

Understanding **CLL/SLL**

**Chronic Lymphocytic Leukemia
and Small Lymphocytic Lymphoma**



**A Guide for Patients,
Survivors, and
Loved Ones**

We understand that a diagnosis of lymphoma may bring about many different emotions but the Lymphoma Research Foundation (LRF) is here to help.

The LRF Helpline is available to help patients and their loved ones better understand their lymphoma diagnosis so that they can feel empowered to make the most informed decisions about their treatment and long-term care.

LRF's Support Services include:

- Individualized information on lymphoma
- Free fact sheets and guides
- Clinical Trial Information Service
- Financial Assistance Program
- Lymphoma Support Network

Contact the LRF Helpline, Monday through Friday, 9:30am - 7:30pm (ET). Call (800) 500-9976 or email at helpline@lymphoma.org

This guide is an educational resource compiled by the Lymphoma Research Foundation to provide general information on chronic lymphocytic leukemia and small lymphocytic lymphoma. Publication of this information is not intended to replace individualized medical care or the advice of a patient's doctor. Patients are strongly encouraged to talk to their doctors for complete information on how their disease should be diagnosed, treated, and followed. Before starting treatment, patients should discuss the potential benefits and side effects of cancer therapy with their physician.

Contact the Lymphoma Research Foundation

Helpline: (800) 500-9976

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ABBREVIATIONS

ABMS	American Board of Medical Specialties	CT	computed tomography
ACIP	Advisory Committee on Immunization Practices	del	deletion
ANC	absolute neutrophil count	DNA	deoxyribonucleic acid; genetic material
app	application	DNR	do not resuscitate
ASCO	American Society of Clinical Oncology	ECOG	Eastern cooperative oncology group
ASH	American Society of Hematology	FDA	U.S. Food and Drug administration
<i>Bcl2</i>	B-cell lymphoma 2	FISH	fluorescence in situ hybridization
BTK	Bruton tyrosine kinase	FL	follicular lymphoma
CAR	chimeric antigen receptor	FNA	fine needle aspiration
CBC	complete blood count	GVHD	graft-versus-host disease
CDC	Centers for disease control and prevention	GVL	graft-versus-lymphoma effect
CLL	chronic lymphocytic leukemia	GVT	graft-versus-tumor effect
CME	continuing medical education	HBV	hepatitis B virus
CMP	comprehensive metabolic panel	HCV	hepatitis C virus
CPR	cardiopulmonary resuscitation	HIV	human immunodeficiency virus
CR	complete remission	HL	Hodgkin lymphoma
CSF	cerebrospinal fluid	IgG	immunoglobulin G
		<i>IGHV</i>	immunoglobulin heavy chain variable region gene

IHC	immunohistochemistry	NSAID	Nonsteroidal anti-inflammatory drug
IRB	institutional review board	PA	Physician assistant
IV	intravenous	PI3K	phosphoinositide3-kinase
LDH	lactate dehydrogenase	PICC	peripherally inserted central catheter
LSRMP	Lymphoma Scientific Research Mentoring Program	PML	progressive multifocal leukoencephalopathy
LRF	Lymphoma Research Foundation	PR	partial remission
MBL	Monoclonal B-cell lymphocytosis	PS	performance status
MR	minor response	PrEP	Pre-exposure prophylaxis
MRD	minimal residual disease	SAB	Scientific Advisory Board
MRI	magnetic resonance imaging	SEER	Surveillance, Epidemiology, and End Results
MUGA	multigated acquisitionscan	slg	surface immunoglobulin
NCI	National Cancer Institute	SLL	small lymphocyticlymphoma
NHL	non-Hodgkin lymphoma	TLS	tumor lysis syndrome
NIH	National Institutes of Health	WBC	white blood count
NK	natural killer cell	WHO	World Health Organization
PET	positron emission tomography		

INTRODUCTION

The purpose of this guide is to educate and support patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and their loved ones. It is designed to allow them to familiarize themselves with this disease and to become active participants in healthcare decisions. Chapters in this guide address different issues faced by patients with CLL/SLL, including what to expect during diagnosis, work-up, and treatment; how to cope with treatment side effects; and what questions to ask doctors, nurses, physician assistants, social workers, and other members of the healthcare team.

In addition to this guide, the Lymphoma Research Foundation (LRF) provides a comprehensive series of expert programs and services for people with lymphoma and their caregivers. Our free services include: Clinical Trials Information Service, Publications focused on lymphoma; Financial Assistance Resources; In-Person Education Conferences; Lymphoma Support Network; LRF's award-winning mobile app Focus On Lymphoma (lymphoma.org/mobileapp); Webinars and Videos. For additional information, please visit our website at lymphoma.org. The LRF Helpline can also provide additional information and copies of LRF educational and support publications free of charge. For individual support, contact the LRF Helpline at (800) 500-9976 or email helpline@lymphoma.org.

Part 1 — Learning the Basics

Chapter 1: Understanding the Disease

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are two types of blood cancers. They are both forms of non-Hodgkin lymphoma (NHL) that affect specialized white blood cells called B lymphocytes. Lymphocytes work together with other cells in the immune system to defend the body against invasion by bacteria, viruses, parasites, and other foreign substances, as well as malignant cells. Lymphocytes travel in the bloodstream and in another network of mostly small vessels called the *lymphatic system*. Lymphocytes are also found in specialized structures called lymph nodes, in the bone marrow, and in the spleen. Lymph nodes are part of the lymphatic system and typically are the sites in which the body develops an immune response to viral or bacterial infections.

CLL and SLL are the same disease. The only difference is location. Patients who have more than 5,000 circulating CLL/SLL cells per microliter of blood have been historically termed CLL. When most of the cancer cells are located primarily in the bloodstream and the bone marrow, the disease is referred to as CLL, although the lymph nodes and spleen may be involved. When the cancer cells are located mostly in the lymph nodes and are rare in the blood, the disease is called SLL. Patients with SLL may develop a rising white blood cell count in the blood (leukemia), and patients with CLL invariably have cancer cells also in the lymph nodes.

This chapter explains these and other terms to help readers better understand CLL/SLL and how it affects a person's health. A better understanding of the disease may allow patients to be active participants in their care.

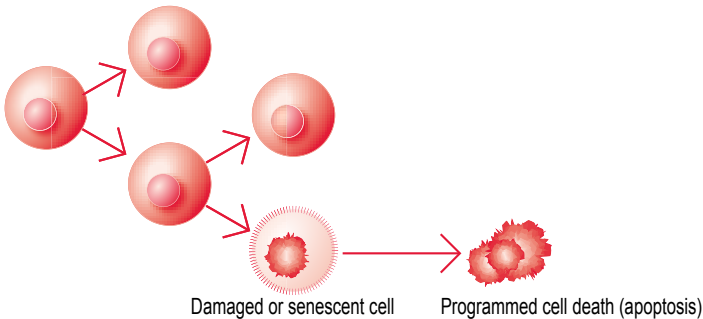
What Is Cancer?

The body is made up of many different types of specialized cells that are organized into tissues and organs that perform the tasks needed to sustain life. To keep the body running smoothly, cells in the body grow, work, and multiply in a very controlled fashion.

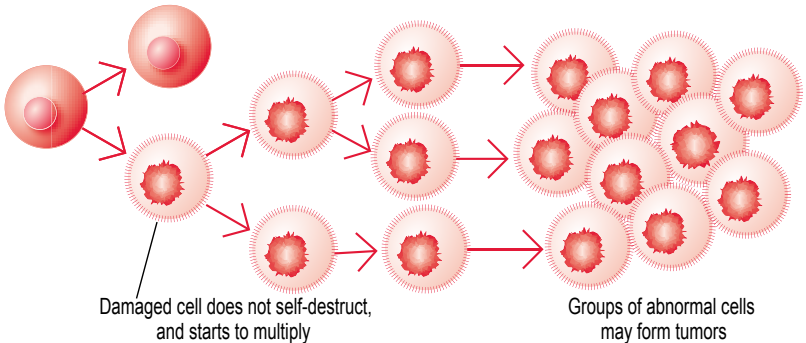
All normal cells have a limited lifespan. A self-destruct mechanism is triggered when cells become senescent (too old) or get damaged; this process is called apoptosis or programmed cell death. However, sometimes damage to the genetic material (DNA) of a cell gives it the ability to override this self-destruct mechanism and allows the cell to continue to live and grow indefinitely, preventing the cell from ever dying. Unless the body's immune system gets rid of these abnormal cells, they can become cancerous.

HOW CANCER FORMS INSIDE THE BODY

Normal cell division



Cancer cell division



Most cancers are named after the organ or cell type of their origin. There are two main types of cancer:

- Hematologic cancers are cancers of the blood cells, such as leukemia, lymphoma, and myeloma.
- Solid tumor cancers originate in body organs or tissues, such as breast, prostate, and lung cancers.

A cancer of the lymphocytes is called a *lymphoma* or *lymphocytic leukemia* depending on whether the cancerous lymphocytes reside primarily in the lymph nodes and other lymphatic tissues (lymphoma) or primarily in the bone marrow and the blood (lymphocytic leukemia).

What Are the Different Types of Blood Cells?

There are three main classes of blood cells:

- Red blood cells (or *erythrocytes*) — Red blood cells carry oxygen from the lungs to all the tissues in the body. Red blood cells also remove the carbon dioxide waste produced by cells and bring it to the lungs to be exhaled. A low number of red blood cells is called *anemia*. A person with anemia may feel tired, weak, and/or short of breath.
- Platelets (or *thrombocytes*) — Platelets are cell fragments that clump together in a blood clot to stop bleeding from broken blood vessels. A low number of platelets is called *thrombocytopenia*. People with thrombocytopenia are more likely to bruise and bleed with minor trauma. They are also more likely to have severe and recurring nosebleeds and bleeding gums.
- White blood cells (or *leukocytes*) — White blood cells work as part of the immune system to help the body fight off infections. The main types of white blood cells are:
 - Granulocytes — There are three types of granulocytes: neutrophils, basophils, and eosinophils. Neutrophils help fight bacterial infections. A low number of neutrophils in the blood is called *neutropenia*. People with neutropenia are more likely to get infections (mostly bacterial infections) than people with normal numbers of neutrophils.

Basophils are cells that take part in inflammatory reactions.

Eosinophils also help fight infections— particularly those caused by parasites—and can become plentiful during allergic reactions.

- Monocytes — These also play an important role in immunity and are usually the first cells to recover after an episode of severe neutropenia.
- Lymphocytes — These are discussed on the following page.

Because blood cells have a limited lifespan, the body needs to constantly replenish its supply of these cells. Red blood cells live for about 120 days; most white blood cells have a much shorter life, ranging from a few hours to a few weeks. New blood cells are made by *hematopoietic* (blood-forming) stem cells, which are *immature* (non-specialized) cells that can develop into nearly any kind of blood cell. Hematopoietic stem cells are found mainly in the *bone marrow* (spongy, fatty material inside large bones such as the pelvis, vertebrae, and ribs).

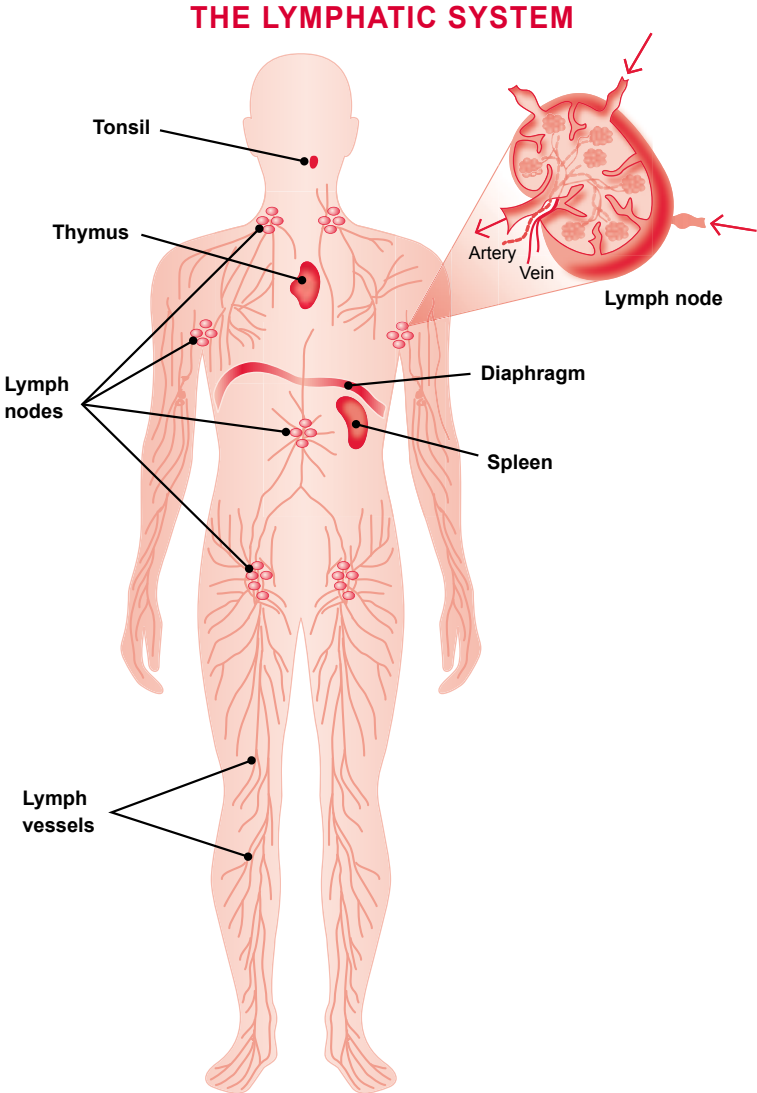
What Are Lymphocytes?

Lymphocytes are one type of white blood cell. There are three main types of lymphocytes:

- B lymphocytes (B cells) — B cells make antibodies or immunoglobulins to fight infections. They are called “B” cells because they were first discovered in the “Bursa of Fabricius” in birds (similar to the appendix in humans). Later, similar cells were found in humans. CLL/SLL is a cancer of B lymphocytes.
- T lymphocytes (T cells) — T cells are the “quarterbacks” of the immune system and help direct immune responses. There are many types of T cells. Some help B cells make antibodies, some attack and kill infected cells, and others help control or regulate the way other parts of the immune system fight infections. They are called “T” cells because they develop in the thymus gland, a small organ in the chest.
- Natural killer (NK) cells — NK cells attack and kill cancer cells and virus-infected cells. They release small particles that contain a group of proteins called cytokines which help the body get rid of cancer cells.

What Is the Lymphatic System?

As shown in the image below, the *lymphatic system* is a circulatory system made up of a spidery network of thin tubes called *lymph vessels* or *lymphatic vessels*. Like blood vessels, lymphatic vessels branch out into all tissues of the body. Lymphatic vessels carry lymph, a liquid that contains lymphocytes to help fight infection.



Within this huge network of vessels are groups of small, bean-shaped organs called *lymph nodes*, which are also commonly known as “glands.” Lymph nodes filter the lymph fluid, removing bacteria, viruses, and other foreign substances from the body. Hundreds of lymph nodes are normally found at locations throughout the body, including the neck, underarms, chest, abdomen, and groin. Lymphocytes can mostly be found in lymph nodes, where they monitor the body’s immune system for signs of infection. Lymph nodes are like warehouses of lymphocytes that scan the lymph for infections. When an infection is detected, those lymphocytes that are preprogrammed to respond to that infection, grow and divide, and fight the infection. This is what happens when a lymph node enlarges and is painful or tender. When the infection is cleared, the lymphocytes reduce in number and the lymph node returns to its normal size. Thus, the lymph nodes can change in size, becoming bigger or smaller, depending on the number of lymphocytes inside them.

Most swollen lymph nodes are a reaction to infection and are not cancerous. Lymph cells can also become enlarged in states of chronic inflammation, such as in autoimmune diseases like rheumatoid arthritis.

How Does the Immune System Work?

The immune system is the body’s defense against things that might cause it harm. The immune system is made up of a network of cells, tissues, and organs that work together to detect and destroy invaders, such as bacteria, viruses, and parasites, that can make people sick.

The immune system provides two different types of immunity:

- **Innate** (meaning “inborn” or “natural”) immunity — This type of immunity is provided by natural barriers in the body, substances in the blood, and specific cells that attack and kill foreign cells. Examples of natural barriers include skin, mucous membranes, stomach acid, and the cough reflex. These barriers keep germs and other harmful things from entering the body. Inflammation (often associated with redness and swelling) is also a type of innate immunity. Blood cells that are part of the innate immune system include neutrophils, macrophages, eosinophils, and basophils.
- **Adaptive** (meaning adapting to external forces or threats) immunity — This type of immunity is provided by the thymus gland, spleen, tonsils, bone marrow, circulatory system, and lymphatic system. B cells and

T cells, the two main types of lymphocytes, carry out the adaptive immune response by recognizing and either deactivating or killing specific invading organisms. The adaptive immune system can then “remember” the identity of the invader, so that the next time the body is infected by the same invader, the immune response will develop more quickly and strongly.

What Is Lymphoma?

Lymphoma is a broad term for cancer that starts in lymphocytes present in the lymph nodes and other tissues in the lymphatic system. There are two major categories of lymphomas: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Both of these categories are further subdivided into numerous types, which differ in the way they develop and spread, as well as in the way they are treated. Physicians may take into consideration the type of lymphoma, the patient’s age, other medical issues, and certain markers that are specific to the individual lymphoma type when making therapy and prognosis decisions.

What Is Non-Hodgkin Lymphoma?

In the United States, NHL (which includes CLL/SLL) is the eighth most common type of cancer affecting adults, with almost 65,000 people newly diagnosed each year. NHL is not a single disease but rather a large group of several closely related cancers that arise from abnormal lymphocytes. The World Health Organization (WHO) estimates that there are more than 60 subtypes of NHL. While these various types share many common features, certain characteristics set them apart from each other, including:

- How they look when examined under a microscope
- Genetic and other molecular characteristics
- How and where they grow in the body
- How their growth and spread affect patients
- How and when the disease should be treated
- Likely outcome of treatment (curable vs not curable [but treatable])

NHL is divided into the following two major groups (as well as some minor groups that are not discussed here):

- B-cell lymphomas — These lymphomas develop from abnormal B lymphocytes and are the most common, comprising about 90 percent of all cases of NHL in western countries (generally North America and Western Europe).
- T/NK-cell lymphomas — These lymphomas develop from abnormal T lymphocytes or NK cells and are less common. T-cell lymphomas account for 10% of patients with an NHL diagnosis, while NK-cell lymphomas account for less than 1% of patients diagnosed with NHL.

Another way to group NHL types is by how quickly they grow:

- *Indolent* (also called low-grade) *lymphomas* usually grow slowly and exhibit few symptoms at first. Indolent lymphomas are generally not curable, but they are usually manageable. Patients can live a long time with these types of lymphomas because they tend to respond well to treatment and can remain in *remission* (disappearance of signs and symptoms) for many years or even decades. However, in a minority of cases, some indolent lymphomas may transform into aggressive lymphomas. Given that these can grow and spread quickly, immediate intervention is required when a diagnosis of transformed disease occurs.
- *Aggressive lymphomas* grow and spread more quickly than indolent lymphomas. However, aggressive lymphomas can often be cured by chemotherapy agents that kill rapidly dividing tumor cells.

Pathologists (doctors who specialize in disease diagnosis) can distinguish among the many different types of NHL by examining biopsy tissue samples and blood and bone marrow samples under a microscope and by carrying out various laboratory tests. This information is critically important in deciding how to treat the disease in each patient.

What Is CLL/SLL?

Until the 1990s, doctors believed that chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) were two different diseases. However, recent research has shown that CLL and SLL are actually the same disease. If the malignant lymphocytes are found mainly in the lymph nodes, the disease is commonly called SLL. If high levels of malignant lymphocytes are found in the bloodstream, then the disease is typically called CLL. However, malignant lymphocytes can often be found in both the lymph nodes and the bone marrow of patients with SLL and CLL and patients with CLL can also have lymph node enlargement at the time of diagnosis. Over time, a patient with *relapsed* (disease returns after treatment) CLL may develop enlarged lymph nodes like a patient with SLL, and a patient with relapsed SLL may have malignant lymphocytes in the blood like a patient with CLL. Patients with CLL may or may not initially have enlarged lymph nodes, while others may develop lymph node enlargement over time. Furthermore, some patients with SLL may initially have very few circulating malignant lymphocytes, but the number might increase as the disease progresses. In fact, most cases of SLL become CLL over time. Because they are essentially the same disease presenting in different parts of the body, the two terms are now usually grouped together as a single condition known as “CLL/SLL.” Since patients with CLL and SLL receive the same treatments and the prognosis is similar, the rest of this guide will use the term CLL/SLL, unless a distinction needs to be made between the two conditions.

Although CLL is a leukemia, CLL and SLL are in the family of B-cell lymphomas within the larger category of NHL. Doctors consider CLL/SLL to be an indolent type of lymphoma because it may remain inactive or *quiescent* over an extended period of time and can be managed like a chronic disease.

However, occasionally CLL/SLL may progress or transform to a more aggressive type of lymphoma, and this transformation from CLL/SLL to a more aggressive lymphoma (usually diffuse large B-cell lymphoma) is called Richter syndrome or Richter transformation.

How Common is CLL/SLL?

About 19 percent of patients with a B-cell lymphoma have CLL/SLL, making it the third most common type of B-cell lymphoma. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data, approximately 21,000 people in the United States are diagnosed with CLL/SLL each year. In 2018, there were approximately 195,000 people living with CLL in the US. This disease is rare in people younger than 40 years. The median age at diagnosis is 70.

What Causes CLL/SLL?

The exact cause of CLL/SLL is not known. Like other types of indolent lymphomas, CLL/SLL develops over a long time after lymphocytes accumulate genetic changes (called *mutations* and *chromosomal abnormalities*) that may cause them to grow abnormally. Some of these mutations make the abnormal lymphocytes divide faster and/or live longer than normal lymphocytes.

These abnormal cells accumulate in the lymph nodes, bone marrow, bloodstream, and other organs. The increasing numbers of cancerous lymphocytes in the blood and bone marrow crowd out healthy white blood cells, red blood cells, and platelets. Patients with CLL/SLL also have low levels of antibodies that fight infections (called gamma immunoglobulins). Because of all these changes, patients with CLL/SLL are more likely to have infections, low levels of red blood cells in the blood, and/or low platelet counts, causing them to bleed more easily.

Just like healthy cells, cancerous lymphocytes can travel through the lymphatic system. This ability to move around lets the cancerous lymphocytes spread and grow in many parts of the body. This is why CLL/SLL and most other types of indolent NHL are already found throughout the body by the time a patient is diagnosed with the disease. This is typical, and is not an indication of a delay in diagnosis.

Why Do Some People Develop CLL/SLL?

The reasons why certain people develop CLL/SLL are not totally understood. However, scientists have found that people with particular characteristics, called *risk factors*, have a slightly higher chance of developing CLL/SLL compared with people who do not have these risk factors. Having one or more risk factors for CLL/SLL does not mean a person will definitely develop the disease. In fact, most people with the known risk factors never develop CLL/SLL, and many people diagnosed with CLL/SLL do not have any of these risk factors. However, there does seem to be a correlation between the risk factors described below and the development of CLL/SLL.

Known risk factors for CLL/SLL include:

- Increasing age
- Male sex
- Having a first-degree relative (parent, sibling, or child) with CLL/SLL
- Having European ancestry
- Being exposed to Agent Orange (an herbicide used during the Vietnam war) and excessive, long-term exposure to some pesticides used in farming. Veterans who have CLL/SLL and were exposed to Agent Orange can contact their local Veterans Affairs office to ask about benefits that may be available.
- Having a diagnosis of monoclonal B-cell lymphocytosis (MBL), a condition characterized by higher than normal levels of lymphocytes, but not high enough to classify as CLL. There is a small risk that these patients may develop CLL in the future, equating to about a 1% chance for each year of MBL diagnosis.

CLL/SLL cannot be caused by injury and cannot be caught from someone who has the disease. CLL/SLL is rarely caused by inherited mutations.

Part 1 — Learning the Basics

Chapter 2: Seeking Medical Attention

This chapter explains the signs and symptoms of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and discusses how a doctor determines whether a person has the disease.

A *sign* is anything unusual that doctors, nurses, or physician assistants notice when they examine their patients or look at their laboratory test results.

A *symptom* is anything unusual in a normal body function, appearance, or sensation that a patient experiences. During a visit with a healthcare practitioner, patients should report all of their symptoms to their doctor, nurse, or physician assistant. Symptoms may indicate the presence of CLL/SLL or another disease.

What Are the Signs and Symptoms of CLL/SLL?

Approximately 50-75% of patients with CLL/SLL do not have any obvious signs or symptoms of the disease at the time of diagnosis. Their doctors might detect the disease during routine blood tests and/or a physical examination. Besides a higher number of white blood cells, the immune system of people with CLL may also produce antibodies against their own red blood cells and/or platelets (autoantibodies, your immune system mistakes your red blood cells and platelets for foreign cells). For others, the lymphoma is discovered when symptoms occur and they go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 2.1, CLL/SLL may cause different signs and symptoms depending on the location of the tumor in the body. Keep in mind that many of these signs and symptoms are not specific to CLL/SLL or other types of non-Hodgkin lymphoma (NHL) and may be due to other conditions.

Table 2.1. Signs and Symptoms Commonly Found in Patients With CLL/SLL

Sign or Symptom	Possible Reason
Shortness of breath, <i>fatigue</i> (extreme tiredness), and pale skin	A shortage of oxygen-carrying red blood cells (<i>anemia</i>)
Severe or frequent infections	Reduced ability to fight infection because of decreased numbers of certain types of white blood cells or a reduction in ability to make infection-directed antibodies, or immunoglobulins (hypogammaglobulinemia)
Frequent nosebleeds, bleeding from the gums, tiny red marks on the skin caused by minor bleeding under the skin (<i>petechiae</i>), and bruising easily	A shortage of platelets in the blood (<i>thrombocytopenia</i>)
“B symptoms” including fever for no known reason, unexplained drastic weight loss, or drenching night sweats that soak clothing and sheets. Patients may also experience chills.	Increased levels of inflammatory chemicals in the blood that are released by leukemia/lymphoma cells or by the immune system reacting to the lymphoma cells
Lumps under the skin on the sides of the neck, above the collarbone, or in the underarms, elbows, or groin	Lymph nodes, or “glands,” that swell because of an increased number of abnormal lymphocytes

When Should a Patient Seek Medical Attention?

Anyone who has an enlarged lymph node in the absence of an infection that does not return to normal size within a few weeks and/or persistent symptoms should see a doctor to make sure that lymphoma or another serious condition is not present. A good rule of thumb is to seek medical attention if any of the signs or symptoms listed in Table 2.1 last longer than two weeks, or sooner if the symptoms are intense enough to impact a person’s daily life. It is important to note that most patients with these symptoms do not have lymphoma, as diseases or conditions not related to lymphoma may cause many of these symptoms.

What Does the Doctor Look For During the Visit?

During their visit, patients should describe all of their symptoms to the doctor. The doctor will ask questions about their medical history and perform a complete physical examination, during which the doctor is likely to:

- Ask details about symptoms including duration, frequency, intensity, and pain; these can be tracked in a mobile device app such as the Lymphoma Research Foundation's mobile app, *Focus On Lymphoma*. This app can keep track of symptoms and make communications with your doctor easier and more accurate.
- Measure blood pressure and pulse
- Listen to the heart and lungs
- Check the throat for enlarged tonsils
- Look for any physical signs of infection or any other cancers, especially on the skin
- Check for swollen lymph nodes under the chin, in the neck and tonsil area, above the shoulders, on the elbows, in the underarms, and in the groin
- Examine other parts of the body to look for swelling or fluid that may be caused by swollen lymph nodes
- Examine the abdomen to see whether the liver and/or spleen are enlarged and to feel for masses
- Look for any weakness or paralysis that may be caused by an enlarged lymph node pressing against nerves or the spinal cord

If the doctor suspects CLL/SLL after reviewing the symptoms reported and the signs noted during the examination, he or she will order tests to confirm the diagnosis. For CLL, it may be best to consult with a hematologist-oncologist, a doctor who specializes in diagnosing and treating blood cancers.

These tests should include a complete blood count (CBC), a comprehensive metabolic panel (a group of 14 tests that measures different substances in blood), assessing the performance status (ability to carry out day-to-day activities through a scoring system). Specific laboratory tests (such as immunophenotyping) and imaging tests (including scans) may also be required. A lymph node biopsy may be needed for patients with suspected SLL. Doctors do not always need a bone marrow test to make the CLL/SLL diagnosis, but they may find it useful prior to treatment and/or to assess the response to therapy. These tests and procedures are discussed in more detail in Chapters 3 and 4.

Part 1 — Learning the Basics

Chapter 3: Receiving a Diagnosis

Doctors need the results of various diagnostic tests to determine whether a patient has chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). This chapter explains the purpose of each test and describes what to expect during and after the test procedures.

Before agreeing to any procedure, patients should make sure that they understand the reasons for the procedure and what will be involved. Here is a list of questions patients may want to ask their doctor.

Questions to Ask Before Having a Diagnostic Procedure

PATIENT TIP

- Why is this procedure necessary?
- What will the procedure tell us about my condition?
- Can the same information be obtained in another way?
- What is involved in this procedure?
- What are the possible risks, complications, and side effects?
- Where will the procedure take place?
- Will I have to do anything to prepare for the procedure?
- How long will the procedure take? Will I be awake? Will I feel pain?
- How long will it take to recover from the procedure?
- May someone else be present when I have the procedure?
- Will I need someone to take me home afterward?
- If I will be receiving a dye, are my kidneys healthy enough to handle it?
- When will I get the results?
- When will we discuss the results?
- How will the results of this test affect my treatment?
- Will my insurance cover the procedure?
- What will be my out-of-pocket costs?

How Is CLL/SLL Diagnosed?

CLL/SLL can be diagnosed using the peripheral blood. Rarely are a bone marrow biopsy, or a lymph node biopsy necessary. Typically, once the diagnosis is made, there is no need to confirm it from additional sites. For example, a patient with an elevated white blood count (WBC) that is proven to be CLL/SLL does not also need a bone marrow biopsy. Most cases of CLL/SLL are diagnosed based on abnormal test results in people who do not have any clinical signs or symptoms of the disease. The doctor might also suspect that a patient has CLL/SLL because of reported symptoms, results of the physical examination, and/or abnormal results from a blood test. The following tests are usually used to confirm the diagnosis:

- Complete blood count (CBC) with *differential*, a test in which the number of the different blood cells are measured. The diagnosis of CLL is characterized by a high blood count of white blood cells, and sometimes low levels of red blood cells and platelets
- Hematopathologic examination of blood smears and sometimes of a bone marrow biopsy
- Immunophenotyping by flow cytometry of the lymphocytes in the blood and lymph nodes (Table 3.2). In these tests, chemicals or dyes are used to understand if certain proteins on the outside of the cell (cell surface proteins) are present. This information allows for the distinction of CLL from other types of leukemia involving lymphocytes. Classic markers found in CLL/SLL include CD5, CD19, CD23 and dimCD20.
- Histopathologic examination of a lymph node biopsy (needed for diagnosis of SLL if the flow cytometry does not provide enough information)

Patients diagnosed with a complicated disease like CLL/SLL will be asked to undergo a variety of procedures before treatment begins, during the course of treatment, and during the follow-up period.

The doctor might also order one or more additional tests such as:

- Genetic tests (like *Fluorescence in situ hybridization* [FISH] or cytogenetic analyses) to look for acquired changes in specific regions of the chromosomes
- Molecular analysis to check on the mutation status of the immunoglobulin heavy chain variable region (*IGHV*) gene
- Blood levels of a protein called Beta-2 microglobulin
- Sequencing (determining the order of *nucleotides*, a component of DNA) of the TP53 gene to see if it contains mutations (changes)
- Other tests that the doctor may deem to be useful for determining therapy.

What Is a Biopsy?

A *biopsy* is a procedure in which a piece of tissue from an area of suspected disease is removed from the body and examined under a microscope. The information provided by this tissue sample is crucial to diagnose the disease correctly and to decide on the best course of treatment. A biopsy might be needed immediately if the size, texture, or location of a lymph node or the presence of other symptoms strongly suggests lymphoma. A biopsy is rarely needed in CLL as the diagnosis can be made from the peripheral blood. However, a node biopsy is needed to confirm the suspicion of Richter transformation.

Table 3.1 describes the three main types of biopsies that may be used for the diagnosis of CLL/SLL and other types of lymphoma.

Table 3.1. The Three Main Types of Biopsies

Excisional or Incisional Biopsy	<ul style="list-style-type: none"> ■ For these procedures, the surgeon cuts through the skin to remove an entire lymph node (<i>excisional biopsy</i>) or a large portion of a lymph node or other tissue (<i>incisional biopsy</i>). ■ If the lymph node that needs to be sampled is close to the skin surface, the procedure can be done using local anesthesia to numb the area. If the lymph node is in the chest or abdomen, the patient is sedated, and the surgeon removes the tissue either <i>laparoscopically</i> (through a tube inserted in the body) or by performing more extensive surgery. ■ This type of biopsy is generally considered the best for establishing an initial diagnosis of lymphatic malignancy because it allows the removal of larger samples than other biopsy procedures. The larger the sample removed, the more tissue the pathologist can examine, which improves the accuracy of the diagnosis. The additional tissue removed can also be used to perform other tests that may direct treatment.
Core Needle Biopsy	<ul style="list-style-type: none"> ■ This procedure is used when the lymph nodes that need to be examined are deep in the chest or abdomen or in other locations that are difficult to reach with excisional biopsy. It may also be used when there are medical reasons for avoiding an excisional or incisional biopsy. ■ A large needle is inserted into a lymph node and a small tissue sample is withdrawn using a syringe attached to the needle. The doctor may use an imaging test like ultrasound or computed tomography (CT) to help guide the needle to the correct place inside the body. This type of biopsy can be done using local anesthesia, and stitches are usually not required. ■ Sometimes the material collected from a core needle biopsy is not adequate for diagnosis, in which case a subsequent excisional or incisional biopsy may be necessary.
Fine Needle Aspiration (FNA) Biopsy	<ul style="list-style-type: none"> ■ This procedure is performed with a very thin needle that is smaller than that used for a core needle biopsy. ■ Because of the small needle size, the sample only contains scattered cells without preserving how the cells are arranged in the lymph node. Therefore, this test may not provide enough information for a definitive initial diagnosis of CLL/SLL. ■ An FNA biopsy is most often used to check for <i>relapse</i> (return of the disease) after treatment.

After a tissue sample has been removed, it is examined by a *pathologist* (doctor who specializes in diagnosing diseases by examining cells and tissues) under a microscope. A *hematopathologist* (pathologist who has undergone additional training in the diagnosis of blood diseases, including lymphoma and leukemia) may also examine the sample. These specialists identify and classify the abnormal cells by looking at their shape and size and how they are arranged in the sample. They also conduct special tests such as flow cytometry, immunohistochemistry, or cytogenetics (see “What Is Immunophenotyping?” and “What Is the Purpose of Genetic Tests?”).

An *oncologist* (doctor who specializes in treating cancer) or *hematologist* (doctor who specializes in treating blood cancers and other blood disorders) uses the pathologist’s report, along with the results of other diagnostic tests, to confirm a diagnosis. A pathologic diagnosis and accurate classification of specific lymphoma types can sometimes be difficult to make. If the pathologist’s interpretation of the biopsy is uncertain, the report should be reviewed by an expert hematopathologist who has particular experience in this type of disorder. An accurate diagnosis is essential for doctors to select the best treatment and predict the most likely outcomes.

What Is a Complete Blood Count (CBC) With Differential Test?

In a CBC with differential test, samples of blood are examined to measure:

- The number of red blood cells
- The amount of *hemoglobin* (the protein that carries oxygen) inside the red blood cells
- The number of total white blood cells, as well as the numbers of each white blood cell subtype (neutrophils, eosinophils, basophils, lymphocytes, and monocytes); the white blood cell count is usually $>5,000/\text{mm}^3$ in patients with CLL/SLL
- The number of platelets

The results of the CBC with differential assist in the diagnosis of CLL/SLL by ruling out other types of blood cancer. Most people with CLL/SLL have *lymphocytosis* (high levels of lymphocytes), and they sometimes have *anemia* (low levels of red blood cells) or *thrombocytopenia* (low levels of platelets). The CBC with differential test is often repeated during the course of treatment to help determine how much the chemotherapy has affected the different blood counts and, in some cases, to help gauge how well the treatment is working against the lymphoma.

What Is Hematopathology?

Hematopathology is the study of blood, lymph node, and bone marrow samples to identify disease. Hematopathologists identify the cancer cells by looking at their shape and size, by studying how they are grouped in the lymph nodes and the bone marrow, and by conducting special tests such as flow cytometry, immunohistochemistry, or cytogenetics (see “What Is Immunophenotyping?” and “What Is the Purpose of Genetic Tests?”).

What Is Immunophenotyping?

Immunophenotyping is a process that can be used to distinguish between different types of cells (for example, normal lymphocytes vs lymphoma cells) based on the presence of *antigens* (cell markers or proteins) on the cell surface. Antigens are specific to different cell types, just as landmarks are specific to different cities. Every antigen can be recognized by a specific type of antibody that locks onto that particular antigen. CLL is defined by an immunophenotype of CD19+, CD5+, CD23+, and light surface immunoglobulin (slg)–positive cells.

Two different procedures (Table 3.2) can be used for immunophenotyping: flow cytometry and immunohistochemistry. Antibodies for a particular antigen are chemically modified in a laboratory so that they either emit fluorescent light (flow cytometry) or show color (immunohistochemistry) when they attach to their corresponding antigens. These modified antibodies are then mixed with cells from the patient’s body. If they light up or change color, that indicates that the cells being studied have the antigen on their surface. Sometimes both immunohistochemistry and flow cytometry are necessary for accurate immunophenotyping.

Table 3.2. Flow Cytometry and Immunohistochemistry Tests

Flow Cytometry	<ul style="list-style-type: none">■ Cells from the biopsy sample are placed in a liquid solution and treated with sets of antibodies that recognize antigens found in different types of malignant cells.■ The cell-antibody mixture is injected into an instrument called a flow cytometer. This machine uses laser beams to detect the different colors of light the cells emit from the antibodies attached to them. This information is measured and analyzed by a computer and interpreted by a hematopathologist or another specialist.
Immunohistochemistry (IHC)	<ul style="list-style-type: none">■ Thin slices of the biopsy sample (or thin layers of fluid) are treated with sets of antibodies that recognize markers found in different types of malignant cells and normal lymphocytes.■ The pathologist examines the slides under a microscope to look for the visible color change that happens when the antibodies attach to the antigens.■ The pathologist identifies and counts the number of cells that are highlighted by color (meaning that they have the antigen on their surface or inside the cell) with each of the different antibodies.

What Is the Purpose of Genetic Tests?

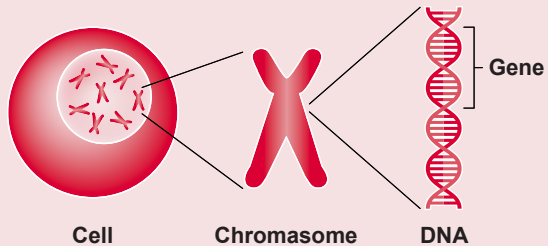
Doctors may order various types of genetic tests to confirm the results of cytogenetic tests or to find out more detailed information about the types of chromosomal abnormalities present in the lymphoma cells. Note that these tests aim to reflect the genetics of the cancer cells themselves, and not the genetics of normal cells, or the genetic material that is passed down from generation to generation. Two common genetic tests that may be used are described in Table 3.3. These genetic tests are important for learning more about a patient's particular disease and what treatments may be most effective for that patient.

Table 3.3. Types of Genetic Tests**Fluorescence In Situ Hybridization (FISH)**

- FISH uses fluorescent chemicals that attach to certain parts of chromosomes to show the presence of translocations and other large abnormalities.
- FISH can be performed on samples of blood, lymph node tissue, or bone marrow.
- The test results from FISH are usually available within a few days, which is quicker than the time required for cytogenetic testing.

Cytogenetic Analysis

- Chromosomes contain genes that are made of very long strands of DNA. Normal human cells have 23 pairs of chromosomes.



- Some lymphoma cells have too many or too few chromosomes, or they may have abnormal chromosomes that have undergone a genetic change.
- Cytogenetic analysis involves looking at chromosomes from lymphoma cells under a microscope to check for missing or extra chromosomes or any other abnormalities.
- The results of the cytogenetic analysis often help doctors distinguish between CLL/SLL and other types of non-Hodgkin lymphoma (NHL). This information can assist in making treatment decisions.

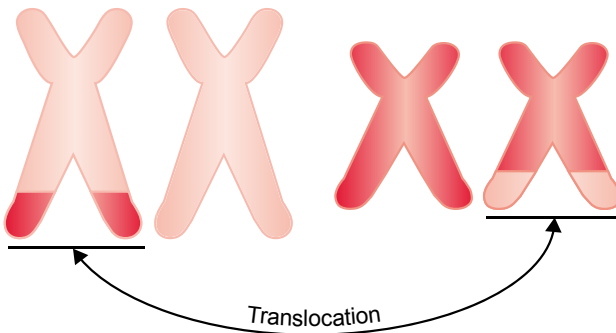
What Are Types of Chromosome Abnormalities?

Translocation

One type of chromosomal abnormality found in some NHL types is called a *translocation*, which occurs when parts of two different chromosomes break off and switch places with each other, as shown in the figure on the next page. Translocations are not very common in CLL/SLL, but other subtypes of NHL such as follicular lymphoma often or always carry a particular translocation.

TRANSLOCATION

Two different chromosomes exchange portions of their genetic material



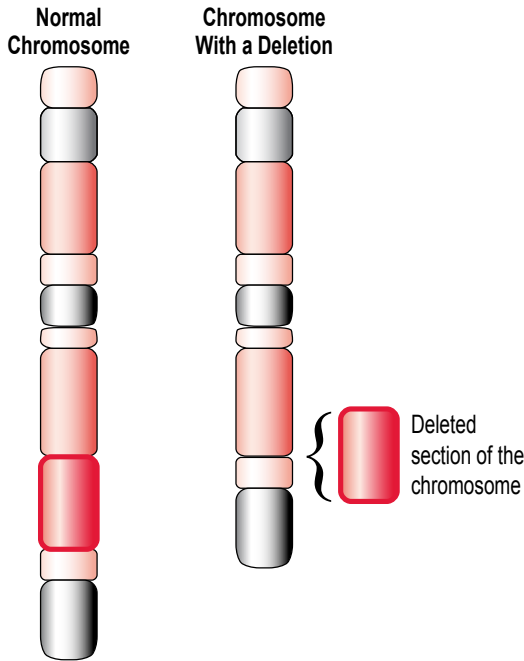
Deletion

Another type of chromosomal abnormality that may be found in CLL/SLL is called a *deletion*, which happens when part of a chromosome is missing (see the figure on the following page). The most common deletions, abbreviated as “del,” in CLL/SLL are seen in chromosomes 11, 13, and 17. Deletions in these chromosomes are written as del(11q), del(13q), and del(17p) in a patient’s FISH or karyotype testing report. The cytogenetic analysis of the malignant lymphoma cells can also change over time. For example, some patients’ malignant cells might have no detectable deletions at first, but they can develop 17p deletions over time. This is called “clonal evolution”. Of all the prognostic markers, the most important to know is whether 17p deletions are present, as this affects treatment selection.

When diagnosing CLL/SLL, the cytogenetic testing looks for very specific changes in only a few places on a few chromosomes. When no abnormalities are identified, the result is called “normal,” but other chromosomal abnormalities may be present that were not tested for.

DELETION

A piece of a chromosome is missing



Trisomy

Another type of chromosomal abnormality that may be present in the DNA of CLL/SLL lymphocytes is trisomy, which indicates the presence of an extra copy of a chromosome. The figure on the next page shows the chromosomes as they look just before the cell divides. Normally there are two pairs of each chromosome, but if a mistake occurs during cell division, a third copy of the chromosome can be created.

TRISOMY

Typical Chromosome Pair
(Two Chromosomes)



Trisomy
(Three Chromosomes)



Chromosomal changes and genetic mutations that are most commonly found in CLL/SLL are shown in Table 3.4.

Table 3.4. Chromosomal Changes and Genetic Mutations Most Commonly Found in CLL/SLL

Chromosome or Gene Mutation	Prevalence in Patients With CLL/SLL ^a
Del(13q14)	51% to 62%
12+ or trisomy 12	10% to 20%
Del(11q23)	5% to 20%
Del(17p)a	3% to 7%

Del means deletion of some of the genetic material. The numbers in parentheses (for example, 11q23) indicate the chromosome and the area on the chromosome where the deletion is located.

^aAt the time of diagnosis; over time, there is clonal expansion and the percentage increases.

Mutations in the *TP53* gene (which is located in chromosome 17) can also be found in CLL. *TP53* provides instructions for the cells to produce a protein called p53, which acts as a tumor suppressor. In CLL, mutations in the *TP53* are associated with a poor prognosis. The most common abnormality affecting the *TP53* gene in CLL is a deletion in chromosome 17p, or del(17p).

It is important for patients to discuss the interpretation of diagnostic tests with their doctor. Some important considerations when interpreting diagnostic tests are listed on the next page.

Cautions About Interpreting Diagnostic Reports

- If patients wish to look at their written or electronic test reports, it is important for them to review and interpret the findings carefully with their doctor.
- Some test results may be reported as “normal” even though CLL/SLL is present.
- Some test results may be reported as “abnormal” even though CLL/SLL is not present.
- Other conditions can produce signs and symptoms similar to CLL/SLL.
- The interpretation of test results, such as imaging studies and scans, can be lengthy, complex, and difficult in some situations.
- Follow-up tests are often needed to determine the significance of previous results, and additional biopsies may be needed to clarify the results.

Part 1 — Learning the Basics

Chapter 4: Evaluation at Diagnosis

After the initial diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), the doctor may order other tests such as blood tests, genetic tests, imaging studies, a bone marrow biopsy, and, less frequently, additional biopsies. This process is often called the *work-up* or *staging studies*. Doctors use some of these test results to determine the disease stage, which is a measure of how much the disease has spread to other parts of the body. Other tests evaluate how the disease has affected a patient's overall health and major organ functions.

Together, these test results provide the information needed to help patients and their doctors make treatment decisions. This chapter explains the reasons for the various tests, how these tests work, what to expect, and how CLL/SLL is staged.

What Tests Are Used in the Work-Up for CLL/SLL?

Patients with CLL/SLL may undergo some or all of the following work-up tests before starting treatment. Many of these tests may be repeated during the course of treatment:

- Physical examination with special attention to the size of the lymph nodes, liver, and spleen
- Assessment of general health status (also called *performance status* or *functional status*) to see how well a patient feels and how well they can carry out normal daily activities, such as getting washed and dressed, going to work, and preparing food
- Identification of any *comorbidities* (other preexisting health problems), such as diabetes, coronary artery disease, or chronic lung disease, that could affect the choice of treatment and the response to treatment
- Questioning about the presence of fever, night sweats, and weight loss (also called “B symptoms”)
- Complete blood count (CBC) with differential
- Comprehensive metabolic panel

- Testing for infection with human immunodeficiency virus (HIV), hepatitis viruses, and other viruses

Other tests that might be useful for some patients include:

- Measurement of levels of an antibody called immunoglobulin G (IgG) that help fight infections
- Reticulocyte count (to determine how fast the bone marrow is making red blood cells), haptoglobin (to determine if red blood cells are being destroyed in the vascular system [network of arteries, veins, and capillaries that supplies blood to the tissues of the body]), and direct Coombs testing (to detect antibodies against the body's own red blood cells)
- Computed tomography (CT) scans of the neck, chest, abdomen, and pelvis. PET scans are rarely indicated in CLL except when there is a suspicion of Richter transformation.
- Blood tests to measure levels of beta-2 microglobulin (a prognostic marker), lactate dehydrogenase (LDH) (which is found in high levels in the blood of many patients with fast-growing tumors), and uric acid (a product of the breakdown of cancer cell DNA, which can accumulate in the blood and damage the kidneys and other organs)
- Bone marrow biopsy and/or aspiration

What Is Performance Status?

Performance status (PS) is a numerical rating of a patient's general health and ability to carry out normal daily activities (such as getting washed and dressed, going to work, and doing chores). Measurement of PS helps doctors determine how well patients will tolerate certain treatments; it also affects eligibility for clinical trials. As shown in Table 4.1, PS is often graded using one of two scales, either the Eastern Cooperative Oncology Group (ECOG) Performance Status, which uses a scale of 0–4, with lower numbers indicating better health, or the Karnofsky Scale, using a scale of 0-100, with higher numbers indicating better health.

Table 4.1. The Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active and able to carry on all pre-disease activities without restriction
1	Cannot perform taxing physical activities, but can move around (ambulatory) and carry out light work (such as light housework) or do things that can be done while seated (such as office work)
2	Can move around and take care of oneself, but unable to do any work; up and about for more than half of awake hours
3	Can only partially take care of oneself; confined to a bed or chair for ore than half of awake hours
4	Completely disabled; cannot take care of oneself; completely confined to a bed or chair

What Is a Comprehensive Metabolic Panel?

A comprehensive metabolic panel (CMP) measures the levels of certain chemicals in the blood and is helpful in assessing the function of body organs. The comprehensive metabolic panel usually includes 14 or more specific tests that measure liver and kidney function, electrolytes, acid/base balance, and the levels of blood sugar and other blood proteins.

The results from these tests can help patients and their doctors choose between possible treatments. The CMP will be repeated frequently during treatment in order to make sure no complications of treatment are developing, in particular a reaction to toxins released by dying lymphoma cells called tumor lysis syndrome (TLS).

What is the Purpose of Testing for Hepatitis Virus and HIV?

It may be necessary to determine whether patients with CLL/SLL carry the hepatitis B virus (HBV), hepatitis C virus (HCV), and/or HIV, because treating these infections will improve how patients do and the effectiveness of treatments.

What Types of Imaging Tests May Be Used?

During the physical examination, doctors can determine by *palpation* (pressing on the outside of the body) whether the lymph nodes, spleen, and liver are enlarged. Imaging studies are only ordered if the doctor has a specific question that cannot be answered another way. Most imaging tests are painless and require no *anesthetic* (numbing medication). The imaging procedures (Table 4.2) may be used to more thoroughly evaluate the extent of disease. PET scans are not indicated in CLL/SLL unless there is a concern for transformation to a more aggressive lymphoma (i.e., Richter transformation). Magnetic resonance imaging (MRI) may be used to see if the disease has involved the bones, brain and spinal cord.

Table 4.2. Types of Imaging Tests

Computed Tomography (CT) Scan	<ul style="list-style-type: none"> ■ A CT scan is created using X-rays (radiation) taken from many different angles around the body. A computer combines the pictures obtained from these different angles to give a detailed image of organs inside the body. ■ Some patients with CLL/SLL may undergo CT scans of the neck, chest, abdomen, and pelvis to find out how many lymph nodes are involved and how enlarged they are, as well as whether any internal organs are affected by the disease. ■ Before a CT scan, the patient may be asked to drink a contrast liquid and/or get an intravenous (IV) injection of a contrast dye to more clearly outline any abnormal areas in the body.
Magnetic Resonance Imaging (MRI)	<ul style="list-style-type: none"> ■ An MRI uses magnets and radiofrequency waves to create images from different angles throughout the body. MRIs do not involve the use of radiation. ■ An MRI can provide important information about certain tissues and organs—particularly bones and the nervous system—that is not available from other imaging techniques, but it is also less helpful in other areas, such as the lungs. ■ Patients may receive intravenous contrast for MRIs, similar to CTs, but this contrast is made of a different substance. Patients who have an allergy to CT contrast, shellfish, or iodine can take MRI contrast. ■ Because this imaging technique works especially well to obtain clear images of the bones, brain, and spinal cord, an MRI may be ordered if a doctor wants to see whether the disease has involved these areas.

Table 4.2. Types of Imaging Tests (continued)

Positron Emission Tomography (PET) Scan	<ul style="list-style-type: none">■ A PET scan evaluates CLL/SLL activity in all parts of the body. A PET scan is not usually needed for patients with CLL/SLL, as CLL masses often cannot be detected with this study, but it might be used if doctors suspect that the disease has developed into a more aggressive form of leukemia/lymphoma.■ PET scans are typically performed with a CT scan and are called PET/CTs. <i>Radioactive fluorodeoxyglucose</i> (a type of sugar) is injected into the body and a positron camera is then used to detect the radioactivity. A CT scan will then take images of the body and a computer superimposes the two on-top of each other to generate images that show the body part and how much sugar uptake is present. The amount of sugar taken up represents the metabolism of the tissue. This test relies on the fact that cancer cells metabolize sugar faster than normal cells, so that more “uptake” on a PET scan indicates more metabolic activity, suggesting the presence of the malignant cells.■ While CT scans provide information about the size of a lymph node, PET scans can better indicate whether the lymph node contains active cancer cells.■ PET scans help distinguish active tumors from scar tissue and may be used to assess a patient’s response to treatment. However, they are not specific for lymphoma and some lymphomas, like CLL, do not light up brightly on a PET scan.
X-ray	<ul style="list-style-type: none">■ X-rays use radiation to take pictures of areas inside the body from a single direction. They are not commonly used in the staging of CLL/SLL.

Why Might Another Type of Biopsy Be Needed?

The diagnosis of CLL/SLL can be made from the blood, a bone marrow biopsy, or a lymph node biopsy. Additionally, biopsies are sometimes performed to confirm the diagnosis or determine the cause of low blood counts. (see Table 4.3).

Table 4.3. Bone Marrow Biopsy

Bone Marrow Aspiration and Biopsy	<ul style="list-style-type: none"> ■ <i>Bone marrow</i> is the soft, spongy material found inside bones. Bone marrow makes the blood cells and by examining it under the microscope, physicians can determine the causes of abnormal blood counts or assess for other problems. ■ A bone marrow aspiration with or without a biopsy may be done to determine the amount of disease in the bone marrow. ■ For the aspiration part of this procedure, the doctor cleans and numbs the skin over the hip, inserts a thin, hollow needle into the hip bone, and removes a small amount of liquid from the bone marrow using a syringe. ■ A bone marrow biopsy is often performed immediately after the aspiration and removes a piece of bone. ■ Although these procedures may be done with local anesthesia, some centers offer light general anesthesia based on patient and doctor preference.
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How Is CLL/SLL Staged?

In patients with CLL/SLL, staging is used to describe where cancer cells are located in the body and to determine how widespread the cancer is in the body. In these circumstances, stage I means the disease is localized, while stage IV indicates the disease is widespread. Because CLL/SLL is almost always widely spread through the body, a very different type of staging system is used. Patients with CLL are staged using either the Rai staging system or the Binet classification system. Doctors in the United States tend to use the Rai system (Table 4.4 on the next page), while the Binet system (Table 4.5 on the next page) is more popular in Europe.

Both of these staging systems are designed to assess the quantity of the disease present and whether the disease is considered active or progressing. Unlike solid tumors, in CLL/SLL treatment is typically not indicated until patients develop advanced disease. This approach is called *active surveillance* (or *watchful waiting*) and is used in patients who would not yet benefit from treatment, since their disease is at an early stage or is stable. Active surveillance is discussed in detail in chapter 6. Additionally, and unlike solid tumors, patients do not need to progress through the stages in order. It is possible for a patient to be Rai stage 0 at diagnosis and then develop a low platelet count and be a Rai stage IV without

being a stage I, II, or III previously. Rai staging establishes risk groups (low, intermediate and high, Table 4.4) that indicate the likelihood that the disease may worsen or require treatment.

Table 4.4. The Rai Staging System for CLL/SLL

Stage	Description	Risk Group
0	<ul style="list-style-type: none"> ■ Blood <i>lymphocytosis</i> (increased lymphocytes) ■ No lymph node enlargement, <i>anemia</i> (decreased red blood cells) and no <i>thrombocytopenia</i> (decreased platelets) 	Low
I	<ul style="list-style-type: none"> ■ Blood lymphocytosis and enlarged lymph nodes ■ No anemia and no thrombocytopenia 	Intermediate
II	<ul style="list-style-type: none"> ■ Blood lymphocytosis and enlarged spleen (<i>splenomegaly</i>) and/or enlarged liver (<i>hepatomegaly</i>) ■ No anemia and no thrombocytopenia 	Intermediate
III	<ul style="list-style-type: none"> ■ Blood lymphocytosis ■ Anemia (hemoglobin less than 11 grams per deciliter) 	High
IV	<ul style="list-style-type: none"> ■ Blood lymphocytosis ■ Thrombocytopenia (platelets less than 100,000 per microliter) 	High

Table 4.5. The Binet Staging System for CLL/SLL

Stage	Description	Match-Up With Rai Stages
A	<ul style="list-style-type: none"> ■ Less than three of five possible enlarged areas* ■ No anemia and no thrombocytopenia 	Rai stages 0, I, and II
B	<ul style="list-style-type: none"> ■ Three or more of five possible enlarged areas* ■ No anemia and no thrombocytopenia 	Rai stages I and II
C	<ul style="list-style-type: none"> ■ Any number of possible enlarged areas ■ Anemia and/or thrombocytopenia 	Rai stages III and IV

*The five possible palpably enlarged areas are the cervical (neck) lymph nodes, the axillary (underarm) lymph nodes, the inguinal (groin) lymph nodes, the spleen, and the liver.

Chapter 5: What to Know Before Starting Treatment

Receiving a cancer diagnosis can be overwhelming. It is perfectly normal to be shocked by the diagnosis, anxious about the future, and confused about the decisions that need to be made. This chapter will help patients who have been diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and their caregivers prepare for the start of treatment by explaining the next steps and providing tips for talking with doctors about any questions or concerns. Patients can also call the Lymphoma Research Foundation's (LRF's) Helpline at (800) 500-9976 or email helpline@lymphoma.org.

PATIENT TIP

First Steps to Take After Receiving a Diagnosis

- Take care of yourself (eat, sleep, rest, and exercise).
- Seek the support of family, friends, and others you trust.
- Learn about the disease and treatment options.
- Find medical care that meets your needs.
- Seek out additional sources of emotional and social support for people with cancer, such as LRF's Lymphoma Support Network that connects patients and caregivers with volunteers who have experience with CLL/SLL, similar treatments, or challenges.
- Research the cost of care, what your insurance will cover, and what financial assistance programs may be available to you.
- Download and start using LRF's Focus On Lymphoma app on your mobile device to learn about and manage CLL/SLL.
- Maintain a copy of your medical records (paperwork, test results, and your own notes).

CLL often presents early enough that there is time for patients to gather information, learn about their disease, and seek out second opinions before needing to make decisions about treatments.

Who Plans and Carries Out the Treatment?

Treatment is usually overseen by a hematologist/oncologist. *Oncologists* are physicians who specialize in diagnosing and treating patients with cancer. *Hematologists* are physicians who specialize in diagnosing and treating patients with disorders of the blood and lymphatic system. Physicians who treat CLL/SLL can be certified in one or both specialties. Depending on the patient's healthcare needs, the primary doctor may refer the patient to other specialists, such as a surgical oncologist or a radiation oncologist. The doctor may also suggest that the patient get a second opinion at a cancer center with particular expertise in managing CLL/SLL or to discuss enrolling in a clinical trial. For more information about clinical trials, contact the LRF Helpline by phone (800-500-9976) or email (helpline@lymphoma.org).

The healthcare team may also include other healthcare professionals such as a hematology/oncology nurse, research nurse, nurse practitioner, physician assistant, clinical research coordinator, social worker, and registered dietitian. The healthcare team works together and consults with the patient to plan, carry out, and monitor the treatment.

What Is a Prognosis?

Prognosis is the medical term for predicting how a patient will ultimately do with their disease. A prognosis is usually based on information gathered from hundreds or thousands of other patients who have had the same disease and were followed. This statistical information provides doctors with a general idea of what to expect when a patient is diagnosed with CLL/SLL, and it helps them select which treatments are most likely to work. It is important to note that many of the prognostic factors used in the past are no longer useful because they may not apply to treatment with newer agents.

Keep in mind that no two patients are alike and that statistics can only predict how a large group of patients will do and cannot predict what will happen to an individual patient. The doctor most familiar with the patient's situation is in the best position to interpret these statistics and understand how well they apply to a patient's particular situation.

Patients should also bear in mind that most published statistics on treatment outcomes may not reflect the benefits of the most recent developments in CLL/SLL treatment.

What Are Prognostic Factors?

The characteristics that help predict a patient's prognosis are called *prognostic factors*. Favorable or good prognostic factors tend to be associated with better outcomes (overall longevity or good response to any treatment), while unfavorable or poor prognostic factors tend to be associated with worse outcomes. Scientists have known about several prognostic factors, called traditional prognostic factors, for many years or even decades, while novel prognostic factors have only been recently identified (Table 5.1).

Table 5.1. Known Prognostic Factors for CLL/SLL

Traditional Prognostic Factors	Novel Prognostic Factors
<ul style="list-style-type: none"> ■ Rai stage ■ Sex ■ Age ■ Beta-2 microglobulin levels in the blood ■ Larger proportion of polymphocytes (active cells) in the blood 	<ul style="list-style-type: none"> ■ CD38 ■ Interphase FISH ■ Immunoglobulin heavy chain variable (<i>IGHV</i>) gene mutation status ■ <i>TP53</i> gene status/17p ■ <i>NOTCH1</i> gene status

There are well over 100 different prognostic markers identified for patients with CLL/SLL. These prognostic markers are studied as independent predictors of outcome, meaning they look at only those who do and do not have the marker. Each prognostic marker will have a different amount of impact upon prognosis, i.e. some will override others.

Two important features of prognostic markers to remember are:

1. What the prognostic marker is predicting. If the prediction is for time to treatment, but everyone does equally well with treatment, then the prognostic marker becomes less important.
2. They are only helpful in the setting in which they were studied. For example, IGHV mutated CLL/SLL patients have longer responses to chemoimmunotherapy than those with unmutated IGHV. But both do equally well in response to targeted therapy with bruton's tyrosine kinase (BTK) inhibitors and therefore, IGHV is no longer prognostic for response to BTK inhibitors.

How to Find an Oncologist and Treatment Center

A patient's primary care doctor usually makes a referral to a medical oncologist, hematologist, or hematologist/oncologist. Before agreeing to treatment by any specific doctor or treatment center, patients and caregivers should make sure that they feel comfortable with the healthcare team and the quality of care they provide. Patients need to feel confident that the providers they select can meet their medical and personal needs. The following questions can be used to help patients select the best medical team.

Questions to Ask to Select the Best Medical Team

- How much experience do the doctor and treatment center have in treating patients with non-Hodgkin lymphoma (NHL), and CLL/SLL in particular?
- How many patients with CLL/SLL are being treated at this center now?
- Does the doctor and/or center participate in clinical trials?
- Is the doctor or clinic affiliated with any major medical center or medical school?
- In case of an emergency, what arrangements are made for medical assistance after hours and on weekends?
- Is my health insurance accepted at this center? Will the treatment center file claims for reimbursement and process the paperwork?
- What kind of patient resources does the clinic or cancer center have for patients with CLL/SLL?
- If I see other specialists (cardiologist, endocrinologist, etc.), will the doctor coordinate my care with my other doctors?

Patients enrolled in a managed care health insurance program may have limited choices. However, patients have the right to choose another healthcare team if they are not entirely satisfied or comfortable with their first consultation visit. They should talk to other patients and caregivers about their experiences and ask them if they would recommend their doctor and healthcare team. Patients and caregivers who are not satisfied with their healthcare team should also share their concerns with their primary doctor and ask for a referral to a different doctor.

How to Decide What Treatment Is Best

With the exception of clinical trials studying early intervention, CLL/SLL is not usually treated at diagnosis (see *What Is Active Surveillance*, page 52). Treatment is initiated when symptoms begin and there are many effective options for patients with CLL/SLL. To identify which treatments may work best, doctors consider the following factors:

- Stage of CLL/SLL
- Results of chromosome analysis and FISH studies
- IGHV mutation status
- TP53 mutation testing
- A patient's overall health, age, and performance status
- A patient's expectations
- Whether the treatment is the first the patient has received for CLL/SLL or the disease has *relapsed* (returned after prior therapy)
- Whether the treatment will impact future treatment options
- Availability of a clinical trial

Doctors discuss the risks, benefits, and side effects associated with the different treatment choices applicable to the patient's particular situation. It is important to also ask about whether treatments are intravenous or oral and whether they involve a great deal of monitoring and travel to the hospital. Patients and caregivers should share questions and concerns with the doctor so that together they can decide which option is best. It is always helpful for patients to write down their questions and go over them with their treating physician and/or team. The questions on the next page can be used to guide the conversation and help patients make an informed decision. LRF also offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and CLL/ SLL including our award-winning mobile app (lymphoma.org/mobileapp).

Questions to Ask Before Treatment Begins

- What is my exact diagnosis? May I have a copy of the report from the pathologist?
- What is the stage of my disease?
- What are my prognostic factors and what do they mean?
- What are my treatment choices? Which do you recommend for me and why? Would choosing one treatment prevent me from getting a different kind of treatment at a later point? How are the different treatment choices administered?
- What is a clinical trial? Are clinical trials available that are studying new treatments for CLL/SLL? Would a clinical trial be appropriate for me? How would I benefit?
- Do I need more than one type of treatment?
- What is the goal of treatment? What are the expected benefits of each type of treatment?
- How will we know if the treatment is working? What tests will I need to determine if treatment is working, and how often will I need to be tested?
- What are the risks and possible side effects of each treatment? Can these side effects be prevented or controlled?
- What should I do to take care of myself during treatment?
- Are there any late or long-term side effects I should be aware of?
- Will treatment impact my ability to have children in the future? Is there time for sperm banking/egg harvesting before starting treatment?
- How long will the treatment last?
- What are the chances the treatment will be successful?
- How will the treatment affect my normal activities (for example, work, school, childcare, driving, sexual activity, and exercise)?
- Is there anything my caregiver needs to do to prepare to care for me while I undergo treatment?
- Will I be able to work during treatment? Will I be able to drive or take public transportation during my treatment?
- Should I take care of other medical or dental issues before I start treatment?
- How much will the treatment cost? Will my insurance cover some or all of it? What will my out-of-pocket costs be?

When to Get a Second Opinion

Before starting any type of treatment, a patient may want to consider getting a second opinion, especially if the diagnosis is rare, complicated, or uncertain. The purpose of the second opinion is not to question the doctor's expertise but to make sure the suggested treatment plan is the best choice for the patient's particular case, as well as to evaluate alternative treatment options, including clinical trials (see Part 5 for more information). Physicians, like everyone else, have opinions regarding which treatment is best for an individual patient and each patient should hear other physicians' opinions. Inform your treating physician if you are seeking a second opinion.

Most doctors are supportive and helpful if patients say they would like to get a second opinion. When informing your treating physician, patients should ask the doctor if it is safe to briefly delay the start of treatment to provide the time needed to get a second opinion. Some insurance programs require second opinions, and others may pay for a second opinion if a patient or doctor requests it.

When getting a second opinion, it is important to consult with a CLL/SLL specialist since CLL/SLL is rare. Patients might want to consider the following tips.

Getting a Second Opinion

- Most hematologists/oncologists who have expertise in CLL/SLL and are associated with medical schools or cancer centers may be willing to provide a consultation and work together with a local hematologist/oncologist to provide treatment and follow-up care.
- As part of the second opinion, another pathologist must review the tissue and blood samples to confirm the diagnosis. The pathology of CLL/SLL is often complex, and some pathologists may have limited experience analyzing CLL/SLL cells, so it is valuable to have the pathology results reviewed by an expert hematopathologist with extensive experience in lymphoma.
- To get a second opinion, you will need to provide the consulting doctor with a complete copy of all medical records, pathology samples, images and scans, and reports. When you set up the appointment, ask the office for a list of all the materials you need to bring. It will be useful to keep your own copy of all these records in case you have questions or concerns later on.

To identify CLL/SLL specialists to contact for a second opinion:

- Ask your current doctors, family members, other patients, friends, and coworkers.
- Contact the patient referral service at your local hospital and at the nearest hospital associated with a medical school; many hospitals have online directories that can be searched to find a specialist in your area.
- Visit the Lymphoma Research Foundation's (LRF's) websites at lymphoma.org or contact the LRF Helpline directly by phone (800-500-9976) or email (helpline@lymphoma.org). However, note that LRF does not provide a physician referral service.
- Visit the American Society of Clinical Oncology (ASCO) website at www.cancer.net to search their oncologist database.
- Visit the American Society of Hematology (ASH) web page at www.hematology.org/patients to search for hematologists with expertise in CLL/SLL.
- Look online for patient reviews of specialists that you are considering.

How to Communicate With the Healthcare Team

Patients and caregivers can ease some of their anxieties by establishing open, honest communication with their healthcare team regarding their diagnosis and treatment. This can help patients and caregivers better understand the treatment regimen, including how it works, what tests are involved, and what side effects and complications may be associated with it.

A good first step for patients is to write down all the questions that come to mind. Before meeting with a doctor, nurse, or physician assistant either for the first time or for follow-up visits, patients should consider organizing their questions into a list to bring to the visit. Since time with doctors, nurses, and physician assistants may be limited, patients should put the two or three most important questions at the top of their list. However, it is also important that a member of the patient's medical team reads all of the questions because some may be more important than the patient realizes. LRF's mobile app (lymphoma.org/mobileapp), *Focus On Lymphoma*, can save and organize your list of questions to review with your healthcare team.

Patients should consider having a family member or close friend accompany them to the doctor's office or clinic to help ask questions and understand and remember answers. This person could also help by taking notes during the visit. If visitors are limited, consider having a family member or close friend on the phone so they can listen and ask questions too. Some patients bring a recording device or a phone or tablet to record the answers. LRF's *Focus On Lymphoma* mobile app enables you to record your session with your doctor. Patients should ask the doctor, nurse, or physician assistant for permission before recording any conversations.

Most oncology nurses and physician assistants (PAs) are also very well informed about cancer treatments and are a good source of information on a wide range of topics. Additionally, oncology social workers are available to assist with practical, emotional, and other support needs throughout the diagnosis and treatment process.

Although family members are often very concerned about their loved ones and want information concerning their care, confidentiality rules prohibit doctors from giving out information to anyone without the patient's permission. For efficiency, one family member should be designated as the family contact, and the healthcare team should know that person's identity and contact information. Most importantly, it is essential for patients and their caregivers or family contact person to have the names, addresses, office numbers, and emergency contact information of the physicians involved in their care, so that they can communicate with the oncologist or hematologist regularly or in the event of an emergency. Adding these phone numbers directly to a cell phone may be helpful so patients or caregivers have the numbers directly on hand if needed.

Open communication between patients and doctors is paramount. The tips on the following page can be used to help patients better communicate with their healthcare team, or for assistance with preparing questions to ask your healthcare team, contact the LRF Helpline at (800) 500-9976 or email helpline@lymphoma.org.

Communicating With Your Doctors

At home:

- Know your medications
- Keep a journal of your symptoms to help you remember the details you want to discuss with your doctor during your next office visit.
- Ask your doctor or nurse ahead of time which symptoms need to be communicated to them immediately and which can wait for your next visit.
- If your questions are urgent, do not wait for the next office visit; call the doctor's office to discuss your concerns.
- Ask whether your healthcare team has an online "patient portal." These portals may provide secure email contact and educational materials, and they often allow patients to check benefits and coverage, schedule non-urgent appointments, and order prescription refills.
- Download the Focus On Lymphoma mobile app from LRF to help you plan appointments, manage medications and blood work, document treatment side effects, record doctor visits, and list questions (lymphoma.org/mobileapp).

At your next doctor's visit:

- Bring your symptom journal and list of questions to discuss with your doctor or nurse.
- Bring a list of the medications you are currently taking, including the dosage and frequency.
- Ask a family member or friend to come with you to provide emotional support and take notes.
- Do not be afraid to ask questions if you do not understand something. Your doctor will want to know if you are uncertain or confused and will be happy to address your concerns.
- Inquire about whom should be contacted for specific questions or weekend support and how you can reach them.
- Inquire whether members of your healthcare team communicate electronically (by email, text, patient portals, etc.). Some providers do not use electronic forms of communication with patients because of concerns about security and patient privacy.
- Make sure you understand the next steps in your care before you leave the doctor's office.
- Request written information that you can take home to help you remember everything your doctor tells you.

How to Be a Self-Advocate

Being a self-advocate and an active participant in healthcare decisions can be a positive experience, help patients regain a sense of control that they may have lost following the lymphoma diagnosis, and ensure the care patients receive is what they want. Patients and caregivers should remember they are partners in their treatment plan. Patients should ask questions, learn about options, and work closely with their healthcare team. Physicians should be comfortable with patients asking questions.

It is important for patients to be comfortable with the doctors and the approaches they take. If patients or caregivers are not comfortable, they should openly discuss their concerns. Confidence in the medical team often leads to confidence in treatment. If patients feel that the team is not a good match, they should ask for a referral to a different healthcare team.

Although each patient is different and each response to therapy is unique, knowing someone who has been through the same situation and who may have had similar concerns can be a source of great comfort. If patients or caregivers are interested in talking to and learning from people who have had similar experiences, they can ask their healthcare team members about support groups in the area or contact LRF for more information about the *Lymphoma Support Network*.

Finally, it is important that the patient not be afraid to talk with the healthcare team about nonmedical issues, such as transportation, finances, insurance, working through treatment or taking time off, and childcare. The tips listed on the next page offer self-advocacy strategies for patients.

Self-Advocacy

- Do not be afraid to ask your doctor or nurses questions about your care. An informed patient asking questions is not 'being a challenge to your physician' (or 'being a difficult patient').
- Learn more about CLL/SLL by asking your doctor for information and visiting reliable websites, such as LRF at lymphoma.org.
- Take advantage of counseling, support groups, nutritional counseling, fitness classes, expressive arts, and other services offered at your doctor's office, cancer center, or hospital.
- Consider joining LRF's Lymphoma Support Network, that connects patients and caregivers with volunteers who have experience with CLL/SLL, similar treatments, or challenges. For individual support or for information about the program, contact the LRF Helpline at (800) 500-9976 or email helpline@lymphoma.org.

Chapter 6: Treatments for CLL/SLL

This chapter reviews the most common therapies currently used in the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was printed. See Chapter 11 to learn more about emerging treatments under investigation.

There are small but important differences in the lymphoma cells found in different patients diagnosed with CLL/SLL. Because of these differences, a treatment that may work very well in one patient may not have the same positive effect in another.

What Types of Treatments Are Used in Patients With CLL/SLL?

There are four general types of treatments for patients with CLL/SLL:

- *Active surveillance*, also known as *watchful waiting* (observation with no treatment), in which the patient is closely monitored to see if/when treatment should be started
- Drug therapy, including one or more of the following types of drugs:
 - Immunotherapy, which helps the body's immune system attack lymphoma cells
 - Targeted therapies, which affect special characteristics or internal workings of lymphoma cells
 - Chemotherapy, which affects general cell growth and *proliferation* (the ability of cells to multiply)
- Cellular therapy like stem cell transplantation and chimeric antigen receptor (CAR) T cell therapy (CAR T cell therapy is FDA-approved to treat some forms of blood cancer, but none are approved to treat CLL/SLL as of May 2022)

Each of these types of therapies is described in detail in this chapter.

What Is Active Surveillance?

With the *active surveillance* (*watchful waiting*) approach, patients' health and disease are monitored through regular checkups and periodic evaluation procedures, such as laboratory and imaging tests, but they do not receive any anti-lymphoma treatments. This approach is used in patients who would not yet benefit from treatment, since their disease is at an early stage. These patients continue to remain untreated if they do not show any signs or symptoms and there is no evidence that the lymphoma is growing or spreading. Once a patient demonstrates symptomatic disease, treatment course would begin.

Doctors use established criteria to help determine when patients with CLL/SLL should no longer remain on active surveillance. These criteria are designed to help the doctor determine when the disease is becoming more active. They include:

- Progressive bone marrow failure; indicated by *anemia* (low levels of red blood cells; Rai stage III) or *thrombocytopenia* (low platelet levels; Rai stage IV)
- Autoimmune cytopenia (body attacks its own blood cells) that is not resolved by treatment with steroids
- B symptoms (fever and/or chills for no known reason, unexplained weight loss, and drenching night sweats that soak clothing and sheets)
- Development of large (bulky) lymph nodes
- Doubling of the lymphocyte count over six months
- Enlargement of the spleen
- Severe *fatigue* (extreme tiredness) due to CLL/SLL
- One or more organs may stop working soon (threatened end-organ function)

Though doctors may recommend active surveillance for selected patients with *indolent* (slow-growing) CLL/SLL, it is not a treatment option for patients with advanced CLL/SLL. While the decision to start treatment depends on the clinical judgment of the treating physician, treatment for these patients should generally start as soon as possible after diagnosis.

Questions to Ask Before Starting Active Surveillance

- What happens if I choose active surveillance and then change my mind?
- Will choosing active surveillance affect my prognosis?
- Will the disease be harder to treat later?
- How often will I have checkups and tests?
- Between checkups, what symptoms and other problems should I report?
- What changes will indicate that I should start active treatment?

What Drugs Are Used to Treat CLL/SLL?

Patients with CLL/SLL are commonly given either a single drug or a combination of drugs. The purpose of combining drugs is to increase how effectively they damage or kill lymphoma cells, to diminish the chances of the lymphoma cells becoming resistant to treatment, and to allow lower doses of each drug to be used to minimize side effects.

During some drug therapy regimens, patients receive the treatment at certain intervals, such as once every two, three, or four weeks, followed by a rest period. This regular treatment schedule is called a *cycle*. The length of the rest period and the number of cycles vary depending on the patient's disease and the types of drugs used. Drugs may be combined to create a *treatment regimen*—a specific schedule that determines which drugs are given in which doses on which days of each treatment cycle. Note that for many drugs given orally (for example, as pills, tablets, or capsules), patients often take them daily for an indefinite amount of time.

Treatment regimens for CLL/SLL may include chemotherapy, immunotherapy, and/or targeted therapy drugs. Table 6.1 lists the drug regimens most often used to treat CLL/SLL. This list is subject to change as the FDA approves new CLL/SLL treatments.

Table 6.1. Common Regimens for CLL/SLL

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)	Delivery Method
Acalabrutinib alone	Acalabrutinib (Calquence)	Oral capsules
Acalabrutinib plus obinutuzumab	Acalabrutinib (Calquence) Obinutuzumab (Gazyva)	Oral capsules IV infusion
Alemtuzumab ^a alone	Alemtuzumab (Campath)	IV infusion
Alemtuzumab ^a with rituximab	Alemtuzumab (Campath) Rituximab (Rituxan)	IV infusion IV infusion
Bendamustine plus obinutuzumab	Bendamustine (Bendeka, Treanda) Obinutuzumab (Gazyva)	IV infusion IV infusion
Bendamustine plus ofatumumab	Bendamustine (Bendeka, Treanda) Ofatumumab (Arzerra)	IV infusion IV infusion
BR	Bendamustine (Bendeka, Treanda) Rituximab (Rituxan)	IV infusion IV infusion
BR plus ibrutinib	Bendamustine (Bendeka, Treanda) Rituximab (Rituxan) Ibrutinib (Imbruvica)	IV infusion IV infusion Oral capsules/tablets
Chlorambucil plus obinutuzumab	Chlorambucil (Leukeran) Obinutuzumab (Gazyva)	Oral tablets IV infusion
Chlorambucil plus ofatumumab	Chlorambucil (Leukeran) Ofatumumab (Arzerra)	Oral tablets IV infusion
Chlorambucil plus rituximab	Chlorambucil (Leukeran) Rituximab (Rituxan)	Oral tablets IV infusion
Duvelisib	Duvelisib (Copiktra)	Oral capsules
FC plus ofatumumab	Fludarabine Cyclophosphamide (Cytoxan) Ofatumumab (Arzerra)	IV infusion Oral tablets or IV infusion IV infusion
FCR	Fludarabine Cyclophosphamide (Cytoxan) Rituximab (Rituxan) or Rituximab hyaluronidase (Rituxan Hycela)	IV infusion Oral tablets or IV infusion IV infusion or SC injection

Table 6.1. Common Regimens for CLL/SLL (continued)

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)	Delivery Method
FR	Fludarabine Rituximab (Rituxan)	IV infusion IV infusion
HDMP-R	High-dose methylprednisolone (Solu-Medrol and others) Rituximab (Rituxan)	IV infusion or intramuscular (IM) injection IV infusion
Ibrutinib alone	Ibrutinib (Imbruvica)	Oral capsules/tablets
Ibrutinib plus obinutuzumab	Ibrutinib (Imbruvica) Obinutuzumab (Gazyva)	Oral capsules/tablets IV infusion
Ibrutinib plus rituximab	Ibrutinib (Imbruvica) Rituximab (Rituxan)	Oral capsules/tablets IV infusion
Idelalisib alone	Idelalisib (Zydelig)	Oral tablets
Idelalisib plus rituximab	Idelalisib (Zydelig) Rituximab (Rituxan)	Oral tablets IV infusion
Lenalidomide alone	Lenalidomide (Revlimid)	Oral capsules
Lenalidomide plus rituximab	Lenalidomide (Revlimid) Rituximab (Rituxan)	Oral capsules IV infusion
Obinutuzumab alone	Obinutuzumab (Gazyva)	IV infusion
Ofatumumab alone	Ofatumumab (Arzerra)	IV infusion
R	Rituximab (Rituxan) Rituximab-abbs ^b (Truxima)	IV infusion IV infusion
Rituximab and hyaluronidase human ^c	Rituximab and hyaluronidase human (Rituxan Hycela)	SC injection
Venetoclax alone	Venetoclax (Venclexta)	Oral tablets
Venetoclax plus obinutuzumab	Venetoclax (Venclexta) Obinutuzumab (Gazyva)	Oral tablets IV infusion
Venetoclax plus rituximab	Venetoclax (Venclexta) Rituximab (Rituxan)	Oral tablets IV infusion

^aAlemtuzumab is provided only through the Campath Distribution Program; it is no longer commercially available. IV, intravenous; SC, subcutaneous.

^bRituximab-abbs is a biosimilar and may or may not be interchangeable. Patients are encouraged to talk to their physician about the option to use a biosimilar for treatment.

^cOne full dose of rituximab must be dosed by IV infusion before a patient may be eligible for rituximab hyaluronidase subcutaneous injection.

How Are Drugs Given?

Depending on the regimen, patients may receive their drug treatments orally (as a tablet or capsule that is swallowed), *subcutaneously* (as an injection just below the skin), *intravenously* (as a liquid that is infused directly into a vein, commonly known as an “IV”), or *intrathecally* (as an injection into the fluid around the spinal cord [lumbar puncture]).

Most chemotherapy and monoclonal antibody drugs used to treat CLL/SLL are IV. One reason for this is that IVs provide flexibility in dosing, allowing the medication to be given all at once or slowly over many hours or days. Another reason is that many chemotherapy drugs cannot be given orally, either because they cannot be easily absorbed from the stomach into the bloodstream, or because they are too harsh for the stomach lining to tolerate. Subcutaneous administration is an alternative method that takes less time than IV methods, and avoids the need for a catheter (discussed below).

To administer IV drug therapy, a doctor, nurse, or physician assistant first inserts an IV catheter, which is a small flexible tube used to deliver medications into a vein. While some catheters are designed for short-term use, others can stay in the patient’s body for weeks or months, making it easier to administer multiple cycles of drug therapy over time. Several commonly used types of catheters are described in Table 6.2 on the next page. Patients and caregivers should discuss with their doctor which catheter, if any, would be best for their particular situation.

Table 6.2. Catheters Used to Administer Drug Therapy

Type of Catheter	Description	Advantages	Disadvantages
Peripheral Venous Catheter	A needle is used to insert a small, flexible tube into a small vein in the hand or arm.	Can be inserted quickly and easily by a nurse; no need for surgical insertion. Good for a single infusion or other temporary use.	Cannot be left in place for more than three days at a time due to infection risk. Sterile dressing needs to be kept clean and dry and replaced daily; the line needs to be injected periodically with a blood thinner (heparin) to prevent blockage. Cannot be used to draw blood for blood tests.

Table 6.2. Catheters Used to Administer Drug Therapy (continued)

Type of Catheter	Description	Advantages	Disadvantages
Peripherally Inserted Central Catheter (PICC line)	A long, thin plastic tube is inserted into a large vein in the arm, and the tip is guided up through the body into the large vein that enters the heart.	Can be kept in place longer than a peripheral venous catheter. Can be used to draw blood sample as well as to give drugs. Good for patients who need to have many short infusions or continuous infusions in a hospital or at home.	Not intended to remain in place as long as some surgically placed catheter types.
Tunneled Catheter (for example, Hickman, Broviac)	One to three tubes are surgically inserted into the subclavian vein (underneath the collarbone). Six to 12 inches of tubing remain outside the skin in the upper chest wall.	Can be left in place for months or years with low infection risk. Easy to draw blood and give drugs using standard needles without having to pierce the skin each time.	Requires a small surgery to be inserted. Patients must learn to clean and take care of the external tubes to prevent infection and blockage. The tubes on the outside of the body make it more obvious that a catheter is in place.
Infusaport or Portacath	A catheter is surgically inserted through the subclavian vein and attached to a small reservoir (port) that lies under the skin. Nothing is visible on the outside except for a bump on the chest.	Patients do not have to do anything to care for it; a nurse keeps the line open by “flushing” it once a month with a small amount of injected liquid.	Requires surgery to be inserted. Patient must be injected through the skin covering the port with a special needle each time it is used. Can be hard to use to draw blood samples because blood clots often cause clogging. Requires another minor surgical procedure to be removed.

What Is Immunotherapy?

The term *immunotherapy* refers to treatments that use the body's own immune response. The immune system normally patrols the body for cancer cells, and when a cancer cell is detected, the immune system launches an attack to eliminate it. However, some cancer cells can “hide” from the immune system and continue to grow in an uncontrolled manner until they form tumors or spread through the body. Immunotherapies help the immune system recognize and attack the lymphoma or CLL/SLL cells and eliminate them from the body. The only type of immunotherapy that is FDA-approved to treat CLL/SLL is monoclonal antibodies.

What Are Monoclonal Antibodies?

Plasma cells are specialized B lymphocytes that make proteins called *antibodies*. Antibodies help fight infection by recognizing and sticking to viruses, bacteria, or other foreign substances in the body. Each antibody is naturally designed to recognize one specific *antigen* (protein on the surface of certain cells).

Monoclonal antibodies are molecules that have been engineered in a laboratory to attach to one specific target (antigen). This target is specifically chosen to be advantageous for the treatment of the cancer. Antibodies generated in the laboratory are all identical in their protein sequence. They are all made from one “mother” B lymphocyte, which is why they are called monoclonal (one clone). Once injected in the patient, the monoclonal antibodies travel through the blood and attach themselves to the cells that have antigens they recognize. This can either stop or slow down the growth of the cancer cell, or it can trigger an “alarm” that makes it easier for other cells in the immune system to recognize and destroy the cancer cell.

The monoclonal antibody therapies used to treat CLL/SLL are given as IV infusions (through a vein) or *subcutaneous* (under the skin) injections at a doctor's office or clinic. To prevent serious allergic reactions to the infusion/injection, patients are usually given an oral antihistamine such as diphenhydramine (Benadryl), as well as acetaminophen (Tylenol), and sometimes corticosteroids before the antibody infusion/injection. Before

beginning monoclonal antibody therapy, all patients are tested for latent hepatitis infection.

Three monoclonal antibodies are used in the treatment of CLL/SLL: rituximab (Rituxan), obinutuzumab (Gazyva), and ofatumumab (Arzerra); a fourth, alemtuzumab (Campath), is provided only through the Campath Distribution Program and is no longer commercially available. With the exception of alemtuzumab (Campath), these treatments are directed against different parts of CD20, an antigen that is almost universally present on the surface of B cells, including the malignant lymphocytes in CLL/SLL. Because they target different parts of CD20, each of these drugs work a bit differently.

Obinutuzumab (Gazyva)

In 2013, obinutuzumab (Gazyva) was approved by the FDA for the treatment of CLL. As of 2021, obinutuzumab is approved by the FDA for use in combination with venetoclax (Venclexta) chlorambucil (Leukeran) and in combination with ibrutinib (Imbruvica) or acalabrutinib (Calquence) for the treatment of patients with previously untreated CLL.

Obinutuzumab (Gazyva) treatment is given as an IV infusion. Patients usually receive the first dose split over two days during the first week, followed by one dose a week for two weeks (this is the first cycle of therapy), then once every 28 days for five more cycles.

Rituximab (Rituxan) and Rituximab Plus Hyaluronidase Human (Rituxan Hycela)

In 1997, rituximab (Rituxan) became the first monoclonal antibody approved by the FDA for the treatment of patients with lymphoma. As of 2021, rituximab is approved by the FDA for the treatment of CLL/SLL in the following situations:

- Previously untreated or treated CD20-positive CLL in combination with FC chemotherapy (fludarabine and cyclophosphamide)
- *Relapsed* (returns after treatment) or *refractory* (does not respond to treatment) low-grade (slow growing) or follicular CD20-positive B-cell NHL as a single agent

- Non-progressing low-grade CD20-positive B-cell NHL as a single agent after *frontline* (initial) CVP (cyclophosphamide, vincristine prednisone) chemotherapy

Rituximab (Rituxan) monotherapy is only considered in rare circumstances and should be avoided in any patient who can be considered for targeted therapies.

The original form of rituximab (Rituxan) is given as an IV infusion, and the treatment regimen varies depending on the combination of drugs used. When combined with chemotherapy, rituximab is usually given during the first day of each chemotherapy cycle.

A subcutaneous formulation of rituximab (Rituxan Hycela or “rituximab and hyaluronidase human”) was approved by the FDA in 2017 for use in patients with previously untreated or treated CLL in combination with FC (fludarabine and cyclophosphamide) chemotherapy.

Subcutaneous administration allows the drug to be given in a shorter period of time. Before patients can receive rituximab and hyaluronidase human (Rituxan Hycela), they must first have at least one full dose of IV rituximab.

Ofatumumab (Arzerra)

In 2009, ofatumumab (Arzerra) was approved by the FDA for the treatment of CLL. As of 2021, ofatumumab was approved by the FDA for the treatment of CLL in the following situations:

- In combination with chlorambucil (Leukeran) for the treatment of previously untreated CLL in patients for whom fludarabine (Fludara)-based therapy is considered inappropriate
- In combination with fludarabine and cyclophosphamide for the treatment of relapsed CLL
- For extended treatment of CLL that is in complete or partial response after at least two lines of therapy for recurrent or progressive CLL
- For the treatment of CLL that is refractory to fludarabine and alemtuzumab (Campath)

Ofatumumab is given as an IV infusion over several weeks. It is administered by itself, in combination with chlorambucil, or in combination with fludarabine and cyclophosphamide. The manufacturer has discontinued the use of ofatumumab (Arzerra) for this indication. Patients who are being treated with ofatumumab (Arzerra) will be able to receive this drug through an oncology patient access program.

What Are Targeted Therapies?

A better understanding of the biology and genetics of CLL/SLL is helping researchers identify specific molecules in lymphoma cells that may be good targets for new drugs. Most of these recently discovered molecules help control the growth and survival of lymphoma cells.

The drugs that target these molecules are broadly called *targeted therapies*. These drugs may kill, slow down or stop the growth of cancer cells. Targeted therapies attack lymphoma cells in a more specific way than chemotherapy drugs.

FDA -approved targeted therapies used in the treatment of CLL/SLL include:

- The Bruton tyrosine kinase (BTK) inhibitors ibrutinib (Imbruvica) and acalabrutinib (Calquence)
- The phosphatidylinositol 3-kinase (PI3K) inhibitor idelalisib (Zydelig) and duvelisib (Copiktra)
- The B-cell lymphoma 2 (Bcl2) inhibitor venetoclax (Venclexta)

LRF's mobile app, *Focus On Lymphoma*, can help with adhering to your medication schedule by sending reminders to take your medication.

Ibrutinib (Imbruvica)

Ibrutinib inhibits the signaling protein BTK to block the growth and survival of cancerous B cells. Ibrutinib was first approved by the FDA in 2013, and as of 2021, it can be used for treatment of CLL/SLL as a single agent, in combination with obinutuzumab (Gazyva) or rituximab (Rituxan), or in combination with bendamustine and rituximab (BR).

Ibrutinib comes in capsules or tablets that must be swallowed whole. It is given once daily.

Acalabrutinib (Calquence)

Acalabrutinib (Calquence) is a small molecule inhibitor of BTK that blocks the proliferation of cancerous B cells. It was approved for the treatment of adult patients with CLL/SLL in 2019, and it can be used in monotherapy or in combination with obinutuzumab (Gazyva).

Acalabrutinib (Calquence) comes in 100 mg capsules that must be swallowed whole. It is given twice daily.

Idelalisib (Zydelig)

Idelalisib inhibits the signaling protein PI3K-delta, blocking the growth and inducing the death of cancerous B cells. Idelalisib (Zydelig) was first approved by the FDA in 2014, and as of 2022 it is indicated in combination with rituximab (Rituxan) for the treatment of relapsed CLL in patients for whom rituximab (Rituxan) alone would be appropriate (because they have received many previous treatments or cannot tolerate chemotherapy)

Idelalisib may only be used in patients who have received other lymphoma treatments; it is not intended to be used as *frontline* (initial) therapy. Idelalisib comes as an oral therapy (tablet) that must be swallowed whole twice daily.

Duvelisib (Copiktra)

Duvelisib inhibits the activity of the PI3K-delta and PI3K-gamma proteins, blocking the growth and reducing survival of cancerous B cells. This drug was approved by the FDA in 2018 for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.

Duvelisib comes as a capsule that must be swallowed whole.

Venetoclax (Venclxta)

Venetoclax targets Bcl2, a protein that plays a major role in cell survival. By inhibiting the activity of Bcl2, venetoclax induces its target cells to die. Venetoclax is approved alone or in combination with obinutuzumab (Gazyva) for the frontline treatment of adult patients with CLL/SLL. It is also approved in combination with rituximab (Rituxan) in the treatment of patients with previously treated CLL/SLL which has relapsed or become refractory.

Venetoclax comes as an oral tablet that must be swallowed whole once a day with a meal and water. Patients should not chew, crush, or break the tablets.

What Is Chemotherapy?

Chemotherapy drugs work by attacking cells that grow and multiply very quickly, which is a common characteristic of cancer cells.

Oncology nurses are usually responsible for administering the chemotherapy prescribed. Most patients receive their chemotherapy treatments in an outpatient clinic, hospital outpatient department, or doctor's office, but sometimes patients must stay overnight in the hospital for their treatment.

While the role of chemotherapy is limited in CLL/SLL, it can be used in combination with other drugs like monoclonal antibodies. Examples of chemotherapy agents used in CLL/SLL include the alkylating agents bendamustine (Treanda) and chlorambucil (Leukeran).

Combined Therapies

Some treatment strategies for CLL/SLL use treatment combinations (e.g. chemotherapy or targeted therapy plus monoclonal antibody). For example, monoclonal antibodies like rituximab (Rituxan) or obinutuzumab (Gazyva) are frequently added to chemotherapy regimens or targeted therapy. Other combination therapies used to treat CLL/SLL are listed on Table 6.1. The treating physician will evaluate which combination will provide optimal clinical benefit and lowest risk for each patient.

What is Cellular Therapy?

Cellular therapy is the introduction of healthy human cells into the patient's body to replace or repair damaged tissue and/or cells. Both stem cell transplantation and CAR T are forms of cellular therapy, and many of the steps in the procedures are similar. Stem cell transplants use unmodified stem cells collected from the patient (autologous transplant) or from a family member or unrelated donor (allogeneic transplant). Allogeneic transplants require immunosuppressant therapy to reduce the risk of rejection of the transplanted cells ("graft") and graft-vs-host disease (where

the graft attacks the patient's healthy cells). The cells used in CAR T cell therapy are genetically reprogrammed to recognize and fight cancer. CAR T cell therapy is FDA-approved to treat some forms of blood cancer, but none are approved to treat CLL/SLL as of May 2022. Current CAR T cell therapies are exclusively autologous, but allogeneic approaches are under investigation. While both procedures require prior chemotherapy, the regimen used in CAR T cell therapy is associated with fewer side effects.

Stem Cell Transplantation

There are three types of stem cell transplantation that differ based on the source of the stem cells: autologous, allogeneic and syngeneic.

In an *autologous stem cell transplant*, patients are their own donor. Autologous stem cell transplantation is not used in patients with CLL/SLL because their stem cells are often contaminated with the disease. Therefore, this type of stem cell transplantation is not discussed further in this booklet.

In an *allogeneic stem cell transplant*, the donor is another person who is genetically similar to the patient; this person is often a brother or sister. Donor stem cells may also come from the patient's child, the patient's parent, an unrelated person, or donated umbilical cord blood. In a syngeneic stem cell transplant, the donor is the patient's identical twin.

A stem cell transplant adds new stem cells back into the body after high-dose chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells. The ability to transplant stem cells allows doctors to use higher doses of chemotherapy than the body would normally tolerate, increasing the probability of treatment success.

For patients who are not candidates for traditional stem cell transplantation, *reduced-intensity* transplantation (also called nonmyeloablative or mini-allogeneic stem cell transplantation) may be an option. In fact, these are the most commonly used types of transplantations in CLL/SLL patients. This approach uses lower doses of chemotherapy and/or radiation prior to transplantation.

CAR T Cell Therapy

A special type of immunotherapy, called chimeric antigen receptor (CAR) T cell therapy, uses patients' own immune cells to treat their cancer. There are many types of immune cells. The ones utilized for this particular type of immunotherapy are called T lymphocytes or T cells.

Briefly, the patients' own T cells are collected and reprogrammed in the laboratory to recognize and attack cancer cells. The reprogrammed (CAR T) cells are then infused back to the patient, where they locate and fight lymphoma.

CAR T cell therapy is a complex procedure that involves specialized care that is only offered at certified treatment centers. If the *hematologist–oncologist* (doctor specializing in treating patients with blood disorders/cancers such as CLL/SLL) thinks a patient is a good candidate for CAR T cell therapy, the patient will be referred to a specialized treatment center. The treatment center staff will conduct their own evaluations to confirm whether the patient is eligible for CAR T cell therapy.

CAR T cell therapy has demonstrated significant efficacy in patients with aggressive lymphoma and is now FDA approved in certain subtypes for treatment of relapsed (disease returns after treatment) or refractory (disease does not respond to treatment) lymphomas. With a median follow-up of about 5 years, this treatment modality has demonstrated durable response in some patients. Patients with aggressive lymphoma who are functionally active and have no significant co-morbidities are eligible for CAR T cell therapy.

Several clinical trials are being conducted to test the efficacy of CAR T cell therapy in *refractory* CLL/SLL. However, currently there are no FDA-approved CAR T cell therapies for CLL/SLL. See Chapter 11 to find more about treatments under investigation in CAR T cell therapy.

What Terms Do Doctors Use to Describe Treatment and Its Outcomes?

Doctors who treat patients with lymphoma use certain terms to describe a patient's treatment and the anticipated outcomes. Some of these are defined in Table 6.3.

Table 6.3. Terms Used to Describe Treatment and Its Outcomes

Cure	This word is cautiously used by doctors when there are no signs of lymphatic malignancy reappearing after many years of continuous complete remission (CR). While cures are rare in CLL/SLL, most patients live for many years.
Complete Remission (CR)	This term is used when all signs of lymphatic malignancy have disappeared after treatment. This does not mean that the cancer is completely cured; rather, it indicates that the symptoms have disappeared, and the lymphatic malignancy cannot be detected using current tests. If complete remission is maintained for a long period, it is called a <i>durable remission</i> . A complete remission is a necessary first step for cure.
Minimal Residual Disease (MRD)	This is a sensitivity test. An MRD-negative status means that are no CLL/SLL cells detected with a sensitivity of 1 in 10,000 (or more, depending on the method used). This can be tested from the blood and bone marrow.
Partial Remission (PR)	This term is used if the lymphatic malignancy has responded to treatment and shrunk to less than one half of its original size.
Stable Disease	This term means the disease has not gotten worse or better following therapy.
Disease Progression	This term means the disease has worsened or has grown or spread during therapy or observation. Other terms used to describe disease progression are relapse, treatment resistance, or resistant disease.
Primary or Frontline Therapy	This term is used to describe the first therapy that a patient receives. The choice of primary therapy depends on the characteristics of the disease, including the factors described in this guide.
Refractory Disease	This term is used to describe a lymphatic malignancy that does not respond to treatment or in which the response to treatment does not last very long.
Relapse	This term refers to disease that reappears or grows again after a period of remission.

What Is Relapsed or Refractory CLL/SLL?

There are many treatment options for patients with CLL/SLL that has relapsed and for those who became refractory to treatment. Exactly what type of treatment is optimal for individual patients with relapsed or refractory CLL/SLL depends on such factors as the patient's age and overall health, the extent and location of disease, the type of previous

therapies received, and the length of response to previous therapies. Many of the therapies already discussed can be effective in patients with relapsed or refractory CLL/SLL.

Patients whose lymphatic malignancy does not go into complete remission (CR) following treatment or does not respond to treatment should not lose hope. Lasting responses to therapy may be achieved after a diagnosis of relapsed or refractory disease. Many patients seek second opinions at any point from diagnosis onward, and some choose to do so if their disease relapses or is considered refractory.

While clinical trials can be a good option for patients at all stages of disease, they are often especially useful for patients with relapsed or refractory CLL/SLL, because many of the novel therapeutic agents most recently approved by the FDA and those being investigated in clinical trials are used specifically for these patients. Lymphoma research continually evolves as doctors and scientists discover new therapies and more effective ways of giving existing treatments. Chapter 11 describes some of the options currently under investigation.

Minimal Residual Disease

Testing for minimal residual disease (MRD, or measurable residual disease) is often done in clinical trials to detect cancer cells that remain in the blood or bone marrow after the completion of treatment. Using very sensitive laboratory techniques, one abnormal cell can be detected among at least 10,000 healthy blood cells. Studies have found that patients with lower levels of MRD (fewer cancer cells remaining after the completion of treatment) may have a longer remission. Studies are underway to investigate whether MRD testing may be used to shorten the course of treatment for patients with undetectable levels of cancer cells in their blood before they have completed a full course of therapy.

When Should a Clinical Trial Be Considered?

Clinical trials are appropriate for patients to consider at all stages of disease, whether newly diagnosed or at the time of relapse (see the section “Overview of Clinical Trials” in Chapter 10). The purpose of a clinical trial is to safely monitor the effects of a new drug or new

combination of drugs on patients over time and to identify more effective therapies for specific diseases. Some trials randomly assign patients to one of two or more treatment arms, each of which receives a different treatment. By participating in a randomized clinical trial, patients may or may not get access to the newest therapies, but at a minimum, they will receive quality standard care in a very carefully controlled and supportive environment.

If patients are interested in participating in a clinical trial, they should ask their doctor if there is an appropriate trial for them and what the potential risks and benefits may be. For more information about clinical trials, contact LRF's Helpline by phone (800-500-9976), or by email (helpline@lymphoma.org).

What Is Transformation of CLL/SLL?

Transformations are very serious and rare complications of CLL/SLL that occur when the disease undergoes additional changes to become a more *aggressive* (fast-growing) lymphoma, such as:

- Richter syndrome (also referred to as Richter transformation), a type of high-grade lymphoma (large-cell is the most common type, but other types can also occur) that is the most common CLL/SLL transformation and is seen in about five percent of patients with CLL/SLL
- Polymorphocytic leukemia, a type of transformation with an increased number of *prolymphocytes* (immature white blood cells) in the blood/bone marrow (>55% of cells)
- Hodgkin lymphoma (HL) is a rare form of transformation seen in about 0.5% of patients with CLL/SLL over 10 years. This transformation has a poor outcome compared to *de novo* cases of HL.

CLL/SLL transformations are generally treated in the same way as aggressive disease.

What Are Complementary and Alternative Therapies?

Complementary therapy may be considered in addition to standard therapy to help improve a patient's quality of life and to relieve the effects of treatment. **It is very important for patients and caregivers to talk to the doctor and healthcare team before starting any form of complementary therapy, because a few of these approaches may interfere with treatment.** Table 6.4 outlines some forms of complementary therapy for cancer, also known as integrative medicine or integrative oncology.

Table 6.4. Forms of Complementary Therapy

Acupuncture	<ul style="list-style-type: none"> ■ Acupuncture uses ultra-thin needles applied to specific points on the body. The process is safe and painless, and the needles are disposed of after one use. ■ Acupuncture may relieve pain, nausea, fatigue, hot flashes, and <i>peripheral neuropathy</i> (numbness or tingling in the hands and feet) associated with chemotherapy. It may also help decrease mild depression and other symptoms and side effects.
Chiropractic and Massage Therapy	<ul style="list-style-type: none"> ■ Chiropractic and massage therapies are the most commonly used modalities and can help relieve side effects and stress. ■ A special type of massage called oncology massage is designed specifically for patients with cancer to help manage stress, pain, swelling, and other side effects without causing harm or interfering with cancer treatments. ■ Patients should look for a massage therapist who is certified in oncology massage. ■ Massage does not cause the CLL/SLL to spread.
Herbal Therapy	<ul style="list-style-type: none"> ■ Patients should talk with their doctor before using herbal therapies, because some herbal therapies, such as St. John's wort, may interfere with cancer medications.
Mind/Body Therapies	<ul style="list-style-type: none"> ■ Examples of mind/body therapies include meditation, guided imagery, self-hypnosis, Tai Chi, and yoga. <ul style="list-style-type: none"> – Meditation, guided imagery, and self-hypnosis can help manage stress. – Yoga and Tai Chi have been shown to minimize stress and improve balance and flexibility.

Alternative therapy refers to any treatment used instead of standard therapy. Alternative therapies are not recognized as effective by the medical profession. **Currently, there are no proven alternative therapies to conventional cancer care for patients with CLL/SLL. Patients should not use alternative remedies to replace the care suggested by their doctors.**

For more information about complementary therapies, please view the *Integrative Oncology* fact sheet on LRF's website at lymphoma.org/publications.

Drug Costs: What to Do if the Insurance Company Will Not Pay

Many patients today face the problem of how to pay for rising healthcare costs. Cancer organizations like the Lymphoma Research Foundation (lymphoma.org) offer help in finding financial assistance resources. Most pharmaceutical companies also have patient assistance programs in place that help provide medications to qualifying patients.

Patients in need of financial assistance should talk to their doctor and social worker about available options and how to enroll in an appropriate program. Before undergoing a medical procedure, patients should check with the insurance carrier to confirm that it is covered. If there is a dispute about coverage or if coverage is denied, patients should ask the insurance carrier about their appeals process. If a claim is repeatedly denied, patients should contact their state's insurance agency. For more information on financial aid, please view the *Resources for Financial Assistance* fact sheet on LRF's website at lymphoma.org/publications. Patients can also call LRF's Helpline at (800) 500-9976 or email helpline@lymphoma.org for assistance in finding financial resources.

Part 3 — Survivorship and Living With the Side Effects of Treatment

Chapter 7: Common Treatment Side Effects

Patients receiving treatment for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) may experience various side effects or toxicities caused by their lymphoma treatment. All treatments have the potential to cause side effects. Fortunately, medications and lifestyle changes can effectively prevent or lessen the severity of most side effects. Before beginning treatment, patients should ask their healthcare team about the most common treatment side effects and how to prevent and manage them. In addition, once treatment has begun, patients need to tell their doctor, nurse, or physician assistant about all side effects they experience. This chapter explains why side effects occur, the types of side effects caused by different treatments, and steps for minimizing these side effects.

What Is the Difference Between Long-Term Effects and Late Effects?

Long-term effects are toxicities that occur during cancer treatment and continue for months or years. *Fatigue* (extreme tiredness), menopausal symptoms, and *neuropathy* (nerve pain) are examples of long-term effects. In contrast, *late effects* of treatment appear only after treatment has ended—sometimes months, years, or even decades after treatment is completed. Infertility, osteoporosis, heart problems, and secondary cancers are examples of late effects.

What Side Effects Are Caused by Drug Therapies?

The drug regimens used to treat CLL/SLL may cause a number of side effects. Some of these side effects are very common and happen to many or most patients, while others affect a smaller number of patients. This section includes explanations of the most common possible side effects that occur during treatment for CLL/SLL and a list of less common possible side effects starts on page 82. (Note: many of these side effects may also be experienced by patients using other treatments discussed in this guide.)

Below is a list of common side effects cause by drug therapies in CLL/SLL:

- Decreased blood cell production (decreased hemoglobin, white blood cells, neutrophils, and/or platelets)
- Diarrhea
- Fatigue
- Infections
- Loss of appetite
- Mouth sores
- Nausea or vomiting
- Peripheral neuropathy (numbness or tingling in hands and feet)
- Problems with sexual function
- *Tumor lysis syndrome* (a reaction to toxins released by dying lymphoma cells)

Decreased Blood Cell Production

The bone marrow constantly produces red blood cells, white blood cells, and platelets. Patients with CLL/SLL may have decreased blood cell production (or shortened survival of these cells) due to their disease. In addition, several types of therapies for CLL/SLL temporarily interfere with the ability of the bone marrow to produce enough of one or more of these different types of blood cells. This is called *myelosuppression*.

To prevent and monitor myelosuppression, samples of a patient's blood are tested with a complete blood count (CBC) with differential, which measures the numbers of red blood cells and platelets, as well as all the different subtypes of white blood cells. These tests are usually done before and sometimes during the treatment process.

Table 7.1 describes the most common conditions involving a decrease in blood cell production.

Table 7.1. Five Common Conditions Caused by Decreased Blood Cell Production

Anemia	<ul style="list-style-type: none"> ■ <i>Anemia</i> is a decrease in the number of red blood cells. ■ Many types of therapy cause mild or moderate anemia. ■ Anemia can make people feel tired and short of breath, especially when it is severe. ■ Although seldom needed, drugs or red blood cell transfusions can be used to treat severe anemia.
Leukopenia	<ul style="list-style-type: none"> ■ <i>Leukopenia</i> refers to a decrease in the number of leukocytes, or white blood cells. Leukocytes include lymphocytes (B cells and T cells), neutrophils, basophils, eosinophils, and monocytes. ■ Patients with low levels of neutrophils are at increased risk of infections.
Lymphopenia	<ul style="list-style-type: none"> ■ <i>Lymphopenia</i>, also called lymphocytopenia, refers to a decrease in the number of lymphocytes. Lymphocytes are white blood cells that produce antibodies and fight bacterial and viral infections. About 20 to 40 percent of white blood cells are lymphocytes. ■ Patients with low levels of lymphocytes are at increased risk of infections.
Neutropenia	<ul style="list-style-type: none"> ■ Neutropenia refers to a decrease in neutrophils, the primary type of white blood cells that fight bacterial infections. ■ Patients with low neutrophil counts are at higher risk of serious and even life-threatening infections. Symptoms of infection include fever and chills. ■ During therapy, doctors regularly monitor the patient's absolute neutrophil count (ANC), the number of neutrophils in the peripheral blood. Because patients with an ANC below 500 cells per microliter are at particularly high risk for infections, doctors modify or hold treatment until the ANC returns to 500 or greater. ■ Some patients with neutropenia require treatment with antibiotics and hospitalization to prevent or treat infections. ■ To avoid a patient missing a dose of therapy, doctors sometimes prescribe drugs like filgrastim (Neupogen, Granix, Zarxio) or pegfilgrastim (Neulasta, Fulphia) to reduce the duration and severity of neutropenia. These drugs can sometimes cause bone pain, which is usually temporary. Bone pain in the chest can mimic heart disease; patients experiencing unexplained chest pain should contact their doctor immediately. ■ Unless contraindicated, bone pain can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil and others) or naproxen (Aleve, Naprosyn), as well as the antihistamine loratadine (Claritin, Alavert). Acetaminophen (Tylenol) can also be used.

Table 7.1. Five Common Conditions Caused by Decreased Blood Cell Production (*continued*)

Thrombocytopenia

- *Thrombocytopenia* refers to a decrease in the number of platelets in the blood. Platelets help start the clotting process when bleeding occurs.
- Patients with low platelet counts may bruise easily; have cuts that bleed more or longer than usual; have nosebleeds or bleeding gums; or bleed from places that have not been injured.
- A platelet transfusion or certain medications may be needed if thrombocytopenia is severe or if the patient develops bleeding.

Diarrhea

While most patients do not experience severe diarrhea, it can occur with certain medications. The most important thing to remember is to stay hydrated. Signs of dehydration include dry mouth or skin, decreased production of urine, or feeling dizzy or lightheaded after standing up. The doctor should be contacted if the patient has bloody diarrhea, fever with diarrhea or if the diarrhea lasts for a long time. Patients may follow the tips below.

PATIENT TIP

Avoiding Dehydration From Diarrhea or Vomiting

- Drink plenty of liquids (eight glasses a day), such as electrolyte replacement drinks like Gatorade, Pedialyte, and Powerade. Sometimes it helps to drink small amounts very frequently rather than to drink a full glass at once.
- Soup, especially broth, is a good source of both water and nutrients.
- Do not drink or eat dairy products because they can worsen diarrhea.
- Do not eat foods that are high in fiber or hard to digest because they can worsen diarrhea.
- Eat plenty of bananas and other high-potassium foods (after checking with your doctor or dietitian to make sure these foods will not interfere with your therapy).
- Take the medicines that your doctor recommends to control diarrhea or vomiting, and call your doctor if symptoms persist.

Fatigue

Fatigue (extreme tiredness) is a common side effect of many therapies for CLL/SLL. Fatigue usually decreases after patients have completed their treatment, but it can take weeks or months for patients' energy levels to return to normal. Patients may use the tips below to help them cope with fatigue.

PATIENT TIP

Coping With Fatigue

- Keep a diary to help you keep track of when you have the most energy and which activities make you feel tired or give you energy. Use this information to plan your activities for the times when you have the most energy.
- Ask for help with housework and other daily activities that are tiring.
- Exercise if your doctor says it is okay to do so, but do not overdo it. Try simple stretching and range-of-motion exercises or a short walk; these activities may energize you without tiring you out. Start slowly and build up to the level that is right for you. Ask your doctor, nurse, or physical therapist to help you create a personalized exercise plan.
- Rest and sleep during therapy are very important, but too much rest may actually decrease your energy levels. An afternoon nap helps some patients feel less tired for the rest of the day, but other patients cannot sleep at night if they nap during the day. If you have trouble sleeping, talk to your healthcare team to find out what you can do to get more rest.
- Be patient. These symptoms usually improve once treatment is completed.

Part 3

Infections

Some CLL/SLL treatments can lower a patient's ability to fight infections. Patients with a fever of 100.5°F or greater should call the doctor. Chills or a chilly sensation often precede fever. Patients should ask their provider what to do if they have a sore throat, rash, diarrhea, cough, or redness, swelling, or pain around a wound. The doctor should be contacted if the patient experiences any painful local rash with or without blisters, as this could indicate an infection of shingles (herpes zoster, the virus that causes chickenpox). If you are having recurrent infections, the doctor may consider giving you gamma immunoglobulins, since patients with CLL/SLL often have reduced antibodies to fight infection.

To reduce the risk of infections, patients may be prescribed antibiotic, antiviral, or antifungal medications. Sometimes doctors also prescribe medication to prevent shingles from developing during therapy. Other ways to reduce the risk of infections are discussed below.

PATIENT TIP

Reducing Your Risk of Serious Infection During Therapy

- Check with your doctor to make sure your vaccinations are up to date before starting treatment.
- Wash your hands diligently and regularly.
- Avoid crowds. Use common sense in crowded or public areas, especially during influenza (flu) season (October–May in North America) and other outbreaks.
- Make sure all foods are thoroughly washed and/or cooked; avoid raw foods that may carry germs.
- Avoid swimming in public pools.
- Do not sleep with pets.

Loss of Appetite

Loss of appetite is sometimes a symptom of CLL/SLL itself, but it can also be a side effect of therapy. Patients may eat less than normal, not feel hungry, or feel full after eating only a small amount of food. Ongoing loss of appetite can lead to weight loss and poor nutrition, which can become serious. Side effects from chemotherapy and other treatments, such as nausea and vomiting, mouth sores or pain, fatigue, depression, dry mouth, and difficulty swallowing can all contribute to a patient's loss of appetite.

The patient's healthcare team should be notified about lack of appetite to determine the underlying cause. Loss of appetite can sometimes be treated with medication or by changing eating habits, such as eating several small meals each day and making nutritious food choices.

Patients may wish to visit a registered dietitian for additional tips. For more information on nutrition, please view the *Nutrition* fact sheet on LRF's website at lymphoma.org/publications.

Mouth Sores

Some chemotherapy drugs can cause a patient's mouth to become red, sore, or irritated, which is called *mucositis*. Additionally, some patients undergoing chemotherapy become more susceptible to viral or fungal infections of the mouth and throat. Often, mouth sores are due to herpes simplex virus.

The doctor should be informed if the patient develops a sore throat. The doctor may examine the patient's throat and take a swab that is sent to a laboratory to check for infection. Several medications are available to treat different types of infections. To help decrease chances of mouth infections, patients should have a complete dental checkup and cleaning before starting therapy. Other tips for preventing and caring for mouth sores caused by CLL/SLL treatment are listed on the following page.

Preventing and Caring for Mouth Sores

- Clean your mouth and teeth regularly. Use a soft-bristle toothbrush, a nonabrasive toothpaste, and lip moisturizer.
- Do not use mouthwashes that contain alcohol. Your doctor may prescribe a gentler mouth rinse that cleans mouth sores without irritating them.
- Do not eat citrus fruits (such as oranges, grapefruit, lemons, or clementines) or drink citrus juices, and avoid other acidic food and sodas. The acids in these foods and drinks can further irritate the lining of the mouth.
- Do not eat spicy foods.
- Eat soft foods to avoid bruising your gums or other soft tissues in your mouth.
- Do not floss your teeth if your blood counts are low, as this may cause your gums to bleed.
- Swish and spit warm salt water (1/4 teaspoon of salt mixed in a coffee cup of warm water) four to six times per day to soothe mouth irritation.
- Viral infections (such as herpes) can be prevented or managed with acyclovir (Zovirax), valacyclovir (Valtrex), and other anti-viral medications.
- Fungal infections (such as Candida and Monilia) can be managed with miconazole (Monistat) or nystatin (Mycostatin). If severe, fungal infections can be treated with the oral treatment fluconazole (Diflucan).

Nausea or Vomiting

Some drugs can cause nausea or vomiting. This typically occurs on the day therapy is administered, but it may also occur one or two days later. The doctor may prescribe an *antiemetic* (drug that prevents nausea and vomiting) before chemotherapy. Examples of antiemetics include aprepitant (Emend), ondansetron (Zofran, Zuplenz), granisetron (Kytril and others), metoclopramide (Reglan and others), prochlorperazine (Compazine and others), dolasetron (Anzemet), and a variety of corticosteroids such as prednisone and dexamethasone. In most cases, these antiemetics are able to partially or completely prevent nausea and vomiting. Tips for controlling or minimizing nausea and vomiting are listed below.

Controlling or Minimizing Nausea and Vomiting

- Before therapy, drink a liquid diet consisting of broth, gelatin, ice pops, and tea. Do not drink milk or have a meal in which the main ingredients are dairy products.
- Do not eat foods that are too hot or too cold, greasy or fatty, or sweet or spicy.
- Eat smaller, more frequent meals instead of fewer, large meals each day.
- Avoid strong or offensive smells. Get plenty of fresh air.
- Take prescribed antiemetics before chemotherapy to prevent nausea.
- If you vomit, make sure to avoid becoming dehydrated (see tips on page 80).
- Finding the best approach is often a process of trial and error. Try different approaches to determine what works best for you.

PATIENT TIP

Part 3

Peripheral Neuropathy

Some drugs may damage the nervous system, causing *peripheral neuropathy* in the hands and feet (sometimes extending to the arms and legs). Symptoms of peripheral neuropathy include pain, numbness, a tingling or prickling sensation, sensitivity to cold and touch, and muscle weakness that can impair fine motor skills such as buttoning a shirt or picking up small objects.

Peripheral neuropathy can be a difficult side effect for patients to manage, and it is a common cause of dose reduction. Furthermore, while neuropathy improves or resolves in most patients after completion of therapy, the symptoms can last beyond the end of the treatment period. Patients should notify their doctor as soon as symptoms begin to develop so the treatment regimen and dosing can be modified appropriately. Specific therapies may be discontinued, or the dosages may be reduced to prevent further complications.

Although no medications have been specifically approved by the U.S. Food and Drug Administration (FDA) to treat chemotherapy-induced peripheral neuropathy, there are several different classes of drugs that doctors may prescribe to help alleviate patients' symptoms. These include antiepileptic agents such as pregabalin (Lyrica) and gabapentin (Gralise, Horizant, Neurontin, and others); local anesthetics such as lidocaine patches; opioid pain relievers; and antidepressants that also target pain such as duloxetine (Cymbalta, Irenka) and amitriptyline (Elavil). Complementary therapy techniques such as acupuncture and massage may also help with neuropathy symptoms (see page 69). Finally, patients should avoid tight-fitting shoes or clothes and exposure to cold, as these may exacerbate neuropathy symptoms in the hands and feet.

Problems With Sexual Function

Psychological factors such as fear about illness and altered body image due to depression, combined with physical side effects of treatment on the body and the brain, often cause a drop in *libido* (sex drive). However, a normal libido usually returns after treatment is finished. Patients should not be embarrassed to talk with their doctor about any problems or concerns they have about changes in their libido or sexual function. The doctor might order tests to track hormone levels or recommend seeing a specialist. Doctors can also prescribe medications to restore erectile function in men, or hormone therapy to alleviate vaginal dryness and other menopausal symptoms in women. It is important for patients to discuss this issue openly with their spouses or partners.

Sterility/Fertility

Since some therapies may damage sperm and egg cells, it can sometimes cause temporary or permanent *sterility* (the inability to have children) in both men and women. The potential for developing sterility depends on the treatment type and dosage, the number of therapies given, and the patient's age at the time of treatment. Options for preserving fertility both before and during treatment include protection of the ovaries or testes, freezing of sperm cells or egg cells, and *in vitro* creation and freezing of fertilized embryos. Patients should speak with their doctor about fertility preservation before beginning treatment.

Despite these risks, it is still possible for female patients with CLL/SLL to become pregnant and for male patients with CLL/SLL to father children during and after treatment. Because some treatments can cause severe birth defects and other pregnancy complications, it is critical that patients receiving these treatments always use reliable birth control methods during treatment and for several months after completion of therapy. The exact duration of this precaution depends in part on the treatment regimen administered. Patients should discuss fertility concerns and pregnancy prevention with their doctor and, if needed, with a fertility specialist.

Tumor Lysis Syndrome

Patients who have large, rapidly growing, or multiple tumors may experience *tumor lysis syndrome* (TLS) during treatment for CLL/SLL. This condition occurs when a drug triggers the quick death of a large number of lymphoma cells, causing the cells to release toxic substances into the blood that can damage the kidneys and other organs. Specific chemotherapy agents used to treat CLL/SLL that may cause TLS include bendamustine (Bendeka, Treanda), cyclophosphamide (Cytoxan), and fludarabine. The targeted agent venetoclax (Venclexta) and the monoclonal antibody obinutuzumab (Gazyva) may also cause TLS. If not properly treated, TLS may lead to kidney failure or damage to the heart and nervous system.

Patients who are receiving medications that commonly cause TLS have frequent blood tests to detect any signs of organ damage or abnormal levels of chemicals in the blood from TLS. Patients may receive extra oral and intravenous (IV) fluids and medications such as allopurinol (Aloprim, Lopurin, Zyloprim) or febuxostat (Uloric) that reduce high blood levels of uric acid. If severe TLS develops it can be treated with rasburicase (Elitek), which rapidly lowers uric acid levels in the blood.

Less Common Side Effects

The following side effects are also possible in patients treated for CLL/SLL:

- *Cardiotoxicity* (heart problems)
- Changes in taste
- *Cognitive problems* (trouble concentrating, impaired memory)
- Hair loss
- Secondary cancers

Cardiotoxicity (Heart Damage)

Cardiotoxicity refers to damage to the cells of the heart or heart muscle. Long-term use of certain chemotherapy drugs can cause cardiotoxicity in some patients. In general, patients with CLL/SLL are rarely treated with potentially cardiotoxic chemotherapy.

A patient's history of heart disease, high cholesterol, or high blood pressure, as well as obesity and lifestyle choices (such as smoking and lack of exercise), may increase the chance of developing chemotherapy-related or radiation-related cardiotoxicity.

Careful monitoring by the healthcare team can reduce the chances of patients developing cardiotoxicity. Before deciding to treat patients with a cardiotoxic drug, most doctors order either an echocardiogram or a multigated acquisition (MUGA) scan to measure the patient's cardiac function. These tests ensure that patients are prescribed a safe chemotherapy dosage given their current heart function. Patients with underlying conditions that put them at high risk of cardiotoxicity may also have their heart function monitored more intensively during the course of treatment for CLL/SLL.

Changes in Taste

Some patients receiving treatment experience a change in the way foods or beverages taste. Familiar foods may taste different (*dysgeusia*), or the flavors of foods may not taste as strong (*hypogeusia*). Some patients may also notice that foods have a metallic taste. These side effects are temporary and usually disappear after completion of chemotherapy. Sometimes this side effect can be helped by dietary changes, such as eating foods that are frozen, cold, or at room temperature; adding extra seasonings or sugar to enhance taste and reduce bitterness; and avoiding metallic silverware.

Cognitive Problems

Treatment can result in mild cognitive impairment, such as trouble concentrating, impaired memory, or issues with motor control. Some patients refer to these side effects as “chemo brain.” Although these side effects can be stressful, they typically disappear over time. Few treatments for CLL/SLL cause cognitive problems.

Hair Loss

Certain drugs can cause *alopecia* (thinning or loss of hair) anywhere on the body, including the scalp, eyebrows, eyelashes, arms, legs, and pelvis. The amount of hair loss varies. Few treatments for CLL/SLL cause hair loss.

When hair loss occurs, it usually starts two to six weeks after the first chemotherapy treatment. Remember that hair loss caused by chemotherapy is usually temporary; hair will most likely grow back after the end of treatment. When the hair first grows back, it may have a slightly different texture or color than it had before treatment. Over time, the texture and color often return to how they looked before treatment started.

Loss of hair in the nose and nasal passages may lead to symptoms of *rhinorrhea* (runny nose). Loss of eyelashes may make eyes more irritated and dry. Patients may follow the tips on the next page for minimizing and managing chemotherapy-induced hair loss.

Managing Therapy-Induced Hair Loss

- After washing your hair, pat it dry instead of rubbing it with a towel.
- Brush your hair with a soft-bristle brush or a wide-tooth comb.
- Do not use curlers or hair dryers.
- Do not color or perm your hair or treat it with other chemicals.
- Use a hat or scarf to protect your scalp when you are out in the sun and to help keep you warm when you are indoors or outside in the cold.
- Many patients choose to use a wig, scarf, turban, soft cotton hat, or head wrap to disguise hair loss. Some health insurance companies cover the cost of wigs with a doctor's prescription. Check your policy to see if it covers this cost.

Secondary Cancers

Secondary cancers are one of the most concerning unwanted effects for patients with CLL/SLL. The risk for a patient with CLL/SLL to develop a secondary cancer after undergoing chemotherapy/monoclonal antibody therapy is more than two times higher than the risk in the general population. Both solid tumors in specific organs and other blood cancers have been noted in various studies. It is not clear why patients with CLL/SLL are at greater risk, or if the risk of these secondary cancers is related to treatments for CLL/SLL. This phenomenon is currently being studied in clinical trials.

Patients with CLL should see their doctors and get routine cancer screening tests and well check-ups regularly. Routine care can help detect any issues early, when they are usually easier to treat.

Other Possible Side Effects

Drug therapies can cause other side effects, such as skin rashes, general weakness, and loss of balance or coordination. Many of these side effects are temporary, but some may last for an extended period. The doctor should be contacted immediately if the patient experiences any painful local rash with or without blisters, as this may be a sign of shingles (herpes zoster).

What Side Effects Are Caused by Monoclonal Antibody Therapies?

The monoclonal antibodies used to treat CLL/SLL—obinutuzumab (Gazyva), ofatumumab (Arzerra), rituximab (Rituxan), and rituximab and hyaluronidase human (Rituxan Hycela)—may cause side effects such as low blood cell counts and infusion reactions, although monoclonal antibodies are less likely than chemotherapy to cause low blood cell counts. These side effects are usually mild, but they can sometimes be severe. Other rare but potentially very serious side effects include infections, tumor lysis syndrome (TLS), and reactivation of past infections such as hepatitis.

Infusion/Injection Reactions

An infusion/injection reaction is a reaction that typically occurs during or within 24 hours after IV infusion or administration of a subcutaneous injection. Symptoms include dizziness, fainting, headache, feeling warm or flushed, fever or chills, hives, itching, shortness of breath, changes in heart rate and blood pressure, pain in the back or abdomen, and swelling of the face, tongue, or throat. Some infusion/injection reactions are true allergic reactions that can cause low blood pressure, difficulty breathing, and anaphylactic shock.

To prevent infusion/injection reactions, patients are given an antihistamine such as diphenhydramine (Benadryl), as well as acetaminophen (Tylenol) and sometimes corticosteroids before or during the antibody infusion/injection. Nurses closely monitor patients during the infusions/injections for signs of an infusion/injection reaction. Patients should immediately report any symptom they experience during or after an infusion/injection.

Infections

Reactivation of hepatitis B virus (HBV) infection is a rare but very serious side effect of treatment with the monoclonal antibodies obinutuzumab (Gazyva), ofatumumab (Arzerra), and rituximab (Rituxan). Reactivation of HBV may also occur with steroids, chemotherapy, or targeted therapies. Patients may not know they are infected with HBV, because a healthy immune system can force the virus to hide without causing noticeable symptoms. However, treatment with CD20- directed monoclonal antibodies can trigger immune system changes that reactivate HBV, which can cause acute liver failure. To prevent HBV from reinitiating, patients are screened for HBV infection before treatment. Patients who have the virus are closely monitored during and after treatment and may be given antiviral medications to control HBV infection. Patients should be mindful of signs of an active HBV infection, such as increasing fatigue, yellowing of the skin or eyes, and dark urine.

Very rare cases of a serious and usually fatal central nervous system infection called JC virus infection (progressive multifocal leukoencephalopathy [PML]) can occur with any of the monoclonal antibodies. Patients should be mindful of neurological symptoms, such as difficulty thinking, loss of balance, changes in speech or walking, weakness on one side of the body, or blurred or lost vision.

What Side Effects Are Caused by Targeted Therapies?

For ibrutinib (Imbruvica), an inhibitor of BTK, the most common side effects include diarrhea, anemia, fatigue, musculoskeletal pain, low blood cell counts, bruising, nausea, and rash; cardiac side effects (for example, atrial fibrillation) and hypertension also occurred in patients with CLL in clinical trials. TLS was less common.

For acalabrutinib (Calquence), an inhibitor of BTK, the most common adverse reactions were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea and musculoskeletal pain.

Patients who receive idelalisib (Zydelig), an inhibitor of PI3K, may experience diarrhea/ colitis, bleeding, liver abnormalities, fever, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash.

The most common side effects for duvelisib (Copiktra), an inhibitor of PI3K, include diarrhea/colitis, neutropenia, rash, fatigue, fever, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia.

Common side effects of venetoclax (Venclexta), an inhibitor of BCL-2, include low blood cell counts, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, edema and fatigue. TLS may be observed in patients who receive venetoclax and requires that the drug be initiated slowly and carefully, with increased dose each week for several weeks, with close monitoring.

Drug Interactions with Targeted Therapies

The main source of interactions are medications that act as CYP3A inhibitors/inducers (like some drugs used to fight infection). By interfering with metabolism, the drugs alter the levels of the above listed targeted therapies in the blood, which can lead to toxicity or reduced efficacy. These interactions include herbal teas like St. John's wort, so be sure to check with your doctor before taking any herbal remedies. Additional concerns regarding drug interaction with targeted therapies used in the treatment of CLL/SLL include the following:

- If you are receiving ibrutinib (Imbruvica) or venetoclax (Venclexta), you should also avoid grapefruit, Seville oranges and starfruit, as these contain CYP3A4 inhibitors
- Venetoclax (Venclexta) increases the blood levels of warfarin (Coumadin, Jantoven), which may increase the risk of bleeding in patients receiving both drugs at the same time.
- Strong/moderate inhibitors of P-glycoprotein (P-gp) may increase the toxicity of venetoclax (Venclexta). Avoid using of venetoclax (Venclexta) and P-gp substrates at the same time.
- Some medications to reduce stomach acid (like proton pump inhibitors, H2-receptor antagonists and antacids) may interact with acalabrutinib (Calquence).

Let your doctor about any medications you may be taking, since you may need to readjust the dose or temporarily interrupt treatment. Your doctor will let you know about strategies to prevent or manage drug interactions.

What Side Effects Are Caused by Chemotherapy?

Chemotherapy has a limited role in the treatment of CLL/SLL. Most chemotherapy drugs work by killing cells that grow and multiply more quickly than typical cells. Cancer cells multiply rapidly, which is why chemotherapy can be effective at killing them. However, a few types of normal cells in the body also multiply quickly, including the cells in hair roots, the mouth, the gastrointestinal tract, and bone marrow, so those cells may also be damaged or killed by chemotherapy. Some chemotherapy drugs can also damage cells in the heart, lungs, or other organs and tissues as described in the common side effects described in the “What Side Effects Are Caused by Drug Therapies?” section at the beginning of this chapter.

The type and severity of side effects caused by chemotherapy vary widely depending on the types of drugs that are given, an individual patient’s tolerance, and the length of time therapy is delivered. The same drug may cause no side effects in one patient, while in others it may cause very mild to very serious side effects.

When Should a Patient’s Doctor Be Contacted?

Patients should talk with their doctor about watching for certain symptoms and side effects. As a general rule, a patient’s doctor should be contacted if the patient experiences:

- A side effect that is unexpected or lasts longer than expected
- A medical problem—such as fever/chills, shortness of breath, prolonged or constant nausea and vomiting, chest pain, and/or dizziness—that cannot wait for a regularly scheduled appointment
- Any unexpected or unusual symptom or medical event.

Part 3 — Survivorship and Living With the Side Effects of Treatment

Chapter 8: Managing Life During and After Treatment

This chapter discusses some general issues that patients may encounter in their daily lives during and after treatment for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Coping Strategies

Each person’s experience with cancer is different, and the way an individual copes with the physical and emotional impacts of CLL/SLL is unique to each patient’s personality and situation. Table 8.1 lists some suggestions for how to cope with common issues that patients may face.

Table 8.1. Coping Strategies

Build a Strong Support System	<ul style="list-style-type: none">■ Communicate your fears and concerns about your disease by talking to your family, friends, doctors, and counselors.■ Write down your concerns in a journal.■ Find a support group or a one-to-one peer support program such as the Lymphoma Research Foundation’s (LRF’s) <i>Lymphoma Support Network</i> or other individuals who are also coping with cancer.
Get Help for Depression	<ul style="list-style-type: none">■ Feeling sad or having a depressed mood from time to time is not unusual in patients living with cancer, but this is not the same as having a psychiatric diagnosis of depression, known as “Major Depressive Disorder.”■ Watch for signs such as sleeping more or less than usual, a loss of interest in preferred activities, crying, or an inability to concentrate.■ If these symptoms last more than two weeks, ask for a referral to a psychiatrist, social worker, psychologist, or counselor who can help you cope with your feelings through talk therapy, medications, or both.

Table 8.1. Coping Strategies *(continued)*

Deal With Physical Changes	<ul style="list-style-type: none"> ■ Some patients with CLL/SLL may feel unattractive because of hair loss and other changes in appearance caused by their treatment. ■ If desired, plan ahead and buy a wig or head covering if hair loss is a possibility. ■ Seek advice from a beautician familiar with the side effects of cancer treatment about makeup if you are concerned about a blotchy complexion. ■ Ask your healthcare team for advice on how to manage other temporary changes in your skin and brittle nails.
Maintain a Healthy Lifestyle	<ul style="list-style-type: none"> ■ Eat a healthy diet that includes fruits, vegetables, proteins, and whole grains. ■ Engage in regular physical exercise, which can help improve mood and reduce anxiety, depression, and fatigue. ■ Get sufficient rest to help combat the stress and fatigue of your disease and its treatment. ■ Quit smoking and reduce alcohol consumption.
Undergo Routine Healthcare and Preventative Care	<ul style="list-style-type: none"> ■ Continue to visit your primary care physician, dentist, eye doctor, skin doctor, and your other regular healthcare providers throughout treatment and afterwards; however, let each one know about your current diagnosis and treatment in case adjustments in your care need to be made. ■ As directed by your healthcare team, continue to receive preventative care, such as vaccines and screenings.
Set Reasonable Goals	<ul style="list-style-type: none"> ■ Having goals for how you want to live your life during and after treatment can help you maintain a sense of purpose. ■ Avoid setting unreasonable goals, such as working full-time if you do not yet have the energy or stamina to do so. ■ Stay as active and involved as you can in work and other activities that interest you.

Maintain a Healthy Lifestyle

Regular physical activity helps keep the cardiovascular system strong and the body muscles flexible. Exercise can also help patients alleviate breathing problems, constipation, and mild depression. Additionally, it may help reduce stress and fatigue. Patients should talk to their doctor before starting an exercise program and consider visiting a physical therapist for advice. The most important point to remember is to avoid overexertion. Patients dealing with cancer do not need to perform activities at the same level of intensity that they did before their lymphoma diagnosis, and they should not push themselves to their limit.

Several types of exercise may be particularly helpful, including:

- General physical activity, such as swimming, dancing, household chores, and yard work
- Aerobic activity to improve cardiovascular fitness, such as walking, jogging, and bicycling
- Resistance training to strengthen muscles, protect joints, and help prevent osteoporosis by building bone mass
- Flexibility exercises such as stretching and yoga to improve range of motion, balance, and stability

Eating a healthy diet is especially important during treatment for CLL/SLL because it helps patients keep up their strength and energy, tolerate treatment-related side effects, decrease the risk of infections, and heal and recover more quickly. Patients should aim for a diet high in fruits and vegetables, protein (such as poultry, fish, and eggs), and whole grains. During or after treatments that can lower white blood cell counts, such as chemotherapy and stem cell transplantation, patients may be instructed to follow a *neutropenic diet*, which involves temporarily avoiding raw fruits and vegetables that may increase the risk of infection. The healthcare team can help develop an appropriate eating plan.

Patients should talk to their doctor before taking any dietary supplements, such as multivitamins or individual vitamin supplements, as well as any herbal or “natural” supplements, because they may interfere with treatments or have unexpected side effects.

The Importance of Pain Control

Patients may occasionally experience pain from the lymphoma itself or from the treatments and procedures. Pain is very treatable, and there is no reason for a patient to endure it without help. Patients should tell their doctors, nurses, or physician assistants if they have any pain, because the healthcare team can help determine whether pain is related to CLL/SLL, and potentially offer advice regarding medications and other ways to reduce and manage the pain.

Different types of pain are best controlled by different types of pain relievers, and some medications may not be appropriate for patients with CLL/SLL. Patients should ask their healthcare team which options are best to help manage their pain. The tips below may help for managing pain.

PATIENT TIP

Managing Pain

- Be specific when you describe your pain to the doctor or nurse.
 - Where do you feel the pain?
 - When did the pain start?
 - What type of pain is it (sharp, dull, throbbing)?
 - Does the pain come and go, or is it steady? How long does it last?
 - How strong is it? Does the intensity change at different times?
 - Does anything make the pain feel better or worse?
 - Which drugs have you taken for the pain? Do they help? If so, for how long?
- Take your pain medication on a regular schedule, even if the pain seems to be better. Do not skip doses.
- Tell your family and friends about your pain so they can help you and understand why you may be acting differently.
- Try deep breathing, yoga, or other ways to relax.
- Ask to meet with a pain specialist or palliative care specialist to help you find better ways to control your pain.
- Tell your doctor or nurse of any changes in your pain.

Part 3

Vaccines

Patients receiving chemotherapy for CLL/SLL need special consideration with regards to the timing of vaccine administration, since these treatments affect the immune system. If possible, all recommended vaccines should be administered before the start of chemotherapy, other immunosuppressive medications when possible.

Vaccination during therapy should generally be avoided because response to the vaccine may be decreased. If patients receive a vaccine within 14 days before starting therapies that affect the immune system, they should be revaccinated at least 3 months after the treatment has stopped and immune function has returned to normal. Patients with altered immune system function should not receive live vaccines, and live vaccines should not be administered for at least 3 months after immunosuppressive treatments. Live vaccines can be administered to patients with leukemia, lymphoma, or other malignancies whose disease is in remission, who have restored immune system function, and whose chemotherapy has been discontinued for at least 3 months. Zoster live vaccine (Zostavax) is not recommended for patients with lymphoma, leukemia, tumors involving bone marrow, and patients receiving chemotherapy. The recombinant zoster vaccine (Shingrix) is in adults aged 18 years and older who are or will be at increased risk of infection with herpes zoster due to immunodeficiency or immunosuppression caused by known disease or therapy. Preliminary results from clinical trials showed that the recombinant zoster vaccine (Shingrix) is safe and can induce immune response in some patients with CLL/SLL.

COVID-19

The currently FDA-approved or FDA-authorized coronavirus disease 2019 (COVID-19) vaccines can be safely administered to patients with compromised immune system function. When possible, COVID-19 vaccine doses should be completed at least 2 weeks before starting or resuming immunosuppressive therapies. An additional dose of an mRNA COVID-19 vaccine administered at least 28 days after completion of an initial 2-dose primary mRNA COVID-19 vaccine series should be considered in patients with moderate to severe immune compromise. Immunocompromised patients eligible for a third dose include those receiving active treatment

for hematologic malignancies, patients who are recipients of CAR T cell therapy or stem cell transplantation (within 2 years of transplantation or receiving immunosuppressive therapy), and active treatment with chemotherapy classified as severely immunosuppressive.

Patients who are immunocompromised should be aware of the potential for a reduced immune response to COVID-19 vaccines and the need to follow currently recommended preventive measures to protect themselves against COVID-19. The information on COVID-19 continues to evolve and vaccination guidelines may change. Please refer to the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) guidance for the most up-to-date information on COVID-19 vaccines for immunocompromised patients, located at: <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>

Additionally, close contacts of patients with lessened immune function should receive all recommended vaccines, including COVID-19 vaccines, with the exception of smallpox vaccine.

Other non-vaccine preventive treatments are available for patients with impaired immunity due to a medical condition who do not mount an adequate response to COVID-19 vaccines (like patients with CLL/SLL). This includes tixagevimab co-packaged with cilgavimab (Evusheld), which is used for pre-exposure prophylaxis (PrEP) of COVID-19 in adults and pediatric individuals 12 years of age and older and weighing more than 40 kgs (88 lbs).

The Importance of Follow-up Care

At the first visit following the completion of treatment, patients should discuss their follow-up schedule with the doctor. This schedule may be different for each patient depending on their disease stage, age, and overall health. It is critical that patients adhere to their schedule of follow-up visits—these are very important for monitoring disease recurrence, as well as detecting and treating any new health problems that might arise because of the treatment.

During these follow-up visits, the doctor asks about any medical changes since the last appointment and conducts a physical examination. The

doctor may also prescribe blood tests and other laboratory tests, molecular diagnostic testing, or imaging.

It is very important to follow all scheduled appointments and comply with your treatments as prescribed, because this will ensure maximum treatment efficacy.

Be Proactive in Healthcare Decisions

To stay proactive in healthcare decisions, patients should write out their questions and bring them to their appointments and take notes during their visits. Patients should also obtain and save the following information from their medical team:

- Copies of all medical records (including electronic records) and a written summary of their treatments in case the patient switches doctors or needs to see a physician who is not familiar with the patient's CLL/SLL history and treatment. LRF's mobile app, *Focus On Lymphoma*, can keep track of the details to share with the healthcare team
- A list of things to watch for, including signs of disease recurrence and late side effects from treatment

At the follow-up care appointments, patients should inform their doctor of:

- Any new symptoms
- Pain
- Physical problems that disrupt their daily life, such as fatigue, insomnia, sexual dysfunction, and weight gain or loss
- Any new health problems, such as heart disease, diabetes, and high blood pressure
- Any new medications and vitamins they are taking, including over-the-counter medications
- Emotional problems, such as anxiety and depression
- Whether they have a medical alert system (particularly for patients over 70 who live alone)
- Any other questions or concerns

Part 4 — Hospital Admission

Chapter 9: Preparing to Go to the Hospital

What Are Some Reasons That Patients May Be Admitted to the Hospital?

Hospital admission usually occurs either from the emergency room or through direct admission by the patient's doctor. In the case of a direct admission, the doctor decides that the patient needs to be admitted and calls ahead to reserve a bed for the patient. If the patient is admitted by a doctor in the emergency room, the patient's doctor is often contacted and informed that the patient is in the hospital.

Treatment teams conduct daily visitation rounds to check on patients admitted to the hospital. The nurse can tell patients when their treatment team is expected to make rounds that day. It is a good idea for family members to know when the treatment team is likely to be coming so they can be there to ask questions.

Whether admitted through the emergency room or a direct admission, patients may be first evaluated by a hospitalist, a resident physician or a nurse practitioner. Hospitalists are doctors employed by or consulting for the hospital. Their specialty is typically internal medicine. Patients are also assigned a case manager (usually a nurse) who works with the patient's healthcare team.

What Should Patients Bring With Them to the Hospital?

When being admitted to the hospital, being prepared can ease the process of admission and positively impact patients' care. A brief list of items for patients to take with them is shown below.

PATIENT TIP

What to Bring if You Are Being Admitted to the Hospital

- Identification (driver's license, student ID) and emergency contact information (relatives' and friends' names and phone numbers).
- List of all allergies and the reaction that occurs in response to exposure (especially important for latex and medication allergies).
- List of all current prescription medications (name, dosage, and frequency) as well as other products taken such as over-the-counter medications and vitamins (instead of making a list, you can also place all medications in a bag and bring them with you).
- List of all medical conditions other than CLL/SLL, such as hypertension, epilepsy, or active ulcer.
- List of all surgeries (even elective plastic surgeries) regardless of how long ago they occurred.
- List of all physicians currently treating you.
- Copy of any completed advance directives (for more information see the section on the following page describing advance healthcare directives).
- All insurance cards, a checkbook, a credit card, and a minimal amount of cash.

Do not bring valuables. Leave most money and jewelry at home.

If patients have access to an up-to-date and complete medical record through a patient portal, flash drive, or phone app, they should bring the security code and the name of the website, or the flash drive, phone app, or other device that contains the health information.

What Is the Purpose of an Advance Healthcare Directive and Appointing a Healthcare Proxy?

Creating an *advance healthcare directive* (a living will) and appointing a healthcare proxy is important for all adults to consider, not just people with cancer, because accidents and other unforeseen circumstances can happen at any time. Ideally, the proxy is the same person who serves as a contact between the patient and the treatment team. This will help the communication flow at its best and avoid redundancy.

Writing down wishes for critical medical care in an advance healthcare directive is a way for individuals to communicate their preferences about what medical treatments they do or do not want if they become critically ill or injured and are unable to communicate their desires.

Besides stating medical care instructions, patients may also consider naming a *healthcare proxy*, or a decision maker, in an advance healthcare directive. This person should be someone who is willing to carry out the patient's healthcare-related wishes, including any do-not-resuscitate (DNR) instructions. It is best to have both an advance healthcare directive and a healthcare proxy.

Before writing an advance healthcare directive, it is important to understand patients' rights and laws regarding advance healthcare directives in each state. Consulting an attorney can provide legal information, but it is not necessary to hire an attorney to prepare an advance directive. An advance healthcare directive may include:

- Specific instructions on medical care, including the type of special treatment that is or is not desired, such as cardiopulmonary resuscitation (CPR), artificial respiration, drugs to make the heart function, kidney dialysis, artificial feeding, and certain surgical procedures
- A choice of a healthcare proxy

For more information about advance healthcare directive laws in each state, please visit the "Advance Care Planning" section of the National Hospice and Palliative Care Organization website at www.caringinfo.org.

What Are Patients' Rights?

Patients' rights are listed in the hospital's Patient's Bill of Rights. See the tips below for more information about these rights.

PATIENT TIP

Your Rights As a Patient

- You must be given a medical screening examination and be evaluated for care whenever you are admitted to a hospital.
- You have the right to considerate and respectful care.
- You have the right to complete information regarding all aspects of your current condition.
- You have the right to know the names of all doctors and healthcare personnel providing your care.
- You have the right to sufficient information about the benefits and risks for all treatments or procedures to enable you to provide informed consent.
- You have the right to refuse any treatment.
- You have the right to privacy—no members of your healthcare team may talk about your condition or care to anyone outside of that team.
- If you must be transferred to another facility, information about why you require transfer must be provided, and the institution that you are being transferred to must have accepted responsibility for your care prior to transfer.
- You have the right to know whether the hospital has any relationship to other healthcare or educational institutions and if/how this relationship impacts your care.
- You have the right to be informed about your continuing healthcare requirements after you are discharged.
- You have the right to examine and receive an explanation of your bill.
- You have a right to know what hospital rules and regulations apply to your conduct.
- You have the right to have a translator present if English is not your first language.

What Do Patients Need to Know About Informed Consent Documents When in the Hospital?

Patients who are admitted to a teaching hospital may be asked to sign informed consent documents. These documents enable patients to make an educated decision about which treatments and procedures they are willing to receive. Patients should read the informed consent documents carefully and request an explanation of anything they do not completely understand. Signing these documents indicates that the patient understands and agrees to the risks and benefits of the treatments/procedures being performed. The tips below may help patients know what to look for in an informed consent document.

What to Look For in the Hospital Informed Consent Document

- Indication of whether you are being enrolled in a clinical trial or research protocol.
- Alternatives to the proposed treatment.
- Names of the physician(s) performing your treatments/ procedures.
- Risks and benefits of the treatments/procedures you are agreeing to.
- An explanation of what will be done with any tissue or fluid samples removed and any photos or videos taken.

PATIENT TIP

Part 4

What Do Patients Need to Know at Discharge?

When the patient is ready to be discharged, make sure the case manager addresses the subjects identified in the following Patient Tip.

PATIENT TIP

Topics for the Case Manager to Address Before Discharge

- Are there any new limitations to what you can do at work or at home? If so, your doctor can provide a note for your employer if needed.
- Will you need physical therapy?
- If you need any new medical equipment, where can it be obtained? Who will order it? Obtain a phone number to ensure you can follow up if there are any problems with equipment delivery.
- Will you need home nursing care or other arrangements? Will this be covered by insurance?
- What new medications will you need to take, and for how long?
- Does your insurance cover the new medication as an outpatient prescription? If not, or if you do not have insurance, what will the cost be?
- If you do not have insurance, does the hospital have a sliding scale fee or charity care?
- Are there alternative medications you can take if the cost is beyond your capacity to pay?
- What are the side effects of the new medications?
- Will they interact with any medications you are currently taking?
- What symptoms might you develop? Which of those symptoms should prompt a call to your doctor?
- Are there other instructions from your doctor or the hospital physician?
- With whom should you follow up and when?
- If you are to schedule your own follow-up, whom do you call?

Itemized hospital bills should be examined carefully to make sure no mistakes were made. If there are discrepancies between the bill and the care the patient received, they should be brought to the attention of both the hospital and the insurance company.

Should Patients Provide Feedback on Their Stay?

Hospitals may send patient satisfaction surveys to patients after discharge. This survey is an opportunity for patients to report problems they had during their stay and/or to recognize staff members whose care and support were exceptional. Hospital administrators pay close attention to these survey responses, so it is worth the time to complete and return the survey so that problems can be addressed and staff members who provided excellent care can be acknowledged. If no survey is sent and patients want to report problems or satisfaction with their care, they can write a letter to the hospital administrator or the appropriate department director.

Chapter 10: Overview of Clinical Trials

There are clinical trials for patients with chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL) now underway in hospitals/ clinics, academic cancer centers, and doctors' offices around the country. The government, pharmaceutical and biotechnology companies, universities, and doctor groups (hematologists/ oncologists) often sponsor clinical trials.

What Is a Clinical Trial?

A *clinical trial* is a carefully designed research study that involves patients who volunteer to participate. The purpose of cancer clinical trials is primarily to answer specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment. The investigators in clinical trials want to determine the safety and effectiveness of the treatment being investigated by making specific assessments before, during, and after the trial. The new treatment may be tested against a more standard and well-known treatment. Strict rules and oversight procedures make sure that clinical trials are designed and run in a way that protects the rights and safety of the people who volunteer to participate. It can sometimes take years for a clinical trial to be completed and for the results to be compiled and published.

In the United States, a new drug must pass through a strict approval process governed by the U.S. Food and Drug Administration (FDA) before it can become a standard and accepted therapy for use in humans. The FDA-regulated approval process for drugs includes preclinical studies (done in laboratories) and clinical trials (done in hospitals and clinics). In addition to the FDA, all trials must be approved by an institutional review board (IRB) consisting of experts and lay persons to ensure that the study is conducted in an appropriate and ethical manner that does not endanger patients in any way. This does not mean that side effects cannot happen but hopefully educates the patient, provides for careful monitoring and reduces the chances of any toxicity to be excessive.

As shown in Table 10.1, there are four main types or phases of clinical trials. The first three (Phase I, Phase II, and Phase III) are usually required before a drug is considered for approval by the FDA. Phase IV trials, sometimes called post-marketing studies, are conducted after a drug has received FDA approval. Each phase is designed to find out certain information, building upon the information learned from the previous phase. Patients may be eligible to participate in different types of clinical trials depending on their health status, stage of CLL/SLL, prognostic risk group, and the types of treatments, if any, they have previously received.

Table 10.1. The Four Phases of Clinical Trials

Phase	Purpose	Number of Volunteer Patients
Phase I	<ul style="list-style-type: none"> ■ To identify a safe dose of a new drug, or of multiple drugs given together in combination ■ To decide on a dosing schedule for the drug ■ To see what side effects are related to the therapy 	<ul style="list-style-type: none"> ■ 15–30 patients with one or more different types of cancer
Phase II	<ul style="list-style-type: none"> ■ To see if a new treatment is effective against a certain type of cancer at the dose determined in Phase I ■ To confirm and learn more about the side effects identified in Phase I 	<ul style="list-style-type: none"> ■ Usually less than 100 patients with the same type of cancer ■ More than 100 patients in two study arms for randomized Phase II studies
Phase III	<ul style="list-style-type: none"> ■ To compare the new treatment or new use of an existing treatment with the current standard treatments ■ To obtain detailed information about how well the treatment works and types and severity of side effects it causes 	<ul style="list-style-type: none"> ■ From 100 to several thousand patients with the same type of cancer ■ Patients are randomly assigned to a treatment group; one group receives the standard therapy, and the other group receives the experimental treatment
Phase IV	<ul style="list-style-type: none"> ■ To find out more information about the long-term safety and efficacy of a new treatment after it has already been approved by the FDA and is being used by patients outside of a clinical trial 	<ul style="list-style-type: none"> ■ Several hundred to several thousand patients with the same type of cancer

Why Is a Placebo Sometimes Used in Phase III Trials?

A *placebo*, or sugar pill/capsule/tablet, is an inactive ingredient that is used as a comparator in some randomized clinical trials. The placebo is made to look and taste the same as the experimental pill/ capsule/tablet, or to have the same appearance as the experimental intravenous/subcutaneous agent, so that patients cannot tell whether they have been randomized to the control group receiving the placebo or the experimental group receiving the new treatment. In some trials, known as *double-blind studies*, the doctors, nurses, and physician assistants who come in direct contact with the patients also do not know who is receiving which type of treatment (although the investigators who are leading the trial have this information).

In clinical trials for cancer therapies, patients are never given a placebo in place of an effective standard therapy. In Phase III cancer trials that use a placebo, the placebo is given in addition to, not instead of, the standard treatment regimen. Clinical trials are never conducted in a way that would deny patients an effective therapy.

Should a Patient Participate in a Clinical Trial?

Clinical trials are not a “last resort” for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments for CLL/SLL must be tested this way before patients can use them in the future. Participating in a clinical trial can help to improve the treatment options for CLL/SLL patients for many years to come. Patients with all stages of CLL/SLL can participate in clinical trials, whether at the time of initial diagnosis or at relapse (disease returns after treatment).

Clinical trials offer both benefits and risks. Patients in clinical trials who are randomized to the experimental group may be able to benefit from a new treatment that is not otherwise available to all patients. However, this new treatment may or may not be more effective than the standard therapy. At the very least, patients who are randomized to the control group receive the standard therapy that they would have received if they had not enrolled in the trial. Another advantage of clinical trials is that the health of enrolled patients is monitored very closely. The healthcare team studying the new treatment can explain all of the possible benefits and risks of a specific clinical trial.

Every clinical trial is led by a principal investigator, who is usually a medical doctor. Clinical trials also have a research team that may include nurses, physician assistants, social workers, medical coordinators, and other healthcare professionals. Patients usually continue regular visits with their current healthcare provider, who may work with the research team to ensure that any investigational treatment does not interfere with current medication or treatments. Clinical trials are carefully supervised by safety monitoring boards, monitoring processes, internal and external audits, and other activities to ensure ongoing safety assessments.

What Is Informed Consent in a Clinical Trial?

Informed consent is a process in which patients learn about the clinical trials they are interested in joining. During this process, members of the clinical trial research team explain:

- The purpose of the study
- The factors used to decide if a patient is allowed to participate in the study
- The tests, procedures, and visits participants are expected to undergo
- The type of treatments provided in the study
- The possible risks, benefits, and alternatives
- The rights of patients to decide whether or not to participate and to leave the study at any time

The research team answers questions and provides written information about the trial. After the team explains all of the details and the patient does not have any more questions, the patient is asked to read and sign an informed consent document before entering the study that details all the trial information discussed, describes how their records are kept private, and confirms that the patient has been given information on the potential risks and benefits and the alternatives to enrolling in the trial. In addition, the healthcare provider also signs the same document.

It is important for patients to remember that even after signing the consent form, they can leave the study at any time. If the patient leaves the study or decides not to take part in the study, the patient's doctor can discuss

the other treatment options available. A list of questions patients might ask their doctor about clinical trials is provided below.

PATIENT TIP

Questions to Ask About a Clinical Trial

- What is the purpose of this clinical trial?
- Why are you recommending this clinical trial for me?
- Who is sponsoring this trial (the National Cancer Institute [NCI], a cancer center, an international study group, another state or national study group, or a pharmaceutical/biotechnology company)?
- Who has reviewed and approved this clinical trial?
- Does this clinical trial include the use of a placebo (no active ingredient/no intervention)?
- How long will the study last? Where will it take place?
- What are the risks involved?
- What are the possible benefits? If I benefit from the intervention, will I be allowed to continue receiving it after the trial ends?
- What are my responsibilities during the clinical trial?
- What kinds of additional tests, procedures, or treatments will be performed? How many and how often?
- Will I be in any discomfort or pain?
- Will I be able to see my own family doctor during the clinical trial?
- What type of long-term follow-up care is part of this trial?
- What costs will I be responsible for? Who will pay for my participation? Will I be reimbursed for other expenses?
- What happens if my health gets worse during the clinical trial?

What Is the Cost of Participating in a Clinical Trial?

Clinical trials are very expensive for the study sponsor, because of all of the monitoring and tests that may be required. However, the cost to the patient varies depending on the trial, who is sponsoring the trial, what

portion of the trial-related expenses the sponsor has agreed to cover, and the patient's health insurance coverage. Often, there are no additional costs to the patient. Patients should ask their doctor about the potential cost of participating in any clinical trial under consideration.

Patients should ask their doctor what clinical trials may be most appropriate for them. Here are some additional sources of helpful clinical trial information:

- LRF's Helpline at (800) 500-9976 or helpline@lymphoma.org whose *Clinical Trials Information Service* provides individualized searches to increase awareness about investigative treatments for CLL/SLL
- The NCI's Cancer Information Center at (888) NCI-1937 or the NCI's Clinical Trials Referral Office at (800) 4-CANCER
- The NIH websites at www.cancer.gov and www.clinicaltrials.gov
- Local cancer centers and institutions affiliated with universities

Chapter 11: Advances in Treatment of Patients With CLL/SLL

Doctors and scientists around the world are working hard to improve currently available treatment options and find better and safer drugs to treat patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Advances are being made in different areas including genetics, molecular biology, immunology, treatments, and supportive care. In particular, recent developments have provided a better understanding of the biology of the disease.

Drugs that are not yet approved by the U.S. Food and Drug Administration (FDA) are said to be investigational. Some of these investigational drugs are being studied in laboratory experiments. This phase is often referred to as the preclinical phase. The drugs in more advanced stages of research, usually due to continued evidence of effectiveness and relative patient tolerance, are being studied in patients in clinical trials; these are referred to as being in the clinical phase of development.

The most common way for a patient to receive an investigational drug is through a clinical trial. To learn more about getting access to investigational drugs, visit the National Cancer Institute's (NCI's) website at www.cancer.gov and search for "access to investigational drugs." Alternatively, visit www.clinicaltrials.gov to search for trials using a particular drug or to find clinical trials nearby.

Today's science on human malignancies, including lymphomas and leukemias, is moving very quickly. Patients should check with their doctor or the Lymphoma Research Foundation (LRF) Helpline *Clinical Trials Information Service* for additional information and recent updates.

For a detailed discussion of currently approved treatment options, please see the "Treatments for CLL/SLL" in Chapter 6.

Immunotherapy

CAR T-Cell Therapy

Researchers have treated patients with *refractory* (disease returns after treatment) CLL/SLL with genetically engineered T cells. T cells are removed from a patient and genetically modified to produce special receptors on their surface called *chimeric antigen receptors* (CARs), which allow the T cells to recognize and kill CLL/SLL cells. The genetically engineered CAR T cells are grown in the laboratory and then infused back into the patient.

Once in the body, the genetically modified cells can grow to large numbers and amplify the antitumor response, persisting for long time and providing ongoing tumor control and possible protection against recurrence. Lisocabtagene maraleucel (Breyanzi) is an example of CAR T cell therapy currently under study for CLL/SLL.

Some patients have had very good responses to CAR T-cell therapy, with no malignant tumor cells detected after treatment. However, this therapy has different types of potentially serious side effects such as *cytokine release syndrome* (a condition caused by a large, rapid release of cytokines into the blood from immune cells). Medicines are now available to suppress or alleviate many of these symptoms. Research is ongoing to continue to improve this novel therapy.

Monoclonal Antibodies

The success of the monoclonal antibody rituximab (Rituxan, an anti-CD20 antibody) directed at cancerous B cells inspired researchers to develop other monoclonal antibodies to treat patients with various types of CLL/SLL. This research led to FDA approval of the monoclonal antibodies alemtuzumab (Campath, an anti-CD52 antibody), obinutuzumab (Gazyva), and ofatumumab (Arzerra) for the treatment of patients with CLL/SLL. New combinations of these monoclonal antibodies and other novel medications are being investigated in clinical trials. Ublituximab (an anti-CD20 monoclonal antibody) and tafasitamab (an anti-CD19 monoclonal antibody) are currently being evaluated in clinical trials for patients with CLL. Other monoclonal antibodies in clinical trials include cirmtuzumab (UC-961), an antibody targeting receptor tyrosine kinase-like orphan receptor 1 (ROR1).

Checkpoint Inhibitors

A newer class of monoclonal antibodies called checkpoint inhibitors has been developed more recently. These agents help develop or enhance the immune system's capacity to kill CLL B cells. Two checkpoint inhibitors, nivolumab (Opdivo) and pembrolizumab (Keytruda), which are FDA-approved for the treatment of Hodgkin lymphoma, are currently being investigated in CLL/SLL clinical trials. Other checkpoint inhibitors, such as durvalumab (Imfinzi) and atezolizumab (Tecentriq), are also under investigation for the treatment of CLL/SLL.

Targeted Therapies

Several targeted therapies for CLL/SLL are being studied in laboratories and in clinical trials, including, umbralisib (Ukoniq), zanubrutinib (Brukinsa), both approved in therapy for some lymphomas, and zandelisib (ME-401). Since research in CLL/SLL advances quickly, patients should check with their doctor or LRF for additional information and updates.

Combination Therapies

Many treatment strategies testing new treatment combinations are currently in clinical trials for patients with newly diagnosed or previously treated CLL/SLL.

Chemotherapy

Researchers are trying to develop new chemotherapy drugs, improve existing drugs, and find better ways to combine different dosages and sequences of existing drugs. The goal is to develop treatment regimens that are better at eradicating CLL/SLL cells while leaving healthy cells alone, decreasing the chance of side effects. Researchers are also investigating the best way to use imaging techniques (for example, positron emission tomography [PET] or computed tomography [CT]) to evaluate responses to chemotherapy and to determine future doses.

Stem Cell Transplantation

Ongoing research in stem cell transplantation is focused on finding better ways to collect stem cells from the bone marrow or peripheral blood; reducing or eliminating graft-versus-host disease in *allogeneic* transplants (i.e., the donor is someone other than the patient); improving ways to remove all lymphoma/leukemia cells from stem cell samples used for autologous (self) transplants; and developing more effective regimens for reduced-intensity stem cell transplantations. For more information on transplantation, please view LRF's *Understanding the Stem Cell Transplantation Process: A Guide for Patients, Caregivers, and Loved Ones* booklet available at lymphoma.org/publications.

Vaccines

Vaccines are commonly used to help protect against viruses and other infections. In these cases, researchers are focused on developing vaccines to help treat, rather than prevent, lymphomas. The hope is that these vaccines might boost the immune system to recognize and kill lymphoma cells early during the course of the disease.

ABOUT THE LYMPHOMA RESEARCH FOUNDATION

The Lymphoma Research Foundation (LRF) is the largest lymphoma-specific non-profit organization in the United States; the Foundation's mission is to eradicate lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and serve those touched by this disease. Through a national education program, innovative research portfolio and numerous outreach and awareness opportunities, we remain dedicated to serving patients with lymphoma and CLL/SLL and to finding a cure.

Awareness and Outreach

LRF offers numerous opportunities for members of the lymphoma community to support one another and the Foundation's vital mission. Team LRF provides active and fun ways to become involved with the organization through a dynamic Fundraise Your Way program, signature Lymphoma Walks, the Research Ride and endurance marathon teams. The LRF Advocacy Program provides volunteer advocates with the resources necessary to raise support for those public policies most important to the lymphoma and CLL/SLL community. There are currently more than 5,000 LRF advocates in all 50 states and the District of Columbia. The Foundation also offers a number of engaging in-person events and virtual outreach initiatives every year.

Education Resources and Support Services

LRF provides a comprehensive series of expert programs and services for people with lymphoma and their caregivers, including: Clinical Trials Information Service; Publications focused on lymphoma subtypes and different treatment options; Financial Assistance Resources; In-Person Education Conferences; LRF Lymphoma Helpline; *Lymphoma Support Network*; Mobile App (lymphoma.org/mobileapp); Webinars; and Videos. All programs and materials are offered free of charge. Learn more at lymphoma.org.

Professional Education

LRF is committed to educating healthcare professionals on the latest developments in lymphoma and CLL/SLL diagnosis and treatment. The Foundation offers a wide range of lymphoma-focused continuing education activities for nurses, physicians, and social workers, including workshops, conference symposia, and webcasts. Our signature Lymphoma Rounds program is CME-accredited and provides a forum for healthcare professionals to meet regularly and address issues specific to the diagnosis and treatment of their lymphoma patients.

Research

LRF is focused on finding a cure for lymphoma and CLL/SLL through an aggressively funded research program. LRF supports early career investigators through the Clinical Investigator Career Development Awards, Lymphoma Postdoctoral Fellowship Grants and Lymphoma Scientific Research Mentoring Program (LSRMP), and senior investigators through several disease-specific research initiatives. These efforts are led by the Foundation's Scientific Advisory Board (SAB), comprised of 45 world-renowned lymphoma experts. The Foundation has awarded more than \$72 million in funding for lymphoma-specific research.

Contact Information

Helpline: (800) 500-9976
helpline@lymphoma.org

Website: lymphoma.org



***Focus on Lymphoma* Mobile App**

The Lymphoma Research Foundation's mobile app, *Focus on Lymphoma*, provides access to lymphoma information and health care tools right at your fingertips.

This first of a kind app changes how patients and their caregivers manage a diagnosis with lymphoma. The app contains three main components—Learn, Track, and Connect—in order to provide comprehensive and helpful content.

Visit lymphoma.org/mobileapp for additional information or visit the App Store or Google Play to download the *Focus on Lymphoma* mobile app today.

Understanding CLL/SLL

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

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