment Outcomes.** Patients will be tested to measure whether they have achieved a complete remission. These tests may include a physical examination, blood tests and, sometimes, a bone marrow test and imaging tests. A complete remission is achieved when:

- Blood cell counts return to normal
- Enlarged lymph nodes and organs return to normal size
- Patients no longer have symptoms of leukemia
- The bone marrow shows no evidence of CLL

**Minimal/Measurable Residual Disease.** Even when a complete remission is achieved, many leukemia cells that cannot be seen with a microscope may remain in the blood and bone marrow. The presence of these cells is referred to as “minimal/measurable residual disease (MRD).”

The tests used most often to detect MRD are flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing. Typically, these three tests use samples of blood or bone marrow cells. The tests are much more sensitive than standard tests that examine cell samples with a microscope.

When patients have less than one CLL cell per 10,000 lymphocytes 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. In research studies, patients who remained MRD-negative after the end of CLL

had better treatment outcomes. An undetectable MRD status after treatment with some drug regimens for CLL is becoming an important factor for predicting prolonged effectiveness of the treatment.

While MRD testing has become widespread in CLL clinical trials, it is not currently part of the routine patient management of CLL. This testing is not done in patients who are receiving acalabrutinib, zanubrutinib or ibrutinib. These drugs are used to control disease. They do not fully eradicate the disease.

**Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS fact sheet *Minimal/Measurable Residual Disease (MRD)* for more information.**

## Relapsed and Refractory CLL

Some patients with CLL do not respond to initial therapy. When this occurs, it is called “refractory” disease. In other patients CLL comes back after a remission. In these cases, it is called “relapsed disease.”

Many patients with refractory disease can achieve a remission with different treatments, and many patients with relapsed disease can obtain another period of remission with additional treatment. This approach can control CLL for many years. Often people with CLL will require several lines of treatment in their lifetime, and they often have a good quality of life for years after receiving additional treatment. Doctors will also consider the side effects of medications and tailor the treatment to each individual patient.

At the time of relapse, patients should be re-tested to find out if their biomarker profile has changed. Doctors need this information to plan the next treatment. Doctors will also consider the side effects of medications and tailor the treatment to each individual patient.

The following drugs and combinations can be used for relapsed or refractory CLL:

- Acalabrutinib
- Bendamustine with rituximab
- Duvelisib
- FCR (fludarabine, cyclophosphamide and rituximab)
- Ibrutinib
- Idelalisib, alone or in combination with rituximab
- High-dose methylprednisolone with rituximab or obinutuzumab
- Obinutuzumab
- Venetoclax, alone or with obinutuzumab or rituximab
- Zanubrutinib



For some patients, the following treatments may also be an option for relapsed or refractory CLL:

- Allogeneic stem cell transplantation (see page 31)
- Chimeric antigen receptor (CAR) T-cell therapy (see page 32)

Acalabrutinib, zanubrutinib, ibrutinib, duvelisib and idelalisib are given for as long as there is a good treatment response, which can be indefinitely. Venetoclax, which is given for a period of 2 years, can be combined with rituximab and in certain circumstances obinutuzumab. 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.

Patients with relapsed or refractory CLL are advised to speak to their doctors about whether treatment in a clinical trial is a good option. Clinical trials involving new treatments may offer more appropriate treatment options (see *Clinical Trials for Blood Cancers* on page 32).

**Allogeneic Stem Cell Transplantation.** For some patients who are in remission and can tolerate intensive chemotherapy, the doctor may recommend stem cell transplantation. The goal of stem cell transplantation is to cure the patient's cancer. Typically, the process involves administering intensive chemotherapy, followed by infusion of healthy stem cells from a donor.

This type of transplant is generally done in high-risk CLL patients with either deletion of the short arm of chromosome 17 (del[17p]) or *TP53* gene mutation identified early in the course of their disease. It is also done in patients with relapsed CLL who have received multiple prior therapies.

Compared to other treatment options, allogeneic stem cell transplantation is associated with a higher rate of side effects and mortality. However, it may be considered for patients with relapsed or refractory CLL categorized as high-risk. The decision to perform an allogeneic transplant also depends on many factors, including the patient's age, physical fitness, comorbidities (other coexisting medical conditions) and social supports (from family members, caregivers, friends, etc), as well as the patient's understanding of the potential benefits and risks.

Allogeneic stem cell transplantation may be an appropriate therapy for carefully selected younger people with CLL who have an available donor. Talk to your doctor to see if this is a treatment option for you.

**Reduced-Intensity Allogeneic Stem Cell Transplantation.** This type of transplantation may be a treatment option for older patients who cannot tolerate the high doses of chemotherapy used in preparation for a standard allogeneic stem cell transplant. The conditioning therapy in a reduced-intensity transplant uses lower doses of chemotherapy and/or radiation. With a reduced-intensity

conditioning regimen, the patient's blood cell counts may not fall as low as they would with high-dose chemotherapy. Additionally, the less toxic regimens put less strain on the patient's organs, making this regimen safer and more tolerable.

**Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation* for more information about stem cell transplantation.**

**Chimeric Antigen Receptor (CAR) T-Cell Therapy.** This therapy is a type of immunotherapy that consists of engineering a patient's own immune cells called "T cells" (white blood cells that help the body fight infections and cancer) to first recognize and then attack cancer cells. Each dose of CAR T-cell therapy is made for a specific patient. The T cells are collected from the patient and then genetically modified in a laboratory to add new genes called "chimeric antigen receptors" (CARs). These receptors recognize and bind to a specific target found on the leukemia cells. The most frequently targeted antigen in CAR T-cell therapy for leukemia is CD19. The CD19 antigen is expressed on the surface of nearly all healthy and cancerous B cells, including CLL cells. The genetically modified CAR T cells are infused back into the patient's body to find and kill leukemia cells with CD19 on their surfaces.

Clinical trials are in progress to study the use of CD19-directed CAR T-cell therapy in the treatment of relapsed or refractory CLL. The results of recent trials have demonstrated that this new approach can induce long-term remissions in some CLL patients.

**Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy* for more information.**

## Clinical Trials for Blood Cancers

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called clinical trials and they are used to find better ways to care for and treat people with cancer.

In the United States, the FDA (U.S. Food and Drug Administration) requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to:

- Treat cancer using
  - A new drug

- An approved drug to treat a different kind of cancer
- A new combination of drugs
- A new way of giving a drug—by mouth (pill), intravenously (IV)
- Manage cancer symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit [www.LLS.org/WhatToAsk](http://www.LLS.org/WhatToAsk) for lists of suggested questions).
- Ask a family member or friend to go with you to your doctor visit—both for support and to take notes.

Clinical trials can be difficult to navigate and figure out, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find potential clinical trials, overcome barriers to enrollment and provide support throughout the entire clinical trial process. Our Clinical Trial Nurse Navigators are registered nurses who are experts in pediatric and adult blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you understand the clinical-trial process, including your rights as a patient
- Ask you for details about your diagnosis (like past treatments, treatment responses, and your cancer genetic profile), your current health, and your medical history—because these might impact whether you can take part in certain clinical trials
- Help you understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials
- Guide you and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
- Help deal with any problems you might have as you enroll in a trial
- Support you throughout the clinical trial process

Call an LLS Information Specialist at (800) 955-4572 or visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information about clinical trials and the Clinical Trial Support Center (CTSC) at LLS.

Also, visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to view the free LLS booklet *Understanding Clinical Trials for Blood Cancers*.

## Financial Concerns

In the past few years there have been significant advances in the treatment of CLL. New targeted therapies have improved outcomes for patients with CLL, improving their survival and quality of life. However, the cost of current medications is significantly higher than the cost of the standard treatments used previously, which raises concerns for both patients and healthcare providers.

The current approved medications for CLL are expensive. In addition, acalabrutinib, zanubrutinib, ibrutinib and duvelisib require continuous daily use until they stop working or the side effects become intolerable. 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.

**Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS booklet *Cancer and Your Finances* for more information and resources to cope with the financial aspects of cancer care.**

# 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”

**Vaccines.** Because of the increased risk of infections, vaccination every 5 years for pneumococcal pneumonia and a yearly flu vaccine are recommended. Current COVID-19 vaccines are also recommended. Patients who have CLL should never receive live vaccines, such as Zostavax (a live shingles vaccine), but they can receive **Shingrix**® because it is an inactivated shingles vaccine.

**Antibiotics and Anti-viral Therapy.** Antibiotics are usually required to treat bacterial infections that may occur during the course of the disease. Patients may also receive other drugs to treat viral and fungal infections.

If you have had a cytomegalovirus (CMV) infection, this virus may be reactivated during CLL treatment with PI3K inhibitors. Rates of reactivation as high as 6 percent have been reported in patients treated with idelalisib. It is important to monitor for this potential problem during idelalisib therapy. Antiviral medications may be given to prevent reactivation of the virus.

Hepatitis B virus (HBV) reactivation has been reported in patients treated with anti-CD20 monoclonal antibody therapy or chemotherapy. HBV reactivation has also been reported in patients treated with acalabrutinib, ibrutinib and idelalisib. Reactivation may be prevented with antiviral medications and continuous monitoring for HBV.

**Intravenous Immunoglobulin Replacement Therapy.** Some people with CLL do not have enough immunoglobulins (proteins made by B cells that help fight infections). This can lead to repeated lung and/or sinus infections. Immunoglobulin levels can be checked with a blood test. If IgG levels are less than 500 mg/dL, immunoglobulins from donors can be given into a vein through an IV to raise patient levels and help prevent infections. This treatment is often given once a month.

**Low Blood Cell Counts.** Supportive 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; deletion of the short arm of chromosome 17 (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 fever and weight loss. Lymphocyte masses may also develop in parts of the body other than the lymph nodes. This transformation is less common in patients who do not receive chemoimmunotherapy for treatment of their CLL.

Typically, patients with Richter transformation of CLL into DLBCL are 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 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](http://www.LLS.org/CTSC) for more information about clinical trials.**

**Autoimmune Cytopenias.** Autoimmune cytopenias are conditions in which the immune system attacks the blood cells. Autoimmune cytopenias occur in 4 to 10 percent of patients with CLL. The most frequent autoimmune cytopenias in CLL patients are:

- Autoimmune hemolytic anemia (AIHA)
- Immune-mediated thrombocytopenia (also known as "immune thrombocytopenia purpura" or ITP)
- Pure red blood cell aplasia (PRCA)

Autoimmune hemolytic anemia 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.

Bone marrow tests may be helpful to confirm the presence of these conditions. The drugs **prednisone**, **rituximab** and **cyclosporine** are sometimes used to treat AIHA and ITP. The drugs **romiplostim (Nplate®)** and **eltrombopag (Promacta®)** are both approved by the FDA for the treatment of ITP that is resistant to other treatments. Splenectomy may be considered for treatment of AIHA and ITP in patients who do not respond to drug therapy.

**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 seen in CLL patients treated with lenalidomide. 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 TLS therapy is given before treatment for CLL 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.

**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 that are either 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 and cyclophosphamide or with FCR: fludarabine, cyclophosphamide and rituximab.

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 increased 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 examination is also strongly recommended.

## Follow-up Care

After you achieve a remission, your doctor will continue to monitor your CLL. You will need to continue regular visits to assess your health and blood cell counts. If indicated, other testing may be required to monitor treatment, as well as to identify signs of disease relapse. You need to keep your treatment team informed of any changes you notice (for example, infections, lymph node changes, etc). These assessments may become less frequent over time.

You are encouraged to:

- Maintain regular follow-up appointments with your hematologist-oncologist. Your doctor will monitor you for signs of disease relapse and also so that you will 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:
  - A list of all healthcare providers
  - A diagnosis summary with specifics such as subtype and/or genetic markers



- A treatment summary with specifics such as the names, dates, and dosages of drugs, site of radiation treatment, surgery and/or transplantation information, response to treatment, and side effects
- Maintenance treatment information, if applicable
- A list of possible late effects
- A schedule for ongoing monitoring with recommended tests, frequency and coordinating provider
- Health and wellness recommendations, such as nutrition guidelines, suggested exercise regimens, as well as other appropriate 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 37).
- 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 survivorship information, visit [www.LLS.org/survivorshipworkbook](http://www.LLS.org/survivorshipworkbook) to view the free LLS booklet *Navigating Life During and After a Blood Cancer Diagnosis*.**

# Drug Information

**Table 8**, below includes information about drug classifications and treatments for CLL. For more information, see the Package Insert and/or the Full Prescribing Information that accompanies each medication on the internet.

**Table 8. Some Drugs Used in the Treatment of CLL and SLL**

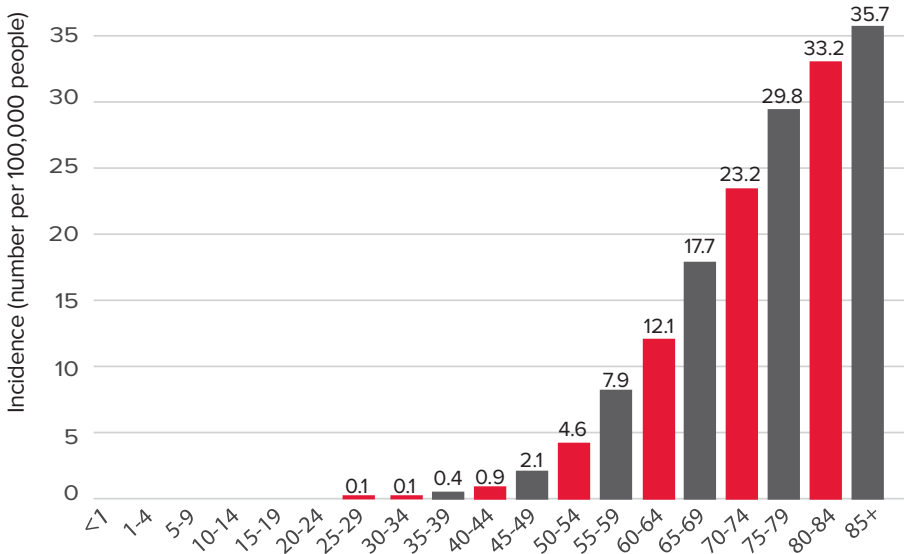
Drug Name Type of Drug Administration	FDA-Approved Indication
<b>Acalabrutinib (Calquence®)</b> BTK inhibitor Oral	Indicated for the treatment of adult patients with CLL or SLL.
<b>Bendamustine (Bendeka®)</b> Chemotherapy Intravenous (IV)	Indicated for the treatment of patients with CLL.
<b>Chlorambucil (Leukeran®)</b> Chemotherapy Oral	Indicated in the treatment of CLL.
<b>Cyclophosphamide (Cytoxan®)</b> Chemotherapy Intravenous (IV) Oral	Approved for the treatment of CLL and malignant lymphomas (Stages III and IV of the Ann Arbor staging system).
<b>Duvelisib (Copiktra®)</b> PI3K inhibitor Oral	Indicated for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.
<b>Fludarabine (Fludara®)</b> Chemotherapy Intravenous (IV)	Indicated for the treatment of adult patients with B-cell CLL who have not responded to or whose disease has progressed during treatment with at least one standard alkylating agent containing regimen.
<b>Ibrutinib (Imbruvica®)</b> BTK inhibitor Oral	Indicated for the treatment of adult patients with CLL/SLL with and without the 17p deletion.
<b>Idelalisib (Zydelig®)</b> PI3K inhibitor Oral	Indicated for the treatment of patients with relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

Drug Name Type of Drug Administration	FDA-Approved Indication
<b>Methylprednisolone</b> Corticosteroid Oral	Indicated for the treatment of leukemias and lymphomas in adults.
<b>Obinutuzumab (Gazyva®)</b> Monoclonal antibody Intravenous (IV)	Indicated: <ul style="list-style-type: none"> <li>• In combination with chlorambucil for the treatment of patients with previously untreated CLL</li> <li>• Off-label combinations with acalabrutinib, ibrutinib and venetoclax</li> </ul>
<b>Rituximab (Rituxan®)</b> Monoclonal antibody Intravenous (IV)	Indicated for the treatment of adult patients with CLL with previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide.
<b>Rituximab and hyaluronidase human (Rituxan Hycela®)</b> Monoclonal antibody Subcutaneous injection	Indicated for the treatment of adult patients with previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide.
<b>Venetoclax (Venclexta®)</b> BCL-2 inhibitor Oral	Indicated for the treatment of adult patients with CLL or SLL.
<b>Zanubrutinib (Brukinsa®)</b> BTK inhibitor Oral	Indicated for the treatment of adult patients with CLL or SLL.

# 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 (see **Figure 4** below).

**Figure 4. Chronic Lymphocytic Leukemia (CLL): Age-Specific Incidence Rates 2015-2019**



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

Source: SEER\*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Cited 2023 February 18]. Available from <https://seer.cancer.gov/explorer/>.

**Causes and Risk Factors.** Although in most cases it is not clear what causes the genetic changes that lead to CLL, there are some known risk factors. A “risk factor” is anything that increases a person’s chance of developing a disease. However, having a risk factor does not mean that a person will develop the disease. Some people with several risk factors never develop a disease, while others with no known risk factors may develop the disease. CLL is not contagious.

The factors that are associated with an increased risk of developing CLL include:

- **Age.** The risk of developing CLL increases with age. The median age at diagnosis is 72 years.
- **Exposure to Certain Chemicals.**
  - Some studies have associated exposure to Agent Orange, an herbicide used during the Vietnam War, with an increased risk of 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, you may want to get a formal evaluation from the VA. Visit [www.publichealth.va.gov/exposures/agentorange](http://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 it is with other blood cancers.
- **Family History.** 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 five to eight times more likely to develop CLL than people who do not have first-degree relatives with the disease. However, the risk is small because the overall chance of getting CLL in a lifetime is low.
- **Sex.** CLL affects more males than females.
- **Race/Ethnicity.** CLL incidence is substantially lower among Asian individuals and higher among Ashkenazi Jews. The reason for these differences is not known.

**Visit [www.LLS.org/DiseaseRegistries](http://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 (B<sub>9</sub>) and vitamin B<sub>12</sub>
- 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 5** on page 45.

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

1. Red blood cells (RBCs) (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 (CO<sub>2</sub>) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO<sub>2</sub> 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.

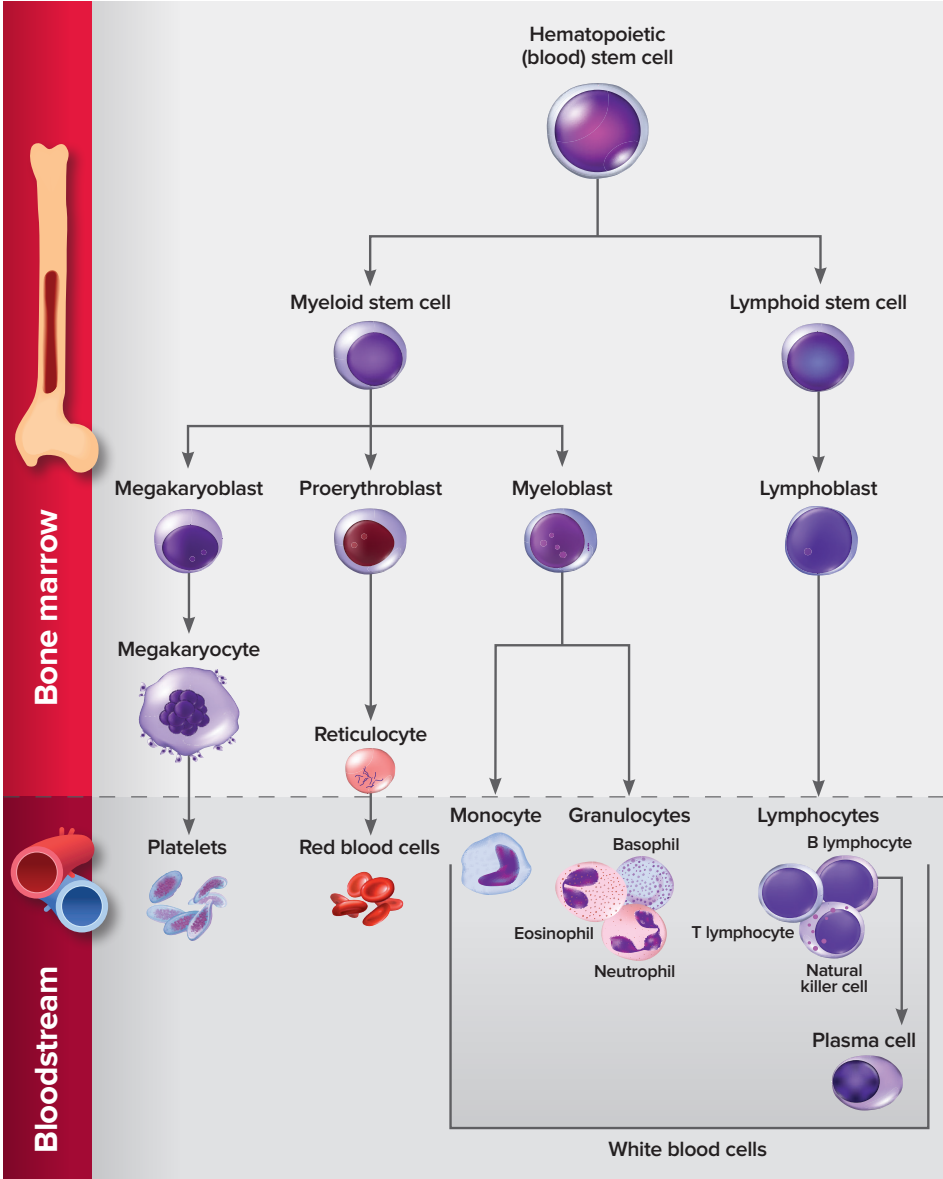
3. White blood cells (WBCs). These are the cells that fight infections.

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 5. Blood Cell & Lymphocyte Development

Most blood cells start as hematopoietic (blood) stem cells in the bone marrow. Hematopoietic stem cells are the most immature blood-forming cells. They must mature (go through many stages) to become a red blood cell, white blood cell or platelet. Some blood cells mature in the bone marrow. Other blood cells leave the bone marrow and travel to other parts of the body to develop into mature blood 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 lymphatic system is the tissues and organs that produce, store and carry lymphocytes (a type of white blood cell) that fight infection and other diseases. This system includes the bone marrow, spleen, thymus. Lymph nodes and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells.) See **Figure 6** on page 47.

The bone 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.

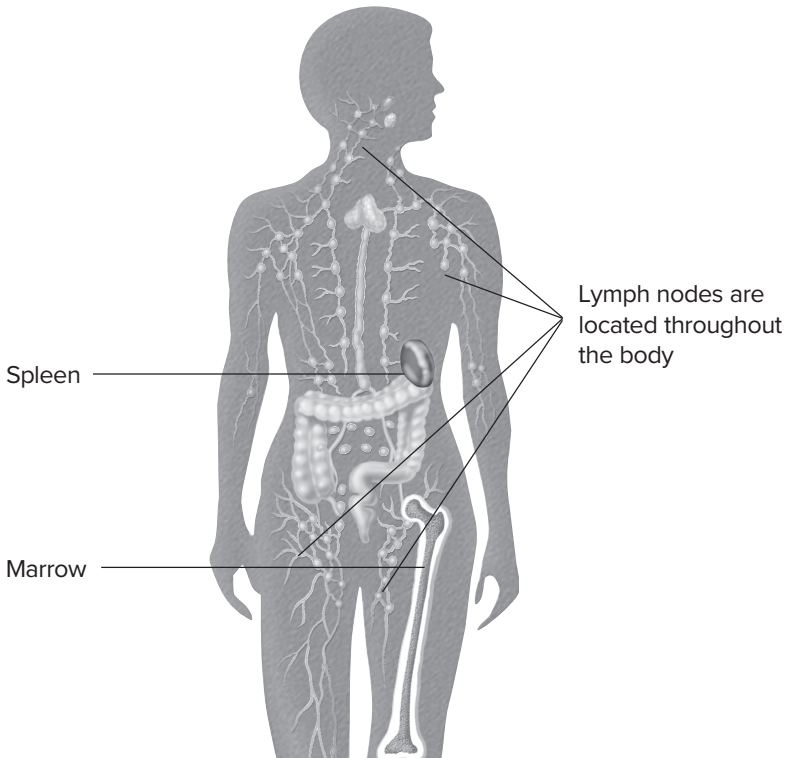
The marrow produces three main types of lymphocytes. They are:

- 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.

**Figure 6. The Lymphatic System**



The lymphatic system is part of the immune system. The normal immune system helps to protect the body from infection. The marrow, lymph nodes and spleen are parts of the immune system. There are about 600 lymph nodes throughout the body

Lymph nodes and other lymphoid tissues that are commonly involved in lymphoma are those around the ears and jaw, in the tonsils and adenoids, in the front and back of the neck, above and below the collar bone, in the armpit, near the elbow, in the chest, in the abdomen, in the pelvis and in the groin. The spleen contains many clusters of lymphocytes that can become malignant and grow, leading to the enlargement of the spleen. The gut-associated (intestinal) lymph tissue may also be the site of lymphoma development.

# Resources and Information

LLS offers free information and services for patients and families affected by blood cancers. This section lists various resources you may find helpful.

## For Help and Information

**Consult with an Information Specialist.** Information Specialists can assist you through cancer treatment, financial and social challenges and give accurate, up-to-date disease, treatment and support information. Our Information Specialists are highly trained oncology social workers and nurses. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. ET)
- Email and Live chat: [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)

**Clinical Trials (Research Studies).** Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Pediatric and adult patients and caregivers can work with our Clinical Trial Nurse Navigators who will help find clinical trials and provide personalized support throughout the entire clinical trial process. Visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information.

**Nutrition Consultations.** Schedule a free one-on-one nutrition consultation with one of our registered dietitians who have expertise in oncology nutrition. Consultations are available to patients of all cancer types and their caregivers. Dietitians can assist with information about healthy eating strategies, side effect management and more. Please visit [www.LLS.org/nutrition](http://www.LLS.org/nutrition) for more information.

**Free Information Booklets.** LLS offers free education and support booklets for patients, caregivers and healthcare professionals that can either be read online or ordered. Please visit [www.LLS.org/booklets](http://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](http://www.LLS.org/programs) for more information.

**Financial Assistance.** LLS offers financial support to eligible individuals with blood cancer for insurance premiums, co-pays, and non-medical expenses like travel, food, utilities, housing, etc. For more information, please:

- Call: (877) 557-2672
- Visit: [www.LLS.org/finances](http://www.LLS.org/finances)

**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. Visit [www.LLS.org/TheBloodline](http://www.LLS.org/TheBloodline) for more information and to subscribe to access exclusive content, submit ideas and topics, and connect with other listeners.

**3D Models.** LLS offers interactive 3D images to help visualize and better understand blood cell development, intrathecal therapy, leukemia, lymphoma, myeloma, MDS, MPNs and lab and imaging tests. Visit [www.LLS.org/3D](http://www.LLS.org/3D) for more.

### **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](http://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](http://www.LLS.org/HealthManager) to download for free.

**Suggested Reading.** LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit [www.LLS.org/SuggestedReading](http://www.LLS.org/SuggestedReading) to find out more.

### **Connecting with Patients, Caregivers and Community Resources**

**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. Visit [www.LLS.org/community](http://www.LLS.org/community) to join.

**Weekly Online Chats.** Moderated online chats can provide support and help cancer patients and caregivers reach out and share information. Please visit [www.LLS.org/chat](http://www.LLS.org/chat) for more information.

**Local Programs.** 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 your region, please:

- Call: (800) 955-4572
- Visit: [www.LLS.org/LocalPrograms](http://www.LLS.org/LocalPrograms)

**Advocacy and Public Policy.** Working closely with dedicated volunteer advocates, LLS's Office of Public Policy elevates the voices of patients to state and federal elected officials, the White House, governors and even courts. Together, we advocate for safe and effective treatments. We pursue policies that would make care more accessible to all patients. And, most of all, we advocate for the hope for a cure. Want to join our work? Visit [www.LLS.org/advocacy](http://www.LLS.org/advocacy) for more information.

**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](http://www.LLS.org/ResourceDirectory) to view the directory.

### **Additional Help for Specific Populations**

**Información en Español (LLS information in Spanish).** Please visit [www.LLS.org/espanol](http://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. For more information, please

- Call: the VA (800) 749-8387
- Visit: [www.publichealth.va.gov/exposures/AgentOrange](http://www.publichealth.va.gov/exposures/AgentOrange)

**Information for Firefighters.** Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit [www.LLS.org/FireFighters](http://www.LLS.org/FireFighters) for resources and information.

**World Trade Center Health Program.** People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help from the World Trade Center (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 in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: [www.cdc.gov/wtc/faq.html](http://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) at (866) 615-6464
- Visit: NIMH at [www.nimh.nih.gov](http://www.nimh.nih.gov) and enter “depression” in the search box

## Health Terms

**Alkylating Agent.** A type of chemotherapy drug that is used in cancer treatment. It kills cancer cells by damaging their DNA, which prevents them from dividing (reproducing).

**Allogeneic Stem Cell Transplantation.** A treatment that uses stem cells from a healthy donor to restore a patient's bone marrow that is damaged or diseased after receiving intensive chemotherapy and/ or radiation therapy. **Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation* for more information.**

**Anemia.** A condition in which the number of red blood cells is below normal. This results in reduced oxygen flow to the body's organs. Severe anemia can cause a pale complexion, weakness, fatigue, dizziness and shortness of breath.

**Antibody.** A type of protein created by blood cells in response to an antigen (a substance that causes the body to mount a specific immune response). Antibodies help the body fight against invaders that make a person sick. They can also be made in the laboratory and are used to help identify certain types of cancer and also to help treat cancer, either alone or attached to toxic substances.

**Antigen.** A substance that creates an immune response in the body, especially the production of antibodies. Examples include allergens, chemicals, bacteria, viruses and other substances outside the body. Cells in the body, including cancer cells, also have antigens on their surfaces that can cause an immune response.

**Antimetabolite.** A type of chemotherapy that interferes with the normal division and functions of cancer cells.

**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. High levels of this protein in CLL patients generally indicate more advanced CLL.

**Bone Marrow.** A spongy tissue in the hollow central cavity of bones, where blood cells form.

**Bone Marrow Aspiration.** A procedure in which a liquid sample of bone marrow is removed for examination by a pathologist. The sample is usually taken from the patient's hip bone using a special needle, after a medication is given to numb the area. Bone marrow aspiration and bone marrow biopsy can be done in a doctor's office or in a hospital and are usually done at the same time.

**Bone Marrow Biopsy.** A procedure in which a sample of bone containing bone marrow is removed for examination by a pathologist. The sample is usually taken from the hip bone, using a special hollow needle, after medication is given to numb the skin and tissue in that area. Bone marrow aspiration and bone marrow biopsy can be done in a doctor's office or in a hospital and are usually done at the same time.

**Bone Marrow Transplantation.** See Allogeneic Stem Cell Transplantation.

**Chemotherapy.** Treatment that stops the growth of cancer cells, either by killing them or stopping them from dividing.

**Chimeric Antigen Receptor (CAR) T-Cell Therapy.** Treatment that uses a patient's own T cells (a type of white blood cell) to identify and attack cancer cells. The T cells are taken from the patient's blood and sent to a laboratory, where they are genetically modified so that they will attack cancer cells. The engineered T cells are then multiplied and later re-infused into the patient's bloodstream. **Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS fact sheet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts* for more information.**

**Chromosome.** Part of a cell that contains genes in a linear order. Human cells have 23 pairs of chromosomes. **Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS booklet *Understanding Genetics* for more information.**

**Cluster of Differentiation (CD).** A term used along with a number to identify a specific molecule found on the surface of cells that help differentiate one cell type from another. It is commonly used in its abbreviated form, for example, "CD20."

**Colony-Stimulating Factor.** See Growth Factor.

**Cytopenia.** A condition in which the number of blood cells is lower than normal.

**Deletion.** In genetics, this refers to a portion of a chromosome that is missing.

**Eosinophil.** A type of white blood cell that is released during infections and allergic reactions.

**FDA.** The abbreviation commonly used to refer to the United States Food and Drug Administration. The FDA is responsible for assuring the safety, effectiveness and security of drugs, medical devices and the nation's food supply.

**Fluorescence In Situ Hybridization (FISH).** A technique for studying abnormal chromosomes in cells and tissues. Pieces of DNA that contain fluorescent molecules are added to cells or tissues on a slide. When the pieces of DNA bind to certain genes or chromosomes, they light up when viewed under a specialized "fluorescence" microscope. This test can help to diagnose some types of cancer and plan treatment.

**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 made by the body that stimulates the growth of specific cells. Some growth factors are made in the laboratory for use in cancer treatment. For example, granulocyte-colony stimulating factor (G-CSF) is a substance used to increase the number of neutrophils, a type of white blood cell.

**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 43.

**Hemoglobin.** A protein inside red blood cells that carries oxygen around the body. Hemoglobin concentration decreases when there is a drop in the number of red blood cells.

**Imaging Test.** A type of test that makes detailed pictures of areas inside the body. Imaging tests use different forms of energy such as x-rays, ultrasound and radio waves.



**Immunoglobulin.** A protein that is made by B cells and plasma cells that helps the body fight infection.

**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.** An organized profile of a person's chromosomes. It shows the size, shape and number of chromosomes in a sample of cells.

**Lymph Node.** A bean-shaped structure that is part of the body's immune system. Throughout the body, there are hundreds of lymph nodes that contain large numbers of lymphocytes, white blood cells that help fight infection and disease.

**Lymphatic System.** The tissues and organs that produce, store and carry white blood cells that fight infections and other diseases. This system includes the lymph nodes, the spleen, thymus and lymphatic vessels (a network of thin tubes that carry lymph and white blood 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 infections; 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 elevated number of lymphocytes in the blood. Technically, all CLL patients have lymphocytosis at the time of diagnosis, but SLL patients may not. Some patients treated with BTK inhibitors may also have an increase in the number of lymphocytes in the blood that occurs soon after the therapy is started.

**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, even when the patient's blood and bone marrow may appear to be normal. These residual cancer cells cannot be seen under a microscope and can only be identified by other very sensitive tests like polymerase chain reaction (PCR), next-generation sequencing or flow cytometry. Also called "measurable residual disease."

**Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS fact sheet *Minimal/Measurable Residual Disease (MRD)* for more information.**

**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 sequence of a cell. A mutation may be caused by an error in cell division or by contact with DNA-damaging substances in the environment.

**Neutropenia.** An abnormal decrease in the number of neutrophils, a type of white blood cell, in the blood. People with low neutrophil counts are susceptible to infections.

**Neutrophil.** A type of white blood cell, and the principal type of phagocyte (microbe-eating cell), in the blood. It is the main type of cell that combats infection.

**Next-Generation Sequencing.** This refers to a number of different gene sequencing technologies that can rapidly examine stretches of DNA or RNA.

**Off-Label.** The legal use of a prescription drug to treat a disease for which the drug has not been approved by the United States Food and Drug Administration (FDA).

**Oncologist.** A doctor who has special training in diagnosing and treating cancer.

**Oral Medication.** Treatment with drugs taken by mouth.

**Pathologist.** A doctor who has special training in identifying diseases by examining cells and tissue samples under a microscope.

**Performance Status.** A measure of how well a person is able to perform ordinary tasks and carry out daily activities.

**Peripheral Blood.** The blood that circulates throughout the body in the arteries, capillaries and veins

**PET Scan.** A procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is taken up. Because cancer cells often take up more glucose than normal cells, the pictures can be used to find cancer cells in the body.

**Platelet.** A small, colorless piece of a cell that helps control bleeding. Platelets are produced from large cells in the bone marrow, called “megakaryocytes.” Platelets travel to and then collect at the site of a wound. The platelets’ sticky surface helps them form clots at the site of the wound and stop bleeding. Also called “thrombocyte.”

**Polymerase Chain Reaction (PCR).** A very sensitive laboratory genetic test that is used to detect and measure some genetic mutations and chromosomal changes that cannot be seen with a microscope. It essentially amplifies (increases) small amounts of specific pieces of either DNA or RNA so that they are easier to detect and measure. This test can find a single cancer cell among more than approximately 100,000 healthy blood cells.

**Red Blood Cell.** A type of blood cell that contains a protein called “hemoglobin,” which carries oxygen from the lungs to the tissues of the body. Red blood cells make up about 40 to 45 percent of blood volume in healthy people. Also called “erythrocyte.”

**Reduced-Intensity Stem Cell Transplantation.** A type of allogeneic stem cell transplantation in which patients receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. The chemotherapy and radiation do not completely kill all the leukemia cells, but the new immune cells that the patient receives in the transplant may attack the leukemia cells. This protocol may be safer than a traditional high-dose conditioning or “myeloablative” allogeneic stem cell transplant, especially for older patients. **Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation* for more information.**

**Refractory.** The term used to describe a disease that does not go into remission or improve substantially after treatment.

**Relapse.** The return of a disease after a period of improvement.

**Remission.** When signs of a disease disappear, usually following treatment

**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.** A rare condition in which CLL changes into a fast-growing type of lymphoma.

**Spleen.** An organ in the left upper portion of the abdomen, just under the left side of the diaphragm. The spleen filters blood, stores blood cells and destroys old blood cells. 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 Cell.** A cell from which other types of cells develop. In the bone marrow, blood-forming stem cells mature into red blood cells, white blood cells and platelets. Stem cells can be collected, preserved and used for stem cell therapy.

**Subcutaneous Injection.** The administration of medication with a needle that goes under the skin into the space between the skin and muscle.

**Thrombocytopenia.** A condition in which the number of platelets in the blood is below normal.

**White Blood Cell.** A type of blood cell that is part of the body’s immune system. The five major types of white blood cells are neutrophils, eosinophils, basophils, monocytes and lymphocytes. Also called “leukocyte.”

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