Understanding CLL/SLL

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

A Guide for Patients, Survivors and Loved Ones

First Edition

LYMPHOMA RESEARCH • FOUNDATION

CLL Education Group

Understanding
CLL/SLL

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

A Guide for Patients, Survivors and Loved Ones

First Edition
Published by: Lymphoma Research Foundation, in collaboration with CLL Information Group
Editorial Board Chairman: Morton Coleman, MD

This guide is an educational resource compiled by the Lymphoma Research Foundation providing general information on chronic lymphocytic leukemia/small lymphocytic lymphoma.Publication of this information is not intended to take the place of medical care or the advice of your physician. Patients are strongly encouraged to talk to their physicians 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.

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Introduction

The Lymphoma Research Foundation (LRF) has previously produced, and now updated, guide books for non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) patients. Non-Hodgkin lymphoma, however, was treated broadly, covering the multiple subtypes of the disease.

In collaboration with the CLL Information Group (CIG), LRF has now prepared the first disease-specific lymphoma information book, focusing on chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). These two entities are essentially the same disease, presenting in two different locations—either the blood (CLL) or the lymph (SLL).

Although the two information books developed by LRF are invaluable in providing much general information to lymphoma patients, this booklet, a first in a series, focuses on one specific disease subtype, CLL.

For more information, visit

lymphoma.org
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Part 1: Learning the Basics

Chapter 1
Cancer Overview

Cancer Overview

Cancer is a group of diseases that develop as the result of uncontrolled growth and spread of abnormal cells. Our bodies consist of millions of cells that grow and divide in an orderly fashion and work in harmony to support thousands of biological functions. These cells divide only when it is necessary to replace worn-out or dying cells to keep the body healthy. Cancer cells are different from normal cells because, instead of dying, they continue to grow and divide, forming new, abnormal cells.

Cancer cells develop when there is damage to the DNA (the building blocks of genetic material found in every cell) that is caused either by inherited DNA cell damage or exposure to something in the environment, such as smoking. Oncogenes are packets of DNA that enable normal cells to turn cancerous. Usually the body is able to destroy these damaged cells, but when the body's natural defense systems do not work, these abnormal cells may grow in an uncontrollable fashion, eventually forming a cancerous tumor.

Overview of Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are considered B-cell malignancies, generally thought of as a non-Hodgkin lymphoma, and are essentially the same disease with slightly different manifestations. The same kind of cell, known as a lymphocyte (a type of white blood cell), is involved in both CLL and SLL. The only difference between the two diseases is where the cancer primarily occurs. When the cancer cells are located mostly in the lymph nodes (small, bean-shaped organs of the lymphatic system found in nearly every part of the body, including the elbows, neck, under the arms and groin), the disease is called SLL. When most of the cancer cells are located in the bloodstream and the bone marrow (the spongy tissue inside bones where blood cells are made), the disease is referred to as CLL, although the lymph nodes and spleen are often involved as well.

Thinking of CLL/SLL as a lymphoma and not a form of leukemia is important because CLL has a clinical course and treatment regimen that is similar to other indolent lymphomas. Chronic lymphocytic leukemia tends to be a slow-growing cancer. However, over time, it can progress to a more aggressive type of lymphoma. According to the American Cancer Society, approximately 15,000 new cases of CLL and 3,600 new cases of SLL are diagnosed annually. This form of cancer is usually diagnosed in older adults over the age of 50—more than half of the people with CLL are over age 70.

Causes of CLL

Normally, bone marrow produces blood stem cells (immature cells) that develop into mature blood cells and become either a myeloid (blood forming) stem cell or a lymphoid (a type of white blood cell) stem cell. The myeloid stem cell develops into one of three types of mature blood cells:

- Red blood cells, which carry oxygen and other materials to tissues in the body

- Neutrophils (white blood cells), which fight infection and disease
- Platelets, which help prevent bleeding by causing blood clots to form

The lymphoid stem cell develops into a lymphoblast cell (a lymphocyte that has become larger after being stimulated by an antigen) and then into one of three types of lymphocytes:

- B-lymphocytes (B-cells), which make antibodies to fight infection
- T-lymphocytes (T-cells), which help B-lymphocytes make antibodies to fight infection
- Natural killer (NK) cells, which attack cancer cells and viruses

When these cells grow old, they die naturally and are continuously replaced by new cells. Chronic lymphocytic leukemia occurs when there is damage to the deoxyribonucleic acid (DNA) of developing cells in the bone marrow. DNA acts as a blueprint for cells, instructing them how and when to grow and divide. Certain genes (packets of DNA), called oncogenes, cause cells to divide, while other genes, called tumor suppressor genes, slow down the process of cell division and cause cells to die normally (apoptosis) at the appropriate time.

In CLL, something occurs to disrupt the process of cell death such that the cells do not die as planned. Instead, the cells accumulate in the lymph nodes, bone marrow, blood stream and other organs. The increasing number of lymphocytes in the blood and bone marrow crowd out healthy white blood cells, red blood cells and platelets, which may result in infection, anemia and easy bleeding.

Although the exact mechanism that causes CLL is unknown, many people with the disease have chromosome abnormalities in their cells. Normal human cells have 23 pairs of chromosomes. Some people with CLL have an extra chromosome or some other abnormality.

Risk Factors for CLL

Anything that increases a person's risk for contracting a disease is called a risk factor. Unlike other forms of cancer, CLL has few known risk factors. Some studies suggest that certain environmental factors might play a role, including exposure to herbicides and insecticides used in farming or the defoliant Agent Orange used during the Vietnam War.

It is important to remember that the presence of one or more risk factors does not mean that CLL will develop. In fact, most people with risk factors never develop the disease and many who are diagnosed have no known risk factors.

How the Immune System Works

The immune system consists of a network of cells, tissues and organs that defend the body against "foreign" invaders (such as bacteria or viruses) or abnormal cells. Our ability to survive exposure to both external invaders and internal cell mutations (abnormalities) largely depends on the immune system. The immune system is the body's first defense against disease. It is made up of highly specialized cells and a circulatory system separate from blood vessels called the lymphatic system. The specialized cells and the lymphatic system work together to rid the body of foreign invaders or abnormal cells before they can harm the body. These invading organisms and abnormal or cancerous cells are generally detected by the immune system through antigens (proteins that are located on the surface of all cells). Special receptors located on the immune cells lock on to these antigens. And just as a lock will only close with the right key, an antigen will only lock with a specific cell from the immune system. When an antigen and an immune cell lock together, the immune response begins, and the body acts to destroy, remove or wall-off the foreign invaders or abnormal cells.

In CLL, the risk of infection is heightened due to a compromised immune system from the cancer and/or its treatment. About 75 percent of CLL patients will have hypogammaglobulinemia, a condition in which the level of immunoglobulins (antibodies) in the blood is low (hypo). This condition increases the risk for infection, despite the fact that CLL patients have the

normal amount of infection-fighting B-cells. One reason may be that the body's T-cells, which help the B-cells make antibodies to fight off infection, are not working properly. CLL patients also have defective activation of a group of blood proteins called the complement system, which help fight common bacteria to which these patients are susceptible. To ward off infections, it is best to stay up-to-date on vaccines for pneumonia and influenza, although they may not work as well because of the impaired immune system resulting from CLL. Chronic lymphocytic leukemia patients should also avoid live vaccines (e.g., chicken pox vaccine).

In addition, T-cell dysfunction may also be responsible for altering the immune system, causing it to attack healthy red blood cells (autoimmune hemolytic anemia) and platelets (thrombocytopenia). This can result in fatigue, shortness of breath and bleeding disorders. (See "Signs and Symptoms of Chronic Lymphocytic Leukemia," on page 11.)

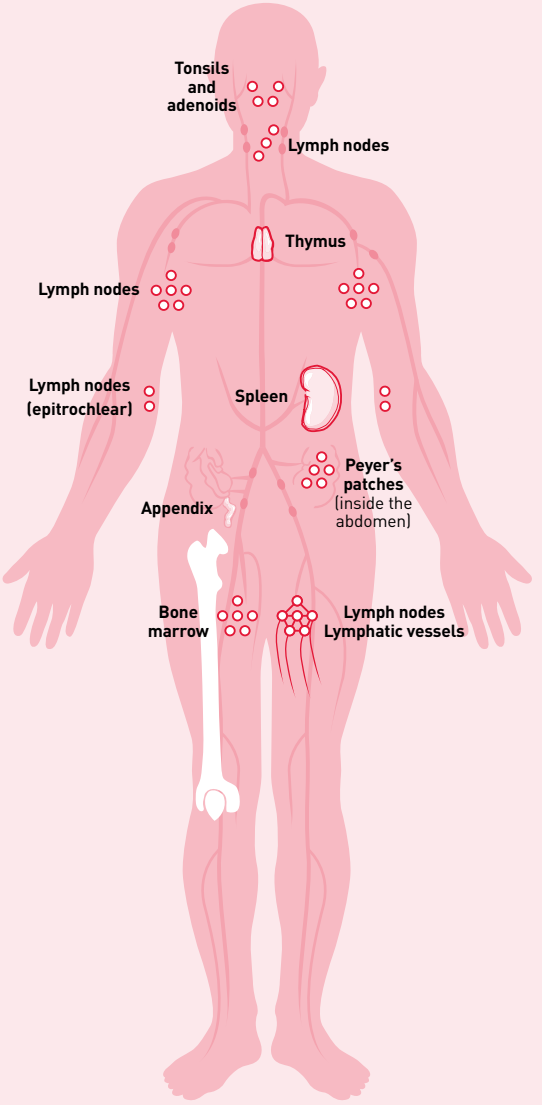
How the Lymphatic System Works

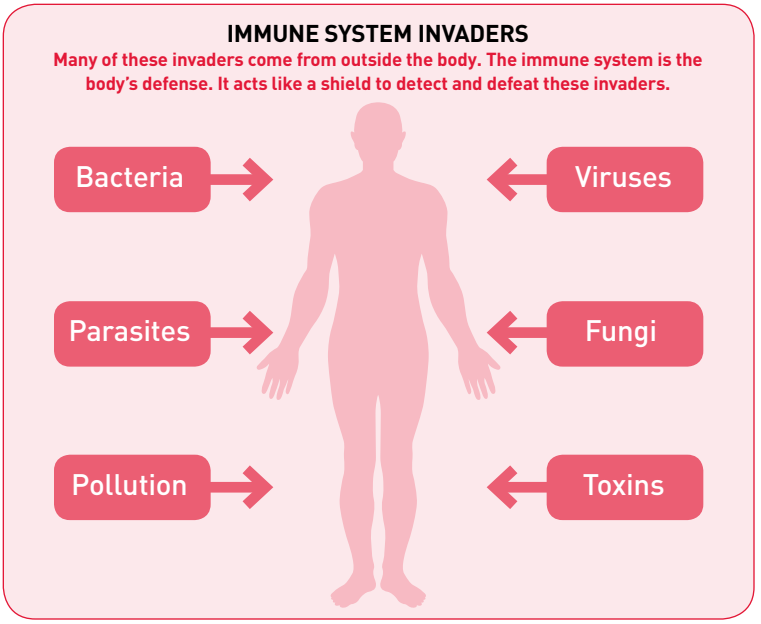
The lymphatic system is one of the most important parts of the immune system because it protects the body from disease and infection. The lymphatic system is a circulatory system made up of a series of thin tubes called lymph vessels that branch like blood vessels into all tissues of the body (see page 8). Lymph vessels carry lymph, a transparent fluid that contains white blood cells called lymphocytes. Within this vast network of vessels are groups of small, bean-shaped organs called lymph nodes. Thousands of lymph nodes are found throughout the body, including the elbows, neck, under the arms and groin. Lymph flows through lymph nodes and specialized lymph tissues such as the spleen, tonsils, bone marrow and thymus gland.

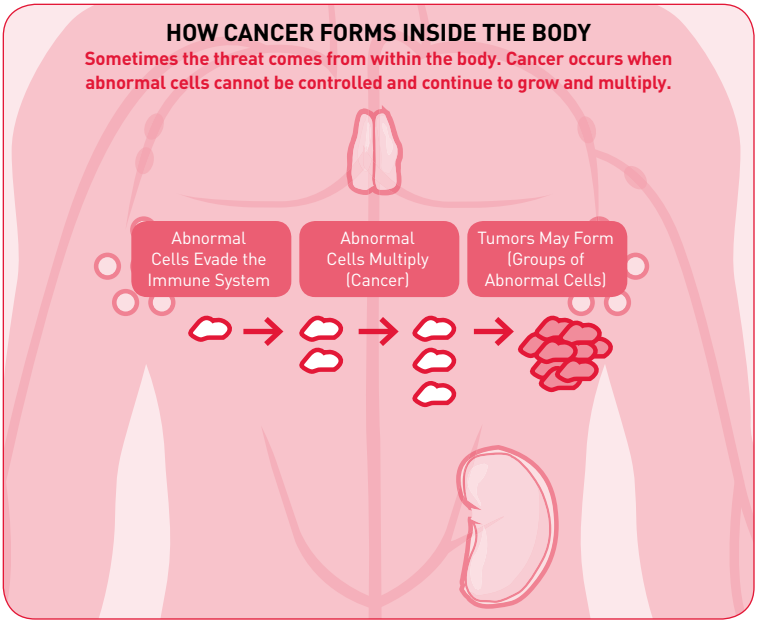
Lymph nodes filter lymph fluid, removing bacteria, viruses and other foreign substances from the body. If a large number of bacteria are filtered through a node or series of nodes, they may swell and become tender to the touch. For example, if a person has a sore throat, the lymph nodes under their jaw and in their neck may swell. Most swollen nodes are a reaction to infection and are not cancerous.

ANATOMY OF THE IMMUNE SYSTEM

The immune system is the body's defense against outside invaders.




IMMUNE SYSTEM INVADERS
Many of these invaders come from outside the body. The immune system is the body's defense. It acts like a shield to detect and defeat these invaders.
Bacteria
Viruses
Parasites
Fungi
Pollution
Toxins


HOW CANCER FORMS INSIDE THE BODY
Sometimes the threat comes from within the body. Cancer occurs when abnormal cells cannot be controlled and continue to grow and multiply.
Abnormal Cells Evade the Immune System
Abnormal Cells Multiply (Cancer)
Tumors May Form (Groups of Abnormal Cells)

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Chapter 2
Signs and Symptoms of Chronic Lymphocytic Leukemia

A symptom is anything out of the ordinary a patient is experiencing that could be caused by a disease. A sign is any abnormality that a healthcare professional discovers upon examination of a patient.

Oftentimes, people with CLL have no obvious symptoms of the disease at diagnosis. In fact, the cancer is usually discovered during a routine medical examination. According to experts, about one-third of all CLL patients will live for years—and even decades—without symptoms or serious ramifications of having the disease. Another one-third of patients will require therapy immediately or will be symptomatic within three to five years, requiring treatment. Another one-third will experience intermediate disease progression in which the cancer is dormant and then becomes active, but will respond to treatment. It is important to remember, however, that every person is unique.

Symptoms of CLL occur because the malignant B-cells accumulate in certain areas of the body, such as in the blood, bone marrow, lymph nodes and spleen, crowding out healthy cells and causing a range of problems. For example, when malignant cells take up space in the lymph node, the lymph node enlarges (lymphadenopathy). When they take up space in the bone marrow, they may affect the blood cells in the following ways:

- Because red blood cells carry oxygen from your lungs to all parts of your body, a shortage of red blood cells (anemia) can cause shortness of breath, fatigue and pale skin.
- A shortage of healthy white blood cells (leukopenia) and/or neutrophils (a type of white blood cell), referred to as neutropenia or granulocytopenia, can make the body prone to developing infections. Even though CLL patients frequently have high white blood cell counts, the cells are not functioning properly and do not protect against infection the way normal white blood cells do.

- Blood platelet cells help prevent and control bleeding and promote blood clotting. When there is a shortage of blood platelets (thrombocytopenia), patients may experience easy bleeding, including frequent nosebleeds, bleeding from the gums or tiny red marks caused by minor hemorrhaging in the skin (petechiae). Patients may also bruise more easily.

Chronic lymphocytic leukemia can also cause swelling of the liver and spleen and enlargement of the lymph nodes in the neck, underarm, stomach or groin. Other symptoms of CLL include:

- Fever and/or chills
- Severe weight loss in which ten percent of the baseline body weight is lost within six months
- Profuse night sweats
- Profound fatigue

It is important to acknowledge that it is not clear what causes these symptoms.

When to Seek Medical Attention

Although symptoms in the early phases of CLL are often vague and nonspecific, it is important that anyone who has persistent symptoms be seen by a physician to make sure that CLL is not the cause. The onset of CLL symptoms is a signal that the cancer is active and an indication that treatment should be started.

What the Physician Looks for During a Physical Examination

Often, CLL does not cause symptoms. The first suspicion that something might be wrong may come from blood tests showing blood cell count abnormalities. However, physical symptoms may also be present and alert physicians of potential disease. Patients should tell their physician if they have been experiencing a general decline in health or have any of the following symptoms:

- Painless swelling of the lymph nodes in the neck, underarm, stomach or groin
- Fatigue
- Pain or fullness below the ribs
- Fever and infection of the skin, lungs, kidneys or other sites
- Weight loss

The physician will take a medical history and perform a complete physical examination, checking for signs of disease, such as swelling of the lymph nodes, spleen and liver, and listening to the heart and lungs. The physician will also measure blood pressure and the pulse and look for any physical signs of infection or any other cancers, especially on the skin. If the physician suspects CLL after reviewing the symptoms and the results from the examination, other tests may be ordered to help confirm the diagnosis. These tests should include a complete blood count (CBC) and may include biopsies from a lymph node and/or the bone marrow and specific laboratory tests.

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Chapter 3
Getting a Diagnosis—What to Expect

Getting an accurate assessment of CLL requires a number of diagnostic tests. First, a hematopathologist (a physician who studies tissues and cells to identify blood diseases) or a hematologist (a physician specializing in blood disorders, including CLL) will examine blood and possibly bone marrow samples under a microscope looking for abnormal cells and changes in the structure or number of chromosomes in the lymphocytes. The hematopathologist or hematologist will also determine whether the lymphocytes are those of CLL or another type of leukemia or lymphoma.

Depending on a patient's situation, a physician may use some or all of the following tests, as well as a medical history and a physical examination, to select the course of treatment with the best chance of controlling the disease.

Laboratory Studies

General Blood Chemistry Studies

After the blood cells have been removed during blood testing, the fluid portion that remains is analyzed to help determine how well vital organs, such as the liver and kidneys, are performing. An unusual (higher or lower than normal) amount of a substance can be a sign of disease in the organ or tissue that makes it. During treatment, general chemistry tests may also be used to identify liver or kidney damage caused by the therapy regimen or other complications of the disease. Levels of immunoglobulin, a blood protein, may also be evaluated to ensure that there are enough antibodies to fight infections. Immunoglobulin levels are often low in people with CLL. Elevated levels of another blood protein, called beta-2-microglobulin, can indicate a more advanced stage of CLL.

LABORATORY TESTS
COMPLETE BLOOD COUNT

Blood tests are routinely performed to diagnose CLL and are later used to determine how well treatment is working and whether the cancer is progressing. Information from a complete blood count (CBC) shows the characteristics and amounts of blood cells, including the number of red blood cells, the amount of hemoglobin (a protein found in red blood cells that carries oxygen), the different types of white blood cells (lymphocytes, monocytes, neutrophils, basophils and eosinophils) and platelets, and whether abnormal cells are present.

Most people with CLL will have high levels of lymphocytes (lymphocytosis). Sometimes, CLL patients may not have enough red blood cells or have abnormal levels of platelets.

Common Tests Used to Evaluate CLL

Laboratory tests:

- General blood chemistry studies
- Flow cytometry
- Immunohistochemistry
- Polymerase chain reaction (PCR)
- Mutational status
- Fluorescence in-situ hybridization (FISH) and conventional chromosomal analysis
- Other tests

Biopsies:

- Lymph node biopsy (not usually necessary and may be performed when clinically indicated)
- Bone marrow examination and aspiration (not necessarily performed to diagnose CLL but is performed when clinically indicated)

Imaging tests:

- X-ray
- CT (computerized axial tomography) scan (not routinely performed)
- PET (positron emission tomography) scan (not routinely performed)

Flow Cytometry

Flow cytometry is performed using samples of blood treated with light-sensitive chemicals, which are then passed in front of a laser beam. The amount of light given off by the sample identifies the presence of various cellular proteins. This technique measures specific proteins and/or antigens on cells and "clusters of differentiation," called CDs. Cells carry these markers on their outer surface. The type and strength of expression of these markers help physicians determine whether the disease is CLL. The markers classically characteristic of CLL are CD5, CD20, CD23 and CD52.

Immunohistochemistry

Immunohistochemistry is a test in which the cells in a sample of lymph node tissue, blood or bone marrow are examined under a microscope to look for the presence of abnormal cells associated with CLL and to determine whether the malignant lymphocytes originated from B-lymphocytes or T-lymphocytes. The tissue samples are treated with fluorescent chemicals that attach themselves to the malignant cells and are then looked at under a microscope to identify the abnormal cells.

Polymerase Chain Reaction (PCR)

Polymerase chain reaction (PCR) is a specialized molecular test performed on either blood or bone marrow samples to identify malignant cells based on the cells' genetic abnormalities. This test is primarily used following treatment to monitor the patient's disease.

Mutational Status

The mutational status of a gene known as IgV_H may predict how quickly CLL might progress. Every B-cell rearranges its genes to make specific antibodies to a particular target (antigen), which, for instance, may be on a bacteria. When CLL is derived from cells that undergo the change to make antibodies (mutated genes), an individual will have a more indolent (slow-growing) course of disease. A person with un-mutated (unchanged) IgV_H will likely have a more progressive and/or aggressive disease than those with the mutated gene.

Fluorescence In-Situ Hybridization (FISH)

Fluorescence in-situ hybridization (FISH) is a test in which special fluorescent proteins are used to detect changes in the structure or number of chromosomes in the lymphocytes in samples of blood or bone marrow. Identifying these abnormalities helps physicians predict how CLL will progress.

In CLL, abnormalities in chromosomes 11, 12, 13 and especially 17 are of particular interest. Chromosome 17 carries the p53 gene, which has an effect on regulating cell death (apoptosis). The normal functioning of the p53 gene is important in the response to chemotherapy. Loss of part of chromosome 17 is associated with particularly aggressive CLL.

Other Tests

Other tests may include lactate dehydrogenase (LDH), tests for anemia and other tests the physician deems necessary.

Biopsies

A biopsy is a procedure in which a piece of tumor tissue or bone marrow is removed from the body and examined under a microscope to look for abnormal cells.

Lymph Node Biopsy

A "core biopsy" is obtained by inserting a needle into a lymph node suspected of being cancerous and removing a small tissue sample. An "excisional biopsy," in which an entire lymph node or a generous wedge of tissue is surgically removed, is often the preferred method because it provides ample tissue for the pathologist to make an accurate diagnosis. A lymph node biopsy is not always necessary, however, it may be performed when clinically indicated.

Bone Marrow Examination and Aspiration

Bone marrow is the spongy, soft material found inside our bones. Bone marrow contains immature cells called stem cells, which develop into three main types of cells found in the body:

- red blood cells that deliver oxygen to all parts of the body and take away the waste product carbon dioxide
- white blood cells that protect the body from infection
- platelets that help blood clot

A bone marrow biopsy is obtained using a needle to remove a sampling of tissue most often from the back of the hipbone. During a bone marrow examination, physicians first numb the area around the skin, tissue and surface of the hipbone with a local anesthetic.

While a bone marrow biopsy is not required to diagnose CLL, it can sometimes be performed when clinically indicated. The procedure can be painful at the moment when the marrow is withdrawn. Patients who are anxious about the test should talk with their physician and nurse to see whether taking a calming medication before the procedure would be helpful.

Imaging Tests

Physicians will often order medical imaging tests to assess the condition of internal organs. These may be done as part of the overall diagnosis, to look for signs of cancer in internal organs, in preparation of treatment or as part of follow-up care. Most of these tests are painless and no anesthetic is required. Several types of imaging procedures may be needed to evaluate the CLL, including:

X-Ray

X-rays use radiation to take pictures of areas inside the body. In CLL, an X-ray may be performed to examine the organs and bones. The amount of radiation used in most diagnostic tests is so small that it poses little risk to the patient.

CT (computerized axial tomography) Scan

A CT scan takes X-rays from different angles around the body and is used to generate detailed cross-sectional images as well as three-dimensional images of the body's internal organs. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. The

pictures obtained are then combined using a computer to give a detailed image. People with CLL may have CT scans of the chest, abdomen and pelvis. These tests are useful in determining how many nodes are involved, how large they are and whether internal organs are affected by the disease.

PET (positron emission tomography) Scans

PET scans evaluate CLL activity in all parts of the body. To perform the test, a radioactive glucose (sugar) tracer substance is first injected into the body. A positron camera is then used to detect the radioactivity and to produce cross-sectional images of the body. PET scans are not routinely performed in CLL except when transformation to a more aggressive disease is suspected.

Other Tests

In addition to these tests, physicians may also order tests to evaluate the health of organs potentially affected by treatments, such as the heart (echocardiograms or radionuclide tests) and lungs (pulmonary function tests).

QUESTIONS TO ASK YOUR PHYSICIAN BEFORE HAVING A PROCEDURE

- Why is this procedure necessary?
- What will the procedure tell us about my condition?
- What is involved in doing this procedure?
- What are the possible risks, complications and side effects?
- Will I feel pain?
- What will my out-of-pocket costs be?
- Will I need someone to take me home afterwards?

Staging

After a CLL diagnosis is confirmed, the stage of the disease will be determined. The Rai Staging System is used in the United States to determine the amount of disease, or tumor burden, that is present in patients with CLL. The Binet Classification System is more commonly used in Europe. It is important to note that the staging system used for CLL is different from other lymphomas because of the involvement of blood and bone marrow from the outset. The Rai Staging System is divided into five stages as follows:

Stage 0 - Low risk. Lymphocytosis (an abnormal increase in the number of lymphocytes, a type of white blood cell, in the blood) is present in the blood or bone marrow only.

Stage 1 - Intermediate risk. Lymphocytosis, plus enlarged lymph nodes.

Stage 2 - Intermediate risk. Lymphocytosis, plus enlarged spleen and/or enlarged liver, with or without enlarged lymph nodes.

Stage 3 - High risk. Lymphocytosis, plus anemia (low red blood cell count), with or without enlarged lymph nodes, spleen or liver.

Stage 4 - High risk. Lymphocytosis, plus thrombocytopenia (low platelets), with or without anemia, enlarged lymph nodes, spleen or liver.

When to Begin Treatment

A physician uses clinical judgment when deciding when to start treatment, although the Rai Staging System often plays a large role in this decision. The standard of care for stage 0 disease is observation. Only when a patient is participating in a treatment research study would he or she be offered any treatment.

Patients with an intermediate risk category (stage 1 or 2) are generally observed. However, patients with poor prognostic markers (such as Zap-70 positive, unmutated IgV_H genes, CD38 positive or certain types of chromosomal abnormalities) may be offered therapy early. It should be noted that confirmatory data for this approach are not currently available. Studies are now being performed to help determine whether early intervention for patients with poor prognostic markers is or is not useful. Patients in stage 3 and 4 generally require treatment.

Getting a Second Opinion

Before starting therapy, patients may want to consider getting a second opinion to confirm the diagnosis and treatment plan, particularly if some aspects of the CLL are complicated or uncertain. Some insurance programs require second opinions; others may cover it if a patient or physician requests it.

Sometimes second opinions are obtained at academic medical centers. The hematologists/oncologists specializing in lymphoma may provide a consultation and establish a collaborative relationship with a local oncologist for treatment and follow-up care.

When seeking a second opinion, patients should remember that it is best to request a complete copy of all medical records and provide original X-rays, pathology materials, scans and reports that are requested by the consulting physician. It may be useful to keep a copy of the medical records. A second opinion is not considered adequate unless another pathologist, preferably one well versed in CLL, reviews the tissue and blood samples. A patient's physician or healthcare team can often recommend an oncologist for a second opinion.

Choosing an Oncologist and Treatment Center

Before agreeing to treatment by a physician or clinic, a patient should be certain that all of their medical and personal needs will be met. Take time to check: (1) the credentials of the physician, the other members of the medical team and the hospital or cancer center, (2) the portion of time the physician spends researching or treating CLL and (3) the patient resources within the cancer center.

Patients should keep in mind that if in a managed care program, choices may be limited. However, if a patient is not entirely satisfied with their first consultation, they have the right to choose another healthcare team. Referrals may be obtained by speaking with other CLL patients or asking their primary physician. It is important that patients feel comfortable with their healthcare team and the quality of care they are receiving.

QUESTIONS TO ASK WHEN CHOOSING A PHYSICIAN AND TREATMENT CENTER

Before beginning treatment, ask these basic questions:

- How much experience does this physician (or clinic) have in treating cancer in general and lymphoma in particular? How many patients with lymphoma are being treated here now?
- Is the physician board certified as an oncologist or hematologist? Has he or she passed qualifying examinations by the American Board of Internal Medicine that certify his or her competency in these specialties?
- How does the physician or clinic stay up-to-date on the latest treatments for CLL?
- Do the oncologists or hematologists in the clinic participate in clinical trials?
- Does this center have state-of-the-art surgical facilities and diagnostic equipment?
- Is the physician or clinic professionally affiliated with any major medical centers or medical schools?
- What arrangements are made for medical coverage after hours and on weekends in case of an emergency?

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Part 2: Treating Chronic Lymphocytic Leukemia

Chapter 4
What You Should Know Before Starting Treatment

Getting a CLL diagnosis is frightening and patients are naturally concerned about what their future may hold. Oftentimes, patients will ask their physician about their outlook or prognosis, the medical term used to describe how the disease will progress and the likelihood of recovery. To be an educated healthcare consumer, it is important to understand the nature of CLL and what to expect from treatments, including any possible effects on quality of life, such as lifestyle, emotions and financial issues.

Prognosis is usually based on information gathered from hundreds or thousands of other patients who have had the same disease. This statistical information provides physicians with a general idea of what to expect when a patient is diagnosed with CLL and also gives guidance on the kinds of treatments that have been most successful in treating CLL. However, it is important to remember that ***no two patients are alike and that statistics from large groups of people do not always accurately***

predict what will happen to a particular patient. A physician most familiar with an individual patient's situation is in the best position to help interpret these statistics and determine their applicability.

It is also important to remember that while progress has been made in understanding CLL there are no known prognostic markers physicians can use to determine how CLL will progress in individual patients, when to begin treatment or which treatments will be most effective. The one exception appears to be in CLL patients with a p53 deletion on chromosome 17. In those patients, the purine analogue fludarabine (Fludara), one of the most commonly prescribed chemotherapy drugs in CLL, may not be effective.

Prognostic Factors Affecting Treatment Outcome

There are several traditional prognostic markers physicians use to determine when to start therapy and the type of treatment for each patient. They include:

- The Rai stage at diagnosis
- Lymphocyte doubling time (doubling in less than 3-6 months is associated with an unfavorable prognosis)
- Pattern of bone marrow involvement
- Age (younger people may tolerate the effects of more aggressive treatment because they generally have fewer health problems, such as heart or lung disease, that could limit the type or dose of therapy)
- The presence of beta-2-microglobulin in the plasma (higher levels imply a poorer prognosis)
- Number of circulating prolymphocytes (precursor of a lymphocyte) in the blood

Novel Prognostic Markers

Over the last decade, several novel prognostic markers have been identified and may be more accurate in predicting disease outcome. They include:

- **CD38 antigen expression -** CD38 is a protein attached on the outside of leukemia cells. The presence of CD38 suggests a faster disease progression, although scientists still do not completely understand why CD38 plays a role in CLL. In addition, the exact level of expression for a cell to be considered "positive" is under debate.

- **Fluorescent in-situ hybridization (FISH) -** This technique is useful in finding common recurring chromosomal abnormalities in CLL, which reflect gene abnormalities. In CLL, chromosomes 11, 12, 13 and 17 are of particular interest. Hematologists pay particular attention to aberrations (variations from the normal) in chromosome 17, where the p53 gene is located, because the normal function of p53 seems to be crucial in how well patients respond to chemotherapy (See page 18 for additional description).

- **Immunoglobulin heavy chain variable gene mutation status (IgV_H) -** The mutational status of the IgV_H gene helps predict how quickly CLL may progress. Patients with mutated IgV_H are more likely to have an indolent (slow-growing) course of CLL. Patients with unmutated IgV_H are more likely to have a progressive and/or aggressive disease.

- **ZAP-70 expression -** ZAP-70 is an intracellular molecule involved with cell activation. The exact level of ZAP-70 seems to be crucial in deciding if a patient is positive or not for ZAP-70. The presence of ZAP-70 is associated with faster disease progression. The absence of ZAP-70 is associated with slower disease progression.

- **CD49d gene expression -** CD49d is a surface protein on the outside of the CLL B-cell. Recent studies have shown that CD49d can be reliable in determining overall survival and when to initiate treatment. CD49d is measured by flow cytometry testing and is a potential therapeutic target.

It is very important to recognize that at this time the use of these novel prognostic markers is not fully understood and research is ongoing.

Performance Status

Performance status is used to describe a person's ability to follow a typical lifestyle. Those with good performance status (people who are active) tend to respond better to treatment than those with poor performance status (people with chronic health problems or those so ill that they are confined to bed), because they can tolerate more intensive therapy. Performance status is ranked on a scale from 0 to 5, with 5 having the poorest performance status.

Communicating With Your Healthcare Team

People who are diagnosed with CLL are often anxious to learn all they can about their disease and treatment choices so they can play an active role in decisions about their care. For many people, getting a CLL diagnosis is shocking and it is normal to feel a lot of physical and emotional stress following diagnosis. Some people are uncertain about how to talk with physicians, and the combination of stress and uncertainty may make it difficult to know what to say or what questions to ask.

Patients can ease their anxieties by establishing an open and honest dialogue with their physician and nurse regarding their diagnosis, and learning 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 of the questions that come to mind. Before meeting with a physician or nurse, whether for the first time or for follow-up visits, organize and write out all questions. Put the two or three most important questions at the top of the list, since time with physicians or nurses may be limited. But 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.

Also, it is helpful for patients to have a member of their family or a close friend accompany them to the physician's office or clinic to help ask questions and understand and remember answers. It can also be helpful to write down the answers to the questions. Some patients bring a

recording device to record the answers. Patients should check with their physician 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. Oncology social workers are also available to assist with practical and emotional needs from the point of diagnosis onward.

Although family members are often very concerned about their loved one and want information concerning his or her care, growing confidentiality rules prohibit physicians from giving out information to anyone without the patient's expressed permission. For efficiency, it is suggested that one family member be designated as the family contact to the physician. However, the patient must inform their physician who this individual will be in advance.

TIPS ON COMMUNICATING WITH YOUR PHYSICIAN

- Keep a journal of your symptoms to help you remember the details you want to discuss with your physician during your office visit and then bring a list of your questions to your appointment.
- During your office visit, take notes or tape record your conversation to help you accurately review the information afterward. Bringing along a family member or friend for support and to take notes for you is also helpful.
- Do not be afraid to ask questions when you do not understand something. Physicians want to know how best to explain information to you.
- Before leaving the physician's office, make sure you understand the next step in your care and ask if there is written information you can take home.

Writing an Advance Healthcare Directive and Appointing a Healthcare Proxy

Writing down wishes for critical medical care in an advance healthcare directive is a way that patients can inform their physician, family members and friends about their healthcare preferences and what special treatment they want or do not want at the end of life. Besides stating medical care instructions, the advance healthcare directive should also include the name of the patient's healthcare proxy, or decision maker. This person should be someone the patient believes will carry out their wishes if they are unable to do so, including do not resuscitate (DNR)

instructions. Before writing an advance healthcare directive, it is important that patients understand their rights and the laws regarding advance healthcare directives in their state. Consulting an attorney can provide the legal information, but patients do not have to use an attorney to write an advance directive. Some things a patient should consider when writing an advance healthcare directive include:

- Specific instructions on the medical care, including the types of special treatment a patient wants or does not want, such as cardiopulmonary resuscitation (CPR), artificial respiration, drugs to make the heart function, kidney dialysis, artificial feeding and certain surgical procedures.
- A patient's choice of healthcare proxy.

How to Be a Self-Advocate

Being a self-advocate and an active participant in healthcare can be a positive experience and may help restore a sense of control that was lost following diagnosis. It is important for patients to remember that they are a partner in their treatment plan and many patients feel better when they actively participate in their care. The first steps in participating in treatment are to ask questions, learn about options and work closely with the physician. Patients must be comfortable with their physician and the approach that they take. If not, patients should openly discuss their concerns. Confidence in the medical team often leads to confidence in treatment. If the patient does not feel that the team is a good match, they should ask for a referral.

Questions will likely vary depending on the purpose of the meeting with the oncologist (e.g., the initial visit to discuss the diagnosis as opposed to a routine visit to monitor a remission). Ask for the timing of office visits, treatments and tests. The physician can help explain what the tests will look for and define the possible responses and the 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 treatment and who may have had similar concerns can be a source of great comfort for patients. If a patient is interested in talking to and learning from people

who have had similar experiences, they should ask their oncologist, hematologist, oncology nurse or the oncology social worker about any support groups in their area. Patients should consider joining the Chronic Lymphocytic Leukemia Information Group (CIG) at cllinfogroup.org and signing up for CLL-specific discussion groups (See page 91 for instructions). The *Lymphoma Support Network*, a nationwide buddy program that matches patients or caregivers, offers the opportunity to share experiences and information, and offers support and encouragement. For more information about this program, call (800) 500-9976 or e-mail support@lymphoma.org.

Before any tests are performed, a patient should check with their healthcare team to determine which costs are covered by insurance and which are not. A patient should not be afraid to broach nonmedical issues, such as transportation, finances, insurance and childcare, with the healthcare team.

TIPS ON SELF-ADVOCACY

- Do not be afraid to ask your physician or nurse questions about your care.
- Learn more about your CLL from reliable websites, such as the Chronic Lymphocytic Leukemia Information Group (cllinfogroup.org) or the Lymphoma Research Foundation (lymphoma.org). Or ask your physician for information specific to CLL.
- Take advantage of other services offered at your physician's office, cancer center or hospital, such as counseling, support groups, nutritional counseling and fitness classes.
- Consider joining the Chronic Lymphocytic Leukemia Information Group (CIG) at cllinfogroup.org
- Sign up for one of several discussion groups (cllsll@yahoogroups.com or cll@acor.listserv.com)
- Contact the *Lymphoma Support Network*, a nationwide buddy program that matches patients or caregivers. For more information about the program, call (800) 500-9976 or e-mail: support@lymphoma.org.

QUESTIONS TO ASK BEFORE TREATMENT BEGINS

- What is my exact diagnosis?
- What is the stage of my CLL?
- What are my treatment options? Which do you recommend for me? Why?
- What are the risks and possible side effects of each treatment?
- What side effects should I report to you?
- Are there any late- or long-term side effects I should be aware of with the treatment?
- How long will the treatment last?
- What are the chances that the treatment will be successful?
- How will the treatment affect my normal activities?
- Are new treatments being studied? Would a clinical trial be appropriate for me?
- What is the treatment likely to cost? Does my insurance cover it?

For more information, visit

lymphoma.org
cllinfogroup.org

Chapter 5
Types of Treatment Currently Available

Fifty years ago, the only therapies available for people with CLL were the alkylating agents chlorambucil (Leukeran) and cyclophosphamide (Cytoxan). Today, there are numerous effective treatment options available to physicians and patients including those recently approved (e.g., bendamustine), although a cure for the disease remains elusive. Generally, CLL manifests as either an indolent (slow-growing), asymptomatic disease that requires no initial treatment or a more aggressive form that requires immediate treatment.

The last decade has seen dramatic advancements made in both better prognostic tests and novel therapies for CLL. A better understanding of the biology of CLL and the microenvironment around the tumor cells is resulting in more effective, less toxic treatments. While the ultimate goal for researchers remains finding a cure for CLL, the goal that appears closer at hand is the ability to turn the disease into a long-term, chronic illness in which patients will be able to experience a high quality of life.

This chapter includes a description of standard and approved therapies, including: (1) watchful waiting, (2) conventional chemotherapy approaches, (3) newer versions of established agents, (4) monoclonal antibodies, (5) stem cell transplantation, (6) radiation therapy, (7) splenectomy and (8) complementary and alternative remedies. For each section, a description of the mechanism of action will be presented, along with the therapies approved by the United States Food and Drug Administration (FDA) at the time of print. It is important to remember that new therapies may have been approved since this book went to print and that additional indications for the therapies discussed in this chapter may be granted as clinical trials reveal new uses. Refer to Chapter 12 for therapies under investigation. For the most up-to-date resources, visit lymphoma.org or fda.gov.

Watchful Waiting

Watch and wait has been the standard approach to care in asymptomatic CLL patients. However, the long-standing approach is coming under closer scrutiny as better targeted, less toxic drugs are making their way to the clinic. Early results from clinical studies are showing that there may be a benefit in treating patients at the time of diagnosis, even some in early stage, when they are healthier and better able to tolerate therapy. There are also some indications that early treatment may give cancer cells less time to develop resistance to the therapy. Studies are underway now in the United States in CLL patients with high-risk prognostic factors as determined, for example, by the presence of an unmutated immunoglobulin heavy chain variable gene, to determine whether they would benefit from immediate therapy with the purine analogue fludarabine (Fludara) and the monoclonal antibody rituximab (Rituxan). A similar study in Europe looks at early therapy of asymptomatic patients with this gene mutation as a well as other poor prognostic factors to see if such intervention with fludarabine (Fludara), cyclophosphamide (Cytoxan) and rituximab (Rituxan) could improve their outcome compared to treatment only at disease progression. However, these studies are ongoing and no conclusions can be drawn at this time.

Results from these studies will not be known for years. In the meantime, CLL patients with so-called high-risk prognostic factors in early stage disease may want to discuss with their hematologists/oncologists the advantages and disadvantages of early treatment and whether to participate in a clinical trial. It is important to keep in mind, however, that prognostic markers predict how well a population of patients will do, but not how one individual patient will do. They are not generally used to determine when to initiate therapy. However, based on recent studies, it appears that the knowledge of these prognostic factors is likely to influence the selection of the most appropriate therapy when it is indicated.

Chemotherapy

Chemotherapy ("chemo") is a cancer treatment with drugs (as opposed to radiation, for example). Many different medications are used to either kill cancer cells or prevent them from growing. Because of how they

work, chemotherapy drugs may also have a similar effect on rapidly dividing normal cells such as hair, nails and the cells in your mouth. People with advanced or symptomatic CLL are generally treated first with chemotherapy in combination with monoclonal antibodies (proteins that bind specifically to the tumor cells and kill them, sparing normal tissues). Chemotherapy regimens in CLL are generally well tolerated.

Combining Chemotherapy Drugs

Chemotherapy for lymphoma often consists of giving several drugs together (combination chemotherapy) in a defined way (schedule), called a treatment regimen. Drug combinations are used because different medications damage or kill cancer cells in different ways, making them more vulnerable to the treatment. Combining chemotherapy drugs provides a more effective way to kill more tumor cells because using the drugs together greatly augments the impact each drug would have if used individually or additively. This is called synergism. In addition, when some drugs are added together in lower doses, it helps reduce the likelihood of side effects without reducing the overall amount of effective chemotherapy.

Chemotherapy Cycles

Chemotherapy is usually given in cycles in which each treatment is followed by several weeks of rest and recovery. Together, each period of treatment and nontreatment is called a chemotherapy cycle. A chemotherapy cycle is typically given every one, two, three or four weeks. The medicines are usually given according to a schedule, with a defined number of days passing between each time the drugs are given.

Clinical trials have determined how often chemotherapy should be given to kill the most tumor cells while minimizing side effects. A typical chemotherapy regimen and cycle for CLL may include fludarabine (Fludara) and rituximab (Rituxan) or fludarabine (Fludara), cyclophosphamide (Cytoxan) and rituximab (Rituxan) given every day for three to five days, followed by no treatment for three to four weeks. Usually up to six cycles of the treatment are given, unless the regimen is ineffective or intolerable side effects develop necessitating the therapy be stopped. Also, fewer cycles are given if additional chemotherapy is thought to be less curative than harmful.

How Chemotherapy Is Given

Depending on the chemotherapy regimen, the type of drugs and the number of cycles, a patient may receive drugs in pill form, as an injection or as an intravenous push or drip. If patients are going to receive intravenous drugs (ones that are given through a vein) for multiple cycles, their physician may recommend having a catheter inserted. An intravenous catheter is a device that is put into a vein to make it easier to give drugs. Catheters may be left in place temporarily or permanently.

There are several types of catheters. One type, called a Hickman-Broviac catheter, consists of one to three tubes inserted through the chest wall into a vein. Six to twelve inches of tubing remains outside the skin. The main advantage of this type of catheter is that blood tests can be drawn and drugs given without having to pierce the skin. Disadvantages include: (1) the possibility of infection, particularly if the catheter is not cared for properly, and (2) the tubes on the outside of the body make it more obvious that a catheter is in place. If patients have this type of catheter, the healthcare team will show them what needs to be done each day to care for it and to make sure it stays clean.

A second type of intravenous catheter, called an Infusa-Port or Portacath catheter, is placed under the skin and appears only as a bump on the chest. The advantage of this catheter is that it is easier for patient care because it only needs to be maintained by a nurse once a month (called "flushing"). However, it also has disadvantages. Each time this type of device is used, an injection through the skin is required, and it may not always be convenient to draw blood samples. These devices may also occasionally clot.

Another type of intravenous catheter is a peripherally inserted central catheter or PICC line, which uses a thin, soft plastic tube to deliver medicines and fluids through a large vein in the arm. The PICC line can be kept in place for months. It is a good option for patients who need to have many short infusions or continuous infusions given in a hospital or at home with a portable pump for a defined, shorter time.

Patients should discuss the pros and cons of the different types of catheters with their physician. A patient's situation and personal preferences will be considered in making this decision.

COMMON TYPES OF DRUGS CURRENTLY AVAILABLE FOR THE TREATMENT OF CLL

Combination Chemotherapy

CHOP
- Cyclophosphamide (Cytoxan)
- Doxorubicin or Hydrodoxydaunorubicin (Adriamycin, Rubex)
- Vincristine (Oncovin)
- Prednisone (Deltasone)

CHOP-R
- Cyclophosphamide (Cytoxan)
- Doxorubicin or Hydrodoxydaunorubicin (Adriamycin, Rubex)
- Vincristine (Oncovin)
- Prednisone (Deltasone)
- Rituximab (Rituxan)

Monoclonal Antibodies
Alemtuzumab (Campath)
Ofatumumab (Arzerra)
Rituximab (Rituxan)

Immunomodulatory Drugs (Imids)
Lenalidomide

Alkylating Agents
Bendamustine (Treanda)
Chlorambucil (Leukeran)
Cyclophosphamide (Cytoxan, Neosar)
Oxaliplatin (Eloxatin)

Purine Nucleoside Analogues
Cladribine (Leustatin, 2-Cda)
Fludarabine (Fludara)
Pentostatin (Nipent)

Steroids
Prednisone, dexamethasone (Decadron, Dexasone)
Methlyprednisolone (Solu-Medrol)
Hydrocortisone

Newer Versions of Established Agents

Scientists continuously examine new uses for established agents and also explore how to create newer versions of existing therapies to make them more effective and less toxic. The drug below represents a therapy recently approved in the United States for CLL.

Bendamustine (Treanda)

Bendamustine (Treanda) is a novel alkylating agent that damages the DNA in tumor cells, thereby disrupting the cell cycle and causing cell death. Approved originally for clinical use in Germany for cancer, the US FDA approved bendamustine in 2008 for the treatment of indolent B-cell NHL that has progressed during or within six months of receiving rituximab (Rituxan) or a rituximab-containing regimen. It has also been approved to treat CLL.

Data based on randomized controlled trials in Europe have now begun to suggest that rituximab (Rituxan) and bendamustine (Treanda) may have a more favorable toxicity profile and equivalent or better efficacy in patients with indolent lymphoma who have been treated with other combination chemotherapy regimens such as R-CVP and R-CHOP. The implications of this data have begun to suggest that this two drug combination regimen may spare patients exposure to multiple chemotherapy drugs and toxicity from these agents without comprising efficacy. Future clinical trials will continue to validate these observations and will begin to study bendamustine (Treanda) in combination with numerous novel therapeutic agents in CLL and other forms of lymphoma.

Monoclonal Antibodies

Plasma cells, the most mature B-lymphocytes in the body, are blood cells that specialize in making antibodies. Each plasma cell is responsible for one antibody, otherwise known as a monoclonal antibody (MAb). Each MAb acts specifically against a particular antigen, which is sort of like a beacon that attracts antibodies produced by immune cells. Using new technologies, scientists can now produce large amounts of monoclonal antibodies that can be directed to a single antigen on the cell's surface. A MAb is similar to a guided missile that homes in on an antigen target on the lymphoma cell and destroys the cell.

A number of strategies involving the use of MAbs to treat cancer are being studied, including: (1) MAbs that react or bind with specific types of cancer cells, thereby enhancing a patient's immune response to the cancer, (2) MAbs that are attached to other anticancer drugs, toxins or radioisotopes, allowing the delivery of these drugs directly to the tumor and bypassing toxicity to most normal cells, and (3) MAbs that are used to help purge and destroy cancer cells remaining in stem cell preparations before the latter is infused in autologous bone marrow transplantation.

Alemtuzumab (Campath)

Alemtuzumab (Campath) was the first Food and Drug Administration (FDA)-approved monoclonal antibody specifically for the treatment of CLL and targets the antigen called CD52. It works very well in patients whose CLL cells are confined to blood and bone marrow. It does not appear to work alone very well in patients with very large lymph nodes or spleen. However, in these situations, it has been used successfully in combination with other MAbs like rituximab (Rituxan) or with chemotherapy. Alemtuzumab (Campath) may increase susceptibility to certain viral, fungal and bacterial infections, and it is mandatory to use medications to prevent these infections while on this drug.

Ofatumumab (Arzerra)

Ofatumumab (Arzerra) is another monoclonal antibody that targets the CD20 antigen, which is found on the surface of CLL cells. The FDA granted the accelerated approval of ofatumumab (Arzerra) for the treatment of patients with CLL whose disease is refractory to fludarabine (Fludara) and alemtuzumab (Campath) in fall 2009. Unlike other monoclonal antibodies, ofatumumab (Arzerra) binds to a specific part of the CD20 protein on the surface of cells called the small loop epitope. This drug kills cells by recruiting proteins called "complement," that lead to cell death. It also induces antibody dependent cellular cytoxicity by recruiting the body's natural killing cells to kill CLL cells. As this drug was just recently approved by the FDA, future editions of this book will provide more detail.

Rituximab (Rituxan)

Rituximab (Rituxan) was the first monoclonal antibody approved for the treatment of lymphoma. It targets the protein antigen called CD20, which

Common Combination Drug Regimens Used to Treat CLL

Regimen Abbreviation	Drugs
CHOP	Cyclophosphamide (Cytoxan) Doxorubicin or Hydrodoxydaunorubicin (Adriamycin, Rubex) Vincristine (Oncovin) Prednisone (Deltasone)
CHOP-R	Cyclophosphamide (Cytoxan) Doxorubicin or Hydrodoxydaunorubicin (Adriamycin, Rubex) Vincristine (oncovin) Prednisone (Deltasone) Rituximab (Rituxan)
FR	Fludarabine (Fludara) Rituximab (Rituxan)
FCR	Fludarabine (Fludara) Cyclophosphmide (Cytoxan, Neosar) Rituximab (Rituxan)
PCR	Pentostatin (Nipent) Cyclophosphmide (Cytoxan, Neosar) Rituximab (Rituxan)
OFAR	Oxaliplatin (Eloxatin) Fludarabine (Fludara) Cytarabine Rituximab (Rituxan)
CFAR	Cyclophosphmide (Cytoxan, Neosar) Fludarabine (Fludara) Alemtuzumab (Campath) Rituximab (Rituxan)
BR	Bendamustine (Treanda) Rituximab (Rituxan)
BCR	Bendamustine (Treanda) Cyclophosphmide (Cytoxan, Neosar) Rituximab (Rituxan)
HDMP + Rituximab	High-Dose Methylprednisolone (Solu-Medrol) Rituximab (Rituxan)

is found on the surface of most CLL cells. Rituximab (Rituxan) is currently approved in Europe for the frontline treatment of CLL. In February 2010, rituximab (Rituxan) in combination with fludarabine (Fludara) and cyclophosphamide (Cytoxan, Neosar) was approved by the United States Food and Drug Administration (FDA) for the treatment of patients with previously untreated CD20-positive CLL as well as previously treated CD20-positive CLL.

Stem Cell Transplantation

Stem cell transplantation is often divided into two types: (1) autologous, where the patient's own hematopoietic stem cells are collected and transfused into the patient following some chemotherapy or radiotherapy (i.e., myeloablative therapy) and (2) allogeneic, when hematopoietic stem cells are collected from a related or unrelated donor and transfused into the patient. Typically, the sources of stem cells used in transplant include bone marrow, peripheral (circulating) blood and cells collected from the umbilical cord after a baby is born.

Depending on the type of transplant (autologous versus allogeneic) and the extent of disease, the type of myeloablative therapy used will vary. Typically, autologous stem cell transplants rely on high doses of chemotherapy to eradicate residual lymphoma. In contrast, allogeneic and umbilical cord transplants rely on an immunologically mediated anti-tumor effect (i.e., graft versus lymphoma) mediated by the donor stem cells.

In CLL, the patient's own hematopoietic stem cells are rarely used because they are often contaminated with the CLL. Usually in CLL, cells from a donor are used, most commonly in a reduced intensity allogeneic transplant. The utility of "reduced intensity" allogeneic transplantation (sometimes referred to as "mini-allogeneic transplantation") in patients with CLL is well established and found to be better tolerated than the fully myeloablative transplants. In reduced intensity transplants, the patient receives low doses of chemotherapy or radiation, usually just enough to allow the body to accept the new cells from a donor. This approach is used to take advantage of the graft versus CLL effect, in which the transplanted donor cells recognize the tumor as a foreign entity and activate T-cells to destroy the cancer. Patients who experience a

graft versus CLL effect may remain in remission for a longer period. Also, because patients receive lower doses of chemotherapy, they may avoid some of the toxicities seen with higher dose chemotherapy.

In CLL, transplantation is a treatment option typically reserved for patients whose CLL does not respond to standard therapies, although for those with high risk features, transplant is being investigated earlier in the disease course. Those patients whose disease has transformed into a more aggressive form of lymphoma, called Richter's syndrome, could potentially benefit from a stem cell transplant.

For more detailed information about stem cell transplantation, please visit the National Marrow Donor Program's website at marrow.org.

Radiation Therapy

Radiation therapy (also called radiotherapy) uses high-energy X-rays to kill cancer cells and shrink tumors. Radiation is a local therapy, which means it only affects cancer cells in the treated area. While radiation therapy is not commonly prescribed in the treatment of CLL, it is sometimes used in patients with limited disease to relieve symptoms associated with bulky lymph nodes that develop as CLL cells accumulate.

Radiation therapy used for localized CLL is called involved-field radiation in which the X-ray beam is directed only at the affected tissues. To prepare for radiation therapy, the skin is marked with tiny ink dots called "tattoos" so the exact same area will be treated every time. Before the first treatment, the healthcare team devotes a substantial amount of time marking the body to make sure that specific areas receive radiation. Normal tissues around the radiation field are shielded by lead, which blocks the path of stray radiation beams. Patients lie still on a table beneath a large machine that delivers the radiation. Props and supports with plastic forms, pillows and rolled blankets help keep patients in position. Once the preparations have been made, it takes only a few minutes to deliver the prescribed dose. Generally, treatment is given five days a week for five to six weeks.

Splenectomy

Some patients with CLL will develop a very large spleen due to an accumulation of CLL cells, which can cause discomfort or pressure. While radiation or chemotherapy are effective in relieving symptoms, removing the spleen usually provides longer lasting benefits, including increases in red blood cells and platelet counts. Patients who have their spleen removed are more vulnerable to certain infections, which, if not treated, could be life threatening. It is important for patients who have their spleen removed to start antibiotics early (almost immediately) if they develop a fever.

Patients should be given the pneumonia vaccine prior to splenectomy even though the immune response by patients with CLL is less than optimal.

Complementary and Alternative Remedies

The concept of holistic medicine to treat the mind, body and spirit became popular in the 1970s and is commonly known today as complementary and alternative medicine, but the terms have distinctly different meanings. Alternative therapy refers to unproven or disproven treatments that are used instead of standard or proven therapy. Complementary therapy is used in addition to standard medicine to help improve a patient's quality of life and to relieve the effects of chemotherapy, radiation and surgery. Currently, there are no viable alternative therapies to conventional cancer care, and CLL patients should never use alternative remedies in lieu of standard care.

Complementary medicine, also known as integrative medicine, includes a vast array of mind/body therapies such as meditation, guided imagery, self-hypnosis, tai chi and yoga; touch therapies, such as massage, reflexology and Reiki; acupuncture; and nutrition. However, because some complementary practices, such as ingesting certain herbs or botanicals, may negatively impact cancer treatment, CLL patients should consult with their healthcare team before embarking on any integrative medicine plan.

How Integrative Medicine Helps

- Acupuncture—Acupuncture may relieve pain, nausea, fatigue, hot flashes and neuropathy (numbness and tingling in the feet and hands) associated with chemotherapy; and may help decrease mild depression. Done using new ultra-thin needles applied to specific points on the body, acupuncture is safe and painless.
- Mind/Body Techniques—Meditation, guided imagery and self-hypnosis may be used to manage stress. Yoga and tai chi minimize stress and improve balance and flexibility.
- Touch Therapies—Massage, reflexology (foot massage) and Reiki involve applying therapeutic pressure to the body and restore a sense of harmony, relaxation and well-being.
- Nutrition—Eating a healthy, well-balanced diet is recommended for patients undergoing treatment.

What to Avoid

Some supplements may increase or reduce the effectiveness of chemotherapy drugs. Patients should speak to their physician about everything they are taking or considering taking, including all over-the-counter medications, vitamins, herbs and other supplements, especially during times of treatment.

Drug Costs: What to Do if Your Insurance Does Not Pay

Many cancer patients today face the problem of how to pay for soaring healthcare costs. Cancer organizations like the Lymphoma Research Foundation (lymphoma.org) and CancerCare (cancercare.org) offer limited financial assistance to patients who qualify. Most pharmaceutical and biotechnology companies have patient assistance programs in place that provide drugs for free to qualifying patients. If you are in need of financial assistance, talk with your physician about available options and how to enroll in an appropriate program. Also, drugs are often free in clinical trials.

Part 3: Disease and Treatment Side Effects

Chapter 6
Transformations, Complications and Side Effects

Chronic lymphocytic leukemia patients may experience a range of side effects from the treatment they receive. The various treatments, including chemotherapy, chemoimmunotherapy (a combination of chemotherapy and monoclonal antibodies), radiation and steroids, cause different side effects. Fortunately, there are many effective ways to make them more tolerable. In many cases, side effects can be lessened with medications or lifestyle changes.

Transformations

One of the most serious complications of CLL is the progression or transformation to a more aggressive form of non-Hodgkin lymphoma known as diffuse large B-cell lymphoma. Also called Richter's syndrome, this type of transformation is rare, with a risk of about one percent per year. CLL can also result in other forms of cancer including Hodgkin lymphoma and multiple myeloma. In some cases, a compromised immune

system and/or the Epstein-Barr virus may be responsible for the transformation. Transformation can be difficult to treat especially in patients who have received prior chemotherapy. Patients with transformation often have fever, night sweats, weight loss, elevated LDH (lactate dehydrogenase) and characteristic changes on the PET scan.

Prolymphocytic Leukemia

Prolymphocytic leukemia (PLL) is a relatively rare transformation of CLL. It is a variant of CLL with a more aggressive course of illness.

Myelodysplastic Syndrome and Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are rare complications of CLL treatment. The transformation may be the result of certain combinations of chemotherapy agents, including chlorambucil (Leukeran) and other alkylating agents such as cyclophosphamide (Cytoxan), which damage the DNA of blood-forming cells. These damaged cells can become malignant leading to MDS and AML.

Complications

Tumor Lysis Syndrome

Tumor lysis syndrome consists of a group of metabolic complications usually occurring at the beginning of therapy when there are a high number of cancerous cells circulating in the body. This syndrome occurs when tumor cells release a number of waste products. Because the kidneys must clear these wastes, the rapid response to therapy can stress the kidneys, sometimes causing renal failure. Tumor lysis syndrome is usually manageable by the administration of fluids and/or slowing down CLL treatment. The drug allopurinol (Zyloprim) is often used prophylactically in patients who may be prone to tumor lysis syndrome. Rasburicase (Elitek) may also be used in high risk cases.

Shingles

Shingles is a reactivation of the varicella-zoster virus, the same virus that causes chickenpox. Shingles usually causes a skin rash that blisters and stops abruptly in the midline of the body. This is associated with pain that can be severe. There are effective treatments for shingles, including the antiviral drugs acyclovir (Zovirax) and valcyclovir (Valtrex). However,

the best results are only achieved when shingles is treated early after onset. Delays in treatment often cause prolonged and even permanent pain in the involved regions of the body. Although vaccines are available to reduce the risk of shingles, they use live viruses and are not advisable for people with compromised immune systems, such as those with blood cancers. Also, patients receiving a purine analog or combination chemotherapy are placed on prophylactic (preventative) antiviral drugs (e.g., acyclovir or famvir) and/or medications (e.g., bactrim or septra) to prevent certain opportunistic infections, such as pneumocystis pneumonia (PCP).

Side Effects

Side Effects Caused by Chemotherapy

Chemotherapy is generally most effective at killing cells that are dividing rapidly, such as cancer cells. However, chemotherapy drugs are not selective. Therefore, they can also affect normal healthy cells, especially cells that are fast growing, such as hair cells and those in the mouth, the gastrointestinal tract and the bone marrow. Some chemotherapy drugs may also damage heart cells. Side effects of chemotherapy can vary widely depending on the types of drugs that are given and an individual patient's response. Side effects can be mild or serious. Some of the most common side effects caused by chemotherapy include the following:

Changes in Taste

Some patients will experience a change in the way foods or beverages taste. Familiar foods sometimes taste differently (called dysgeusia) or the flavors of foods are not as strong (called hypogeusia). Some patients may also feel that foods have a metallic taste. These side effects are temporary and typically disappear after chemotherapy is completed.

Decreased Blood Cell Production

Red blood cells, white blood cells and platelets are constantly being produced in the bone marrow. Both chemotherapy and chemoimmunotherapy treatment may temporarily interfere with the ability of the bone marrow to produce adequate numbers of blood cells. When this occurs, it is called myelosuppression.

SOME COMMON SIDE EFFECTS CAUSED BY CHEMOTHERAPY

- Changes in taste
- Decreased blood cell production
- Diarrhea
- Fatigue
- Hair loss
- Mouth sores
- Nausea/vomiting
- Sexual dysfunction
- Sterility
- Secondary cancers

Anemia is the term used when myelosuppression causes a reduction in the number of red blood cells. Anemia can cause people to feel very tired and have shortness of breath. Mild or moderate anemia is common with many chemotherapy regimens, and treatment for the anemia may be necessary.

Neutropenia is the term used when myelosuppression causes a decrease in neutrophils—the primary type of white blood cells found in the blood. Because neutrophils play a very important role in fighting infection, a low count may cause patients to develop serious or even life-threatening infections that require hospitalization or antibiotic therapy. Also, if the absolute neutrophil count (ANC) is too low, the chemotherapy dosage may need to be reduced or treatment delayed rather than risk infection. Infection is often accompanied by fever. Other symptoms of infection may include chills and night sweats.

To prevent and control neutropenia, physicians will check patients' white blood cell and neutrophil counts before and during each chemotherapy cycle. When neutropenia threatens a patient's ability to receive the planned dose of chemotherapy, drugs such as filgrastim (Neupogen), pegfilgrastim (Neulasta) or sargramostim (Leukine) can be given after chemotherapy to reduce the duration and severity of neutropenia. These drugs can sometimes cause bone pain and, if in the chest, may make patients think they are having a heart attack. Nonsteroids may relieve this pain rapidly. By keeping the white blood count from dipping too low, these medications can help keep your chemotherapy doses on schedule. Occasionally, oral antibiotics are given to help prevent infection when neutrophil counts are low.

Thrombocytopenia is the term used when myelosuppression depletes the number of platelets in the blood. Platelets help start the clotting process when bleeding occurs. If platelet counts are low, patients may bruise easily. A low platelet count may also cause prolonged or excessive bleeding from cuts, nose bleeds, bleeding from the gums or bleeding without a previous injury. A platelet transfusion may be needed in some cases.

Risk of Infections

A normal white blood cell count ranges from 4,000 to 10,000. Physicians regularly monitor the absolute neurtophil count (ANC), the number of neutrophils in the peripheral blood. When the ANC drops below 1,500, patients are at high risk for contracting infections. If a fever of 100.5°F or greater develops, patients should immediately contact their physician or go to the emergency room.

TIPS FOR DETECTING INFECTION DUE TO LOW BLOOD CELL PRODUCTION

Report these symptoms immediately to your healthcare team:

- Fever (greater than 100.5°F)
- Sore throat
- Rash
- Diarrhea
- Redness, swelling or pain around a wound
- Cough

Diarrhea

Diarrhea can be a side effect of chemotherapy. While most patients do not experience severe diarrhea, the most important thing to remember is to avoid dehydration (a loss of body fluids). Report any bloody diarrhea or fever with diarrhea to your healthcare team.

Fatigue

Fatigue is a common side effect of many types of chemotherapy. Fatigue should go away after treatments are over, but it can take weeks or months until it is completely gone.

Hair Loss

One side effect of chemotherapy is hair loss (also called alopecia). Thinning or loss of hair can occur at any place on the body, including the scalp,

TIPS FOR AVOIDING DEHYDRATION FROM DIARRHEA OR VOMITING

- Drink plenty of liquids.
- Look for signs of dehydration, including dry mouth or skin, decreased urine and dizziness or lightheadedness when you stand up.
- Avoid milk products, which can worsen diarrhea.
- Avoid hard-to-digest foods, such as those high in fiber, which can worsen diarrhea.
- Eat plenty of bananas and other high-potassium foods (check with your physician or dietitian to make sure these foods will not interfere with your chemotherapy or other medications you are taking).
- Take the medicines that your physician recommends to control diarrhea (notify your healthcare team if diarrhea occurs).

eyebrows, eyelashes, arms, legs and pelvis. The hair loss may be variable. It is important to note that hair loss does not occur with all drugs. Remember that hair loss due to chemotherapy is usually temporary. At first, the new hair growing in may be a slightly different texture or color than it was before treatment, but it oftens returns to normal.

Mouth Sores

The membranes of the mouth may become red, sore or irritated during chemotherapy, which is referred to as mucositis. Infections of the mouth and throat caused by viruses or fungi may also occur. If throat soreness occurs, the healthcare team will examine the throat and may do a swab (called a culture) to check for infection, particularly herpes, fungus and bacterial infections. If an infection is present, several medications are available to treat it.

To help reduce the risk of mouth infections, a physician may request a complete dental checkup and cleaning before receiving chemotherapy.

Nausea or Vomiting

Chemotherapy can cause nausea or vomiting. Drugs that prevent vomiting (called antiemetics) include aprepitant (Emend), ondansetron (Zofran), granisetron (Kytril), metoclopramide (Reglan), prochloperazine (Compazine)

TIPS FOR COPING WITH FATIGUE

- Keep a diary to help you identify when you have the most energy and what activities make you feel fatigued or give you energy. This can help you plan your activities for the times when you have the most energy.
- Ask for help. This may be difficult for many people. Accept help if someone offers to assist you or if you need something you do not have the energy to do for yourself. Many family members or friends are happy to give assistance.
- Exercise if your physician says it is okay to do so. But do not overdo it. Simple stretching, range-of-motion exercises or a short walk may give you more energy and not decrease the energy you have. Begin slowly and build up to the level that is right for you. Your physician, nurse or physical therapist can help you create a personal exercise plan.
- Rest and sleep during therapy are very important, but try not to rest more than necessary, because it may decrease your energy level. Many patients find that taking an afternoon nap leaves them feeling less fatigued for the rest of the day, but others find that napping causes less restful nighttime sleep. If you are having trouble sleeping, talk to your healthcare team to determine the reason and what you can do about it.

TIPS FOR CARING FOR HAIR LOSS

These steps can help alleviate chemotherapy-induced hair loss:

- Pat your hair dry rather than rub it with a towel after shampooing.
- Use a soft-bristle brush and a wide-tooth comb when grooming your hair.
- Avoid curlers and hair dryers.
- Avoid coloring your hair or using chemicals on it.
- Some people use a wig, scarf, turban or soft cotton hat or head wrap. Some health insurance companies cover the cost of wigs with a prescription from your physician. Check your policy to see if you are covered.
- Use a hat or scarf to protect your scalp when out in the sun.

TIPS FOR PREVENTING OR CARING FOR MOUTH SORES

- Keep your mouth clean. Use a soft-bristle toothbrush, nonabrasive toothpaste and lip moisturizer.
- Avoid mouthwashes that contain alcohol. Your physician or nurse may recommend a swish-and-swallow mouth rinse.
- Avoid citrus fruits and juices.
- Avoid spicy foods.
- Eat soft foods while you are taking chemotherapy to avoid bruising the membranes in your mouth.
- Avoid flossing your teeth if your blood counts are low.

TIPS FOR CONTROLLING OR MINIMIZING NAUSEA AND VOMITING

- Consume a liquid diet before chemotherapy such as broth, consommé or water. Avoid milk.
- Avoid foods that are too hot, cold, sweet or spicy.
- Eat smaller and more frequent meals rather than a few large meals each day.
- Avoid strong or offensive odors. Get plenty of fresh air.
- Take prescribed antiemetics **before** chemotherapy to prevent nausea.
- If vomiting occurs, be careful to avoid dehydration (loss of body fluids).

and dolasetron (Anzemet), and a variety of corticosteroids, such as Deltasone (prednisone). Nausea most frequently occurs on the day chemotherapy is administered, but it can also start several days later.

Physicians may prescribe an antiemetic before chemotherapy to prevent nausea. In most cases, antiemetics can partially or completely prevent nausea and vomiting.

Sexual Dysfunction

Chemotherapy can cause a drop in libido (sex drive). Usually, a normal libido returns after treatment is finished. (See "Sexuality," on page 59.)

Sterility

Chemotherapy (and radiation) can sometimes cause either temporary or permanent sterility (the ability to have children) in both men and women, because the treatment may damage sperm and egg cells. The specific dose of treatment, whether the patient has received one or several therapies and the patient's age at the time of treatment are all contributing factors to infertility side effects.

Patients should speak with their physicians about fertility presevation before starting treatment. (See "Fertility Risks," on page 61.)

Other Possible Side Effects

Some of the other possible side effects of chemotherapy include cough, a decrease in lung function, skin rashes and general weakness. Some drugs may also cause damage to the nervous system called peripheral neuropathy. Nerve damage can cause side effects such as constipation or a tingling sensation in the fingers and toes. Patients should immediately report any painful local rash (which sometimes may be accompanied by blisters) to their physician. Other possible side effects include a sore throat and a loss of balance or coordination. Although many of these effects are temporary, some may last for an extended period.

Side Effects Caused by Radiation

In CLL, radiation therapy (or radiotherapy) is sometimes used to shrink an enlarged spleen or swollen lymph nodes, eliminating symptoms stemming from those growths. Radiation therapy uses an invisible radioactive ray or beam of high-energy particles aimed at specific sites to kill cancer cells. While radiotherapy is painless, there are side effects associated with the treatment. The consequences of radiation therapy depend on the treatment dose, the part of the body being treated (usually side effects occur only in the specific area of the body being radiated) and the age of the patient, among other factors. Some common side effects caused by radiation therapy in CLL patients include:

- Diarrhea or constipation
- Fatigue
- Nausea
- Secondary cancers
- Skin reactions

Radiation may also cause a drop in the number of white blood cells, which help protect the body against infection. Therefore, white blood cells will be monitored during treatment.

Fatigue

The likelihood that patients will experience fatigue depends on their disease and the specific radiation plan. (See page 51 for tips on overcoming fatigue.)

Nausea

Nausea may occur after radiation treatment, especially in patients who have radiation to the abdomen. Some people can avoid nausea if they eliminate eating (especially sweet, spicy or fatty foods) a few hours before radiation treatment. Taking a medication that prevents nausea (an antiemetic) before each radiation therapy session may be recommended. (See page 52 for additional tips regarding coping with nausea and vomiting.)

Skin Reactions

Radiation can cause a slight to moderate reddening of the skin and is often accompanied by discomfort, itching and flaking. These skin changes usually diminish and disappear over a few weeks.

During radiation treatment, patients can protect their skin by:

- Avoiding exposing areas of the skin that are receiving radiation to the sun. These areas will always need extra protection, even after treatment is completed.
- Wearing a T-shirt and using plenty of sunscreen (with a high SPF) when out in the sun.

Side Effects Caused by Steroids

Steroid drugs, such as cortisone, dexamethasone and prednisone, may cause a variety of side effects, including insomnia (the inability to fall asleep), increased appetite, mood or personality changes, high blood pressure and weight gain. Prednisone may also trigger diabetes in patients

prone to that disease or make the diabetes worse in patients who already have the disease. High-doses of steroids may also cause osteoporosis in at-risk patients. Patients are advised to alert family and friends that personality changes may occur. Patients should avoid making hasty decisions. If personality changes occur, the physician should be informed—the dose may need to be reduced.

Long-Term Effects and Late Effects of CLL

Long-term effects are defined as toxicities that happen during cancer treatment and continue for months or several years, such as fatigue, flu-like symptoms and chronic infections due to decreases in red and white blood cells and/or platelets. Late effects are side effects of cancer treatment that become apparent only after treatment has ended and may arise many months, years or even decades after treatment is completed, such as, infertility, osteoporosis and secondary cancers. People with CLL are at an increased risk for contracting secondary cancers, especially malignant melanoma and other skin cancers, soft-tissue sarcomas, lung cancer as well as other common cancers (e.g., breast, colon). People with CLL are also at risk for developing secondary leukemias. The combination of B-lymphocyte and T-lymphocyte defects and low gammaglobulin levels all conspire to make people with CLL more susceptible to infections, which can alter the immune system's ability to fight off cancer cells. In addition, there is some evidence to suggest that the purine analogue cladribine (Leustatin, 2-Cda) and some alkylating agents used in the treatment of CLL may further damage the immune system, possibly raising the risk for secondary cancers.

The risk for developing secondary cancers from radiation therapy depends on a number of factors, including the amount of radiation given and the part of the body treated. For example, CLL patients with more extensive disease in lymph node groups below the diaphragm are at greater risk for developing gastrointestinal cancers such as colon cancer. Less common secondary cancers include basal cell skin cancer and sarcomas of the bone and soft tissue.

Combating Side Effects

Pain Management

Pain may result from treatment. For example, pegfilgrastim (Neulasta), given to stimulate white blood cells, may cause bone pain. Pain may also occur as a result of procedures or tests (such as bone marrow biopsy). Pain may be acute (comes on quickly) or chronic (lasts over a long period of time).

Living with pain can have a negative effect on overall quality of life. However, many medical advances have been made in the treatment of pain, including an improved understanding of how medication works to relieve it. Many healthcare teams now include pain specialists. Several techniques, such as relaxation, guided imagery and biofeedback, may also relieve pain. Keeping a journal of when pain occurs, what it feels like (sharp, throbbing, etc.), how strong it is and how long it lasts will help physicians develop the most appropriate pain management plan. For more information on managing pain, visit the American Pain Foundation's website at painfoundation.org.

WHEN TO SEE YOUR PHYSICIAN

Your physician or a member of your healthcare team will discuss possible treatment side effects with you prior to initiating therapy. If you experience a side effect that is not expected or if your complications are prolonged, see your physician. If you experience a medical problem that cannot wait for a regularly scheduled appointment, such as high fever, shortness of breath, unremitting nausea and vomiting, chest pains and dizziness, call your physician, who will evaluate your situation and decide your next course of action. If you cannot reach your physician or a member of your medical team, go to your hospital emergency room for a medical assessment and place another call to your physician.

Exercise

Regular physical activity helps keep the cardiovascular system strong and body muscles flexible. Exercise can also help alleviate breathing problems, constipation, poor appetite and mild depression. It also helps reduce stress and fatigue. Several types of exercise are particularly helpful:

- General physical activity, such as swimming, dancing, mowing the lawn
- Aerobic activity to improve cardiovascular fitness, such as walking, jogging, bicycling
- Resistance training to strengthen muscles, protect joints and help remedy osteoporosis by building bone mass, such as lifting weights or using resistance-training equipment, push-ups, carrying and lifting
- Flexibility practices to improve range of motion, balance and stability, such as stretching and yoga

Patients should consult their physician before starting an exercise program.

Diet

Eating a healthy diet is important during CLL treatment. Nutritionists specializing in oncology care can be helpful in developing individualized nutrition plans. Patients should consult their physician before taking dietary supplements such as multivitamins or individual vitamin supplements because they may interfere with treatments.

For more information, visit

lymphoma.org
cllinfogroup.org

Chapter 7
Sexuality

Sexual Function During Treatment

The causes of sexual dysfunction experienced by men and women during and after a cancer diagnosis are varied. Psychological factors, such as fear about illness, altered body image due to hair loss and depression, and the physical side effects of treatment, can all conspire to reduce sexual desire (libido) and function. Besides fatigue, some chemotherapy treatments can interfere with testosterone levels in men, resulting in low libido. In women, decreased estrogen production may cause vaginal dryness, hot flashes and other menopausal symptoms. In women, radiation therapy to the pelvis can cause a narrowing of the vagina, painful intercourse and ovarian failure, resulting in infertility (see "Fertility Risks," on page 61). Some antidepressants and over-the-counter medications also lower sexual desire, as do certain lifestyle choices, such as smoking and drinking.

Be assured that the lack of sexual desire and function due to treatment is usually temporary. Although many people are often too embarrassed to raise the issue of sexual function with their physician, it is important to recognize that sexuality is an integral part of life and patients should discuss this with their physician. Physicians may order tests to track hormone levels and make recommendations to see a specialist and/or prescribe medications to restore erectile function in men and hormone therapy to alleviate vaginal dryness and other menopausal symptoms in women.

When to Use Contraceptives

Lymphoma is not a contagious disease, and it cannot be caused by or transferred through sexual intercourse. However, because small quantities of chemotherapy may be found in semen or vaginal fluid of people undergoing treatment, using condoms is recommended during sexual intercourse. It is especially important for men to use condoms and women

to use birth control if they are getting chemotherapy and should be mandatory when taking immunomodulatory drugs, such as thalidomide (Thalomid) and lenalidomide (Revlimid), a derivative of thalidomide, which may cause birth defects in developing fetuses. Avoiding pregnancy while on chemotherapy is necessary since chemotherapy drugs may affect the fetus. Women should alert their physician if they suspect they have become pregnant.

It is also recommended that people who have undergone stem cell transplants use condoms to reduce their risk for contracting cytomegalovirus and other infections, due to a compromised immune system. To further reduce risk of infection, patients should avoid sexual intercourse if their blood counts (hemoglobin, white blood cells and platelets) are low. Patients should ask their physician when it is safe to engage in sexual intimacy.

QUESTIONS TO ASK YOUR PHYSICIAN ABOUT SEXUAL FUNCTION

- How will my treatment affect my sexuality?
- Will sexual function be restored after my treatment is completed?
- How long will it take for sexual function to be restored?
- Are there successful treatments for my sexual dysfunction?
- What can I do to restore sexual desire and function?

Chapter 8

Fertility Risks

Treatment for CLL, such as certain types of chemotherapy, especially alkylating agents, and radiation therapy, can interfere with fertility in several ways. In addition to killing cancer cells, these treatments can also affect healthy cells and reproductive organs, like the ovaries and testes, which produce the eggs and sperm crucial to fertility. Whether the infertility is temporary or permanent depends on a number of factors, including the patient's sex, age at the time of treatment, the specific type and dose of radiation therapy and/or chemotherapy used and treatment duration.

Patients considering having children in the future should consult their physician before treatment begins. A fertility specialist may also be consulted.

How to Protect Fertility in Men

Infertility occurs in men when the testes stop producing normal sperm cells. Currently, preserving fertility in men is much easier and more effective than preserving fertility in women. It involves collecting a sampling of semen and then freezing and storing it in a process known as sperm banking. The sperm can later be thawed and used for intrauterine insemination or in vitro fertilization. For men with low sperm counts, a procedure called testicular sperm extraction (TESE) can be performed in which testicular tissue is removed. The sperm extracted from the tissue can then be frozen and stored for later use.

Some men who lose fertility immediately following treatment may regain fertility in the future, although the chance of recovering fertility depends on several factors such as age (younger people are more likely to get their fertility back than older people) and the amount and duration of radiation and chemotherapy treatments.

How to Protect Fertility in Women

Cancer treatment may cause women to go into early menopause or may result in other damage that does not allow for a successful pregnancy. Although preserving fertility in women is more difficult than it is in men, the emerging field of oncofertility—a melding of two medical specialties, oncology and assisted reproduction—is providing new hope for lymphoma survivors concerned about their ability to conceive following treatment.

To date, the most widely available and successful way of preserving fertility before cancer treatment begins is by removing eggs, fertilizing them in vitro with the sperm of a spouse or donor and then freezing and storing the embryos for future use (embryo banking). Eggs may also be stored unfertilized (egg banking). Banking and using unfertilized eggs is more difficult, but it is a technique that has been recently developed. Because both of these techniques require a number of weeks of treatment to complete, they may not be advisable for women needing immediate treatment of their lymphoma.

Another fertility preservation method under active investigation is ovarian tissue cryopreservation (OTC) in which an ovary is removed laparoscopically and tissue from the ovary is frozen. Eggs from the tissue follicles are then fertilized and implanted.

Lupron (leurolide) injections are sometimes given to halt production of hormonal function before chemotherapy begins, limit ovarian exposure to the treatment and protect the quality of the eggs. However, evidence of its success is highly controversial. Before treatment begins, all women of childbearing age should talk to their physician and a fertility preservation expert about the options available to them.

For more more information on fertility preservation techniques, visit:

- Fertile Hope (Fertilehope.org)
- Institute for Fertility Preservation (Fertilitypreservation.org)
- Myoncofertility.org

Chapter 9

If You Relapse or Do Not Respond to Treatment

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Although the majority of CLL patients respond favorably to initial treatment, achieving either a complete or partial remission, they may relapse (the cancer recurs) or become refractory (the cancer is resistant to treatment). In general, if a patient's cancer becomes resistant to treatment, a more aggressive form of second-line therapy, such as a stem cell transplant, may be necessary. In the relapsed setting, if the patient has a low-burden of disease, it may not be necessary to immediately restart treatment and a period of observation, or watch and wait, may be appropriate. If there is evidence of progressive disease occurring after approximately 12 months following the discontinuation of treatment, patients can usually be successfully retreated with either the same therapy or other therapies.

Treatment for Relapsed/Refractory CLL

The type of relapse experienced, when it occurs, the extent of the disease, overall health and the previous therapies received, all influence the type of treatment prescribed. For relapsed patients, the second-line treatment protocol will usually include a combination of chemotherapy and immunotherapy agents. There are many single-agent monoclonal antibodies being tested in clinical trials in relapsed CLL patients.

Some common single-agent therapies currently used in the relapsed setting include:

- Alemtuzumab (Campath)
- Fludarabine (Fludara)
- Chlorambucil (Leukeran)
- Rituximab (Rituxan)
- Ofatumumab (Arzerra)
- Bendamustine (Treanda)

Some common combination treatment regimens used in the relapsed or refractory setting include:

- CVP (Cytoxan, Vincristine, Prednisone)
- FR (Fludarabine, rituximab)
- FCR (Fludarabine, Cytoxan, rituximab)
- R-CHOP (Rituximab, Cytoxan, Adriamycin, Vincristine, Prednisone)
- BR (Bendamustine and rituximab)

There are many novel therapies currently under clinical trial investigation in the relapsed/refractory setting and include:

- ABT-263 (an inhibitor of the Bcl-2 protein)
- Flavopiridol (a cyclin-dependent kinase inhibitor)
- Oblimersen sodium (Genasense)
- Lumiliximab (anti-CD23 antibody)
- Lenalidomide (Revlimid)
- TRU-016 (anti-CD37 protein)

Additional agents emerge regularly. For a complete list, patients should contact *Lymphoma Helpline* (800-500-9976) or speak with their physician.

Part 4: Living With Chronic Lymphocytic Leukemia

Chapter 10
Regaining Your Life After Cancer

Coping with CLL varies among individuals. Some common coping strategies are highlighted below.

Coping

Communicating

It is important that patients communicate their fears and concerns about having CLL with their loved ones, friends, physicians, nurses or social workers. Writing down their fears in a journal may also help.

Overcoming Depression

It is not unusual for people living with cancer to feel sad or depressed. Being diagnosed with CLL and undergoing treatment can be challenging both physically and emotionally. Signs of sadness or depression include sleeping more or less than usual, lack of energy, crying and an inability

to concentrate. In addition to challenging life circumstances, depression may also be caused by certain medications. Patients who experience any symptoms of depression that last longer than two weeks should contact a psychiatrist, social worker, psychologist or counselor. The CLL Information Group, cllinfogroup.org, also offers online group discussions with patients and medical advisors.

Coping with Physical Changes

Hair loss, weight loss/gain and changes in physical appearance may occur as a result of treatment. To cope with these changes, patients should speak with their healthcare team, get ideas from other CLL survivors and use techniques most comfortable to them.

Maintaining a Healthy Lifestyle

Eating a healthy diet, engaging in regular physical exercise and getting sufficient rest can help combat the stress and fatigue of CLL and its treatment (see "Combating Side Effects," on page 56).

Life After Remission and Follow-Up Care

Although finishing CLL treatment can be significant, it is normal to experience ongoing feelings of anxiety and worry about a relapse. Adjusting to the "new" normal routines of life during and after cancer may take a few weeks or months to complete. Developing a wellness plan with guidance from the healthcare team may lead to a better sense of overall well-being.

Some changes to consider making:

- Quit smoking
- Reduce alcohol consumption
- Exercise (walking, biking, swimming)
- Eat a healthy diet

Follow-Up Care

Most people with CLL will have a favorable response to initial treatment, enabling them to achieve either a complete remission or a partial remission. However, regardless of the type of remission achieved, it is important that each patient adhere to a schedule of regular follow-up office visits established by his or her physician. Follow-up visits can range in frequency from every few months to once a year depending on the patient's disease progression, age, general health and time from last treatment.

Upong completing treatment, the healthcare team will develop a follow-up care schedule. This will include appointments with the hematologist/oncologist as well as regular visits with the general practitioner, OB-Gyns, etc. The hematologist/oncologist will monitor the status of the CLL through physical examination and various tests (e.g., blood, imaging, etc.).

STAYING PROACTIVE

To stay proactive in your healthcare, be sure to get the following information from your medical team:

- Copies of your medical records and a written summary of your treatment in case you switch oncologists or need to see a primary care physician for routine medical care
- A list of signs of disease recurrence and late side effects from treatment

At your follow-up care appointments, be sure to tell your physician about:

- Any new symptoms
- Pain
- Physical problems that disrupt your daily life such as fatigue, insomnia, sexual dysfunction, weight gain or loss
- Any new health problems, such as heart disease, diabetes or high blood pressure
- Any new medications or vitamins you are taking
- Emotional problems, such as anxiety or depression

For more information, visit

lymphoma.org
cllinfogroup.org

Part 5: Clinical Trials

Chapter 11
Clinical Trials

A clinical trial is a research study designed to answer basic questions about a new treatment or a new way of using an old treatment. There are hundreds of CLL clinical trials now underway in hospitals, cancer centers and physicians' offices around the country. The government, pharmaceutical and biotechnology companies, universities and physician groups often sponsor clinical trials. The Food and Drug Administration (FDA) and the institutional review board of participating hospitals or institutions must approve each phase in a clinical trial.

Basics of Clinical Trials

Clinical trials are performed to study new drugs and treatment strategies. Clinical trial investigations may study the following:

- A novel drug
- A new indication (use) for a drug already approved by the FDA as a treatment for a different disease
- Compare a new treatment with a standard treatment to determine which one is more effective or has fewer side effects

New drugs must pass through a rigorous approval process governed by the Food and Drug Administration (FDA) before it becomes a standard therapy for use in hospitals and clinics. The trials used to assess these drugs are typically divided into three types, called phases, each of which is designed to answer certain questions. Phase I tries to determine whether a potential treatment is well tolerated; phase II tests the drug's effectiveness in a small group of patients; and phase III tests the drug's effectiveness compared to standard therapies or other available treatments in a large, varied group of patients with a specific cancer. Patients may be eligible to take part in different stages depending on their condition, type and stage of lymphoma and the type of treatment, if any, previously given.

Phase I

Phase I studies (first in human studies) are designed to assess the maximum tolerated dose (MTD), frequency of treatment and overall safety of the drug in a small number of patients.

Phase II

Once the therapy dose is determined and shown to be safe in a phase I trial, it is then ready to be tested in a phase II study. Phase II studies aim to establish whether the therapies have any evidence of effectiveness in a larger group of patients with a particular type of cancer (e.g., CLL).

Phase II studies might be used to generate preliminary data on a drug or to confirm data to obtain FDA approval. Phase II studies also investigate whether a therapy already approved for one type of disease is effective treatment for another.

Phase III

Phase III trials are performed to determine whether the treatments developed in phase I and II studies are better than what is currently considered the "standard of care" for a specific disease. Phase III studies often require a large number of patients. Once a patient elects to enroll in a phase III study, he or she is assigned to one of two groups in a process called "randomization." In randomization, a computer assigns the treatment the patient is to receive. One group receives the standard

therapy and the other group receives the experimental treatment. It is important to remember that this randomization process is done so that each treatment arm will have patients with similar characteristics and be free of bias. The randomization in phase III trials allows researchers to determine whether or not the new treatment is any more effective or less toxic than the standard of care.

Use of a Placebo in Phase III Trials

A placebo, or sugar pill, is an inactive ingredient that is used is some types of clinical trials to ensure that the test results are unbiased. It is important to note that clinical trial participants will never receive a placebo in phase III trials if standard therapy exists. Patients would only potentially receive a placebo if there were no standard therapies to test against. Placebo-controlled trials are never done in a manner to deny patients an effective therapy. They are often done to add a new therapy to what might be the standard therapy.

Participating in a Clinical Trial

Clinical trials should not be considered a "last resort" by patients. Chronic lymphocytic leukemia patients can often benefit from participation in clinical trials both in the frontline treatment setting and in the relapsed treatment setting. Clinical trials offer patients therapies that are not otherwise available to all patients and are monitored very closely.

Informed Consent

During the informed consent process, the healthcare team will review the design of the study, possible risks and benefits and what will be expected of the participant. The healthcare team will answer any questions and ask the patient to sign a consent form, indicating their desire to particpate in the study.

The Cost of Being in a Clinical Trial

Clinical trials are very expensive undertakings for the study sponsor. Patient costs vary 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. Some health insurance and managed healthcare providers will pay for the basic medical procedures associated with the trial, such as lab 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 physician visits, tests or treatments. The costs vary depending on the study and the health plan. Medicare provides coverage for patient care associated with government-sponsored clinical trials.

If a patient is taking part in a National Cancer Institute (NCI) trial being conducted at the National Institutes of Health (NIH) in Bethesda, Maryland, the NCI will pay for the study drug and the costs related to the study. A stipend for travel, food and lodging 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, provide financial assistance for treatment-related expenses. (See "Drug Costs: What to Do If Your Insurance Does Not Pay," on page 44.)

Patients should ask their physician what clinical trials may be most appropriate for them. Here are some additional ways to find information:

- Contact the *Lymphoma Helpline* at the Lymphoma Research Foundation at (800) 500-9976 to request a clinical trial search.
- Cancer centers in your area may also have information about trials.
- Coalition of Cancer Cooperative Groups (CancerTrialsHelp.org).
- NIH websites (Cancer.gov and Clinicaltrials.gov).

QUESTIONS TO ASK YOUR PHYSICIAN

- What is the purpose of this clinical trial?
- Who is sponsoring the trial (National Cancer Institute, a cancer center, a pharmaceutical company)?
- How long does the study take?
- What are the risks involved?
- Will I be in any discomfort or pain?
- What kinds of tests, procedures or treatments will be performed; how many and how often?
- Will I be able to see my own physician during the trial?
- What costs will I be resonsible for?

Chapter 12
Therapies Under Investigation

Many drugs are approved by the United States Food and Drug Administration (FDA) for very specific and often restricted indications. This chapter will focus exclusively on those drugs that are *not* currently FDA approved for CLL and may represent major advances in our efforts to cure or manage cancer better. Therefore, patients may find that these drugs are only available in clinical trials. This chapter will forego detailed discussions about presently approved agents in CLL and efforts to expand their indications in specific subtypes of the disease. Refer to Chapter 5 for more detailed description of already approved agents in CLL. It is critical to remember that today's science is moving very fast. Therefore, the charts in this chapter may not be entirely comprehensive or accurate depending on when this information is being read. Please check with the Lymphoma Research Foundation or your physician for additional information and recent updates.

Therapy	Predominant Mechanism of Action	Comments
Monoclonal Antibodies		
MDX-1342	CD19	Relapsed/refractory
Veltuzumab	CD20	Relapsed/refractory
GA-101	CD20	Relapsed/refractory
Lumiliximab	CD23	Relapsed/refractory
Ontak (denileukin)	CD25	Relapsed/refractory
Lucatumumab (HCD-122)	CD40	Relapsed/refractory
Galiximab	CD80	Relapsed/refractory
TRU-016	CD37	Relapsed/refractory

Monoclonal Antibodies

A monoclonal antibody (MAb) targets a specific antigen, which is like a beacon that attracts antibodies and immune cells. Large amounts of antibodies can now be directed to a single antigen on the cell's surface like a guided missile. The MAb homes in on its target, the antigen on the lymphoma cell, and destroys the cell.

In addition to the two monoclonal antibodies approved for CLL, alemtuzumab (Campath) and ofatumumab (Arzerra), many other monoclonal antibodies are currently under investigation. These include MAbs targeting antigens such as CD19, CD20, CD23, CD25, CD37 and CD40.

Immunomodulatory Agents (IMids)

Immunomodulatory agents, referred to as IMids, may not only impact the nourishing environment of the cancer cells, but may also inhibit the formation of new blood vessels (angiogenesis). They may also induce both apoptosis (programmed cell death) and growth arrest in resistant cancer cells. These drugs have also been shown to increase the numbers of tumor fighting natural killer (NK) cells in patients' blood. These NK cells then mount a cellular response against the lymphoma. Thalidomide (Thalomid) and lenalidomide (Revlimid) are oral agents that have been approved by FDA for other blood disorders. Recent studies have shown that they work well in patients with CLL. Particularly impressive is their efficacy in patients with certain adverse prognostic factors where conventional therapies do not seem to work well. Side effects include lowering of platelet counts, neuropathy and increased risk of blood clots. There are several ongoing studies looking into the most effective use of these agents in CLL.

Therapy	Predominant Mechanism of Action	Comments
Immunomodulatory Agents (IMids)		
Thalidomide (Thalomid)	Immunomodulatory Agents (IMids)	FDA indications in myeloma; preceded approval of lenalidomide
Lenalidomide (Revlimid)	Immunomodulatory Agents (IMids)	FDA indication in myeloma and disease of bone marow failure; now being investigated in many forms of NHL

Proteasome Inhibitors

Nearly all cells in the body continually break down their own protein components to remove improperly made or damaged proteins and to control cell growth and other vital processes. The "cellular disposal" system which handles these proteins is called the "proteasome." In this form of cellular housekeeping, the proteasome cuts up protein molecules that are no longer needed by the cell. Recently, physicians and scientists have learned that certain cancer cells are particularly vulnerable to a new class of molecules called proteasome inhibitors. Bortezomib (Velcade), a therapy first approved for a type of blood cancer called multiple myeloma, was the first drug of this type approved to treat cancer. This drug has been approved for relapsed mantle cell lymphoma and is currently being tested as a therapy for follicular lymphoma and relapsed/refractory CLL.

Therapy	Predominant Mechanism of Action	Comments
Proteasome Inhibitors		
Bortezomib (Velcade)	Proteasome Inhibitor	Approved for treatment of multiple myeloma and mantle cell lymphoma; being investigated in relapsed/ refractory CLL
Dasatinib	Proteasome Inhibitor	Relapsed/refractory

Purine Analogs

Purine analogs belong to a class of drugs called antimetabolites. These drugs enter the cell and are transformed into an active form of the drug that is incorporated into cellular DNA, interfering with its function and its ability to repair itself. This effect results in cell death.

Therapy	Predominant Mechanism of Action	Comments
Purine Analogs		
Forodesine	Purine analog	Relapsed/refractory
Clofarabine	Purine analog	Relapsed/refractory

Bcl-2 Directed Therapies

Perhaps one of the most exciting new areas in cancer drug discovery over the last decade has revolved around the discovery and development of new small molecules which appear to be able to "teach" cancer cells how to die. One intrinsic feature of every tumor cell is its ability to divide when it should not and to resist dying when it should die. This "cell death thermostat" is established by the expression of a variety of proteins in the cell known as pro- and anti-apoptotic modulators. Pro-apoptotic proteins induce cell death while anti-apoptotic proteins resist cell death. Clearly, tumor cells contain an overabundance of those anti-apoptotic proteins which help the tumor cells survive even despite very toxic environments including those imposed by chemotherapy.

One of the first of these drugs is called oblimersen (Genasense). Since the development of oblimersen (Genasense), a variety of new small molecules, many of which are orally available, have been developed (e.g., ABT-263 and AT-101). These drugs appear to inhibit the anti-apoptotic influence of many different proteins within the tumor cell, thereby increasing the sensitivity of the tumor cell to the induction of cell death by chemotherapy. Though these agents are now in very early development, they have so far demonstrated very promising activity in early phase clinical trials across a whole range of lymphoma. The future development of these agents will be oriented toward studying them in combination and lowering the threshold required to induce cell death when given in combination with other drugs known to be active in lymphoma. These agents have the value that they target biology that is selectively overrepresented in tumor cells and therefore are not associated with the same toxicity seen with combination chemotherapy and to date have been found to be very tolerable in early phase I and II clinical trials in patients with lymphoma.

Agent	Predominant Mechanism of Action	Comments
Other New Agents		
Oblimersen (Genasense)	Bcl-2	Being studied in melanoma and CLL
ABT-263	Bcl-2	Lowers threshold necessary to kill cancer cells; active in CLL; may make chemotherapy more effective; broad applicability
AT-101	Bcl-2	Similar to ABT-263 above; orally available
Obatoclax mesylate (GX15-070)	Bcl-2	Relapsed CLL, MCL and other forms of lymphoma

Other Agents

Numerous other small molecules are under investigation in CLL.

Therapy	Predominant Mechanism of Action	Comments
Other New Agents		
Fostamatinib Disodium (FosD)	Syk inhibitor	Relapsed/refractory
Flavopiridol	Cyclin-D Kinase inhibitor	Relapsed/refractory
GRN-163L	Telomerase inhibitor	Relapsed/refractory
CAL-101	PI3K inhibitor	Relapsed/refractory

For more information, visit

lymphoma.org
cllinfogroup.org

GLOSSARY OF MEDICAL TERMS

Absolute neutrophil count (ANC): A measurement of the number of mature neutrophils (a type of white blood cell) that are available for fighting infection. A low ANC increases the risk for infection.

Advanced disease: Disease that has spread to multiple locations.

Aggressive lymphomas: Lymphomas that are fast growing and generally need to be treated immediately. Also called intermediate-grade or high-grade lymphomas.

Allogeneic transplant: A procedure in which a patient receives bone marrow or stem cells donated by another person.

Alopecia: Hair loss. Alopecia from chemotherapy is almost always temporary; hair grows back when therapy is finished.

Anemia: A shortage of red blood cells, causing weakness and fatigue.

Angiogenesis: The process of developing new blood vessels.

Antiangiogenesis therapies: Drugs that prevent tumors from developing new blood vessels, thereby stopping or limiting tumor growth.

Antibody: A substance made by B-lymphocytes that reacts with antigens on toxins, bacteria and some cancer cells and either kills or marks them for removal.

Antiemetic: A drug that reduces or prevents nausea and vomiting.

Antigen: Identifying proteins located on the surface of all cells. The immune system uses antigens to determine whether cells are a necessary part of the body or need to be destroyed.

Apheresis: The part of the stem cell transplantation procedure in which stem cells are removed from the blood.

Autologous transplant: A type of bone marrow or stem cell transplantation in which a patient receives his or her own cells.

Beta (2) microglobulin (B2M): A protein found in the blood. Higher levels of B2M suggest that the lymphoma may be more aggressive.

Biologic therapy: Treatment that uses or stimulates the immune system or other body systems to fight infection and disease.

Biopsy: Removal of a small piece of tissue for evaluation under a microscope.

Bone marrow: Spongy material found inside the bones containing stem cells that develop into three types of cells: red blood cells that deliver oxygen to the body and take away carbon dioxide; white blood cells that protect the body from infection; and platelets that help the blood to clot.

Bulky tumor: A large tumor, usually greater than five, seven or ten centimeters.

Cancer: Abnormal cell growth that cannot be controlled by the body's natural defenses. Cancerous cells can grow and eventually form tumors.

Catheter (intravenous access): A device that is temporarily or permanently put into a vein that makes it easier to give medications.

Cerebrospinal fluid: Fluid that is present around the spine and brain. It may be examined to determine if NHL has spread to these parts of the body.

Chemotherapy: Treatment with drugs to stop the growth of rapidly dividing cancer cells, including lymphoma cells.

Chemotherapy cycle: Term used to describe the process in which chemotherapy is given, followed by a period of rest in which the body is allowed to recover.

Chemotherapy regimen: Combinations of anticancer drugs given at a certain dose in a specific sequence according to a strict schedule.

Clinical trial: A research study in which a new treatment is given to patients to determine whether it is safe, more effective or less toxic than current therapies.

Combination Chemotherapy: Several drugs given together to increase response rate of certain tumors.

Complete remission (CR): Term used when all signs of the disease have disappeared after treatment.

CT or CAT (computerized axial tomography) scan: This imaging test provides a series of detailed pictures of inside the body using an X-ray machine linked to a computer.

Cure: There are no signs or symptoms of lymphoma, and a significant period of time (usually defined by years) has passed during which there are no relapses.

Decreased blood cell production: A decrease in the production of red blood cells, white blood cells and platelets that may occur as a side effect of cancer or cancer therapies. Also called myelosuppression.

Diaphragm: The muscle below the lungs and heart that separates the abdomen from the chest.

Disease progression: The term used if the disease worsens despite treatment (also called treatment failure).

DNA: Abbreviation for deoxyribonucleic acid, an essential component of genes.

Dose intensity: A term used to describe giving the highest possible doses of drugs over a specific period of time with acceptable side effects.

Durable remission: When a complete response lasts for years.

Dysgeusia: When familiar foods taste differently.

Echocardiogram: Use of ultrasound to examine the heart. It is ordered when potential cardiotoxic chemotherapy is used.

Etiology: The study of the causes of a disease.

Extranodal disease: NHL that has spread outside the lymphatic system.

Fatigue: A decreased capacity for activity that is often accompanied by feelings of weariness, sleepiness or irritability.

Gallium (radioisotope) scan: When injected into the body, radioactive gallium is a chemical that collects in some tumors. The body is then scanned to see whether the gallium has collected in a tumor.

Generalized disease: A cancer that has spread throughout the body.

Genes: The basic building blocks of heredity that are present in all cells. Genes are comprised of DNA and other materials.

Gene therapy: Therapy approaches that alter the genetic structure of tumor cells, making them more susceptible to either the immune system or chemotherapy drugs.

Grade: A method of classifying a tumor on the basis of how aggressively it is growing.

Graft versus host disease (GVHD): Occurs when a donor's bone marrow (graft) recognizes the recipient of the marrow (the host) as foreign. In response, the immune cells in the donor marrow attack the foreign cells in the host.

Harvesting: A procedure in which stem cells are obtained from the blood or bone marrow for use in repopulating the body's cells after high-dose chemotherapy.

Hematologist: A physician who specializes in treating diseases of the blood and blood-forming tissues.

Histology: The study of tissue characteristics that may lead to identifying a specific type of tumor.

Hodgkin lymphoma: One of the two major types of lymphoma that begin in the lymph nodes and tissues of the lymphatic system. All other lymphomas are classified as non-Hodgkin lymphomas. Hodgkin lymphoma has a characteristic cell, the Reed-Sternberg cell, seen by the pathologist under the microscope when looking at the tissue from the biopsy.

Hypogeusia: When the flavors of foods are not as strong as normal.

Hypothyroidism: A condition in which there is lower than normal production of thyroid hormone. Low thyroid levels can lead to a variety of effects, including mild weight gain, dry skin, fatigue and sleepiness.

Idiotype: A unique "fingerprint" portion of an antibody present on the surface of B-cells.

Idiotype vaccine: A lymphoma vaccine that is custom-made to attack an individual patient's lymphoma and contains idiotype (unique) tumor material and an immune stimulant.

Immune system: One of the body's defense mechanisms. All lymphomas are diseases of the immune system.

Immunological tests: Blood tests that detect the presence of diagnostic proteins or antigens on a tumor.

Immunotherapy: See biologic therapy.

Improvement: This term is used if a tumor shrinks following therapy but is still more than one-half of its original size.

Indolent lymphoma: Lymphoma that is slow growing and has few symptoms. Also called low-grade lymphoma.

Lactate dehydrogenase (LDH): An enzyme found in the blood. Higher levels of LDH suggest that the lymphoma may be more aggressive.

Laparoscopy: Passing a tube through the abdominal wall to obtain a small sample of tissue for examination under the microscope.

Leukemia: Disease generally characterized by the overproduction of abnormal or immature white blood cells that circulate or are present in the blood.

Leukopenia: A shortage of white blood cells, resulting in the inability to fight infecting organisms such as bacteria, fungi and viruses.

Localized disease: A cancer that is only present in a limited part of the body, for example, the neck or armpits.

Local therapy: A therapy that only affects a small area.

Low-grade lymphoma: Lymphoma that grows slowly and has few symptoms. Also called indolent lymphoma.

Lymph: The watery fluid in the lymph system that contains white blood cells (lymphocytes).

Lymph nodes: Small bean-shaped glands located in the small vessels of the lymphatic system. There are thousands of lymph nodes located throughout the body, with clusters of them in the neck, under the arms, the chest, abdomen and groin. Lymph nodes filter lymph fluid, trapping and destroying potentially harmful bacteria and viruses.

Lymphatic system: The channels, tissues and organs that store and carry lymphocytes that fight infection and other diseases.

Lymphocyte: A type of white blood cell. Lymphocytes, carried along by the lymph fluid, are part of the immune system and fight infection.

Lymphoma: A malignant disease that begins in the lymph nodes, organs and tissues of the lymphatic system (immune system). Hodgkin lymphoma is one type of lymphoma; the other major type is called non-Hodgkin lymphoma. There are approximately 61 types of non-Hodgkin lymphoma.

Malignant: Cancerous—a malignant tumor is a cancerous tumor.

Medical oncologist: A physician who specializes in the use of chemotherapy, hormone therapy and many other types of biologic therapies to treat cancer.

Memory cells: Memory cells are types of B-lymphocytes and T-lymphocytes. After a foreign invader or unwanted cell has been destroyed, surviving B- and T-lymphocytes develop into specialized memory cells that remain on watch and can provide protection if the invader is encountered in the future.

Metastasize: To spread to other organs of the body. Cancer may spread from its primary site to other sites or organs.

Monoclonal antibodies: Biologic therapies that act specifically against a particular antigen. Scientists can produce large amounts of antibody that can be directed to a single target (or antigen) on the cell's surface. Monoclonal antibodies have been developed to help combat specific cancers, including some forms of non-Hodgkin lymphoma.

MRI (magnetic resonance imaging): MRI uses magnets and radio frequency waves to produce images of inside the body. MRIs can provide information about tissues and organs that is not available from other imaging techniques.

Mucositis: Inflammation of the lining of tissues and organs. In the mouth, it is characterized by sores or inflammation.

Myelosuppresion: A reduction in the bone marrow's ability to make red blood cells, white blood cells and platelets.

Neutropenia: An abnormally low level of neutrophils (the white blood cells responsible for fighting bacterial infections).

Neutrophils: The primary type of white blood cells found in the blood that fight bacteria, etc.

Non-bulky tumor: A small tumor, usually less than five centimeters (approximately two inches)

Non-Hodgkin lymphoma (NHL): A group of several closely related cancers that arise from the lymphatic system. Although the different types of NHL have some things in common, they differ in what the cancer cell looks like under a microscope, how the cells grow and how the tumor affects the body.

Oncologist: A physician who specializes in treating cancer. Some specialize in chemotherapy (medical oncologists), radiotherapy (radiation oncologists) or surgery (surgical oncologists).

Palliation: Treatment that is given to remove or relieve symptoms.

Para-aortic: The area close to the aorta. The aorta is the largest vessel in the body and rises from the heart.

Partial remission (PR): The term used when a cancer has shrunk in size by at least half but has not totally disappeared. The cancer can still be detected, and other treatments may be recommended.

Pathologist: A physician who specializes in studying disease through microscopic evaluation of body tissues and organs. Any tissue suspected of being cancerous must first be examined by a pathologist to confirm the diagnosis.

PCR (Polymerase chain reaction): A molecular test that can identify small amounts of genetic material. This test is done if looking for minimal residual disease.

Performance status: A term used to describe a person's ability to follow a typical lifestyle.

Peripheral neuropathy: Damage to the nerves. This condition can be caused by some drugs and is usually characterized by tingling and weakness or numbness in the extremities.

PET (positron emission tomography) scan: A type of test that may be used instead of gallium scans to identify areas in the body that are affected by non-Hodgkin lymphoma. This test evaluates metabolic activity in different parts of the body using a radioisotope.

Plasma cell: A mature B-cell that makes antibodies—these antibodies help the body destroy or remove toxins, bacteria and some cancer cells.

Primary therapy: The first therapy given after a diagnosis of cancer.

Prognosis: The likely outcome of a disease, including the chance of recovery.

Pulmonary function test: A procedure for determining the capacity of the lungs to exchange oxygen and carbon dioxide efficiently.

Radiation field: The part of the body that receives radiation therapy.

Radiation oncologist: A physician who specializes in treating cancer with radiation.

Radiation therapy: The use of radiation beams (X-rays) to treat a cancer. High doses of high-energy radiation beams carefully focused on a tumor will kill cancer cells. Radiation therapy (with or without chemotherapy) is used to treat certain lymphomas.

Radioimmunotherapy: A therapy that is prepared by attaching a radioactive isotope to a monoclonal antibody.

Radionuclide tests: Tests that use radioactive substances to help evaluate the function of tissues.

Refractory disease: A cancer that is resistant to treatment.

Regimen: A specific combination of drugs (chemotherapy), their doses and their schedules of administration. A regimen may also include radiotherapy.

Relapse: The return of cancer after treatment. Lymphoma may recur in the area where it first started, or it may occur in another place.

Remission: The absence of disease. A patient is considered in remission when the lymphoma has been treated and tumors have diminished by at least 50 percent (partial) or have totally disappeared (complete). Remission does not necessarily mean cure. Patients with intermediate or aggressive lymphomas must achieve a complete remission and maintain it for a period of time, usually five or more years, before there is consideration of cure. Patients with low-grade tumors are usually not considered cured because the disease can reappear even with a long remission of many years. Patients may have a complete or partial remission.

Risk factors: Factors that may increase the chance that a person will develop NHL. It is important to note that most people with risk factors never develop lymphoma, and many who are diagnosed have no identifiable risk factors.

Salvage therapy: Therapy that is given if the primary therapy is not successful or if the disease disappears and then comes back.

Spleen: An organ on the left side of the upper abdomen, near the stomach. A key component of the lymphatic system, the spleen produces and stores lymphocytes and releases them when required as part of the body's response to infections and other stimuli. The spleen may store blood and remove old blood cells from circulation.

Stable disease: The disease does not get better or worse following therapy.

Stage: The extent of cancer in the body, including whether the disease has spread from the original site to other body parts.

Standard therapy: The most widely used primary therapy.

Synergism: The term used when two or more drugs given together provide a better anti-cancer effect than expected from the additive effects from the medications alone.

Systemic symptoms: Symptoms that affect the entire body. Examples of these include fever, night sweats and weight loss.

Thrombocytopenia: A shortage of platelets in the blood, which reduces the ability of the blood to clot.

Thymus gland: A gland located behind the sternum (breastbone) that enhances the reproduction and development of lymphocytes. T-lymphocytes are processed in the thymus.

Toxicities: The unwanted side effects of cancer therapies, such as a decrease in blood cells, nausea and vomiting, and hair loss.

Tumor: An abnormal mass or swelling of tissue. Tumors may occur anywhere in the body. A tumor may be benign (non-cancerous) or malignant (cancerous).

Vaccine: A substance or group of substances meant to cause the immune system to respond. A vaccine can help the body recognize and destroy cancer cells. Lymphoma vaccines often combine cancer antigens with a substance to stimulate the patient's own natural defenses to fight the disease. These vaccines in lymphoma are custom-made for each patient, using a sample of tumor obtained from the patient's lymph nodes.

VEGF (Vascular Endothelial Growth Factor): One of a number of substances that stimulate angiogenesis, blood vessel formation—a process necessary for tumor growth.

Watchful waiting: An approach in which no immediate medical, surgical or radiation therapy is given. Patients are followed closely to make sure the cancer does not progress. Watchful waiting is an appropriate option for some patients with indolent (slow-growing) non-Hodgkin lymphoma.

Xerostomia: A temporary reduction in the production of saliva or "dry mouth."

X-ray: Radiation that is used in low doses to provide images of the inside of the body and in high doses to treat cancer.

For more information, visit

lymphoma.org
cllinfogroup.org

About CLL (Chronic Lymphocytic Leukemia) Information Group (CIG)

The CLL Information Group (CIG) was created in the autum of 2004 to provide disease-specific information to CLL/SLL patients and their caregivers. The CLL Information Group is a membership network of CLL patients and currently serves nearly 1,000 members.

The CLL Information Group organizes teleconferences with renowned CLL specialists, provides educational webcasts on CLL-specific topics and assists in the creation of various seminars and workshops for CLL patients.

Website (cllinfogroup.org)

In 2007, CIG launched an educational website. The site is frequently updated with the latest information on CLL-specific treatments and research, making it a complete and comprehensive resource for CLL patients.

Internet Discussion Group

An internet-based discussion group exists in relation to CIG (CLLSLL@yahoogroups.com), which focuses on the medical, educational and technical issues CLL patients currently face. The group is regularly joined by CLL expert Richard Furman, MD, of the New York-Presbyterian Hospital, Weill Medical College of Cornell University.

Contact Information

To join CIG, send an e-mail to jb50192@aol.com, or log on to the web site above.

To join the discussion group, send an e-mail to cllsll-subscribe@yahoogroups.com and follow instructions.

For more information, visit

lymphoma.org
cllinfogroup.org

About the Lymphoma Research Foundation

The Lymphoma Research Foundation (LRF) is the nation's largest lymphoma-focused nonprofit health organization devoted exclusively to funding lymphoma research and providing patients and healthcare professionals with the most current information on the disease. The Foundation's mission is to eradicate lymphoma and serve those touched by this disease.

The Lymphoma Research Foundation was formed in 2001 with the merger of the Cure For Lymphoma Foundation (CFL) and the Lymphoma Research Foundation of America (LRFA). Both organizations were founded by lymphoma advocates who wanted to turn a life-altering diagnosis into a positive experience for others with the disease. Ellen Glesby Cohen founded LRFA in Los Angeles in 1991. Until her death in 2000, Ellen was a tireless champion for patients and their families who created new education and support programs and served as a staunch advocate for improved government legislation. Jerry and Barbara Freundlich founded CFL in 1994 in New York City. Jerry is a long-term survivor of non-Hodgkin lymphoma.

Resources for Patients, Survivors and Loved Ones

Receiving a diagnosis of lymphoma can be challenging. Whether you or someone you love is newly diagnosed or a long-term survivor, understanding the latest medical information and accessing appropriate support services may help. Lymphoma Research Foundation offers a wide array of programs and support services to assist you from the point of diagnosis through long-term survivorship.

Patient Services and Support

Lymphoma Helpline and Clinical Trials Information Service
Through this phone and email service, trained staff members are available to answer your questions and provide individual support to you and your loved ones. Services are available in any language.

Lymphoma Support Network (LSN)

This national one-to-one peer support program matches lymphoma patients or caregivers with volunteers who have had similar lymphoma-related experiences.

Lymphoma Newsline

Lymphoma-related news can be distributed to you directly through this free electronic news services. Sign up by clicking on the "register" icon on LRF's homepage at lymphoma.org.

In-Person Patient Education Programs

North American Educational Forum on Lymphoma

This two-day national forum is held annually and provides critical information about the latest in lymphoma research, making the best decisions about treatment options and patient support issues.

Lymphoma Workshop: Understanding Lymphoma Basics and Current Treatment Options

These regional, full-day educational programs provide the latest information about lymphoma, current treatment options and patient support issues.

Multimedia Programs

Because LRF understands that information about lymphoma continually changes throughout the year, the ongoing production of webcasts, podcasts and teleconferences enable you to access the latest information on specific topics anywhere, anytime.

Webcasts

Webcast programs offer you the opportunity to navigate through a synchronized audio and slide presentation.

Podcasts

Podcasts (video format) can be viewed on LRF's website.

Teleconferences

Teleconferences are hour-long interactive telephone programs that provide an opportunity to learn more about lymphoma, treatments and promising research from leading lymphoma experts. These are conducted live, and the archived version is available after the program.

Publications

Patient Guides

In addition to this publication, LRF also produces *Understanding Non-Hodgkin Lymphoma: A Guide for Patients, Survivors and Loved Ones* and *Understanding Hodgkin Lymphoma: A Guide for Patients, Survivors and Loved Ones.*

Fact Sheets

Fact sheets with the latest disease- and treatment-specific information are available in either hard copy or in PDF on LRF's website. New topics are added on a regular basis; check to see if the topic you are looking for is available.

Newsletters

To keep you abreast of LRF research and news in the wider lymphoma community, you can sign up to receive any of LRF's regular newsletters either electronically or via mail.

Any of LRF's publications may be ordered by visiting lymphoma.org. Individual and bulk copies are available free of charge.

Resources for Children and Young Adults

Lymphoma in Your Teens, 20s and 30s

The Foundation offers a wide array of webcasts and podcasts for individuals affected by lymphoma as teens or young adults, including topics specifically designed to help friends and family. Visit lymphoma.org/youngadults to access these programs.

LIVESTRONG Young Adult Alliance

The Lance Armstrong Foundation's LIVESTRONG Young Adult Alliance is a coalition of organizations with the goal to improve the survival rates and quality of life for young adults with cancer between the ages of 15 and 40. By visiting livestrong.org/yaa you can access the websites of all member organizations that specifically provide services for young adults with cancer.

Planet Cancer

Planet Cancer (a program of the Lance Armstrong Foundation) is a peer support community for young adults going through the tremendously isolating experience of cancer between the ages of 18 and 40. On Planet Cancer, young adult patients and survivors connect 24 hours a day, 7 days a week through a dynamic and irreverent social networking website and face-to-face retreats. Planet Cancer also provides advocacy programs to build awareness about the unique medical and psychosocial needs of this often-overlooked age group. Visit planetcancer.org to access these services.

Ulman Cancer Fund for Young Adults

This organization focuses on how cancer affects young adults and offers scholarships, community grants, advocacy services and a guidebook. Visit ulmanfund.org for more information.

How to Access Programs and Services

Many of the aforementioned programs are available on LRF's website at lymphoma.org. For additional information about these resources, call (800) 500-9976 or email us at helpline@lymphoma.org.

If you would like to order additional copies of *Understanding CLL/SLL: A Guide for Patients, Survivors and Loved Ones*, please call (800) 500-9976 or visit lymphoma.org.

HOW TO GET INVOLVED AND GIVE BACK

Take Action to Make a Difference

The LRF Advocacy Program is a network of people and programs dedicated to increasing awareness and support for the lymphoma community. The Advocacy Program focuses on taking action on laws, policies and positions that affect every lymphoma patient and survivor. By contacting elected officials via phone calls, email and letters in support of these priorities, local advocates help LRF to make lymphoma a national health priority. To become involved, visit lymphoma.org/advocacy.

Start or Join a Local Chapter

Chapter volunteers work tirelessly to educate people about lymphoma, conduct outreach, raise funds for research and participate in public policy and advocacy initiatives. To learn more about a chapter in your area or how to start one, please visit lymphoma.org/chapters or call (800) 235-6848.

Raise Funds and Awareness

Raise funds and awareness by participating in a variety of events being held across the country such as Lymphomathon walks, bike rides, golf tournaments, galas, lunches, young professional social events and much more! Visit lymphoma.org/events for more information.

Join Team LRF

Team LRF is a program through which people across the country raise much-needed funds and awareness for lymphoma research through sporting events such as marathons, half marathons, triathlons, hiking adventures, bowling tournaments, soccer matches, bike rides, lacrosse tournaments, paddling events, dance-a-thons, spin-a-thons, yoga-a-thons and much more. Join Team LRF in an existing LRF-partnered event in your area, or join Team LRF Teammates Across the Country if you wish to raise funds by starting your own event or by participating in an event in which LRF does not have official charity entries. For more information, visit lymphoma.org/teamlrf.

Notes

Donate Now

The Lymphoma Research Foundation (LRF) is a nonprofit health organization with 501(c)(3) status. If you would like to support LRF, your generous gift will help us move closer to finding a cure, while helping those affected by the disease.

Three easy ways to give:

Website: lymphoma.org/donatenow

Call: (800) 235-6848

Mail: Cut out this form and mail it to Lymphoma Research Foundation, 115 Broadway, 13th Floor, New York, New York 10006
or
FAX Fax: (212) 349-2886

Amount of donation $ _____

Make checks payable to the Lymphoma Research Foundation. You may also specify that your gift be used for CLL-specific research, or that it be channeled to the CLL Information Group (CIG). If so, please indicate this on your check or enclose a note.

Charge my ☐ Amex ☐ Visa ☐ MasterCard

Credit Card # Exp. Date

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Notes

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