

Understanding **CLL/SLL**

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma



A Guide for Patients,
Survivors, and
Loved Ones

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October 2016

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.

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ABBREVIATIONS

ABMS	American Board of Medical Specialists	CBC	complete blood count
ACA	Affordable Care Act	CLL	chronic lymphocytic leukemia
AFib	atrial fibrillation	CMV	cytomegalovirus
AML	acute myeloid leukemia	CNS	central nervous system
ANC	absolute neutrophil count	CPR	cardiopulmonary resuscitation
app	application	CR	complete remission
ASCO	American Society of Clinical Oncology	CSF	cerebrospinal fluid
ASH	American Society of Hematology	CT	computed tomography
Bcl2	B-cell lymphoma 2	del	deletion
BTK	Bruton tyrosine kinase	DNA	deoxyribonucleic acid; genetic material
CAR	chimeric antigen receptor	DNR	do not resuscitate

FCR	fludarabine, cyclophosphamide, and rituximab	MUGA	multigated acquisition scan
FDA	U.S. Food and Drug Administration	NCI	National Cancer Institute
FISH	fluorescence in situ hybridization	NHL	non-Hodgkin lymphoma
FL	follicular lymphoma	NIH	National Institutes of Health
FNA	fine needle aspiration	NK	natural killer cell
GVHD	graft-versus-host disease	PCR	polymerase chain reaction
GVT	graft-versus-tumor effect	PET	positron emission tomography
HBV	hepatitis B virus	PI3K	phosphoinositide 3-kinase
HL	Hodgkin lymphoma	PICC	peripherally inserted central catheter
IgG	immunoglobulin G	PML	progressive multifocal leukoencephalopathy
<i>IGHV</i>	immunoglobulin heavy chain variable region gene	PR	partial remission
IHC	immunohistochemistry	PS	performance status
IRB	institutional review board	SEER	Surveillance, Epidemiology, and End Results
IV	intravenous	SLL	small lymphocytic lymphoma
LRF	Lymphoma Research Foundation	TLS	tumor lysis syndrome
MDS	myelodysplastic syndromes		
MR	minor response		
MRI	magnetic resonance imaging		

INTRODUCTION

The purpose of this booklet is to assist patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) patients and their caregivers to become active participants in healthcare decisions. CLL and SLL are forms of slow-growing cancers of the white blood cells called lymphocytes. Chapters in this book address different issues faced by patients with CLL/SLL, including what to expect after diagnosis, work-up, and treatment; how to cope with treatment side effects; and what questions to ask their doctors and other healthcare providers. In addition to this booklet, information is available online at the Lymphoma Research Foundation's website at www.lymphoma.org, and the Foundation's CLL-specific website at www.FocusOnCLL.org. The Helpline can also provide additional information and copies of LRF educational and support publications. For Helpline assistance, call (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 names for a cancer that affects the same 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. Lymphocytes travel in the bloodstream and in another network of 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 viruses or bacterial infections.

Historically, when small lymphocytic lymphoma cells were found mostly in a patient's blood, the disease was called CLL; when small lymphocytic lymphoma cells were found primarily in the lymph nodes, the disease was called SLL. However, CLL and SLL are highly similar, and both typically also involve the bone marrow. In fact, CLL and SLL are really the same disease. Sometimes patients with SLL can develop a rising white blood cell count in the blood (or leukemia), and patients with CLL invariably have CLL cells also in the lymph nodes. In addition, most cases of SLL become CLL over time. Today, CLL and SLL are grouped together, acknowledging that the malignant lymphocytes found in the bone marrow, blood, and lymph nodes are considered the same disease.

This chapter explains these and other terms that will help you understand CLL and SLL and how they affect a person's health. A better understanding of the disease may help patients take a more active role in their treatment.

What Is Cancer?

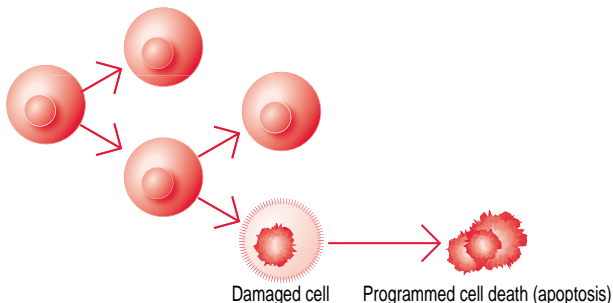
The body is made up of many different types of specialized cells that are organized into tissues and organs to perform all the different tasks needed to sustain life. To keep the body running smoothly, cells in the body grow, work, and divide in a very controlled fashion.

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 (deoxyribonucleic acid, abbreviated DNA) of a cell gives it the ability to override this self-destruct mechanism and to continue to live and grow, making the cell “immortal” in many ways. This means that the cells that would normally be unable to divide and grow continue to grow indefinitely. Unless the body’s immune system gets rid of these abnormal cells, they can become cancerous.

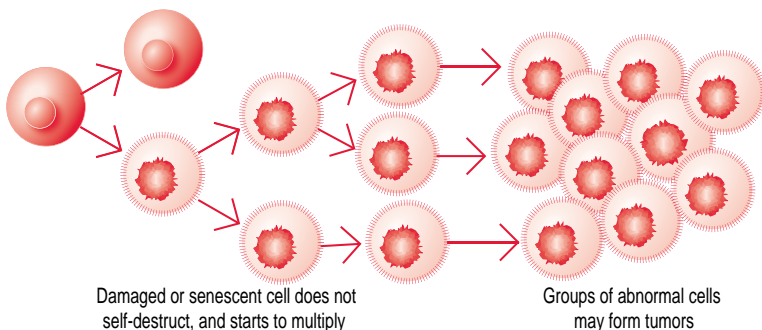
Cancer, or malignancy, is a disease whereby abnormal cells gain the ability to divide uncontrollably and without stopping. When these cells accumulate, they can form a mass called a *tumor*, which can then interfere with normal organ function.

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. For example:

- A cancer that started in the pancreas is called *pancreatic cancer*.
- A cancer of the lymphocytes is called a *lymphoma* or *lymphocytic leukemia* depending on whether the cancer resides only in tissues/ lymph nodes (lymphoma) or also in the blood (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 sweep up the carbon dioxide waste produced by cells and bring it to the lungs to be exhaled. A low number of red blood cells causes *anemia*. A person with anemia may feel tired, weak, and short of breath.
- 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:
 - Lymphocytes — These are discussed on Page 7.
 - Granulocytes — There are three types of granulocytes (neutrophils, basophils, and eosinophils). Neutrophils help fight off 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 and in fighting infections due to parasites. Eosinophils also help fight infections and can become plentiful in allergic reactions.
 - Monocytes — These also play an important role in immunity.
- Platelets (or *thrombocytes*) — These 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.

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 an even 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 any kind of blood cell. Hematopoietic stem cells are found mainly in the *bone marrow* (the spongy, fatty material inside large bones such as the pelvis, vertebrae, and ribs). Healthy bone marrow produces blood stem cells that change and divide, becoming either a “myeloid” stem cell (myeloblast or precursor myeloid cells) or a “lymphoid” stem cell (lymphoblast or precursor or lymphocytes).

What Are Lymphocytes?

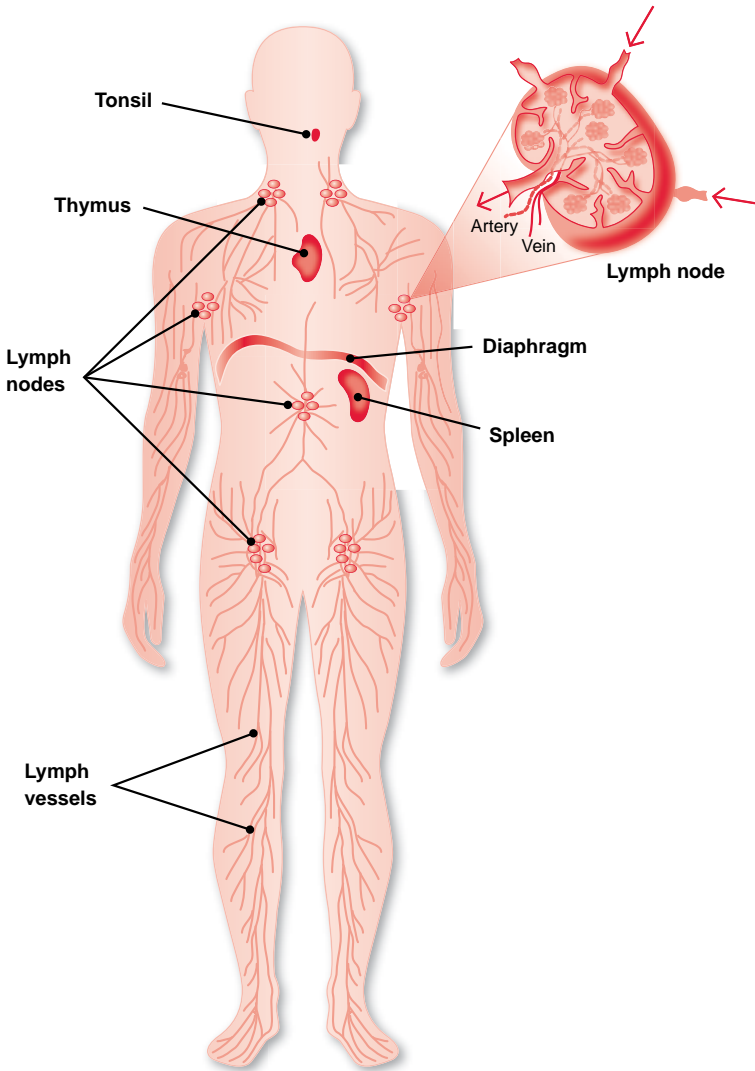
Lymphocytes are one type of white blood cell. There are three main types of lymphocytes:

- 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. Later, similar cells were found in humans.
- T lymphocytes (T cells) — There are many types of T cells. Some help B cells make antibodies, some attack and kill infected cells, and others help control 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 also make chemicals called cytokines that help the body get rid of viruses and tumor cells.

What Is the Lymphatic System?

As shown in the image on the following page, the *lymphatic system* is a circulatory system that is made up of a spidery network of thin tubes called *lymph vessels* or *lymphatic vessels*. Similar to blood vessels, lymph vessels branch out into all tissues of the body. While people can clearly see blood vessels, especially at their wrists and on the top of their hands, most lymph vessels are invisible to the naked eye. However, there is one larger vessel of the lymphatic system called the *thoracic duct*.

THE LYMPHATIC SYSTEM



Lymph vessels carry *lymph*, a type of 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.” Thousands of lymph nodes are found at locations throughout the body, including the neck, underarms, elbows,

and groin. Lymphocytes can mostly be found in lymph nodes, where they monitor the body and its immune system for signs of infection. The lymph nodes can change in size, becoming bigger or smaller depending on the number of lymphocytes inside them.

Lymph fluid flows through lymph nodes and specialized lymph tissues such as the spleen, tonsils, bone marrow, and thymus gland. Lymph nodes filter the lymph fluid, removing bacteria, viruses, and other foreign substances from the body. The liquid in lymph vessels often drains into the thoracic duct.

If a large number of foreign substances are filtered through a node or series of nodes, swelling may occur and the nodes may become tender to the touch. Most swollen nodes are a reaction to infection and are not cancerous. Lymph cells can also multiply (and lymph nodes can become enlarged) in states of inflammation, such as autoimmune diseases like rheumatoid arthritis.

How Does the Immune System Work?

The immune system is the body's defense against things that might harm it. 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 immunity** — This is provided by natural barriers in the body, substances in the blood, and specific types of cells that attack and kill foreign cells that invade the body. Examples of natural barriers include skin, mucous membranes (in the nose, mouth, eyelids, windpipe, lungs, stomach, intestine, and bladder), stomach acid, and the cough reflex. These barriers keep germs and other harmful things from entering the body. *Inflammation* (redness and swelling) is also a type of innate immunity. Blood cells that are also part of the innate immune system include neutrophils, macrophages, eosinophils, and basophils, among others.

- Adaptive immunity — This type is provided by the thymus gland, spleen, tonsils, bone marrow, circulatory system, and lymphatic system. These systems work together to make, store, and move specialized cells (such as B cells and T cells) and molecules (such as antibodies) that recognize specific identifying parts (*antigens*) of invading organisms, ridding the body of viruses, bacteria, or parasites that have these antigens. For the immune system to destroy foreign invaders, it has to be able to recognize what things are part of the body (“self”) and what things are not part of the body (“non-self”). In other words, the immune system has to recognize what is foreign and what is not. Through a complicated process, the body’s adaptive immune system can “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 be even stronger. Vaccinations prevent disease by turning on the adaptive immune response before the body is exposed to a disease, ensuring it is prepared to recognize and fight the disease.

What Is Lymphoma?

A *lymphoma* is a type of cancer that affects lymphocytes. There are two major categories of lymphomas: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Both of these major categories of lymphoma are further subdivided into many different types, which are different in the way they develop and spread and how affected patients are treated. The particular type of lymphoma a patient has may need its own plan of treatment. Unlike other cancers, therapy and prognosis are not based solely on the stage at which the disease is diagnosed but is rather determined by the lymphoma subtype in addition to a variety of other factors (age, other medical issues, etc.).

What Is Non-Hodgkin Lymphoma?

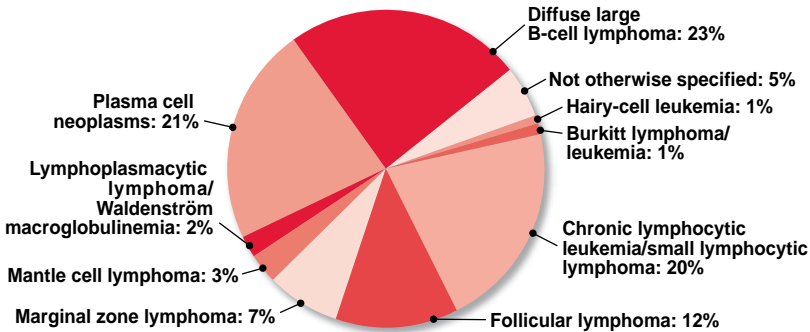
In the United States, NHL (which includes CLL/SLL) is the fifth most common type of cancer affecting adults. NHL is not a single disease but rather a group of several closely related cancers that occur in lymphocytes. The World Health Organization estimates that there are more than 60 subtypes of NHL. While these various subtypes 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 patients should be treated
- Likely outcome with treatment (curable vs. not)

NHL is categorized into the following two major groups:

- B-cell lymphomas — These develop from abnormal B lymphocytes and are the most common, representing about 92 percent of all patients diagnosed with NHL.
 - CLL and SLL are in the family of B-cell lymphocyte malignancies. About 20 percent of patients with a B-cell lymphocyte malignancy have CLL or SLL.
- T/NK-cell lymphomas — These develop from abnormal T lymphocytes or NK cells, are less common, and account for about 6 percent of patients with an NHL diagnosis.

RELATIVE PREVALENCE OF B-CELL LYMPHOMAS



Percentages are based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data, 2004-2013. Some very rare types are not shown in the graph.

In addition, NHL types are often grouped according to how quickly they grow:

- **Indolent** (also called *low-grade*) lymphomas usually grow slowly and tend to initially cause few symptoms. While indolent lymphomas are generally not curable (similar in some ways to diabetes, which is not curable but manageable), patients can live a long time with these types of lymphomas, because they may respond well to treatment and remain in *remission* (disappearance of disease signs and symptoms) for many years, even decades. Over time, some indolent lymphomas may “transform” or develop into aggressive lymphomas.
- **Aggressive** lymphomas grow and spread more quickly than indolent lymphomas. However, patients with 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 a patient.

What Is CLL/SLL?

Until the 1990s, doctors believed that CLL and SLL were two different diseases, so patients were diagnosed with either CLL or SLL. However, research has shown that CLL and SLL are essentially the same disease, but they are called different names depending on where the malignant lymphocytes are found in the body. If the malignant lymphocytes are found mainly in lymph nodes, the disease is called SLL. If the malignant lymphocytes are found in the bloodstream and cause the blood lymphocyte count to be elevated, then the disease is called CLL. The malignant lymphocytes of both SLL and CLL can often be found in the lymph nodes, spleen, and bone marrow. Over time, a patient with *relapsed* (disease returns after treatment) CLL may have 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.

Since patients with CLL and SLL receive the same treatments, the rest of this booklet will use the term CLL/SLL, unless a distinction needs to be made between the two conditions.

CLL/SLL causes signs and symptoms in four ways. The overgrowth of malignant lymphocytes takes up space in the blood, bone marrow, and other organs that is needed for normal cells to function, resulting in loss of the normal blood cells. CLL/SLL also inhibits the normal function of the immune system, especially the production of antibodies, increasing a patient's risk of infection. Patients with CLL/SLL may also have increased autoimmunity, which occurs when a person's own immune cells attack their normal, healthy cells. Autoimmunity can cause *anemia* (low red blood cell levels) or *thrombocytopenia* (low platelet levels). Finally, CLL/SLL may sometimes cause *fatigue* (tiredness) and/or "B symptoms." These symptoms include fever and chills, night sweats, and weight loss. Because of the way CLL/SLL behaves, doctors consider it to be a type of chronic disease, meaning that it may remain inactive or *quiescent* over an extended period or may worsen over time. This is different from acute disease, in which symptoms appear and change or worsen

rapidly. Over time, CLL/SLL may occasionally progress to a more aggressive type of lymphoma called Richter syndrome.

According to the National Cancer Institute's SEER data, approximately 19,000 people in the United States are diagnosed with CLL/SLL each year. An average person has a three in 500 (0.6 percent) lifetime risk of developing CLL/SLL. This disease is rare in people younger than 40 years. The average age at diagnosis is 71.

What Causes CLL/SLL?

The exact cause of CLL/SLL is not known. Like other types of indolent lymphoma, CLL/SLL develops over a long period of 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 reproduce 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. 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.

Also, like their healthy siblings, 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.

Why Do People Develop CLL/SLL?

The characteristics that make a person possibly more susceptible to developing any type of disease are called *risk factors*.

Having one or more risk factors for CLL/SLL does not mean a person will 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 connection between these risk factors and the development of CLL/SLL.

Known risk factors for CLL/SLL include:

- Having a first-degree relative (parent, sibling, or child) with CLL/SLL
- Being exposed to Agent Orange (an herbicide used during the Vietnam war) and long-term exposure to some pesticides used in farming
- Ancestry – CLL/SLL is more common in North America and Europe and is less common in Asia

Like other types of cancer, CLL/SLL cannot be caused by injury and cannot be caught from someone who has the disease.

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 or not a person has the disease.

A *sign* is anything unusual that doctors or nurses notice when they examine a patient.

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

What Are the Signs and Symptoms of CLL/SLL?

Some patients with CLL/SLL do not have any obvious symptoms of the disease. Their doctors might detect the disease during routine blood tests and/or a physical examination. For others, the disease is detected when symptoms occur and the patient goes to the doctor because he or she is worried, uncomfortable, or does not feel well.

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

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

Symptoms	Possible Reason
Shortness of breath, <i>fatigue</i> (tiredness), and pale skin	A shortage of the oxygen-carrying red blood cells (<i>anemia</i>)
Increased susceptibility to infections	A shortage of different types of healthy white blood cells. Depending on the type of white blood cell affected, this condition is called <i>leukopenia</i> , <i>neutropenia</i> , or <i>granulocytopenia</i>
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>); these blood cells help prevent and control bleeding, and promote blood clotting
Swollen, tender abdomen ("belly" or "stomach")	Enlarged lymph nodes in the abdomen, liver, and/or spleen that may press on the stomach, making a person feel full after eating only a small amount of food
"B symptoms" including fever and/or chills for no known reason, unexplained weight loss, and drenching night sweats that soak clothing and sheets	Increased levels of inflammatory chemicals in the blood
Enlarged lymph nodes in the neck, underarms, and/or groin	Lymph nodes or "glands" swell when the lymphocytes inside them sense that something is wrong, like an infection, or because of an increased number of lymphocytes

Having one or more of these symptoms does not mean that a person has CLL/SLL. Infections or other conditions (including other cancers) may also cause these symptoms.

When Should a Patient Seek Medical Attention?

Anyone who has an enlarged lymph node that does not go away 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 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. 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?

There are no specific tests that doctors can use to routinely screen patients for CLL/SLL.

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

- Ask details about symptoms—including duration, frequency, and intensity—and in particular about any pain the patient is experiencing
- 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 see if there is swelling or fluid in the chest and/or abdomen that may be caused by swollen lymph nodes

- Examine the abdomen to see if the liver and/or spleen are enlarged and 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 signs they have uncovered during the examination, he or she will order other tests that can confirm the diagnosis.

These tests should include a complete blood count (CBC) and may also include specific laboratory tests, imaging tests (including scans), and a bone marrow evaluation. Biopsies from lymph nodes may be needed for patients with SLL. Doctors do not 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 Chapter 3.

Part 1 — Learning the Basics

Chapter 3: Receiving a Diagnosis

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

How Is CLL/SLL Diagnosed?

Most cases of CLL/SLL are diagnosed on the basis of abnormal blood tests 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
- Hematopathology of blood smears and sometimes of a bone marrow biopsy
- Immunophenotyping by flow cytometry of lymphocytes in the blood
- Histopathology of a lymph node biopsy (needed for SLL diagnosis, but not usually for CLL unless 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 for the initial diagnosis and work-up before treatment begins, during the course of treatment, and during the follow-up period. Before patients agree to a procedure, they should make sure that they understand the reasons for the procedure and what will be involved.

Questions to Ask Before Having a Diagnostic Procedure

- 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 doing this procedure?
- What are the possible risks, complications, and side effects?
- Where will I have the procedure done?
- 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 for me to recover from the procedure?
- Should anyone else be present during the procedure?
- Will I need someone to take me home afterward?
- When will I get the results?
- When will we discuss the results?
- Will my insurance cover the procedure?
- What will be my out-of-pocket costs?
- If I will be receiving a dye, are my kidneys healthy enough to handle it?
- If I'm allergic to seafood or a dye, can I have this procedure?

To help determine the most effective treatment, the doctor might also order one or more additional genetic tests such as:

- *Fluorescence in situ hybridization* (FISH) or cytogenetics to look for changes at the genetic level in specific regions of the chromosomes. This important test should be done before any therapy
- Molecular analysis to check on the mutation status of the immunoglobulin heavy chain variable region (*IGHV*) gene
- Flow cytometry or immunohistochemistry to determine expression of specific proteins
- Sequencing of the *TP53* gene to see if it contains *mutations* (changes)

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 so that a *pathologist* (doctor who specializes in disease diagnosis) can examine it using a number of tests to establish a diagnosis. The information provided by this tissue sample is crucial to correctly diagnose the disease and decide on the best course of treatment.

Table 3.1 shows the four main types of biopsies used, when necessary, for the diagnosis of patients with CLL/SLL and other types of lymphoma.

Table 3.1. The Four Main Types of Biopsies

Bone Marrow Aspiration

- This procedure involves the removal of bone marrow, blood, and a small piece of bone via the insertion of a hollow needle into the hip bone or breast bone.
- While bone marrow evaluation is often necessary for diagnosis, the diagnosis of CLL/SLL can sometimes be accomplished without it.

Table 3.1. The Four Main Types of Biopsies (*continued*)

Excisional or Incisional Biopsy	<ul style="list-style-type: none"> ■ This type of biopsy is generally considered the best to establish an initial diagnosis of lymphoma, because it allows the removal of larger samples than other biopsy procedures do. The larger the sample, the more tissue the pathologist can examine, which improves the accuracy of the diagnosis. ■ A 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 is close to the skin surface, the procedure can be done under 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.
Core Needle Biopsy	<ul style="list-style-type: none"> ■ This procedure is used when the lymph nodes are deep in the chest or abdomen or in other locations that are difficult to reach with excisional biopsy, or when there are medical reasons for avoiding an excisional or incisional biopsy. ■ A large needle is inserted into a lymph node suspected to be cancerous, and a small tissue sample is withdrawn using a syringe attached to the needle. ■ A needle biopsy can be done under local anesthesia, and stitches are usually not required. ■ Sometimes the material collected may not be adequate for diagnosis and a subsequent excisional or incisional biopsy may be necessary. ■ Often the core needle biopsy will be directed by an imaging test, such as an ultrasound, computed tomography (CT) scan, or positron emission tomography (PET) scan.
Fine Needle Aspiration (FNA) Biopsy	<ul style="list-style-type: none"> ■ As its name implies, this procedure is performed with a very thin needle (smaller than that used for a core needle biopsy). ■ Because of the small needle size, the sample will only contain scattered cells, without preserving how the cells are actually arranged in the lymph node. Therefore, this test cannot provide enough information for an initial diagnosis. ■ An FNA biopsy is most often used to check for return of the disease (<i>relapse</i>) after treatment.

After a tissue sample has been removed, a pathologist examines it and develops a report. An *oncologist* (doctor specialized in treating patients with cancer) or *hematologist* (doctor specialized in treating patients with blood disorders including blood cancers) then uses this report, along with 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 a *hematopathologist* (a specialist in the identification of blood diseases), since an accurate diagnosis is essential.

What Is a Complete Blood Count With Differential?

For a complete blood count (CBC) with differential, samples of blood are examined to find out the following:

- The number of red blood cells
- The amount of *hemoglobin* (the oxygen-carrying protein) in red blood cells
- The number of total white blood cells and the different subtypes of white blood cells (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)
- The number of platelets

The results from the CBC with differential will help the doctor in determining a diagnosis of CLL/SLL. 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 find out how well the treatment is working against the cancer and to assess the impact of therapy on normal cells.

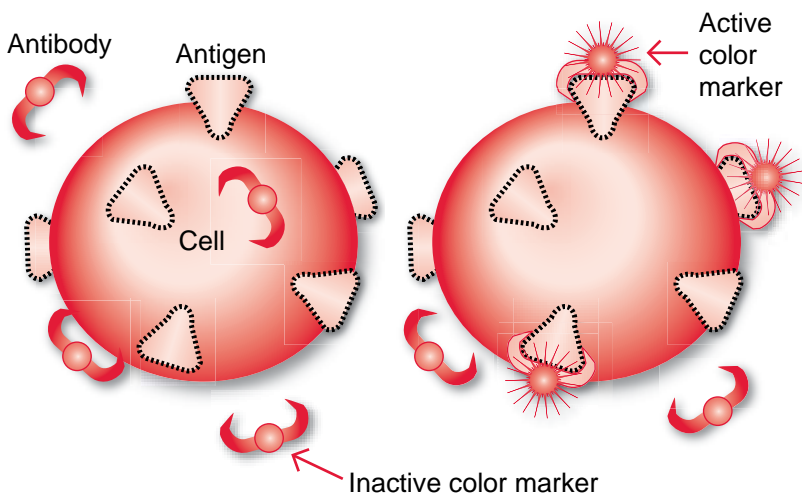
What Is Hematopathology?

Hematopathology is the study of blood, lymph node, and bone marrow samples to identify disease. Hematopathologists are doctors who specialize in the diagnosis of blood diseases. These specialists identify the cancer cells by looking at their shape and size, by studying how they are grouped in samples from lymph nodes and the bone marrow, and by conducting special tests, such as flow cytometry, immunohistochemistry, or cytogenetics (see sections labeled “What Is Immunophenotyping?” and “What Is Cytogenetic Analysis?”).

What Is Immunophenotyping?

Immunophenotyping is a process used to distinguish between different types of cells (e.g., between normal lymphocytes and lymphoma/leukemia cells) by detecting small identifying substances, called cell “markers” or *antigens*, expressed in or on the cells. These antigens are detected using special antibodies, which lock onto the antigens like a lock and key. The antibodies are made and chemically modified in the laboratory so they will show color or emit light when they stick to their corresponding markers.

IMMUNOPHENOTYPING



Upon binding to specific antigens inside the cells or on the cell surface, the antibodies can be detected by chemicals. The markers may appear as different colors and can be studied under a microscope using immunohistochemistry analysis. Alternatively, a fluorescent molecule can be attached to the antibody so that it can be made to emit light when it binds to the antibody, allowing the cells to be sorted and counted using a process called flow cytometry. Sometimes, both immunohistochemistry and flow cytometry are necessary for accurate immunophenotyping (see Table 3.2).

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 different antigens found in different types of lymphoma cells. ■ The cell-antibody mixture is injected into an instrument called a flow cytometer. This machine uses laser beams to sense the different colors the cells emit from the different antibodies attached to them. This information is measured and analyzed by a computer and interpreted by a doctor. ■ The results from the flow cytometry analysis will distinguish between different types of lymphoma, other cancers, and some other diseases.
Immunohistochemistry (IHC)	<ul style="list-style-type: none"> ■ Thin slices of the biopsy sample (or thin layers of fluid or blood) are placed on slides and treated with sets of antibodies that recognize different markers found in different types of lymphoma cells and normal lymphocytes. ■ The pathologist examines the slides under a microscope to look for the visible color change that happens when the antibody sticks to the marker. ■ The pathologist identifies and counts the number of cells that change color (meaning that they are positive for the marker) with each of the different antibodies and uses that information to identify the specific type of lymphoma.

What Is Cytogenetic Analysis?

Chromosomes contain genes that comprise long strands of deoxyribonucleic acid (DNA). Healthy human cells have 23 pairs of chromosomes. Chromosomes are divided into two regions called “arms,” which are called *p* (short arm) and *q* (long arm). Some lymphomas and other types of cancer have too few chromosomes or have chromosomes with an abnormal structure. Most commonly, chromosome pieces are misconnected, leading to activation of tumor growth signals.

In cytogenetic analysis, chromosomes from cancer cells are examined under a microscope to check for changes in their number (too few or too many) or the presence of other abnormalities. It usually takes two to three weeks to obtain the results from cytogenetic testing, because a sufficient number of cancer cells must be grown in the laboratory to get enough genetic material for the analysis.

The results of the cytogenetic analysis can help distinguish between CLL/SLL and other types of non-Hodgkin lymphoma (NHL).

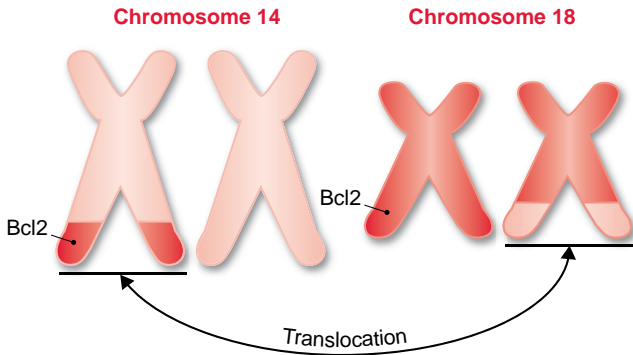
What Are Types of Chromosome Abnormalities?

Translocation

One type of chromosomal abnormality found in some NHL types is called a *translocation*, which occurs when part of the chromosome breaks off from its normal location and becomes attached to another chromosome, as shown in the figure below (an example of a translocation that occurs in follicular lymphoma patients). This helps to differentiate CLL/SLL (in which translocation is much less common) from a subtype of NHL called mantle cell lymphoma, which always carries a particular translocation.

TRANSLOCATION

Two different chromosomes exchange portions of their genetic material

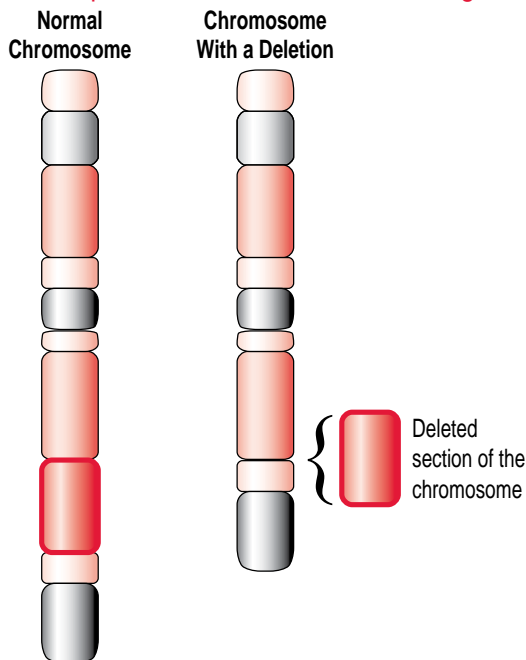


Deletion

Another type of chromosomal abnormality 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 would be written as del(11q), del(13q), and del(17p) on a patient’s chart. The cytogenetic analysis of the malignant lymphoma cells can also change over time. For example, some patients’ malignant cells might develop 17p deletions over time. The cytogenetic test looks for very specific changes in only a few places on a few chromosomes. When no abnormalities are seen, the result is called “normal,” but other chromosomal abnormalities may be present but are not seen because they were not tested for.

DELETION

A piece of a chromosome is missing



Trisomy

Another type of chromosomal abnormality in CLL/SLL is *trisomy*, which indicates the presence of an extra copy of a chromosome. The figure below shows the chromosomes as they look during a phase of the cell cycle called metaphase, which occurs just before the cell divides. In metaphase chromosomes, the DNA of the chromosomes is tightly packaged or condensed and two pairs of chromosomes are joined together. Sometimes in cell division a mistake can occur resulting in the extra chromosome (trisomy).



What Is the Purpose of Other Genetic Tests?

Doctors may order other genetic tests to confirm the results of cytogenetic tests or find out more detailed information about the types of damage to the genetic information of the lymphoma cells in the patient's body. The two main types of genetic tests used are shown in Table 3.3. These genetic tests are important for learning more about an individual's particular disease and what treatments may be most effective for them.

Table 3.3. Other Types of Genetic Tests

Fluorescence In Situ Hybridization (FISH)	<ul style="list-style-type: none">■ FISH uses fluorescent chemicals to specifically attach to certain parts of chromosomes to show the presence of translocations and other large abnormalities.■ FISH can be done on blood, lymph node, or bone marrow samples, and the test results are usually available within a few days (quicker than cytogenetic testing).
Polymerase Chain Reaction (PCR)	<ul style="list-style-type: none">■ PCR is a test that can detect changes in DNA that are too small to be seen under a microscope.■ PCR tests can be done on a very small quantity of lymphoma cells, and it usually takes about a week to get the results.

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

Chromosome or Gene Mutations	Prevalence in Patients With CLL/SLL	Possible Impact on Patient Outcomes
12+ or trisomy 12	10% to 20%	Undetermined impact on outcomes
Del(11q23)	5% to 20%	Poor outcomes may be overcome by chemoimmunotherapy
Del(13q14)	51% to 62%	Good outcomes if this is the only cytogenetic change
Del(17p)	3% to 7% of untreated patients	Poor outcomes; resistant to FC/FCR chemotherapy

Del means deletion of some of the genetic material. The numbers in parentheses (e.g., 11q23) indicate the chromosome and the area on the chromosome where the deletion is located. FC/FCR, which stands for fludarabine (Fludara) plus cyclophosphamide (Clafen, Cytoxan, Neosar) with or without rituximab (Rituxan), is a type of treatment.

PATIENT TIP

Cautions About Interpreting Diagnostic Reports

Some patients like to review their written reports. When doing so, it is important for the patient to carefully review the findings with their doctor. The following are points to keep in mind when reviewing a pathology report:

- Some tests can be reported as “normal” even though CLL/SLL may be present.
- Some tests 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 tests, such as imaging studies or scans, can be lengthy and difficult in some situations.
- Follow-up tests such as additional biopsies may be needed to determine the significance of previous results or to clarify the results.

Part 1 — Learning the Basics

Chapter 4: Work-Up Before Treatment Can Begin

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. Some of these work-up studies are needed to see if and how much the disease has spread to other parts of the body. Doctors will use these test results to determine the state of advancement, or *stage*, of a patient's disease. Other tests, such as quantitative immunoglobulin G (IgG) and uric acid, will check how the disease has affected a patient's overall health and major organ functions.

Together, all of these tests will provide the information needed to help patients and their doctors decide on the best course of treatment. This chapter will help you understand how CLL/SLL is staged, the reason for these tests, how these tests work, and what to expect. Patients should speak with their doctor to better understand why he or she ordered a particular test.

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, and many of these tests may also be repeated during the course of treatment:

- Physical examination with special attention to the size of the lymph nodes, liver, and spleen
- Determination of general health status (also called *performance status*) to see how well a patient feels and how well he or she can carry out normal daily activities (such as getting washed and dressed, going to work, and doing chores); this topic is discussed in additional detail in Chapter 5

- Determination of the presence or absence of *fatigue* (tiredness) and of fever, night sweats, and weight loss; these latter symptoms are called “B symptoms.” (Many patients do not experience these symptoms.)
- Complete blood count (CBC) with differential and platelets
- Comprehensive metabolic panel
- Testing for signs of infection with hepatitis viruses or other viruses

Other tests that might be useful for some patients include:

- Quantitative IgG to make sure that there are enough antibodies to fight infections (people with CLL/SLL often have low levels of immunoglobulins)
- Reticulocyte count (to help determine if the bone marrow is producing enough red blood cells), haptoglobin (to see how fast red blood cells are being destroyed), and direct Coombs test (to see if there are antibodies against the body’s own red blood cells)
- Neck, chest, abdominal, and pelvic computed tomography (CT) scans
- Blood tests for beta-2 microglobulin (can indicate a more advanced stage of CLL/SLL), serum lactate dehydrogenase (which is found in high levels in the blood of many patients with fast-growing tumors), and uric acid
- Bone marrow biopsy and/or aspiration

Positron emission tomography (PET) is not usually helpful in evaluating patients with CLL/SLL, unless the physician suspects that the disease might be changing into a *fast-growing* (aggressive) type of lymphoma called Richter transformation.

What Is a Comprehensive Metabolic Panel?

A comprehensive metabolic panel measures the amount of different chemicals in the blood that will show if the CLL/SLL is affecting any of the main organs. The comprehensive metabolic panel usually includes specific tests that measure liver and kidney function, electrolyte balance, acid/base balance, and the levels of blood sugar and different blood proteins. Calcium, magnesium, potassium, and sodium are some of the electrolytes found in the body; abnormal levels of electrolytes can make a patient sick.

The results from these tests will help patients and their doctors decide between different types of treatments. Many of these blood tests will be repeated during the course of treatment to check if and how the treatment and the cancer are affecting body functions.

What Types of Imaging Tests May Be Used?

The diagnosis of CLL/SLL does not require any imaging studies. A doctor determines by palpation (pressing on the outside of the body) during the physical examination if lymph nodes, spleen, and liver are enlarged. Imaging studies should only be ordered when a doctor has a specific question. Most imaging tests are painless and require no anesthetic. The imaging procedures described in Table 4.1 may be needed to more thoroughly evaluate the extent of disease.

Table 4.1. Types of Imaging Tests

Computed Tomography (CT) Scan

- A CT scan takes X-rays 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.
- Patients with CLL/SLL often have CT scans of the neck, chest, abdomen, and pelvis to find out how many lymph nodes are involved, how large they are, and whether 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 injection of a contrast dye that will more clearly outline abnormal areas that may be present in the body.

Table 4.1. Types of Imaging Tests (*continued*)

Magnetic Resonance Imaging (MRI)	<ul style="list-style-type: none"> ■ Like a CT scan, an MRI takes images from different angles around the body, but an MRI does not use radiation (X-rays) like a CT scan; instead, it uses magnets and radiofrequency waves. ■ An MRI can provide important information about tissues and organs, particularly the nervous system, which is not available from other imaging techniques. ■ Because this testing technique works 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 lymphoma has spread to these areas.
Positron Emission Tomography (PET) Scan	<ul style="list-style-type: none"> ■ A PET scan evaluates NHL activity in all parts of the body. A PET scan is not usually recommended for patients with CLL/SLL, but it might be used if doctors suspect that the disease has developed into a more aggressive form. ■ Radioactive fluorodeoxyglucose (a type of sugar) is injected into the body. A positron camera is then used to detect the radioactivity and produce cross-sectional images of the body. ■ PET scans help distinguish active tumors from scar tissue and may be used to assess a patient's response to treatment. ■ While CT scans show the size of a lymph node, PET scans show if the lymph node is active (still has disease).
PET/CT Scan	<ul style="list-style-type: none"> ■ PET scans and CT scans can be combined into a single test called a PET/CT scan. A PET/CT machine produces a single image that shows both the structure and the function of affected lymph nodes. ■ PET/CT scans are rarely needed for the initial diagnosis of CLL/SLL. ■ For assessing response to treatment, CT scans with a contrast dye tend to be more effective than PET/CT scans at detecting CLL/SLL remaining in the body.
X-ray	<ul style="list-style-type: none"> ■ X-rays use radiation to take pictures of areas inside the body. The amount of radiation used in most diagnostic tests is so small that it poses little risk to the patient.

Why Might Another Type of Biopsy Be Needed?

Once the diagnosis is made, the doctor may order other types of biopsies for additional pathology studies and other tests to see if and how the disease has spread to other parts of the body (see Table 4.2). These additional tests are not usually necessary for patients with CLL/SLL.

Table 4.2. Other Types of Biopsies

Bone Marrow Aspiration and Biopsy	<ul style="list-style-type: none">■ This procedure may be done to determine if CLL/SLL has spread to the bone marrow.■ Bone marrow is the soft, spongy material found inside our bones. CLL/SLL and other NHLs can spread to the bone marrow or start in the bone marrow.■ For the aspiration part of this procedure, the doctor cleans and numbs the skin over the hip and inserts a thin, hollow needle into the bone. The doctor uses a syringe to remove a small amount of liquid from the bone marrow. Even with the numbing local anesthetic, this procedure can briefly cause pain when the marrow is withdrawn.■ For the biopsy part of this procedure (which is usually done right after the aspiration), the doctor inserts a slightly larger needle to take out a small piece of bone and marrow. This procedure can also briefly cause pain.■ Patients who are anxious about the test should talk with their doctor and nurse to see whether taking a calming medication before the procedure would be helpful.
Lumbar Puncture (Spinal Tap)	<ul style="list-style-type: none">■ This procedure is used to determine if the lymphoma has spread to the cerebrospinal fluid (CSF), the liquid found in the brain and spinal cord. Most types of indolent NHL like CLL/SLL do not spread to the CSF.■ The doctor will order this test only for patients with certain types of lymphoma or those who have symptoms suggesting that the disease has reached the brain.■ The doctor inserts a thin needle into the lower back after the area has been numbed with a local anesthetic. A small needle is used to remove a sample of fluid that will be sent to a laboratory for analysis.

Table 4.2. Other Types of Biopsies (*continued*)

Pleural or Peritoneal Fluid Sampling	<ul style="list-style-type: none"> ■ This procedure is used to find out if the lymphoma has spread to the chest or abdomen, where it can cause liquid to accumulate. ■ The doctor numbs the skin with a local anesthetic, inserts a small needle, and uses a syringe to remove a sample of the liquid for laboratory analysis. ■ The liquid is called <i>pleural fluid</i> when found inside the chest and <i>peritoneal fluid</i> when found inside the abdomen.
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How Is CLL/SLL Staged?

Staging is used to describe how widely the cancer has spread in patients with CLL/SLL. Because of how blood and bone marrow are involved in CLL, these staging systems are different from those used for other types of NHL, including SLL. 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 4.3), while the Binet system (Table 4.4; on the next page) is more popular in Europe.

Table 4.3. The Rai Staging System for CLL

Stage	Description	Risk Group
0	<ul style="list-style-type: none"> ■ Blood <i>lymphocytosis</i> (increased lymphocytes). No <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 and anemia (hemoglobin less than 11 grams per deciliter) 	High
IV	<ul style="list-style-type: none"> ■ Blood lymphocytosis and thrombocytopenia (platelets less than 100,000 per microliter) 	High

Table 4.4. The Binet Classification System for CLL

Stage	Description	Match-Up With Rai Stages
A	Less than three* enlarged areas (lymph nodes or spleen and liver) without low hemoglobin (<i>anemia</i>) and low platelet count (<i>thrombocytopenia</i>)	Rai stages 0, I, and II
B	Three* or more areas of lymph node involvement without anemia and thrombocytopenia	Rai stages I and II
C	Anemia and/or thrombocytopenia, along with any number of enlarged areas	Rai stages III and IV

*There are five possible palpably enlarged areas: lymph nodes (cervical, axillary, and inguinal), spleen, and liver.

Part 2 — Treatment of CLL/SLL

Chapter 5: What to Know Before Starting Treatment

Receiving a cancer diagnosis can be an overwhelming experience. It is perfectly understandable to be shocked by the news, to become anxious about the future, and to feel confused about the medical information and decisions that need to be made. This chapter will help patients and caregivers prepare for the start of treatment by explaining the next steps and providing tips for talking with a patient's doctor about any questions or concerns.

PATIENT TIP

First Steps to Take After Receiving a Diagnosis

- Seek a second opinion to confirm the diagnosis.
- Take care of yourself (eat, sleep, rest, and exercise).
- Seek the support of family, friends, and others whom you trust and rely on.
- Learn about the disease and treatment options.
- Find medical care that meets your needs.
- Research the cost of care, what your insurance will cover, and what financial assistance programs may be available to you.
- Maintain a copy of your medical records (paperwork, test results, your own notes).
- Ask your physician or healthcare provider to help you prepare a *Lymphoma Care Plan*, available on the Lymphoma Research Foundation's (LRF's) website at www.lymphoma.org/publications.

Who Will Plan and Carry Out the Treatment?

Treatment is usually overseen by a medical oncologist or hematologist. It is important for all patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) to identify hematologists or medical oncologists who specialize in the treatment of patients with lymphoma or leukemia. A doctor may suggest a

second opinion from an oncologist or hematologist who specializes in CLL/SLL and/or possible participation in a clinical trial.

The healthcare team may also include other healthcare professionals such as an oncology nurse, nurse practitioner, physician assistant, social worker, and registered dietitian. The healthcare team will work together and consult with the patient to plan, carry out, and monitor the treatment and plan the patient's cancer care.

How to Find an Oncologist and Treatment Center

A patient's primary care doctor will probably make a referral to a specialist—likely a medical oncologist, hematologist, or hematologic 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.

Before agreeing to treatment by a specific doctor and treatment center, make sure that they will be able to meet all of the patient's medical and personal needs. Patients and caregivers should feel comfortable with the healthcare team and the quality of care they provide. The following questions can be used to help patients select the best medical team.

- What are the credentials of the doctor, the other members of the medical team, and the hospital or cancer center?
- How much experience does the doctor and treatment center have in treating patients with non-Hodgkin lymphoma (NHL), and CLL/SLL in particular?
- How many patients with this disease are being treated here 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?
- What arrangements are made for medical assistance after hours and on weekends, in case of an emergency?

- Is the patient's 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 the patient sees other specialists (cardiologist, endocrinologist, etc.), will the center coordinate the patient's cancer care with the 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 with their first consultation visit. They should talk with other patients and caregivers about their experiences and ask them if they would recommend their doctor and healthcare team. Also, patients and caregivers who are not satisfied should share their concerns with their primary doctor and ask for a referral to a different doctor.

What Is a Prognosis?

Prognosis is the medical term that doctors use for predicting how the disease will progress and the likelihood for recovery, which is often one of the first things that patients ask their doctor. A prognosis is usually based on information gathered from hundreds or thousands of other patients who have had the same disease. This statistical information provides doctors with a general idea of what to expect when a patient is diagnosed with CLL/SLL, and it also gives guidance on the kinds of treatments that have been most successful in treating this disease.

Keep in mind that no two patients are alike and that statistics from large groups of people cannot accurately predict what will happen to a specific individual patient. The doctor most familiar with the patient's situation is in the best position to help interpret these statistics and understand if and how they may apply to a patient's particular situation.

What Are Prognostic Factors?

The characteristics that help predict a person's prognosis are called *prognostic factors*. Favorable prognostic factors tend to be associated with a better outcome, while adverse prognostic factors tend to be associated with a worse outcome. Prognostic factors provide information about expected responses to treatment, including progression-free survival and the probability of transformation to a more aggressive type of cancer. Prognostic factors are different for different therapies.

Table 5.1. Known Prognostic Factors for CLL/SLL

Favorable Prognostic Factors	Adverse Prognostic Factors
<ul style="list-style-type: none"> ■ Limited replacement of normal bone marrow by lymphoma cells (non-diffuse bone marrow involvement) ■ Deletion of part of chromosome 13 and no other chromosome abnormalities ■ CLL/SLL cells with <i>mutated</i> (changed) gene for <i>IGHV</i> (immunoglobulin heavy chain variable) ■ Less than 20% of CLL/SLL cells have ZAP-70 ■ Less than 30% of CLL/SLL cells have CD38 	<ul style="list-style-type: none"> ■ Widespread replacement of normal bone marrow by lymphoma cells (diffuse bone marrow involvement) ■ Advanced age ■ Male sex ■ Deletions in parts of chromosomes 17 (del[17p]) or 11 (del[11q]) ■ CLL/SLL cells with a normal (not mutated, also called wild type) gene for <i>IGHV</i> ■ High blood levels of beta-2 microglobulin ■ Lymphocyte doubling time shorter than 6 months ■ Larger proportion of an early form of lymphocytes (prolymphocytes) in the blood ■ Greater than 20% of CLL/SLL cells have ZAP-70 ■ Greater than 30% of CLL/SLL cells have CD38

What Is Performance Status?

Performance status (PS) is a numerical way to describe a patient's general health, presence or absence of chronic health problems, and ability to carry out normal daily activities (such as getting washed and dressed, going to work, and doing chores). As shown in Table 5.2, which depicts the Eastern Cooperative Oncology Group PS scale, PS is graded on a 0 to 4 scale, with the lower numbers indicating a better PS. Doctors do not generally use PS values unless the patient is part of a clinical study. Many clinical studies of new agents restrict participation to the more physically fit patients (those with lower PS grades).

Table 5.2. The Eastern Cooperative Oncology Group PS Scale

Grade	Description
0	Fully active; 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 house work) or do things that can be done while sitting (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 bed or chair for more than half of awake hours
4	Completely disabled. Cannot take care of oneself. Completely confined to bed or chair

How to Decide What Treatment Is Best

Many patients with CLL/SLL do not need to be treated when they are first diagnosed. If the patient's doctor decides it is time to begin treatment, there are many effective treatment options for patients with CLL/SLL. To identify what treatments may work best, doctors consider the following factors:

- The stage (see "How is CLL/SLL Staged?" on Page 37)
- A patient's prognostic factors (see Table 5.1 on Page 42)
- The presence or absence of symptoms caused by CLL/SLL

- A patient's overall health, age, and performance status (see Table 5.2 on Page 43)
- A patient's preferences and goals for treatment
- Whether the treatment is the first the patient has received or if the disease has *relapsed* (returned after prior therapy)
- Availability of a clinical trial

A doctor will discuss the risks, benefits, and side effects associated with the different treatment choices applicable to the patient's particular situation. Patients and caregivers should share questions and concerns with the doctor so that together they can decide which option is best. The following questions can be used to guide the conversation and help make an informed decision.

Questions to Ask Before Treatment Begins

PATIENT TIP

- 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 how might they impact my prognosis?
- What are my treatment choices? Which do you recommend for me and why? Will the recommended treatment disqualify me from any other treatment options I may need if I relapse or are *refractory* (disease does not respond to treatment) to this current treatment?"
- What is a clinical trial? Are clinical trials available that are studying new treatments? Would a clinical trial be appropriate for me? How would I benefit?
- 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 have to see if it is working? How often will I need to be tested?
- What are the short-term risks and possible side effects of each treatment? Can these side effects be prevented or controlled?

Questions to Ask Before Treatment Begins

(continued)

- What are the long-term 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 before and during treatment?
- Are there any late or long-term side effects that I should be aware of? Will treatment impact my ability to have children?
- How long will each treatment session last? How long will the entire treatment process last?
- What are the chances that the treatment will be successful?
- How will the treatment affect my normal activities (for example, work, school, childcare, driving, sexual activity, exercise)?
- Is there anything my caregiver needs to do to prepare while I undergo treatment?
- Will I be able to drive or take public transportation after my treatment?
- Should I take care of other medical or dental issues before I start treatment?
- Do I need radiation?
- How often will I need a checkup?
- How much will the treatment cost? Will my insurance cover it?

When to Get a Second Opinion

Before starting any type of treatment, a patient may consider getting a second opinion—especially if some characteristics of the diagnosis are complicated or uncertain. The purpose of the second opinion is not to question the doctor's expertise, but to make sure that the suggested treatment plan is reasonable and optimal for the patient's particular case and to learn about additional alternative treatments, including those offered in clinical trials (see Part 5 for more information).

Most doctors will be supportive and helpful if patients tell them that they would like to get a second opinion. It is important to remember that the only person to be concerned about is the patient. Do not worry about “hurting the doctor’s feelings.” Physicians understand the importance of second opinions. Patients should ask the doctor if it would be okay to briefly delay the start of treatment to provide the time needed to get a second opinion. Keep in mind that some insurance programs require second opinions; others may provide coverage for the cost of a second opinion if a patient or doctor requests it.

When getting a second opinion, patients might want to consider the tips outlined below and on the following page.

Getting a Second Opinion

PATIENT TIP

- Some hematologists/oncologists who have an expertise in CLL/SLL, especially those associated with medical schools or cancer centers, may provide a consultation and be willing to work together with a local 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. Try to find a pathologist with a lot of experience diagnosing patients with lymphoma.
- To get a second opinion, you will have to provide the consulting doctor a complete copy of all medical records, original X-rays, pathology materials, scans, and reports. When you set up the appointment, ask their office for a list of all the materials they will need. It may be useful to keep your own copy of all these records in case you have questions or concerns later on.

Getting a Second Opinion *(continued)*

To identify lymphoma specialists to contact for a second opinion:

- Ask your current doctors, family members, other patients, friends, and coworkers. Also, speak to your primary care doctor/ internist, who will have an important perspective on the quality of care and demeanor of each physician, so that you can select the one who might be the best fit for you.
- 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 LRF's websites at www.lymphoma.org or www.FocusOnCLL.org, or contact the LRF Helpline at (800) 500-9976 or email (helpline@lymphoma.org) to discuss resources and referrals.
- 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) website at www.hematology.org/patients to search for hematologists with an interest in lymphoma.
- Visit the National Cancer Institute (NCI) at <https://www.cancer.gov/research/nci-role/cancer-centers/find> to identify the nearest NCI-designated cancer center, and call (800-4-CANCER or 800-422-6237) or visit their website to find out about their lymphoma specialists.
- Visit the American Board of Medical Specialists (ABMS) Certification Matters website at www.ABMS.org to find out if doctors are board certified in a particular specialty.

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. Open communication with the healthcare team can help patients and caregivers better learn about what the prescribed treatment regimen is, how it works, what tests are involved, and what side effects and complications may be associated with it.

A good first step is to write down all questions that come to mind. Before meeting with a doctor or nurse, for the first time or for follow-up visits, consider organizing questions to bring to the visit. The two or three most important questions should be put at the top of the list, since time with doctors or nurses may be limited. However, make sure that a member of the medical team reads all of the questions, because they may see some that are more important than the patient realizes.

Patients should consider having a family member or close friend accompany them to the doctor's office or clinic. A companion could help by asking additional questions, remembering answers, and taking notes during the visit. Some patients use LRF's *Focus On Lymphoma* mobile application (app) to record sessions; visit www.FocusOnLymphoma.org to download this free mobile app from the App Store or Google Play. Patients should ask the doctor or nurse for permission before recording any conversations.

Most oncology nurses 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 also available to assist with practical and emotional needs from the time diagnosis is received and onward.

Although family members are often very concerned about their loved one and want information concerning his or her care, confidentiality rules prohibit doctors from giving out information to anyone without the patient's expressed permission. For efficiency, designate one family member as the family contact. The patient must remember to

specifically tell the doctor the identity of the primary family contact. Most importantly, patients should have the names and addresses of all physicians involved in their care so the hematologist/oncologist will be able to communicate with them regularly.

Open communication between patients and their healthcare team is paramount. You should feel comfortable with the doctor and healthcare team. The following tips can help improve those discussions.

Communicating With Your Doctors

At home

- 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 which symptoms need to be communicated immediately to them and which can wait for your next visit.
- Make a list of questions that you want to ask your doctor. However, if the questions are urgent, do not wait for the next visit; call the doctor's office to discuss your concerns.
- Review patient portals for contacting your healthcare team. They may provide secure email contacts and educational materials, and they may allow patients to check benefits and coverage, schedule non-urgent appointments, and order prescription refills. Confirm that they have safeguards in place to protect patient privacy.
- Download the free *Focus On Lymphoma* mobile app from LRF to help you plan appointments, keep track of medications and blood work, track symptoms, and document treatment side effects (www.FocusOnLymphoma.org).

Communicating With Your Doctors *(continued)*

At your next doctor's visit

- Bring your symptom journal and list of questions, and discuss them with your doctor or nurse.
- 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 for weekend support and how you can reach them.
- Inquire whether members of your healthcare team communicate electronically (by email, patient portals, etc.).
- 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.

How to Be a Self-Advocate

Being a self-advocate and an active participant in healthcare decisions can be a positive experience and may help restore a sense of control that may have been lost following the diagnosis. Patients and caregivers should remember that they are partners in their treatment plan. Many patients feel better when they actively participate in their own care. Ask questions, learn about options, and work closely with the doctor.

It is important to be comfortable with the doctors and the approach that 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 there is a feeling that the team is not a good match, patients should ask for a referral to a different healthcare team.

Questions will likely vary depending on the purpose of the meeting with the doctor (such as the initial visit to discuss the diagnosis or a routine visit to monitor a remission). Patients should inquire about the scheduling of office visits, treatments, and tests. The doctor can help explain what the tests will look for and define the possible responses and options for further care depending on treatment response.

Although each person 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, ask the oncologist, hematologist, oncology nurse, or the oncology social worker about any support groups in the area.

Before agreeing to any tests, patients should continue to check with the healthcare team to determine which costs are covered by insurance and which are not. It's important that the patient not be afraid to talk to the healthcare team about nonmedical issues, such as transportation, finances, insurance, working through treatment or taking time off, and childcare. The tips on the following page offer some self-advocacy strategies for patients.

Self-Advocacy

- Do not be afraid to ask your doctor or nurses questions about your care.
- Learn more about CLL/SLL by asking your doctor for information and visiting reliable websites, such as the Lymphoma Research Foundation at www.lymphoma.org or www.FocusOnCLL.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, a nationwide buddy program that matches patients and caregivers with people who have had similar experiences. For information about the program, call (800) 500-9976 or email support@lymphoma.org.

Part 2 — Treatment of CLL/SLL

Chapter 6: Treatments for CLL/SLL

In this chapter, you will learn about the most common therapies that are currently used in the treatment of patients with 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 book went to print. Read Chapter 11 to learn more about new agents under investigation.

Cancer refers to a large group of very complicated diseases. There are many different ways for a cell to become abnormal enough to cause cancer. Because of this, the path taken by a healthy liver cell to become a malignant liver cell can be quite different from the path taken by a lymphocyte to become lymphoma or leukemia. This is why a treatment that works against one type of cancer may not necessarily work against another.

There are also small but important differences in the cancer cells found in different patients diagnosed with the same type of cancer. 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 five general types of treatments for patients with CLL/SLL:

- Watchful waiting (no treatment given) in which the patient is closely monitored to see if/when treatment should be started. This is usually the first treatment approach taken with patients.

- Medications, which includes one or more of the following types of agents:
 - Chemotherapy, which affects general cell growth and division
 - Immunotherapy, which uses parts of the immune system to specifically attack cancer cells
 - Targeted therapy, which targets specific enzymes and proteins
- Radiation therapy
- *Splenectomy* (surgical removal of the spleen)
- *Allogeneic stem cell transplantation* (donor)

These types of therapy are described in detail throughout this chapter.

What Is Watchful Waiting?

About one-third of patients with CLL/SLL never need treatment for their disease. With the *watchful waiting* (also known as *observation* or *active surveillance*) approach, patients do not receive any anti-lymphoma treatments, but their health and disease are monitored through regular checkup visits and follow-up evaluation. These patients continue to remain untreated as long as they do not develop symptoms or show any signs of their disease becoming active.

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

- Development of worsening *anemia* (low levels of red blood cells; Rai stage III) or *thrombocytopenia* (low platelet levels; Rai stage IV)
- Development of large bulky lymph nodes
- Development of significant *splenomegaly* (enlarged spleen)
- Development of B symptoms (fever and chills, drenching night sweats, and weight loss)
- A doubling of the lymphocyte count over six months
- Severe *fatigue* (tiredness)

This approach may be started after the initial diagnosis or after initial treatment. Active treatment is started if the patient begins to develop disease-related symptoms or if there are signs that the disease is progressing.

Though doctors recommend watchful waiting for selected patients with *indolent* (slow-growing) CLL/SLL, it is not a treatment option for patients with *aggressive* (fast-growing) or advanced CLL/SLL.

Questions to Ask Before Starting Watchful Waiting

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

What Medications Are Used for CLL/SLL?

The list on Page 56 shows the medication regimens most often used to treat people with CLL/SLL. Many of these regimens combine chemotherapy medications with *monoclonal antibodies* such as rituximab (Rituxan, abbreviated by the letter “R”), ofatumumab (Arzerra), or obinutuzumab (Gazyva). All medications have two names, a brand name (capitalized) and a generic name (lower case). When medications are no longer patented, multiple companies can manufacture the same medication (indicated by the generic name), but often under different brand names. Regimens that combine both chemotherapy agents and monoclonal antibodies are called *chemoimmunotherapy*.

This list is subject to change as new approvals are made by the FDA.

Table 6.1. Common Regimens for CLL/SLL

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)
B	Bendamustine (Treanda)
BR	Bendamustine (Treanda) Rituximab (Rituxan)
2CDA	Cladribine (Leustatin)
C	Cyclophosphamide (Clafen, Cytoxan, Neosar)
ChI	Chlorambucil (Leukeran)
CyPred-R	Cyclophosphamide (Clafen, Cytoxan, Neosar) Prednisone (Deltasone) Rituximab (Rituxan)
D	Dexamethasone (Decadron, Dexasone)
F	Fludarabine (Fludara)
FR	Fludarabine (Fludara) Rituximab (Rituxan)
FCR	Fludarabine (Fludara) Cyclophosphamide (Clafen, Cytoxan, Neosar) Rituximab (Rituxan)
HDMP-R	High-dose methylprednisolone (Depo-Medrol, Medlone 21, Medrol, Meprozone, Metrocort, Metypred, Solu-Medrol, Summicort) Rituximab (Rituxan)
Ibrutinib alone	Ibrutinib (Imbruvica)
Idelalisib plus rituximab	Idelalisib (Zydelig) Rituximab (Rituxan)
Obinutuzumab plus chlorambucil	Obinutuzumab (Gazyva) Chlorambucil (Leukeran)
OFAR	Oxaliplatin (Eloxatin) Fludarabine (Fludara) Cytarabine (Cytosar-U, Tarabine PFS) Rituximab (Rituxan)

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

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)
Ofatumumab alone	Ofatumumab (Arzerra)
Ofatumumab plus chlorambucil	Ofatumumab (Arzerra) Chlorambucil (Leukeran)
PCR	Pentostatin (Nipent) Cyclophosphamide (Clafen, Cytoxan, Neosar) Rituximab (Rituxan)
R	Rituximab (Rituxan)
RChI	Rituximab (Rituxan) Chlorambucil (Leukeran)
RCHOP	Rituximab (Rituxan) Cyclophosphamide (Clafen, Cytoxan, Neosar) Doxorubicin/hydroxydaunorubicin (Adriamycin, Rubex) Vincristine (Oncovin, Vincasar PFS) Prednisone (Deltasone)
Venetoclax	Venetoclax (Venclexta)

Chemotherapy

Chemotherapy agents work against general characteristics of cancer cells such as their tendency to grow and multiply very quickly. Depending on the agent, patients may have to swallow a pill or receive a liquid infused directly into a vein (*intravenous infusion* or *IV*). Bendamustine (Treanda), chlorambucil (Leukeran), cyclophosphamide (Clafen, Cytoxan, Neosar), cytarabine (Cytosar-U, Tarabine PFS), and fludarabine (Fludara) are some of the chemotherapy agents used to treat patients with CLL/SLL.

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

Immunotherapy

Immunotherapy uses parts of the immune system to help the body fight cancer. The only type of immunotherapies that are FDA-approved to treat patients with CLL/SLL are monoclonal antibodies. Other kinds of immunotherapies used to treat patients with other cancers include adoptive cell transfer, genetically engineered T cells (see Chapter 11), cytokines, and treatment vaccines (also called therapeutic vaccines).

As part of our immune system, specialized white blood cells (plasma cells) make proteins called *antibodies*. Antibodies help fight infection by recognizing and binding to bacteria, viruses, or other foreign substances to kill or neutralize them. Each antibody our body makes is naturally designed to recognize one specific type of molecule.

Monoclonal antibodies are molecules engineered in the laboratory. They are designed to recognize and stick to a specific target (called an *antigen*). For example, by selecting a target on the surface of cancer cells, it is possible for the antibodies to attack only the cancer cells, leaving normal cells alone. When a monoclonal antibody attaches itself to a cancer cell, it can stop or slow down its growth or it can make it easier for the immune system to recognize and kill it.

Monoclonal antibody therapies are given to patients as IV infusions or *subcutaneous* (under the skin) injections during visits at the doctor's office or clinic. Once injected in the patient, the monoclonal antibodies travel through the blood and stick to the cells that have the antigen they recognize. Most of these will be CLL/SLL cells. Once they stick, the antibodies trigger an alarm that draws cells from the immune system to help destroy and kill the tumor cells.

The monoclonal antibodies rituximab (Rituxan), obinutuzumab (Gazyva), and ofatumumab (Arzerra) are being used to treat patients with CLL/SLL. A fourth monoclonal antibody, alemtuzumab (Campath), is no longer commercially available, although it is available to patients with CLL/SLL who are still benefitting from this medication through a special distribution program. Rituximab, obinutuzumab, and ofatumumab recognize the CD20 antigen, a molecule found on the

surface of almost all B cells. CD20 is also found on the surface of malignant lymphocytes in CLL/SLL, which are B cells.

To prevent serious allergic reactions, patients are given oral antihistamines (e.g., Benadryl), acetaminophen (Tylenol), and sometimes steroids before the antibody infusion. All patients should be tested for active hepatitis before starting any treatment for CLL/SLL. To avoid life-threatening infections, patients being treated with monoclonal antibodies should not be vaccinated with live attenuated virus vaccines, such as those for *shingles* (herpes zoster), yellow fever, and the Sabin vaccine for polio. The sections that follow provide additional information about a few monoclonal antibodies.

Rituximab (Rituxan)

In 1997, rituximab (Rituxan) became the first monoclonal antibody approved by the FDA for the treatment of patients with cancer—specifically for patients with relapsed or refractory low-grade or follicular, B-cell non-Hodgkin lymphoma (NHL). In 2016, the FDA approved rituximab for the treatment of patients with the following:

- NHL
- CLL/SLL
- Rheumatoid arthritis, Wegener granulomatosis, and microscopic polyangiitis

Rituximab (Rituxan) is used in various combinations with chemotherapy agents or other monoclonal antibodies (see Table 6.1). Rituximab treatment is given as an IV infusion usually once every 28 days, but the schedule varies depending on the type of combination regimen used. Rituximab is usually given during the first day of each chemotherapy cycle.

The most common side effects caused by rituximab (Rituxan) include infusion reactions, fever, *lymphopenia* (low number of lymphocytes), *neutropenia* (low number of white blood cells), chills, infection, and *asthenia* (feeling weak).

Rarer, more serious side effects (some of which have caused death) include severe allergic reactions (usually during the first infusion), severe skin and mouth reactions (painful sores, ulcers, blisters on skin, lips, or mouth, peeling skin, rash, and pustules [small pus-filled bumps on the skin]), reactivation of hepatitis, progressive multifocal leukoencephalopathy (PML; a rare but serious neurologic disease), bowel stoppage and bowel injuries, and *tumor lysis syndrome* (TLS; a condition in which fast-growing cells break apart and release their contents into the blood; see Page 91).

Rituximab (Rituxan) treatment can make a person more susceptible to infection during and for up to six months after treatment. Because of this, rituximab is not recommended for use in patients with severe, active infections.

Obinutuzumab (Gazyva)

In 2013, the FDA approved obinutuzumab (Gazyva) for the treatment of patients with previously untreated CLL/SLL when given together with the oral chemotherapy agent chlorambucil (Leukeran).

Obinutuzumab also has an FDA-approved indication for patients with follicular lymphoma.

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.

The most common side effects caused by obinutuzumab (Gazyva) include infusion reactions, *neutropenia* (low number of neutrophils), thrombocytopenia, anemia, fever, cough, and muscle and joint pain. Serious side effects include severe allergic reactions (usually to the first infusion), and rarely reactivation of hepatitis B virus (HBV) that can lead to liver failure. Another rare but serious side effect of obinutuzumab is TLS (Page 91).

Ofatumumab (Arzerra)

In 2009, the FDA approved ofatumumab (Arzerra) for the treatment of patients with CLL/SLL that has not responded to previous therapy with the chemotherapy agent fludarabine (Fludara) and the monoclonal antibody alemtuzumab (Campath; no longer commercially available). Ofatumumab is sometimes used as *monotherapy* (alone, not in combination with other medications) for patients with relapsed or refractory CLL/SLL. In 2014, ofatumumab was also approved in combination with chlorambucil (Leukeran) for the treatment of newly diagnosed patients with CLL/SLL for whom fludarabine-based therapy is not considered appropriate. In 2016, the FDA approved ofatumumab for the extended treatment of patients who are in complete or partial responses after at least two lines of therapy for recurrent or progressive CLL/SLL.

When given as a monotherapy, ofatumumab (Arzerra) is administered as an IV infusion once a week for eight weeks and then once every four weeks for four more doses. When given in combination with chlorambucil (Leukeran), it is administered on the first and eighth day of treatment during the first cycle, then on the first day of each 28-day cycle. When given for extended treatment, ofatumumab is administered as an IV infusion once a week for two weeks, once on week seven, and then every eight weeks for up to two years.

The most common side effects caused by ofatumumab (Arzerra) include neutropenia, thrombocytopenia, anemia, pneumonia, fever, cough, diarrhea, fatigue, difficulty breathing, rash, nausea, bronchitis, and infections. Rare but serious side effects include severe allergic reactions (usually to the first infusion), reactivation of HBV that can lead to liver failure, and the potentially deadly brain disorder progressive multifocal leukoencephalopathy (PML). Another rare but serious side effect of ofatumumab is TLS (Page 91).

Targeted Therapy

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 medications. Most of the recently discovered molecules help control the growth and survival of leukemia cells. The agents that target these molecules are broadly called *targeted therapies*, because they attack cancer cells in a more specific way than chemotherapy agents. Targeted therapies may kill the lymphoma or leukemia cells, or they may slow down or stop their growth. Another important way targeted therapies differ from chemotherapy is that they are typically given on a continuous basis, until the cancer develops resistance to the treatment or the patient develops problems tolerating the medication.

Most of the targeted therapies used in the treatment of lymphoma, leukemia, and other cancers are called *tyrosine kinase inhibitors* (or more broadly, *small-molecule enzyme inhibitors*). Tyrosine kinases are specialized proteins found inside cells that conduct signals from the cell surface to the interior of the cell. These signals play key roles in determining how cells behave. The specificity of this subgroup of targeted therapies relies on the tyrosine kinase only being present in and responsible for the growth and survival of particular lymphoma or leukemia cells; these cells are therefore sensitive to inhibition of the kinase.

As of the publication of this booklet, ibrutinib (Imbruvica), idelalisib (Zydelig), and venetoclax (Venclexta) are the only targeted therapies the FDA has approved for the treatment of patients with CLL/SLL. Additional information about ibrutinib, idelalisib, and venetoclax is provided on the next few pages. These medications are also called oral targeted therapies because they are taken by mouth. For more information on oral agents, please view the *Oral Agents in Lymphoma* fact sheet on the Lymphoma Research Foundation's (LRF's) website at www.lymphoma.org.

Ibrutinib (Imbruvica)

Ibrutinib (Imbruvica) blocks a tyrosine kinase called Bruton tyrosine kinase (BTK). BTK normally helps B cells grow and form blood in tissues, especially the lymph nodes; it also does this in CLL/SLL cells. Consequently, by blocking the function of BTK, ibrutinib helps stop or slow down the growth of CLL/SLL cells.

Ibrutinib (Imbruvica) is FDA-approved as monotherapy for the treatment of patients with previously treated CLL/SLL or CLL/SLL with a 17p deletion. In March 2016, the FDA approved ibrutinib for the initial treatment of patients with CLL/SLL. This latest approval for CLL was based on results from a clinical study that showed better progression-free survival and anticancer response with ibrutinib compared with chlorambucil. Ibrutinib is also indicated for the treatment of patients with previously treated mantle cell lymphoma and Waldenström macroglobulinemia, two other types of B-cell lymphomas.

Ibrutinib (Imbruvica) comes in capsules that must be swallowed whole with water at about the same time once a day, every day. Ibrutinib is dosed on a continuous basis until a patient's disease becomes resistant to it or the patient has a problem taking the medication. Patients should not open, break, or chew the capsules. During the course of treatment with ibrutinib, patients should not eat or drink grapefruit products or Seville oranges, as these substances interfere with the breakdown of ibrutinib. With oral therapies, it is very important for patients to consistently take their medications and follow the cautions and prescribing information as discussed with their doctor. Poor adherence can interfere with the medication's effectiveness.

Some of the most common side effects caused by ibrutinib (Imbruvica) are decreased neutrophils and platelets, diarrhea, and muscle and bone pain (see Chapter 7).

Rarer, more serious side effects (some of which have caused death) include internal bleeding (in the brain or intestines), infections, *atrial*

fibrillation (AFib; irregular and rapid heartbeat), *hypertension* (high blood pressure), secondary cancers (such as skin cancer), and TLS (on Page 91).

Idelalisib (Zydelig)

Idelalisib (Zydelig) inhibits the delta isoform (type) of the enzyme phosphoinositide 3-kinase (PI3K). PI3K is present in every cell in the body. Idelalisib's specificity for CLL and lymphoma cells comes from the delta isoform only being present in cells of the immune system. The other PI3K isoforms (alpha, beta, and gamma) are present in all body cells. Like BTK, the main job of PI3K-delta is to transmit signals that help B cells grow, move, divide, and survive. By inhibiting the signal from PI3K-delta, idelalisib helps stop or slow down the growth of CLL/SLL cells.

In July 2014, idelalisib (Zydelig) was approved by the FDA to be used in combination with rituximab (Rituxan) for the treatment of patients with CLL that has *relapsed* (returned after treatment) for whom treatment with single-agent rituximab would be considered due to other comorbidities, and to be used as monotherapy for the treatment of patients with SLL or follicular lymphoma (FL; another B-cell NHL) who have relapsed after at least two prior therapies. The approval for CLL was based on results from a clinical study that showed improved survival and anticancer response when idelalisib was given together with rituximab compared with rituximab alone. The approvals for SLL and FL were based on results from clinical studies that showed improved anticancer responses with this medication. In March 2016, the manufacturer issued a warning for healthcare providers stating that idelalisib should not be used for the initial treatment of patients with CLL/SLL and indolent NHL.

Idelalisib (Zydelig) comes in tablets that must be swallowed whole, twice a day, and they can be taken with or without food. Patients should not break or chew the tablets. If a dose is missed by less than six hours, the missed dose should be taken right away and the next one should be taken at the usual time. If a dose is missed by more than six hours, the patient should wait and take the next dose at the usual time.

Some of the most common side effects caused by idelalisib (Zydelig) are diarrhea, fever, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash (see Chapter 7).

Rarer, more serious side effects (some of which have caused death) include severe liver toxicity, diarrhea or *colitis* (colon inflammation), *pneumonitis* (lung inflammation), *intestinal perforation* (holes in the intestine), skin reactions, allergic reactions, neutropenia, and infections (including pneumocystis and cytomegalovirus).

Venetoclax (Venclexta)

Venetoclax (Venclexta) is a small molecule that inhibits a protein called B-cell lymphoma 2 (Bcl2). In contrast to ibrutinib (Imbruvica) and idelalisib (Zydelig), venetoclax is not a tyrosine kinase inhibitor. CLL cells make large amounts of Bcl2, which help them survive longer and resist even the effects of chemotherapy. The inhibition of Bcl2 by venetoclax triggers the self-destruction of CLL cells by a natural process called *apoptosis*.

In early studies, venetoclax (Venclexta) resulted in several episodes of tumor lysis syndrome (TLS), where the tumor cells broke down all at once and overwhelmed the kidneys, which can be life threatening. The dosing schedule for venetoclax was subsequently changed to start at 20 mg daily, and increased every week over five weeks to the maximum dose of 400 mg to avoid the possibility of tumor lysis. This change markedly lessened the risks of TLS. If a dose is missed by eight or less hours, the missed dose should be taken right away and the next one should be taken at the usual time. If a dose is missed by more than eight hours, the patient should wait and take the next dose at the usual time.

In April 2016, the FDA approved venetoclax (Venclexta) for the treatment of patients with CLL who have the chromosomal abnormality 17p deletion (as detected by an FDA-approved test) and who have received at least one prior therapy. The approval was based on results from a clinical study that showed a very good anticancer response

with this medication. Clinical studies have yet to compare venetoclax with other treatments for CLL.

Venetoclax (Venclexta) comes in tablets that must be swallowed whole once a day with a meal and water. The tablets should be taken at about the same time every day. Patients should not chew, crush, or break the tablets. Patients should not drink or eat grapefruit, Seville oranges, or starfruit while on venetoclax treatment. Because venetoclax can interact with other chemicals, patients should tell their doctor about all of the prescription medications, over-the-counter medications, vitamins, and herbal products they are taking.

Some of the common side effects caused by venetoclax (Venclexta) are neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue.

Rarer, more serious side effects (some of which have caused death) include TLS and severe neutropenia.

What Is a Treatment Regimen?

Patients take or receive their prescribed medication(s) at specific intervals, such as once every 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 medications used.

Some patients with CLL/SLL are treated with combination therapy, meaning two or more medications, instead of a single medication. The medications are given in a specific order (or *schedule*) during certain days of each treatment cycle—this is called a *treatment regimen*. The reason to combine medications is to increase how effectively they damage or kill cancer cells. Other agents, such as ibrutinib (Imbruvica) and venetoclax (Venclexta), may be given for prolonged periods.

How Are Medications Given?

Depending on the regimen, patients will receive their medication(s) in pill or capsule form, as an injection, or as an IV drip through a vein. If given in capsule form, the capsules should not be opened or broken, and it is best to take them at the same time each day. To make it easier to give and receive multiple cycles of chemotherapy by IV, the doctor may insert an IV catheter that will stay in place for a few weeks or for the duration of the treatment. There are several types of catheters, which are described in the following table. 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 Chemotherapy

Type of Catheter	Description	Advantages	Disadvantages
Peripheral Venous Catheter	A needle is used to insert a small, flexible tube (the catheter or cannula) into a vein in the hand or arm. Drugs and other fluids are given through the various types of attachments	No need for surgical insertion A good option for patients who require few infusions spaced wide apart	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 To minimize the risk of infections, the catheter needs to be replaced at least every 3 days or sooner if it becomes blocked Cannot be used to draw blood for blood tests
Hickman and Broviac	Consists of one to three tubes surgically inserted through the subclavian vein (the vein that runs underneath the collar bone) in the chest wall. Six to 12 inches of tubing remain outside the skin	It makes it easy to draw blood and give drugs using standard needles and without having to pierce the skin	Requires proper care to reduce the risk of infection and blockage The tubes on the outside of the body make it more obvious that a catheter is in place Patients need training and instructions to learn how to clean and take care of the external tubes

Table 6.2. Catheters Used to Administer Chemotherapy (continued)

Type of Catheter	Description	Advantages	Disadvantages
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; once a month a nurse keeps the line open by “flushing” with a small amount of injected liquid	The patient must be injected through the skin with a special needle each time it needs to be used Sometimes it is hard to use it to draw blood samples because of clogging (due to a blood clot) If an infection occurs, the catheter may need to be removed through a minor surgical procedure
Peripherally Inserted Central Catheter (PICC line)	A thin, soft plastic tube is inserted in a large vein in the arm	A good option for patients who only need to have many short infusions or continuous infusions given in a hospital or at home with a portable pump	This is more temporary than the other types of catheters

Why Is it Important to Adhere to the Medication Treatment Schedule?

Patients should adhere to their medication treatment schedule because a full course of therapy given on time works best in the treatment of their disease. In clinical studies, doctors have found that reducing the medication dose or delaying therapy may decrease the chance of a cure and long-term survival for patients with certain types of lymphomas. Changing the regimen to reduce short-term side effects may actually be harmful in the long run.

Some side effects may be unpleasant but tolerable. Other side effects may be serious, but they can often be anticipated and prevented. It is very important that medication schedules be maintained to the greatest extent possible.

Radiation Therapy

Radiation therapy (also called *radiotherapy*) uses X-rays or other types of radiation to kill cancer cells and shrink tumors. The term is used to describe *external beam radiotherapy*, in which radiation is delivered using an external radiation beam.

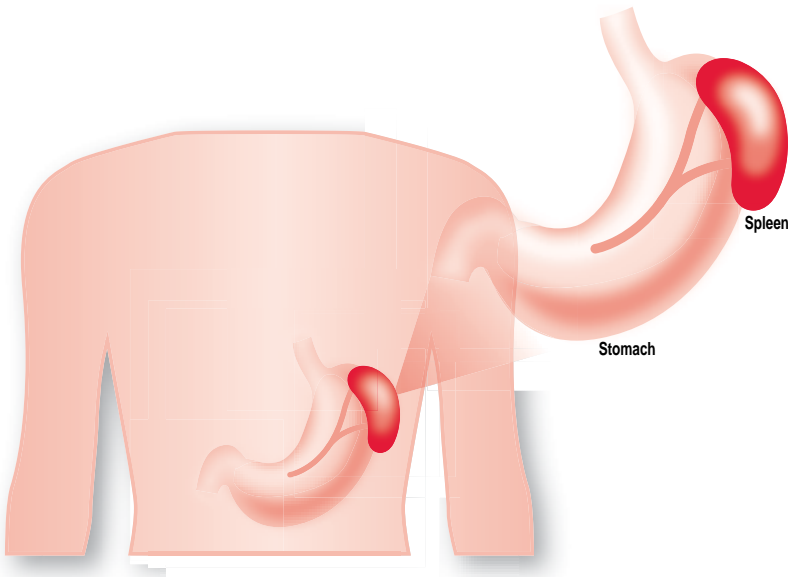
A radiation oncologist will be in charge of the radiation therapy. The area of the body selected to receive the radiation therapy is called the *radiation field*. Doctors usually limit the radiation field to affected lymph nodes, the areas immediately surrounding lymph nodes, or other non-lymph node areas where the lymphoma started. Doctors will decide on the type and size of the radiation field depending on the type of tumor and the extent of disease.

To prepare for radiation therapy, the healthcare team will precisely mark the patient's body with tiny ink dots (called *tattoos*) to make sure that only the targeted areas receive radiation. During the day of treatment, they will use lead shields to protect a patient's normal tissues around the radiation field. They use plastic forms, pillows, and rolled blankets to make the patient comfortable and keep him or her in the proper position. Patients need to lie still on a table beneath a large machine that delivers the radiation painlessly. Once the preparations have been made, it takes only a few minutes to deliver the prescribed dose. The total dose of radiation is usually divided and given over one to six weeks. During and after the radiation treatment, patients will have to carefully protect the radiation site from the sun.

Radiation therapy is rarely used to treat patients with CLL/SLL.

Splenectomy

A *splenectomy* is the surgical removal of the spleen, a small organ found inside the rib cage, near the far upper-left side of the stomach. The spleen filters the blood to recycle old and abnormal red blood cells. It also stores platelets and white blood cells until they are needed. While the spleen works as part of the lymphatic system to fight off infections, it is possible to lead a normal life without it. Sometimes the surgeon may decide that the operation can be done by a laparoscopic approach, thus avoiding the need to do a larger open surgical procedure.



The spleen becomes enlarged in some patients with CLL/SLL and causes discomfort or pressure. A splenectomy is an option if other treatments do not provide enough relief or if the patient has autoimmune complications associated with CLL/SLL. Removing the spleen might also improve low blood counts.

People without a spleen have an increased risk of developing serious bacterial infections and should promptly call their healthcare team at the first symptoms of infection. These symptoms might include pain, swelling, fever, and/or redness. To reduce the risk of infection, doctors

recommend that patients who have had a splenectomy receive vaccines, particularly to help prevent pneumonia. They may also advise patients to take antibiotics promptly when they develop a fever.

Stem Cell Transplantation

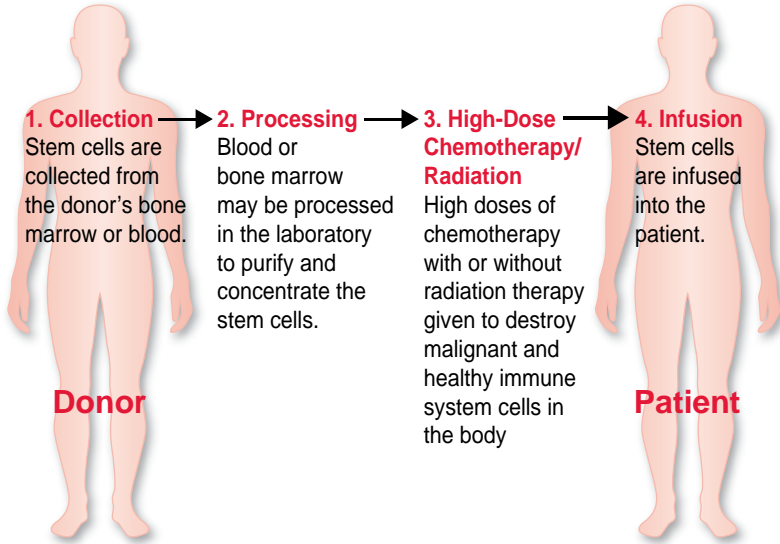
There are different types of stem cell transplantation, depending on who donates the stem cells. In an *autologous stem cell transplant*, the patient is his or her own donor. Autologous stem cell transplantation is not used in patients with CLL/SLL because their stem cells are often contaminated with the disease. Therefore, this type of stem cell transplantation is not discussed in this booklet.

In *allogeneic stem cell transplantation*, the donor is another person who is genetically similar to the patient; this is typically a brother or sister, but the donor can also be an unrelated person, or the cells can come from umbilical cord blood. Allogeneic stem cell transplantation may be an option for some relatively physically fit patients with advanced or *refractory* (does not respond to treatment) CLL/SLL who have a suitable donor.

Patients undergoing a standard stem cell transplant receive high doses of chemotherapy, often in combination with radiation therapy, that destroy their bone marrow cells. This method is used in an attempt to eliminate all of the cancer cells. Because high-dose therapy and allogeneic stem cell transplantation place great strain on a patient's body, they are not options for everyone. In deciding if transplantation is a good option, doctors will consider the patient's health status, age, medical history, cancer stage, prognostic factors, and responses to previous therapy.

ALLOGENEIC STEM CELL TRANSPLANTATION

Stem cells from a donor who is genetically similar to the patient.



Reduced-intensity transplantation (also called non-myeloablative or mini-allogeneic stem cell transplantation) uses lower doses of chemotherapy and/or radiation prior to allogeneic transplantation. This approach takes advantage of the *graft-versus-tumor* (GVT) effect, in which the transplanted cells (the “graft”) recognize the remaining cancerous cells in the patient’s body as foreign and destroy them. Patients receiving reduced-intensity transplants may avoid some of the side effects seen with higher-dose chemotherapy.

Questions to Ask Before Deciding to Undergo Allogeneic Stem Cell Transplantation

- Why do you think this is a good idea?
- What are the risks versus benefits associated with this procedure?
- Why do you recommend this particular type of transplantation?
- Would I jeopardize the possibility of other therapies?
- How will a donor be found?
- How long will I need to be in the hospital?
- Once I'm back home, will I need special care?
- Will I need someone to care for me immediately after the transplant?
- Will my insurance cover this procedure?
- What type of special care will I receive?
- How sick will this treatment make me?
- What will you do to lessen the side effects?
- How will we know if the treatment is working?
- How and for how long will the treatment affect my normal activities (for example, work, school, childcare, driving, sexual activity, exercise)?
- What is my chance of making a full recovery?

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 www.lymphoma.org/publications.

What Terms Do Doctors Use to Describe the Outcome of Treatment?

Table 6.3. Terms Used to Describe Treatment and Its Outcomes

Front-Line (Initial) Therapy	This is the first therapy that a patient receives. The choice of front-line therapy depends on the pathologic characteristics of the disease, including the factors described previously in this booklet.
Complete Remission (CR)	This term is used when all signs of the lymphoma have disappeared after treatment. This does not mean that the lymphoma is completely cured; it means that the symptoms have disappeared and the lymphoma cannot be detected using current tests. If this response is maintained for a long period, it is called a durable remission.
Cure	This word is cautiously used by doctors when there are no signs of the lymphoma reappearing after many years of continuous CR. While cures are rare in CLL/SLL, most patients live for many years.
Disease Progression	This term means that the disease has worsened or the tumor has grown during therapy or observation. Other terms used to describe this are treatment resistance or resistant disease.
Partial Remission (PR)	This term is used if the lymphoma has responded to treatment and shrunk to less than one-half of its original size.
Minor Response (MR)	This term is used if the tumor has shrunk following therapy but is still more than one-half of its original size.
Stable Disease	This term means that the disease has not gotten worse or better following therapy (the tumor has not grown or shrunk), but has stayed about the same.
Refractory Disease	This refers to a lymphoma that is resistant to treatment (meaning that the cancer cells continue to grow) 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?

Relapsed CLL/SLL means that the disease has returned after responding to treatment—this is sometimes also called a *recurrence*. Most patients who relapse do not require immediate treatment.

Refractory CLL/SLL means that the patient's disease does not respond to a specific treatment or that the response to the treatment does not last very long. There are many treatment options for patients with relapsed or refractory CLL/SLL. Exactly what type of treatment is optimal for individual patients with relapsed or refractory CLL/SLL depends on factors such as age, extent and location of disease, overall health, type of previous therapies received, and length of response to previous therapies.

Some centers will consider using allogeneic stem cell transplantation for some patients with relapsed or refractory CLL/SLL, depending on a patient's age, overall health, and other characteristics.

Patients who do not go into complete remission (CR) following treatment or who do 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 often choose to do so if their disease relapses or is considered refractory. Clinical trials are a good option for patients at all stages of disease.

Many of the novel therapeutic agents most recently approved by the FDA and those being investigated in clinical trials are used specifically for patients with relapsed or refractory disease. 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.

When Should a Clinical Trial Be Considered?

Clinical trials are appropriate for patients at all times in their disease (see “Overview of Clinical Trials”). The overall goal of clinical trials is to improve the treatment of patients. There are many excellent treatments available, but since none are perfect, clinical researchers are always trying to do better. Additional goals of clinical trials are to safely monitor the effects of a medication or a new combination of medications in patients over time and to identify more effective therapies for specific diseases. By participating in a randomized clinical trial, patients may or may not get access to the newest therapies but will, at a minimum, receive quality care and the standard treatment 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 “Clinical Trials Information Service” online (www.lymphoma.org/clinicaltrials_forpatients), by phone (800) 500-9976, or email (helpline@lymphoma.org).

What Are Transformations of CLL/SLL?

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

- Richter syndrome – A diffuse large cell lymphoma; this is the most common CLL/SLL transformation and is seen in about five percent of patients with CLL/SLL
- Prolymphocytic leukemia
- Other rarer transformations such as Hodgkin lymphoma, acute lymphocytic leukemia, and acute myeloid leukemia

Patients with these CLL/SLL transformations are treated in the same way as patients whose disease originated as one of these types of cancers. Patients with CLL/SLL transformations have more aggressive disease which will impact treatment goals and therapy decisions.

What Are Alternative and Complementary Therapies?

Alternative therapy refers to treatments that are used instead of standard therapy recognized as effective by the medical profession.

Currently, there are no proven alternative therapies to conventional cancer care for patients with CLL/SLL and other types of NHL. Patients are strongly urged to discuss alternative remedies they are considering with their doctors.

Complementary therapy may be able to help improve a patient's quality of life and to relieve the effects of medications, radiation, and surgery. **Patients and caregivers should talk to their doctor and healthcare team before starting any form of complementary therapy, because some of these practices can make their cancer treatment less effective.** Table 6.4 outlines some forms of complementary therapy also known as integrative medicine or integrative oncology.

Table 6.4. Forms of Complementary Therapy

Acupuncture	<ul style="list-style-type: none"> ■ Acupuncture may relieve pain, nausea, fatigue, hot flashes, and <i>neuropathy</i> (numbness or tingling in the hands and feet) associated with chemotherapy and may help decrease mild depression. ■ Using ultra-thin needles applied to specific points on the body, acupuncture is safe and painless. Needles should only be used once and disposed of after use.
Chiropractic and Massage Therapy	<ul style="list-style-type: none"> ■ Chiropractic and massage therapies are the most commonly used modalities, and they can help relieve side effects and stress. ■ A special type of massage called <i>oncology massage</i> 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.
Herbal Therapy	<ul style="list-style-type: none"> ■ Ask your doctor before using herbal therapies. Some herbal therapies may interfere with other medications, particularly St. John's wort.

Table 6.4. Forms of Complementary Therapy (*continued*)

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.
Nutrition	<ul style="list-style-type: none">■ Patients undergoing lymphoma treatment should eat a healthy, well-balanced diet that contains five to seven servings of fruits and vegetables a day, fish or poultry, and whole grains.

Medication Costs: What to Do if Insurance Will Not Pay?

Many patients today face the problem of how to pay for rising healthcare costs. Cancer organizations such as LRF (www.lymphoma.org) offer limited financial assistance to patients who qualify. Most pharmaceutical companies have patient assistance programs in place that help provide medications to qualifying patients.

Patients in need of financial assistance should talk with their doctor and social worker about available options and how to enroll in an appropriate program. Before undergoing a medical procedure, check with the insurance carrier to ensure that it is covered. If there is a dispute about coverage or if coverage is denied, ask the insurance carrier about their appeals process. If a claim is repeatedly denied, the patient 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 www.lymphoma.org. You may also call LRF's Helpline at (800) 500-9976 or email helpline@lymphoma.org.

Part 3 — Living With the Side Effects of Treatment

Chapter 7: Common Treatment Side Effects

Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) may experience various side effects or toxicities caused by their cancer treatment. All treatments, including chemotherapy and biologic or targeted therapies, can cause side effects. Fortunately, medications and lifestyle changes can effectively prevent or lessen the severities of most side effects. Ask the healthcare team about possible treatment side effects and how to prevent and manage them, and tell the doctor or nurse about any side effects experienced. This chapter explains the causes of these side effects, the types of side effects caused by different treatments, and steps to take to minimize these side effects.

Why Does Chemotherapy Cause Side Effects or Toxicities?

Chemotherapy agents cause side effects because of the nonspecific way these medications attack cancer cells. Most chemotherapy agents are designed to kill cells that divide rapidly like cancer cells (meaning that they are multiplying quickly). Most normal cells in the body do not divide as quickly as cancer cells do. However, healthy cells in hair roots and cells in the mouth, gastrointestinal tract, and bone marrow do divide rapidly and can be damaged or killed by chemotherapy. Some chemotherapy agents can also damage cells in the heart or other organs and tissues.

The type and severity of side effects caused by chemotherapy vary widely depending on the types of medications that are given and an individual patient's response. The same agent may cause no side effects in one patient, while in others it may cause anything from very mild to very serious 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 several years. *Fatigue* (tiredness), menopausal symptoms, and cardiovascular problems are examples of long-term effects.

Late effects of treatment become apparent after treatment has ended and may arise many months, years, or even decades after treatment is completed. Infertility, osteoporosis, and secondary cancers (such as leukemia) are examples of late effects.

What Side Effects Are Caused by Chemotherapy?

Side effects vary depending on the type of chemotherapy; additionally, things other than chemotherapy can cause these same adverse effects.

Some of the most common side effects caused by chemotherapy used to treat patients with CLL/SLL include:

- Decreased red blood cell production, leading to anemia; decreased white blood cell production, leading to increased risk of infection; or a decrease in platelet production, leading to bleeding, diarrhea, or constipation
- Fatigue
- Fever
- Loss of appetite
- Mouth sores
- Nausea and vomiting
- *Peripheral neuropathy* (tingling or numbness in the hands and feet)
- Problems with sexual function
- Sterility
- *Tumor lysis syndrome* (TLS; abnormalities in electrolytes in the blood due to rapid death of lymphoma cells)

The following side effects are rarely seen in chemotherapy-treated patients with CLL/SLL:

- Cardiotoxicity (damage to the heart)
- Changes in taste
- Cognitive problems (trouble concentrating, impaired memory)
- Hair loss

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 due to their disease. However, some types of chemotherapy and immunotherapy also 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* and is very common during the course of CLL/SLL.

To monitor myelosuppression and treat it if needed, samples of a patient's blood are tested with a *complete blood count* (CBC), which measures the number of white blood cells, red blood cells, and platelets, and the differential, which measures the numbers of the different subtypes of white blood cells. These tests are usually done before, and sometimes during, each chemotherapy cycle. Table 7.1 (on the next two pages) describes the main conditions caused by decreased blood cell production.

Table 7.1. The Four Main Conditions Caused by Decreased Blood Cell Production

<p>Anemia</p>	<ul style="list-style-type: none"> ■ This condition is caused by a decrease in the number of red blood cells. Normal levels of red blood cells are 4.7 to 6.1 million per microliter for men and 4.2 to 5.4 million per microliter for women. ■ Additional indicators of red blood cell count include hemoglobin level and hematocrit. Hemoglobin is a protein that is present in all red blood cells. Normal hemoglobin levels are 13.5 to 17.5 g/L for men and 12.0 to 15.5 g/dL for women. A hematocrit test measures the amount of blood that is occupied by red blood cells. Normal hematocrit values are 39 to 50 percent for men and 34 to 44 percent for women. ■ Many chemotherapy drugs cause mild or moderate anemia. ■ Anemia can make people feel tired and short of breath, especially when it is severe. Although seldom needed, anemia can be treated with drugs or red blood cell transfusions.
<p>Lymphopenia</p>	<ul style="list-style-type: none"> ■ <i>Lymphopenia</i>, also called <i>lymphocytopenia</i>, refers to a decrease in the number of lymphocytes. It should be noted that reduction in the number of lymphocytes is a desired aim of treatment in patients with CLL/SLL and, therefore, lymphopenia is not always a side effect; however, the degree of lymphopenia can occur which poses increased risks for the patient. Lymphocytes produce antibodies and fight bacterial and viral infections. Usually, of all white blood cells, about 20 to 40 percent are lymphocytes. ■ Patients with low levels of lymphocytes are at risk of latent infections. For example, if the patient had chicken pox as a child, he or she could get shingles if he or she has low levels of lymphocytes.

Table 7.1. The Four Main Conditions Caused by Decreased Blood Cell Production (*continued*)

Neutropenia	<ul style="list-style-type: none">■ <i>Neutropenia</i> refers to a decrease in neutrophils—the primary type of white blood cells that fight bacterial infections.■ Patients with low neutrophil counts are at risk of serious and even life-threatening infections. Symptoms of infection include fever, chills, and night sweats.■ A normal white blood cell count ranges from 4,000 to 10,000 cells per microliter. Doctors regularly monitor the <i>absolute neutrophil count</i> (ANC), the number of neutrophils in the peripheral blood. Because patients with an ANC below 500 are at high risk for infections, their doctors may decrease the chemotherapy dosage or delay the next treatment in order to keep the ANC above 500.■ Some patients require treatment with antibiotics and hospitalization to prevent or treat infections.■ To avoid a patient missing a dose of chemotherapy, doctors sometimes prescribe drugs like filgrastim (Neupogen and Granix) and pegfilgrastim (Neulasta) to reduce the duration and severity of neutropenia. These drugs can sometimes cause bone pain, which is usually temporary.
Thrombocytopenia	<ul style="list-style-type: none">■ <i>Thrombocytopenia</i> refers to a decrease in the number of platelets in the blood; platelets help start the clotting process when bleeding occurs. Normal platelet count levels are 150,000 to 450,000 per microliter.■ Patients with low platelet counts may bruise easily; have cuts that bleed for too long or too much; have nosebleeds or bleeding gums; or may bleed from places that have not been injured.

Diarrhea

Some types of therapy may cause diarrhea. While most patients do not experience severe diarrhea, the most important thing to remember is to avoid dehydration, which is a loss of body fluids. The doctor should be contacted if the patient has bloody diarrhea or fever with diarrhea.

PATIENT TIP

Avoiding Dehydration From Diarrhea or Vomiting

- Drink plenty of liquids (8 glasses a day) such as water or electrolyte replacement drinks like Gatorade, Pedialyte, and Powerade. Sometimes it helps to drink small amounts very frequently rather than too much at once. Soup, especially broth, is a rich source of nutrients as well as fluids.
- Look for the following signs of dehydration: dry mouth or skin, decreased urine, or feeling dizzy or lightheaded when you stand up.
- Do not drink or eat milk products, because they can worsen diarrhea.
- Eat plenty of bananas and other high-potassium foods (check with your doctor or dietitian to make sure that these foods will not interfere with your chemotherapy or other medications that you are taking).
- Take the medicines that your doctor recommends to control diarrhea or vomiting (call your doctor if symptoms persist).

Fatigue

Fatigue is a common side effect of many types of therapy. Fatigue should decrease after patients complete their lymphoma treatment, but it could take weeks or months until they return to their normal energy levels.

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.
- 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 do not rest more than you need because it may decrease your energy levels. An afternoon nap helps many patients feel less tired for the rest of the day. 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 why and what you can do about it.
- Be patient. These symptoms usually improve once treatment is completed.

Increased Chance of Infections

Some kinds of treatments can lower a patient's ability to fight infections. Patients are sometimes at increased risk for viral infections, particularly *shingles* (herpes zoster), and sometimes the doctor will prescribe medication to prevent a shingles outbreak during therapy. Many of these side effects are temporary, but some could last for an extended period.

Patients with a fever of 100.5°F or greater should seek medical attention. They should ask their doctor 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.

To reduce the risk of infections, patients may be prescribed antibiotic medications. Other ways to reduce the risk of infections are included below.

Reducing Your Risk of Serious Infection During Chemotherapy

PATIENT TIP

- Check with your doctor to make sure your vaccinations are up to date prior to beginning treatment.
- Wash your hands diligently and regularly.
- Avoid crowds.
- Make sure all foods are thoroughly washed and/or cooked; avoid raw foods that may carry germs, as your body is more sensitive to them.
- Do not sleep with pets.

Loss of Appetite

Loss of appetite is sometimes a symptom of the lymphoma, or it may be a side effect of chemotherapy. 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, such as nausea and vomiting, mouth sores or pain, fatigue, depression, or 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 other medications or by changing eating habits, such as eating several small meals each day and making nutritious food choices. For more information on nutrition, please view the *Nutrition* fact sheet on the Lymphoma Research Foundation's (LRF's) website at www.lymphoma.org. It is a good idea to contact a dietitian.

Mouth Sores

Some chemotherapy agents can cause a patient's mouth to become red, sore, or irritated—this is called *mucositis*. Some patients undergoing chemotherapy also become more susceptible to viral or fungal infections of the mouth and throat.

The doctor should be informed if the patient develops a sore throat. The doctor will examine the patient's throat and may take a swab to send to the laboratory to check for infection. Several medications are available to treat different types of infections. To help decrease chances of infection, patients should have a complete dental checkup and cleaning before starting chemotherapy.

Preventing and Caring for Mouth Sores

- Clean your mouth and teeth. Use a soft-bristle toothbrush, nonabrasive toothpaste, and lip moisturizer.
- Do not use mouthwashes that contain alcohol. Your doctor or nurse may recommend a particular mouth rinse.
- Do not eat citrus fruits (such as oranges, grapefruit, lemons, or clementines) or drink citrus juices.
- Do not eat spicy foods.
- Eat soft foods while you are receiving chemotherapy 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.

Nausea or Vomiting

Some chemotherapy agents can cause nausea or vomiting, which typically occurs on the day chemotherapy is administered but may also occur one or two days later. The doctor may prescribe an *antiemetic* (a medication that prevents nausea and vomiting) before chemotherapy. Examples of antiemetics include: aprepitant (Emend), ondansetron (Zofran), granisetron (Kytril), metoclopramide (Reglan), prochlorperazine (Compazine), dolasetron (Anzemet), and a variety of corticosteroids, such as prednisone (Deltasone) or dexamethasone (Decadron). Some of these medications are also sold under other brand names. In most cases, these antiemetics are able to partially or completely prevent nausea and vomiting. Additional tips for minimizing nausea and vomiting are shared on the next page.

Controlling or Minimizing Nausea and Vomiting

- Before chemotherapy, drink a liquid diet such as broth, consommé, or water. Do not drink milk or have a meal whose 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 and 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.
- Finding the best approach is often a process of trial and error. Try different approaches to determine what works best for you.

Peripheral Neuropathy

Some chemotherapy agents may damage the nervous system by affecting signaling between the *central nervous system* (CNS; the brain and spinal cord) and the rest of the body through all the nerves that make up the *peripheral nervous system*. This damage causes *peripheral neuropathy* symptoms such as numbness, a tingling or prickling sensation in the fingers and toes, sensitivity to touch, and muscle weakness.

Problems With Sexual Function

Psychological factors, such as fear about illness, altered body image due to hair loss and depression, and the physical side effects of treatment can cause a drop in *libido* (sex drive). However, a normal libido usually returns after treatment is finished. Some therapies (such as the fludarabine [Fludara], cyclophosphamide [Clafen, Cytoxan, Neosar], and rituximab [Rituxan] regimen; FCR) may trigger early menopause in premenopausal women. Doctors, oncology nurses, and oncology social workers are prepared to help with any problems or concerns about changes in libido or sexual function. Seeing a specialist, administering tests to track hormone levels, taking medications to restore erectile function, and using hormone therapy to alleviate vaginal dryness and other menopausal symptoms are some of the strategies the doctor may recommend.

Sterility

Since chemotherapy may damage sperm and egg cells, it can sometimes cause temporary or permanent *sterility* (inability to have children) in both men and women. The potential for developing sterility depends on the treatment type and specific dose, the number of therapies given, and the patient's age at the time of treatment. Options to preserve fertility include possible protection of the ovaries or *cryopreservation* (freezing) of sperm cells, egg cells, or in vitro-fertilized embryos. Speak with the doctor about fertility preservation before beginning chemotherapy. For more information and resources about sterility, visit the LRF's web page on "Fertility" available at www.lymphoma.org/fertility.

Patients of childbearing age who are receiving chemotherapy should always use birth control, since these medications may harm a developing fetus or cause birth defects.

Tumor Lysis Syndrome

Patients who have rapidly growing tumors or those who have developed many tumors may experience tumor lysis syndrome (TLS) in response to chemotherapy. TLS occurs when an anti-lymphoma agent triggers the quick death of a large number of lymphoma cells, making them break apart and spill their contents into the blood. The spilled cellular material floating in the blood can damage the kidneys and other organs. If not properly treated, TLS may lead to kidney failure and damage to the heart and nervous system. TLS has been a concern with venetoclax, so doctors administering this agent must be familiar with the detection and management of this potential complication.

To prevent TLS, patients may receive extra fluids and medications such as allopurinol (Zyloprim) to prevent *hyperuricemia* (high levels of uric acid). If hyperuricemia develops, it can also be treated with medications such as rasburicase (Elitek).

Cardiotoxicity

Cardiotoxicity refers to damage to the cells in the heart or heart muscle. Long-term use of certain chemotherapy agents can cause heart damage in some patients.

In general, patients with CLL/SLL are rarely treated with potentially cardiotoxic chemotherapy. The few patients who do receive these medications get them at low dose levels and few cycles, so cardiotoxicity is usually not a problem.

A patient's history of heart disease, high cholesterol, and 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 developing cardiotoxicity. Before deciding to treat patients with a cardiotoxic agent, most doctors will prescribe either an echocardiogram or a multigated acquisition (MUGA) scan to measure their cardiac function. This test will ensure that patients are prescribed a safe chemotherapy dose given their current heart function and that they are monitored more intensively if needed.

Changes in Taste

Some patients will experience a change in the way foods or beverages taste. Familiar foods may taste differently (*dysgeusia*), or the flavors of foods may not be as strong (*hypogeusia*). Some patients may also feel that foods have a metallic taste. These side effects are temporary and usually disappear after the end of chemotherapy. Sometimes this side effect can be helped with dietary changes.

Cognitive Problems

Chemotherapy can result in mild cognitive impairment such as trouble concentrating, impaired memory, or issues with motor control. Although these side effects can be stressful, they typically disappear over time.

Hair Loss

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

If hair loss occurs, it often starts two to six weeks after the first chemotherapy treatment. Remember that hair loss caused by chemotherapy is usually temporary. Hair will probably grow back after the end of chemotherapy treatments. 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 may return to normal. Loss of hair in the nose and nasal passages may lead to symptoms of *rhinorrhea* (runny nose). Patients may follow the tips on the next page for managing chemotherapy-induced hair loss.

Managing Chemotherapy-Induced Hair Loss

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

Other Possible Side Effects

Chemotherapy can also cause other side effects such as cough, skin rashes, general weakness, sore throat, and loss of balance or coordination. Many of these side effects are temporary, but some could last for an extended period. The doctor should be contacted 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 patients with CLL/SLL may cause similar side effects to those seen with chemotherapy, such as low blood cell counts and infusion reactions. These are usually mild but can sometimes be severe. Other rare, but potentially very serious, side effects include infections and TLS.

Infusion Reactions

When infusion reactions occur, they typically happen during or within 24 hours after the infusion, and they are most likely to happen after the first infusion. Symptoms of infusion reactions 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.

To prevent infusion reactions, patients are given antihistamines (e.g., Benadryl) and acetaminophen (Tylenol), and sometimes corticosteroids, before or during the antibody infusion. Nurses closely monitor patients during the infusions. Patients should report any new symptom that they experience during or after an infusion as soon as it occurs.

Infections

Reactivation of hepatitis B virus (HBV) infection is a rare but very serious side effect of obinutuzumab (Gazyva), ofatumumab (Arzerra), and rituximab (Rituxan) therapy. Reactivation of hepatitis B may also occur with steroid or chemotherapy treatment. People may not know that they have HBV because a healthy immune system can force the virus to hide without causing noticeable symptoms. Treatment with the CD20-directed monoclonal antibodies can effect immune system changes that enable reactivation of HBV. If unchecked, this reinitiation of HBV infection can cause acute liver failure. To prevent HBV from reinitiating, patients are screened for HBV infection before treatment. People who have the virus are closely monitored during and after treatment. Patients should be mindful of signs of an active HBV infection, such as increasing fatigue and yellowing of the skin or eyes. Patients treated with monoclonal antibodies very rarely can develop *progressive multifocal leukoencephalopathy* (PML), which is a serious brain infection thought to be caused by a virus known as the “JC virus.”

Secondary Cancers

Secondary cancers are one of the most concerning unwanted effects following chemotherapy/monoclonal antibody therapy. The risk for a CLL/SLL patient who underwent chemotherapy/monoclonal antibody therapy developing a secondary cancer is about 2.4 times higher than the expected risk in the general population. The most common secondary cancers include aggressive lymphomas, myelodysplastic syndromes (MDS), and acute myeloid leukemia (AML). How treatment leads to the development of these cancers is not well understood. This phenomenon is currently being studied in clinical trials.

What Side Effects Are Caused by Targeted Therapies?

Ibrutinib (Imbruvica)

The most common side effects caused by ibrutinib (Imbruvica) are decreased neutrophils and platelets, diarrhea, anemia, muscle and bone pain, rash, nausea, bruising, fatigue, and fever. Serious side effects include bleeding problems, infections, atrial fibrillation (AFib), hypertension, and TLS.

Patients taking ibrutinib (Imbruvica) should notify their doctor if they are considering any surgical procedure or if they have undergone any emergency procedure, because ibrutinib treatment will have to be stopped for a short period of time before and after these procedures due to an increased risk of bleeding. Patients should also notify their doctor if they experience:

- Any signs or symptoms of bleeding (severe headache, blood in stool or urine, or prolonged or uncontrolled bleeding)
- Any signs or symptoms of serious infection (fever, chills, weakness, or confusion)
- Any signs of heart palpitations, lightheadedness, dizziness, fainting, shortness of breath, or chest discomfort

Idelalisib (Zydelig)

The most common side effects caused by idelalisib (Zydelig) are diarrhea, fever, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash. Rarer but serious side effects include severe skin reactions, *anaphylaxis* (life-threatening allergic reaction), and neutropenia. Very serious and potentially life-threatening side effects such as liver problems, colitis with severe diarrhea, *pneumonitis* (inflammation of the lungs) with lung or breathing problems, infections, and tears in the intestinal wall (*perforation*) have also occurred in patients receiving idelalisib.

Before and during idelalisib (Zydelig) treatment, the doctor will order blood tests to check for liver problems. Patients should notify their doctor if they experience:

- Any symptoms of liver problems (yellow skin, dark or brown urine, pain in the upper-right side of the stomach, bleeding or bruising more easily than normal)
- An increase in the number of bowel movements to six or more per day
- A new or worsening cough, shortness of breath, difficulty breathing, or wheezing
- A new or worsening pain in the stomach area, chills, fever, nausea, or vomiting

In March 2016, the manufacturer issued a warning for healthcare providers stating that idelalisib (Zydelig) should not be used for the frontline treatment of patients with CLL/SLL and indolent NHL. The reason for this warning was that three clinical trials of idelalisib added to standard therapies found lower overall survival and increased side effects in patients with previously untreated CLL and in patients with first-relapse indolent NHL or SLL. Most of the increased side effects were infections such as sepsis and pneumonia. To reduce the risk of serious infection for all patients taking idelalisib, doctors give patients medicines to prevent infection with pneumocystis pneumonia, and they will stop treatment at the first signs of infection. Doctors will also

monitor blood counts very closely. Patients receiving idelalisib should also be regularly monitored for cytomegalovirus (CMV) infection.

Venetoclax (Venclexta)

The most common side effects caused by venetoclax (Venclexta) are neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue. Venetoclax also can cause very serious and potentially life-threatening side effects such as TLS and very low white blood cell count.

To decrease the risk of TLS, which is a real risk especially in the first five weeks of therapy, patients should drink plenty of water (six to eight glasses each day, about 56 fluid ounces), starting two days before the start of treatment. They should have their blood and urine checked by their doctor several times, on the day they start treatment, on the subsequent day, and each week while the dose is being increased. Patients should notify their doctor if they experience any sign or symptom of TLS (fever, chills, nausea, vomiting, confusion, shortness of breath, seizure, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle pain, joint discomfort) or any signs of infection.

What Side Effects Are Caused by Steroids?

Steroids, such as dexamethasone and prednisone, can cause side effects such as *insomnia* (the inability to fall asleep), increased appetite, mood or personality changes, anxiety, high blood pressure, fluid retention, and weight gain.

Prednisone can also trigger diabetes in patients prone to that disease or worsen diabetes in patients who already have the disease. Long-term steroid use can also cause osteoporosis in at-risk patients. Patients should alert family and friends that personality changes may occur during their treatment. Patients should avoid making hasty decisions. If personality changes do occur, the doctor should be informed, as the dose may need to be reduced.

What Side Effects Are Caused by Radiation Therapy?

Radiation therapy itself is painless, but it can cause short-term and long-term side effects. The side effects caused by radiation therapy vary depending on the type of radiation, the radiation dose used, and the part of the body treated. Side effects are usually worse when radiation therapy and chemotherapy are given at the same time, which is not normally done for patients with CLL/SLL. Side effects from radiation include dry mouth, fatigue, loss of appetite and taste, nausea, diarrhea, and skin reactions.

What Side Effects Are Caused by Allogeneic Stem Cell Transplantation?

Patients treated with chemotherapy and/or radiation before undergoing an allogeneic stem cell transplant are at increased risk for developing infection, bleeding, and other side effects as described previously (see “What Side Effects Are Caused by Chemotherapy?” and “What Side Effects Are Caused by Radiation Therapy?”)

These patients are also at risk of developing *graft-versus-host disease* (GVHD), a condition in which the donated bone marrow attacks the patient’s healthy tissues. GVHD can happen at any time after the transplant. Medications can be used to reduce the risk of developing GVHD or to treat the problem once it develops.

For more information about stem cell transplantation and its effects, including GVHD, view the Lymphoma Research Foundation’s *Understanding the Stem Cell Transplantation Process: A Guide For Patients, Caregivers, and Loved Ones* booklet at www.lymphoma.org/publications.

When Should a Patient's Doctor Be Contacted?

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.
- The patient experiences a medical problem—such as high fever, shortness of breath, prolonged or constant nausea and vomiting, uncontrolled diarrhea, chest pains, and/or dizziness—that cannot wait for a regularly scheduled appointment.

Part 3 — 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 while they live their life during and after treatment.

Coping Strategies

Each person's experience with cancer is different, and how he or she copes with the physical and emotional impact of having chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is unique to a patient's personality and situation. Here are some suggestions for how to cope with some issues that patients may face.

Table 8.1. Coping Strategies

Maintain a Strong Support System	<ul style="list-style-type: none">■ Communicate your fears and concerns about your disease by talking with your family, friends, doctors, and counselors.■ Writing down your concerns in a journal may also help.■ Find a support group or other individuals who are also coping with cancer such as the Lymphoma Research Foundation's Lymphoma Support Network that matches lymphoma patients or caregivers with volunteers who have had similar lymphoma-related experiences.
Get Help for Depression	<ul style="list-style-type: none">■ Feeling sad or depressed is not unusual in people living with cancer.■ Watch out for signs of depression: sleeping more or less than usual; feeling a lack of energy; crying; inability to concentrate.■ Ask for a referral to a psychiatrist, social worker, psychologist, or counselor who will help you cope with your feelings through talk therapy, medications, or both.■ Find a support group of people who have had similar experiences.

Table 8.1. Coping Strategies (*continued*)

Deal With Physical Changes	<ul style="list-style-type: none"> ■ Some patients with cancer feel unattractive because of hair loss and other changes in appearance caused by their treatment. ■ Ask your doctor what changes you should expect; plan ahead and buy a wig or head covering if hair loss is a possibility. ■ Get advice from a beautician about makeup for the areas that you consider a problem. ■ Ask your healthcare team for advice on how to manage temporary changes such as dry skin, brittle nails, and a blotchy complexion.
Maintain a Healthy Lifestyle	<ul style="list-style-type: none"> ■ Eat a healthy diet that includes fruits, vegetables, protein, and whole grains. ■ Engage in regular physical exercise; this can reduce anxiety, depression, and <i>fatigue</i> (tiredness), and improve mood. ■ Get sufficient rest to help combat the stress and fatigue of your disease and its treatment. ■ Quit smoking and reduce alcohol consumption.
Set Reasonable Goals	<ul style="list-style-type: none"> ■ Having goals for how you want to live your life during and after treatment will help you maintain a sense of purpose. ■ Avoid setting unreasonable goals, such as deciding to work full-time while part-time would be much better for your health. ■ Stay as active and involved as you can in work and other activities that interest you.

The Importance of Pain Control

In some situations, patients may experience pain from the cancer itself or from the treatments and procedures. Cancer pain is very treatable, and there is no reason for a patient to endure this pain without help. Patients should tell their doctors and nurses if they have any pain, because they can offer advice regarding medications and other ways to relieve the pain, as some medications may not be appropriate for their disease.

Different types of pain are best controlled by different types of pain relievers. Patients should ask their healthcare team what options are best to help manage their pain. Some of the following tips can be used for managing pain.

PATIENT TIP

Managing Pain

- Tell your doctor or nurse about your pain. Be specific when you describe it.
 - In what part of your body do you feel the pain?
 - When did the pain start?
 - What type of pain is it (sharp, dull, throbbing)?
 - Does it come and go, or is it steady?
 - How strong is it? How long does it last?
 - Does anything make the pain feel better or worse?
 - Which medications 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.

Maintain a Healthy Lifestyle

Regular physical activity helps keep the cardiovascular system strong and body muscles flexible. Exercise can help alleviate breathing problems, constipation, and mild depression. It also helps to reduce stress and fatigue. Patients should talk to their doctor before starting an exercise program and consider visiting a physical therapist for advice.

Several types of exercise are particularly helpful:

- 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 remedy osteoporosis by building bone mass
- Flexibility exercises such as stretching and yoga to improve range of motion, balance, and stability
- Breathing exercises to create a feeling of relaxation and well-being as well as to support your cardiovascular system

However, patients should not feel it is necessary to push themselves physically to the same level as before the CLL/SLL, due to how the toxicities from the drugs affect their bodies.

Eating a healthy diet is especially important during treatment for CLL/SLL because it will help patients keep up strength and energy, tolerate treatment-related side effects, decrease risk of infection, and heal and recover more quickly. Patients should aim for a diet high in fruits and vegetables, protein (poultry, fish, legumes, and eggs), and whole grains. During chemotherapy and after a stem cell transplant, the patient may be asked to temporarily avoid raw fruits and vegetables that may increase the risk of infection if they have a low white blood cell count (“neutropenic diet”). The healthcare team can help develop an eating plan that is appropriate.

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 Follow-up Care

At the first visit following the completion of treatment, patients should discuss their follow-up schedule with the doctor. This will be different from patient to patient depending on their disease stage, age, and general health. Patients should adhere to their schedule of follow-up visits—these are very important for monitoring disease recurrence and detecting and treating any health problems that might have been caused by the treatment.

During these follow-up visits, the doctor will ask about any medical changes since the last appointment and give a physical examination. The doctor may also prescribe blood, molecular diagnostic, imaging, or other laboratory tests.

Be Proactive in Healthcare Decisions

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

- Copies of all medical records and a written summary of treatment(s) in case the patient switches oncologists or needs to see a primary care physician for routine medical care
- A list of 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
- 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 in the emergency room or through direct admission by the patient's doctor. Patients with CLL/SLL may be admitted to the hospital for diagnostic testing or for treatment. In the case of a direct admission, the patient has seen their doctor and he/she feels that the patient should be admitted to the hospital. The doctor will call ahead and reserve a bed for the patient.

Most doctors make daily visitation rounds at about the same time each day. The nurse can tell you when the patient's doctor usually makes rounds. It is a good idea for family members to know when the doctor is likely to be making visitation rounds so they can be there to ask questions.

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

What Should Patients Bring With Them When Being Admitted to the Hospital?

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

What to Bring if You Are Being Admitted to the Hospital

- Identification (driver's license, student ID) and emergency contacts (relatives' and friends' names and phone numbers).
- List of all allergies and the reaction that occurs in response to allergen exposure (especially important for latex and pharmaceutical allergies).
- List of all current medications (name, strength, frequency) and "treatments" (include over-the-counter medications, such as Tylenol, vitamins, herbals, and any other items such as energy enhancers). If you do not have a list, place all medications in a bag and bring them with you.
- List of all medical conditions (name all conditions, not just cancer, for example: hypertension, epilepsy, active ulcer).
- List of all surgeries (even elective plastic surgeries) regardless of how long ago they occurred.
- Name(s) of all physicians currently treating you.
- Copy of any completed advance directives (for more information see Page 108 describing Advance Healthcare Directives).
- All insurance cards, a checkbook, and/or a credit card.
- If the patient has access to an up-to-date and complete medical record through a patient portal, flash drive, or mobile application (app), bring the security code for these medical records and the name of the website, or the flash drive, mobile app or device that contains the health information. Patients may also want to use the Lymphoma Research Foundation's free *Focus On Lymphoma* mobile app to help plan appointments, keep track of medications and blood work, track symptoms, and document treatment side effects (www.FocusOnLymphoma.org).

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

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

Having an *Advance Healthcare Directive* (a living will) and appointing a *healthcare proxy*, or a decision maker, is important for all adults to consider, not just people with cancer, because accidents and other unforeseen circumstances can happen at any time.

Writing down wishes for critical medical care in an Advance Healthcare Directive is a way to formally tell the doctor, family members, and friends about healthcare preferences and what special treatments someone does or does not want if they become critically ill or injured and are unable to make or communicate their decisions.

Besides stating medical care instructions, people may also consider naming a healthcare proxy, in an Advance Healthcare Directive. This person should be someone who will carry out their 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 an attorney is not required to write 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, medications 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 for your state, please visit the "Planning Ahead" 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 know 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—none of your healthcare team can talk about your condition.
- If you must be transferred to another facility, the information on why you require transfer must be provided and the institution that you are being transferred to must have accepted you 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.

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

If the patient is admitted to a teaching hospital, he/she may receive informed consent documents. These documents should enable patients to decide which treatments/procedures they are willing to receive. Signing these documents indicates that the patient understands the risks and benefits of the treatments/procedures being performed. The tips below will help patients know what to look for in informed consent.

PATIENT TIP

What to Look For in Informed Consent Documents

- Read the informed consent documents carefully.
- Request an explanation of anything you do not completely understand.
- Be sure to determine whether you are being enrolled in research.
- Treatment alternatives should be covered as well so you are aware of all options.
- The documents should provide the names of the physician(s) performing your treatments and/or procedures and the risks and benefits of the treatments/procedures you are agreeing to.
- The documents should identify what will be done with any tissue/fluid samples and photos or videos (if taken).

What Do Patients Need to Know at Discharge?

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

PATIENT TIP

Issues For the Case Manager to Resolve 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 to maintain functions?
- 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? How can you find home-based care?
- What new medication(s) will you need to take, and for how long?
- Does your insurance cover the new medication as an outpatient? If not, or if you don't have insurance, what will the cost be?
- If you don't have insurance, does the hospital have a sliding-scale fee or charity care?
- Are there alternative medications 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?
- Are there other instructions from your doctor or the hospital physician?
- Whom should you follow up with and when?
- If you are to schedule your own follow-up, whom do you call?
- Who is responsible for paying for your care?

For itemized hospital bills, make sure no mistakes were made. If there are discrepancies between the bill and the care the patient actually received, bring it to the attention of both the hospital and the insurance company.

When the patient is being discharged to hospice care at home or in a hospital, the case manager will also make these arrangements for the patient.

Should Patients Look For An Opportunity to Provide Feedback on Their Stay?

Hospitals may send patient satisfaction surveys to patients after discharge. This survey is an opportunity for patients to share issues they had with their care during their stay and/or to recognize those staff members whose care and support they felt were exceptional. Believe it or not, hospitals and their administrators pay close attention to these surveys, so it is worth the time to complete and return the survey so issues can be addressed and staff members providing excellent care can be acknowledged. If no survey is sent and you still want to report problems or satisfaction with the patient's care, you can write a letter to the hospital administrator or appropriate department director.

Part 5 — Clinical Trials and Advances in Treatment

Chapter 10: Overview of Clinical Trials

There are a large number of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) clinical trials now underway in hospitals, cancer centers, and doctors' offices around the country. The government, pharmaceutical and biotechnology companies, universities, and doctor groups often sponsor clinical trials.

What Is a Clinical Trial?

A *clinical trial* is a carefully designed research study that involves people who volunteer to participate. Clinical trials are also sometimes referred to as clinical studies. However, the term “clinical study” is broadly used to describe many different sorts of studies in addition to those described in this chapter.

The purpose of clinical trials in cancer is 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. In fact, new cancer treatments can only be identified through clinical trials. 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. Strict rules and oversight procedures make sure that clinical trials are designed and run in a way that protects the right 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 medication must pass through a strict approval process governed by the U.S. Food and Drug Administration (FDA) before it can become a standard therapy for use in people. The FDA-regulated approval process for medications 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 determine the correctness of the study.

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 medication is considered for approval by the FDA. Phase IV studies are performed after a medication has received FDA approval; these trials are sometimes called *postmarketing studies*. Each phase is designed to find out certain information, building upon the information learned from the previous phase. Patients may be eligible to take part in different types of clinical trials depending on their health status, stage of CLL/SLL, and type of treatment, if any, they previously received.

Table 10.1. The Four Main Types (or Phases) of Clinical Trials

Phase	Purpose	Number of Volunteer Patients
Phase I	<ul style="list-style-type: none"> ■ To identify a safe dose. ■ To decide on a schedule. ■ To see what side effects are related to the therapy. 	<ul style="list-style-type: none"> ■ 15–30 people with one or more different types of cancer.
Phase II	<ul style="list-style-type: none"> ■ To find out if a new treatment has an effect against a certain type of cancer. ■ To see if the treatment causes any side effects. 	<ul style="list-style-type: none"> ■ Usually less than 100 people with the same type of cancer. ■ Randomized Phase II studies involve more than 100 people in two study arms.
Phase III	<ul style="list-style-type: none"> ■ To compare new treatments or new uses of existing treatments with current standard treatments. ■ The main comparisons are usually how well the treatment works and what types of side effects it causes. 	<ul style="list-style-type: none"> ■ From 100 to several thousand people 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 effectiveness of a new treatment. ■ These trials take place after the drug has been marketed. 	<ul style="list-style-type: none"> ■ Several hundred to several thousand people with the same type of cancer.

Should a Patient Participate in a Clinical Trial?

Clinical trials are not a “last resort” for patients, and it may be important to note that all approved medications underwent evaluation before they were approved through the clinical trials process. Patients with all stages of CLL/SLL can participate in clinical trials, whether at the time of initial diagnosis or at relapse. Clinical trials offer both benefits and risks. Patients in clinical trials may be able to try new treatments that are not otherwise available to all patients. However, participating in the trial may mean that the patient receives the standard therapy. If the patient receives the new treatment, it may or may not be more effective than the standard therapy. Although new treatments are tested very carefully in animals and in the laboratory before they are used in a clinical trial, they may still have undesirable and/or unexpected side effects. The health of patients enrolled in clinical trials is monitored very carefully. The healthcare team studying the new treatment will 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, social workers, 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 would not interfere with current medication or treatments.

All of these trials are reviewed by a human rights committee comprised of lay people and doctors (IRB). No one can conduct a clinical trial without oversight.

Some professional organizations, like the National Comprehensive Cancer Network (which develops guidelines for doctors to use in treating patients with all types of cancers), actively encourage patients with cancer to participate in clinical trials because, in their opinion, clinical trials often provide the best management for difficult-to-treat cancers. Participating in clinical trials also means that a patient is providing a benefit to all future patients with CLL/SLL by helping researchers to test new and potentially better therapies for this disease.

What Is Informed Consent In a Clinical Trial?

Informed consent is a process through which patients learn all about the clinical trials they are interested in joining. During this process, members of the clinical trial research team will 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 will be expected to agree to
- The type of treatment provided in the study
- The possible risks, benefits, and alternatives
- The rights of patients to decide whether or not to participate, as well as their right to leave the study at any time

The research team will answer questions and provide written information about the trial. After the team explains all of the details and the patient does not have any more questions, he or she will be asked to read and sign an informed consent document before entering the study that details all the trial information discussed, describes how their records will be kept private, and shows that he or she was given information on the risks, potential benefits, and alternatives.

Remember that even after signing the consent form, patients can stop participating in the study at any time. If the patient leaves the study or decides not to take part in the study, the doctor will discuss the other treatment options available to them. Refer to the Patient Tip on Page 117 that outlines some helpful questions to ask the doctor about clinical trials.

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 (a sugar pill or saline solution with 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 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 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?

Why Is a Placebo Sometimes Used in Phase III Trials?

A *placebo* is an inactive ingredient that is used as a comparator in some clinical trials. Depending on whether the investigational agent is given by mouth or intravenous (IV) a placebo can be a sugar pill or an IV bag filled with an inactive saline solution. The placebo will be made to look and taste the same as the experimental pill or have the same appearance as an intravenous agent. The patients and the doctors and nurses treating them may not know what type of treatment is being given.

In cancer clinical trials, patients are never given a placebo in place of an effective standard therapy. Placebo-controlled trials are NEVER DONE in a manner that would deny patients an effective therapy. In most cases that a placebo is used, it is added to a standard regimen to compare the standard regimen to the standard regimen combined with an investigational agent. By using a placebo in addition to the standard regimen, patients cannot tell whether they are receiving the investigational agent or not.

In Phase III trials, patients are usually selected at random for either the experimental group receiving the study medication or the control group receiving the current treatment(s) for their particular lymphoma. Therefore, patients who are in the placebo group will still benefit from receiving the standard of care.

What Is the Cost of Participating in a Clinical Trial?

Clinical trials are very expensive undertakings for the study sponsor. However, the cost to the patient varies depending on the study, who is sponsoring the trial, what portion of the trial-related expenses the sponsor will cover, and the patient's health insurance coverage. A patient should ask his or her doctor about the potential cost of participating in any clinical trial under consideration.

In most instances, the law requires the healthcare plan to cover clinical trials. The March 2010 Affordable Care Act (ACA) states that all healthcare plans (offered through an employer or purchased through

an ACA exchange) that were newly issued or renewed on or after January 1, 2014, are not allowed to limit or deny coverage for people who decide to participate in an approved clinical trial. However, this patient protection provision does not apply to healthcare plans that existed before January 1, 2014. Some of these “grandfathered” plans do pay for the basic medical procedures associated with the trial, such as laboratory tests, scans, and hospitalization when required, while others may define clinical trials as “experimental” or “investigational” and not cover some of the routine costs, such as doctor visits, tests, or treatments. Medicare provides coverage for patient care associated with most clinical trials.

If a patient is taking part in an NCI trial being conducted at the National Institutes of Health (NIH) campus in Bethesda, Maryland, the NCI will pay for the study medication and the costs related to the study. Additional funding to assist with travel, food, and lodging expenses is also provided. Some cancer centers provide financial assistance or discounted rates for room and board and have special research units that will pay for study-related costs. Some organizations, including the Lymphoma Research Foundation (LRF), provide some financial assistance for treatment-related expenses. For more information on financial aid, please view the *Resources for Financial Assistance* fact sheet on LRF’s website at www.lymphoma.org.

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

- The LRF “Clinical Trials Information Service” can help conduct a search for potential lymphoma treatment trials. Contact the LRF Helpline at (800) 500-9976, email helpline@lymphoma.org, or visit LRF online at www.lymphoma.org/clinicaltrials_forpatients
- 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
- Cancer centers in the area

Part 5 — Clinical Trials and Advances in Treatment

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

Doctors and scientists around the world are working very hard to improve currently available treatment options and find better and safer medications 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, epidemiology, and supportive care. In particular, recent developments have provided a better understanding of the biology of the disease.

Medications that are not yet approved by the U.S. Food and Drug Administration (FDA) are considered to be investigational. Some of these investigational agents are being studied in laboratory experiments using tissue culture cells and laboratory animals. This phase is often referred to as the preclinical phase. The medications in more advanced stages of research are being studied in patients in clinical trials and are then referred to as being in the clinical phase of development.

The most common way for a patient to receive an investigational medication is through a clinical trial. To find out more about getting access to investigational medications, visit the National Cancer Institute's (NCI's) website at www.cancer.gov and search for "access to investigational drugs." Alternatively, visit the website at www.clinicaltrials.gov to search for trials using a particular medication or to find clinical trials nearby, or access the Lymphoma Research Foundation's (LRF's) "Clinical Trials Information Service" by phone (800) 500-9976 or email (helpline@lymphoma.org).

Remember that today's science is moving very fast. Please check with your doctor or LRF for additional information and recent updates.

For detailed discussion of currently approved treatment options, please see the "Treatments for CLL/SLL" chapter of this booklet on Page 53.

Chemotherapy

Researchers are trying to develop new chemotherapy agents, make improved versions of existing medications, and find better ways to combine different doses and sequences of existing medications. The goal is to make medications that are better at killing CLL/SLL cells while leaving healthy cells alone (decreasing the chance of side effects).

Monoclonal Antibodies

Monoclonal antibodies are medications that mimic our own immune proteins but they are designed to recognize and stick to specific target molecules on the surface of cancer cells. When a monoclonal antibody attaches itself to a CLL/SLL cell, it can stop or slow down its growth, or it can make it easier for the immune system to recognize and kill the cell.

The success of the monoclonal antibody rituximab (Rituxan) inspired researchers to develop other monoclonal antibodies to treat patients with various types of non-Hodgkin lymphoma (NHL), including CLL/SLL. This research led to the FDA approvals of the monoclonal antibodies alemtuzumab (Campath), obinutuzumab (Gazyva), and ofatumumab (Arzerra) for the treatment of patients with CLL/SLL. New combinations of some of these monoclonal antibodies and other medications are being investigated in clinical trials.

Targeted Therapies

A better understanding of the biology and genetics of CLL/SLL is helping researchers identify specific molecules within lymphoma cells that may be good targets for new medications. These molecules usually help control the growth and survival of lymphoma cells. The medications that target these molecules are broadly called targeted therapies. These medications may kill the lymphoma cells or slow down or stop their growth. Targeted therapies attack cancer cells in a more specific way than chemotherapy agents. Some targeted therapies are less likely to kill or damage healthy cells. This characteristic makes it less likely that these agents will cause serious side effects.

The first targeted therapy approved by the FDA for CLL/SLL was ibrutinib (Imbruvica), a tyrosine kinase inhibitor, which stops signals from BTK, a molecule inside B cells that is important for sending signals that are critical for the CLL/SLL cells to grow, move, divide, and survive. Idelalisib (Zydelig) was the first phosphoinositide 3-kinase (PI3K) inhibitor to receive approval from the FDA. The main job of PI3K (which comes in four forms: alpha, beta, delta, and gamma) is to transmit signals that help B cells grow, move, divide, and survive. Venetoclax (Venclexta)—an inhibitor of B-cell lymphoma 2 (Bcl2) which helps cancer cells survive and become resistant to treatments—was the first FDA-approved targeted medication for CLL that triggers cellular self-destruction by the process of apoptosis. Future clinical trials will help doctors determine the best ways to use these medications to treat CLL/SLL.

New Medications and Combinations in Clinical Trials

Many currently FDA-approved medications and new investigational agents for CLL/SLL are being studied in laboratories and in clinical trials. Some new regimens and agents are in Phase III clinical trials. For example:

- Duvelisib (IPI-145)
- Ibrutinib (Imbruvica) plus rituximab (Rituxan)
- Ibrutinib (Imbruvica) plus ublituximab (TG-1101)
- Obinutuzumab (Gazyva) plus chlorambucil (Leukeran) versus acalabrutinib (ACP-196) plus obinutuzumab versus acalabrutinib alone
- Obinutuzumab (Gazyva) plus venetoclax (Venclexta)
- Ublituximab (TG-1101) plus TGR-1202
- Venetoclax (Venclexta) plus rituximab (Rituxan)

Since research in CLL/SLL advances quickly, check with your doctor or LRF for additional information and updates.

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; to reduce or eliminate *graft-versus-host disease* in *allogeneic* (donor) transplantations; and to develop more effective reduced-intensity chemotherapy regimens for allogeneic 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 www.lymphoma.org/publications.

Genetically Engineered Autologous T Cells

Researchers have treated a small number of patients with CLL/SLL with genetically engineered immune cells, or T cells. T cells are removed from the patient and genetically modified to produce special receptors on their surface called *chimeric antigen receptors* (CARs), which allow them to recognize and kill CLL/SLL cells. The genetically engineered T cells that produce CARs are grown in the laboratory until they number in the billions and then are infused back into the patient (autologous). The CARs on the surface of T cells allow them to recognize a specific protein (antigen) on the tumor cells called CD19, so that the patient's own immune system can selectively kill CD19-positive B cells. CD19 is an ideal tumor target for CAR therapy because it is expressed on almost all CLL/SLL cells. This type of treatment is sometimes called CAR T-cell therapy and is only available through clinical trials.

Once infused into the body, the genetically modified cells can grow to large numbers and amplify the antitumor response, persisting for long periods of time and providing ongoing tumor control and possible protection against recurrence. Some patients have had very good responses, with no malignant tumor cells detected after treatment. However, this therapy can also result in significant side effects such as tumor lysis syndrome (TLS; described on Page 91) or cytokine release syndrome. Some patients have reduced *immunoglobulins* (antibodies) after treatment and require monthly gamma globulin supplementation.

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 advocacy, awareness, and fundraising programs—including the signature Lymphoma Walk program and Team LRF—which allow members of the lymphoma and CLL/SLL community to become involved with the organization and support the LRF mission. The LRF Advocacy Program provides volunteer advocates with the resources necessary to raise attention and 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.

Patient Education and 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 each lymphoma subtype and different treatment options; Financial Assistance Programs; In-Person Education Conferences; LRF Lymphoma Helpline; Lymphoma Support Network; Mobile App (www.FocusOnLymphoma.org); Teleconferences; and Videos, Webcasts and Podcasts. All programs and materials are offered free of charge. Learn more at www.lymphoma.org or www.FocusOnCLL.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.

Research

LRF is focused on finding a cure for lymphoma and CLL/SLL through an aggressively-funded research program and by supporting the next generation of lymphoma investigators. LRF supports Clinical Investigator Career Development Awards, Lymphoma Fellowships, and 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 funded nearly \$60 million in lymphoma-specific research.

Contact Information

Helpline: (800) 500-9976

National Headquarters: (212) 349-2910

Email: LRF@lymphoma.org

Websites: www.lymphoma.org or www.FocusOnCLL.org

Understanding CLL/SLL

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

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